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Editor's corner: Nutrición Hospitalaria *2017*

"Scientific information is of no value without dissemination"
J. Loscalzo, Editor Jefe de Circulation

Como es habitual, coincidiendo con el comienzo de un nuevo ejercicio, el Comité Editorial da cuenta del último año en *Nutrición Hospitalaria (NH),* de su situación general, de los cambios producidos y de los resultados obtenidos. Dos son los aspectos relevantes durante 2017, en apariencia, contrapuestos: el incremento en la visibilidad de la revista y, a la vez, la disminución en el factor de impacto *Journal Citation Report* (JCR).

Escribe Valentín Fuster en el prólogo de su libro *El círculo de la motivación* (Planeta 2013): "El desánimo y la incertidumbre, los descalabros y las adversidades, son elementos inseparables de nuestra existencia. Es imposible estar siempre arriba. Quien alcanza la cúspide fácilmente puede caer, pero luego puede alzarse de nuevo solo o con la ayuda de otros. La buena y la mala noticia es que el proceso es cíclico. Es un círculo en continua rotación, un empeño constante. Una vida satisfactoria es una conquista cotidiana". Podríamos asumir esta frase a la vista de la bajada en el factor de impacto de la revista en 2016. Esa es también la existencia cotidiana de una revista científica: esforzarse por mejorar, demostrar ser útil para los lectores, influir en la sociedad civil.

El resumen del año que acaba de terminar

En el año 2017, el número de manuscritos recibidos fue de 418, una cifra discretamente inferior a la de los dos años anteriores, en consonancia con el rigor en la evaluación de originales y en la concreción de las materias de interés para los lectores de *Nutrición Hospitalaria*. La tasa de aceptación general ha sido de un 48%. Desde mediados del año es posible acceder a los artículos ya aceptados antes de ser publicados ("on-line first"), tal y como nos habíamos propuesto en el comienzo del año (1). Se han publicado 217 manuscritos en los seis números de 2017, además de 4 números extraordinarios o suplementos, dos de ellos directamente relacionados con el Congreso Anual SENPE.

Nutrición Hospitalaria es la segunda revista española de la especialidad, ocupando el puesto 68 de 81 revistas agrupadas en la categoría *Nutrition & Dietetics* de la *Journal Citation Report* (JCR), en el cuartil 4 de esta disciplina y en el Q2, cuando nos referimos a revistas médicas. Frente a los 735 artículos citables en 2015, en 2016 fueron 175, con una media de 31,5 referencias por artículo. El número de citas recibidas en el año 2016 fue de 2.501. Sin embargo, si nos referimos a la puntuación "Eigenfactor", que es un índice basado en el número de veces que los artículos publicados en los cinco años previos han sido citados en el presente año, el número de orden sube al 37/81, señalando la vigencia en el tiempo de lo publicado.

En cuanto al índice H Google Scholar Metrics (que intenta medir el balance entre el número de publicaciones y las citas a estas) de 2016 fue de 32, en el puesto nº 4/87 de todas las revistas publicadas en España (2). Cuando se analiza en Scimago, (Scimago Journal & Country Rank [SJR]) su índice H es de 37, y es la primera dedicada a Nutrición y Dietética, en el Q2 de la clasificación de las revistas españolas, por encima de *Medicina Clínica* o *Revista Clínica Española.*

Nutrición Hospitalaria cumple 35/36 de los criterios de calidad establecidos por Latindex, que es el Sistema Regional de Información en Línea para Revistas Científicas de América Latina, Caribe, España y Portugal. La revista, que se publica en acceso abierto ("Open Access"), está disponible tanto en el Sistema de Información Científica Redalyc, Red de Revistas Científicas de América Latina y el Caribe, España y Portugal, como en SciELO, *Scientific Library on Line*.

editorial

editorial

Un comentario sobre el papel de *Nutrición Hospitalaria*

Mejorar el posicionamiento de la revista en el conjunto mundial de las publicaciones científicas es una tarea ardua, pero no imposible. Entre las dificultades para *Nutrición Hospitalaria* destacan, por una parte, el que la disciplina de la Nutrición Clínica y la Dietética comparte su ámbito de trabajo con otras especialidades y áreas de conocimiento –reflejo, a su vez, de la sociedad científica de la que es órgano de expresión; y por otra, su publicación –y difusión– en español en una gran mayoría de sus artículos.

Probablemente eso que parecen debilidades constituyen, a su vez, sus fortalezas, como señalan, por ejemplo, el número de autores y de lectores de la revista en todo el planeta (Fig. 1) y el de descargas (el número de mayo-junio de 2016 recibió más de 50.000) (Fig. 2). El surgimiento de métricas alternativas como indicadores

Figura 1.
Distribución geográfica de la procedencia de artículos en 2016.

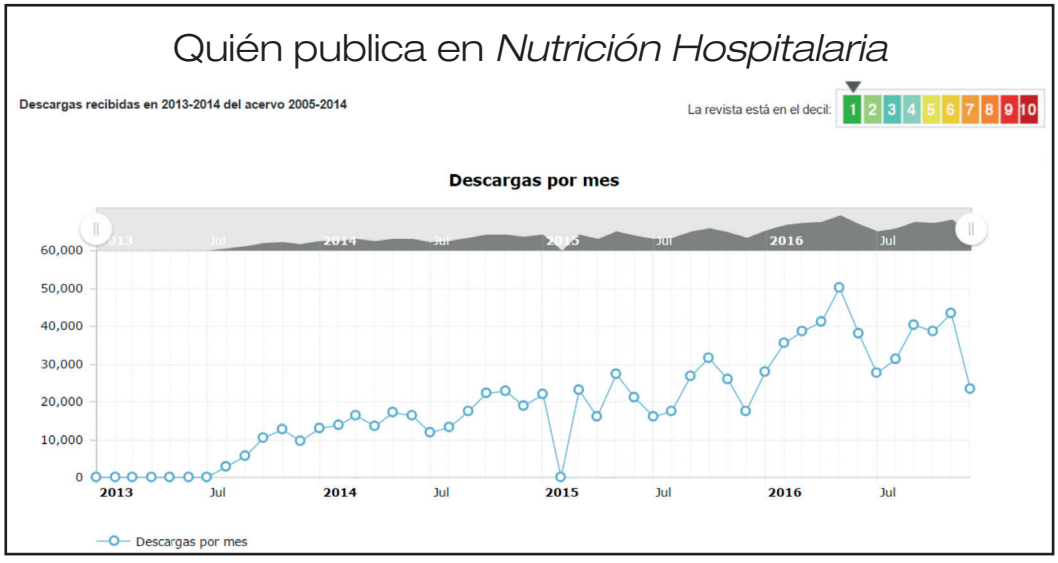

Figura 2.
Volumen de descargas de cada número de Nutrición Hospitalaria.

complementarios para evaluar el valor y el impacto de los artículos científicos está en revisión (3,4). Las menciones en los medios sociales, la cobertura en los medios de comunicación tradicionales y en línea, las descargas del texto completo son alternativas, cada vez, más reales a las que *Nutrición Hospitalaria* ha de adherirse. Nuevos indicadores como el impacto de descarga o de citas ponderado por campo que algunos repositorios internacionales han comenzado a valorar son el futuro. Conocer la bibliometría es ya parte de las tareas de cualquier investigador o cualquier profesional que pretenda publicar. También lo es para los editores de *Nutrición Hospitalaria.*

En 2018 cambiaremos la plataforma de manejo de manuscritos para hacerla más amigable tanto a los autores como a los revisores, trabajaremos en aumentar el número de repositorios internacionales en los que la revista se encuentra y buscaremos activamente artículos de revisión escritos por líderes de opinión en su campo. Todo esto no es posible sin el trabajo desinteresado del equipo de redactores adjuntos y del número creciente de revisores, cuya base de datos hemos actualizado a finales de 2017.

José Manuel Moreno Villares, Director
Gabriel Olveira, Subdirector

Bibliografía

1. Moreno Villares JM, Olveira G. Logros y retos de Nutrición Hospitalaria 2016-2017. Nutr Hosp 2016;34(1):1-3.
2. Delgado López-Cózar EM, Martín- Martín A, Orduña-Malea E. Índice H de las revistas científicas españolas según Google Scholar Metrics (2012-2016). EC3 Reports, 20. Granada, 26th November 2017.
3. Loscalzo J. The future of medical journal publishing. The Journal Editor's perspective: looking back, looking forward. Circulation 2016;133:1621-4.
4. Sanz Valero J, Wanden-Berghe C. El acceso a la documentación científico-técnica en ciencias de la nutrición. Nutr Clin Med 2016;3:140-52.

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Un paso más en seguridad en nutrición parenteral pediátrica

On step more in safety in pediatric parenteral nutrition

editorial

La seguridad del paciente es uno de los grandes retos de la asistencia sanitaria y en el uso de los medicamentos tenemos uno de los grandes campos de actuación, ya que los errores relacionados con la medicación suponen un alto porcentaje de los problemas de seguridad del sistema.

La nutrición parenteral pediátrica (NPP) es una tecnología sanitaria especialmente sensible en el aspecto de seguridad tanto por el tipo de paciente al que se destina, como por la gran complejidad del medicamento, en este caso la mezcla nutriente. Proveer de una mezcla segura y de calidad supone garantizar requerimientos, compatibilidad, estabilidad, esterilidad y exención de contaminantes, entre otros (1).

Afortunadamente, para la elaboración de mezclas seguras contamos con procedimientos, documentos y estándares de calidad en el proceso, que nos proporcionan nomogramas, gráficos, tablas y ecuaciones, y que forman parte de los sistemas informáticos de soporte a la validación de la mezcla de nutrición parenteral (2,3), ya que cubrir las elevadas necesidades de calcio y fosfato de la población pediátrica candidata a NP, supone un elevado riesgo de precipitación y, por lo tanto, de inestabilidad de las mezclas. La posibilidad de uso de sales orgánicas de calcio (gluconato y glucobionato) y de fósforo (glicerofosfato) ha conseguido resolver estos problemas de seguridad y/o minimizarlos (4).

Otro problema de seguridad importante en la NPP es la presencia de aluminio como contaminante procedente de sus componentes, lo que puede ocasionar toxicidad neurológica, hepática, ósea y de otros tejidos. Este hecho ha motivado que organismos como la FDA haya incluido el contenido en aluminio como de declaración obligatoria en sus preparados y haya establecido unos aportes máximos diarios. En determinados grupos de población candidatos a NPP, estos límites máximos pueden alcanzarse fácilmente dado los requerimientos elevados necesarios en pacientes pediátricos y neonatales (5,6).

La Guía de Práctica Clínica SENPE/SEGHNP/SEFH sobre NPP, publicada recientemente, trata esta problemática y recomienda tenerlo en cuenta sobre todo en recién nacidos pretérmino, por su inmadurez y bajo peso, y también en los niños con NP prolongada donde se han observado niveles plasmáticos de aluminio elevados. Este grupo de trabajo tiene en marcha estudios centrados en este problema de investigación (7).

Todas las iniciativas que aporten luz sobre este tema son muy importantes y serán bien recibidas por los equipos multidisciplinares que atienden a este grupo de pacientes, ya que precisamos esclarecer la falta de consenso que en este sentido encontramos en la bibliografía.

El primer punto a resolver es el conocimiento de las cantidades presentes en cada uno de los componentes utilizados para la elaboración de las mezclas, algo que solo depende de las autoridades sanitarias hacerlo posible. Existen estudios que muestran contenidos de aluminio en soluciones de gluconato cálcico 10 veces superiores a volúmenes equivalentes de cloruro cálcico (8). La aportación del grupo de estandarización de la SENPE en cuanto a la cuantificación de la contaminación en los preparados, naturaleza del envase como factor predisponerte, como ya nos adelantan respecto al vidrio o tipo de soluciones y sales con mayor riesgo, supondrá una información muy valiosa para la mejora de la seguridad.

En la bibliografía encontramos recomendaciones de expertos sobre la no utilización del cloruro cálcico como componte de la NP (9), así como estudios de estabilidad que muestran la utilización del cloruro de calcio en mezclas nutrientes parenterales con fosfato orgánico (glicerofosfato de sodio), a diferentes concentraciones y

con distintos aportes de macronutrientes, como una opción factible para disminuir la carga de aluminio contaminante (5).

En este sentido, en este número de *Nutrición Hospitalaria* se publica un trabajo de Watrobska-Swietlikowska y cols. (10), en mezclas de NPP prolongada de administración domiciliaria, donde tras un exhaustivo estudio de estabilidad fisicoquímica, concluye que la sal inorgánica de calcio podría ser una opción que minimice estos riesgos. Es importante a la hora de extrapolar resultados tener en cuenta las condiciones de elaboración de las mezclas y reproducirlas exhaustivamente, en cuanto a ingredientes y envases, diferentes composiciones cualitativas y cuantitativas que pudieran influir en el riesgo de agregación de partículas, así como manipulaciones posteriores de la mezcla que refieren en su metodología. Todos ellas podrían ser variables que sin duda podrían modificar la estabilidad y, por tanto, la seguridad para el paciente. Son innumerables los factores que intervienen en la precipitación de las sales calcio-fosfato además del tipo de sal utilizada, y que tienen que ver con otras propiedades fisicoquímicas del medio, como el pH, concentración de macronutrientes, temperatura, orden de adición, tiempo desde la elaboración y tiempo de infusión.

El debate sobre las ventajas e inconvenientes del uso de las sales de calcio y fosfato sigue abierto y enriqueciéndose gracias a las evidencias que van apareciendo. Tradicionalmente, la principal preocupación en su manejo era alcanzar los requerimientos sin riesgo de precipitación, algo que quedó prácticamente resuelto con las sales orgánicas, pero los riesgos asociados a la contaminación con aluminio ha desviado nuestra atención hacia la posibilidad de volver a contar con las sales inorgánicas de calcio.

Seguiremos atentos a las nuevas aportaciones y es que como decía George Bernard Shaw, dramaturgo irlandés del siglo XIX: "La ciencia nunca resuelve un problema sin crear otros 10 más".

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Bibliografía

1. Gallego C, Serrano J. Nutrición parenteral. En: Errores en Nutrición Infantil. Madrid: Ergon; 2014. pp. 121-32.
2. Consenso español sobre preparación de mezclas nutrientes parenterales. Grupo de Trabajo Nutrición de Farmacia SENPE-SEFH 2008. Disponible en: http://www.senpe.com/GRUPOS/farmacia/ConsensoPreparacion2008.pdf. [consultado: enero 2018].
3. Gomis P, Rodriguez I, Inaraja MT, et al. Formulación y elaboración. En: Estándares de práctica del farmacéutico de hospital en el soporte nutricional especializado: desarrollo y criterios de evaluación. Farm Hosp 2009;33(Extr. 19):36-48.
4. Gomis P. Componentes de las mezclas de nutrición parenteral en pediatría. Nutr Hosp 2017;34(Suppl. 3):32-9.
5. Poole RL, Pieroni KP, Gaskari S, et al. Aluminum exposure in neonatal patients using the least contaminated parenteral nutrition solution products. Nutrients 2012;4:1566-74.
6. Wier HA, Kuhn RJ. Aluminum toxicity in neonatal parenteral nutrition: what can we do? Ann Pharmacother 2012;46:137-40.
7. Pedrón Giner C, Cuervas-Mons Vendrell M, Galera Marinez, R, et al. Grupo de Estandarización de la SENPE. Guía de Práctica Clínica sobre Nutrición Parenteral Pediátrica. Nutr Hosp 2017;34(3):745-58.
8. Physical Compatibility of calcium chloride and sodium glycerophosphate in pediatric parenteral nutrition solutions. Collin Anderson, Mark MacKay. J Parenter Enteral Nutr 2016;40(8):1166-9.
9. Newton DW, Driscoll DF. Calcium and phosphorus compatibility revisited again. Am J Health Syst Pharm 2008;65:73-80.
10. Watrobska-Swietlikowska D, MacLoughlin R, Szlagatys-Sidorkiewicz A. The presence of inorganic calcium in pediatric parenteral admixtures. Nutr Hosp 2018;35(1):11-8.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

Monitorización de la nutrición enteral como indicador clínico para la evaluación de la calidad en unidades de cuidados intensivos

Tube feeding monitoring as a clinical quality indicator at intensive care units

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Resumen

Introducción: la desnutrición es particularmente prevalente en unidades de cuidados intensivos (UCI), asociándose con malos resultados clínicos. La nutrición enteral (NE) presenta múltiples beneficios en pacientes críticos y su monitorización ha sido establecida por la Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias (SEMICYUC) como indicador clínico de calidad (ICC; pacientes con NE correctamente monitorizados/todos los pacientes con NE, en %). Sin embargo, no se han publicado resultados sobre su monitorización reglada.

Objetivos: evaluar el cumplimiento del ICC "monitorización de la NE", identificando dificultades y posibilidades para su utilización.

Metodología: durante 18 meses, el ICC fue monitorizado en pacientes de UCI según criterios de SEMICYUC.

Resultados y conclusión: el ICC, aunque se presenta como único, tiene múltiples componentes, originando múltiples resultados difíciles de compilar. El estándar establecido (100%) solo fue alcanzado en control de la sonda y verificación de vómitos, regurgitación y broncoaspiración. Proponemos elaborar un listado de verificación diaria, incluyendo todos los aspectos contemplados, para su puesta en común entre los estamentos médicos y de enfermería, para cada paciente con NE.

Palabras clave:

Soporte nutricional.
Nutrición enteral.
Calidad asistencial.
Indicadores clínicos.
Paciente crítico.
Unidad de cuidados intensivos.

Abstract

Background: Malnutrition is particularly prevalent among intensive care unit (ICU) patients, being associated with poor clinical results. Enteral nutrition (EN) offers multiple benefits on critically ill patients and its monitoring was established by the Spanish Society of Critical Care (SEMICYUC) as a clinical quality indicator (CQI; EN patients correctly monitorized / all EN patients, as %). However, no results have been published on its regulated monitoring.

Objectives: Assessing CQI's compliance, identifying difficulties and possibilities for its use.

Methods: In a recent 18-month period, the CQI was assessed in ICU patients following SEMYCIUC criteria.

Results and conclusion: This CQI, although offered as a unique indicator, has different components, giving rise to multiple results. The settled standard (100%) was only reached by some of these components, i.e.: feeding tube position control plus verification of vomiting, regurgitation and aspiration. We propose to elaborate a daily checklist, including the different components that integrate this CQI, for its joint completion by nurses and physicians for all patients receiving EN.

Key words:

Nutritional support.
Enteral nutrition.
Quality of care.
Clinical indicators.
Critically ill patient.
Intensive care unit.
Tube feeding.

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INTRODUCCIÓN

La desnutrición en unidades de cuidados intensivos (UCI) presenta mayor prevalencia que entre el resto de pacientes hospitalizados (1,2), asociándose con empeoramiento clínico, aumento de complicaciones, estancia hospitalaria y mortalidad (2). Por ello, su detección, prevención y tratamiento son particularmente importantes. La nutrición enteral (NE) ha demostrado notables beneficios, especialmente si se inicia durante las primeras 24-48 horas desde el ingreso en UCI, destacando disminución de mortalidad, estancia hospitalaria y algunas complicaciones como hiperglucemia, fallo orgánico o infecciones (1,3). Sin embargo, el paciente crítico frecuentemente presenta dificultades para tolerar la NE. De la intolerancia a la NE puede derivarse un empeoramiento de la desnutrición y situación clínica del paciente (2). Por ello, el mantenimiento y control de medidas orientadas a conseguir su tolerancia, así como la oportuna identificación de complicaciones características de esta modalidad terapéutica son esenciales (4).

Los indicadores clínicos de calidad (ICC) son herramientas que valoran la adecuación, efectividad y seguridad de la práctica clínica, dimensiones primordiales de la calidad asistencial, identificando problemas y oportunidades de mejora (4,5). Los ICC generalmente se definen bajo fórmulas compuestas por un numerador –fácilmente identificable– y un denominador –más amplio, que puede ser el total de la muestra, o una parte de esta–, y suelen llevar asociado un estándar de cumplimiento como referencia (5). La Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias (SEMICYUC), en estrecha y extensa colaboración con la Fundación Avedis Donabedian, ha definido 120 ICC, nueve relativos a Nutrición y Metabolismo, y dos de estos referidos a NE. Los ICC de SEMICYUC han sido reproducidos y adoptados por numerosas sociedades médicas internacionales. El indicador número 53 NE precoz, considerado por SEMICYUC como uno de sus 20 indicadores relevantes, ha sido recientemente analizado (6).

Mediante el presente estudio, nos proponemos evaluar el ICC número 54 de SEMICYUC Monitorización de la nutrición enteral. Este ICC, de acuerdo con sus creadores, mide fundamentalmente la efectividad de la NE, siendo de gran utilidad para verificar su tolerancia y la detección de complicaciones. El indicador está integrado por la monitorización de los distintos aspectos recogidos en la tabla I (4) y no se han publicado resultados sobre su monitorización reglada.

PACIENTES Y MÉTODO

La población del estudio se obtuvo a partir de todos los pacientes ingresados en UCI en el Hospital Clínico San Carlos de Madrid durante un periodo reciente de 18 meses. De estos pacientes, 800 recibieron NE y tras excluir casos duplicados por reingreso en UCI, pacientes sin clarificación de historia clínica y aquellos con ingesta oral o nutrición parenteral previa a la NE durante el ingreso, se obtuvo una muestra final de 386 pacientes (edad media 63 ± 15, mediana 66, rango 17-88; varones 64%).

Tabla I. Desglose de resultados sobre la evaluación del indicador Monitorización de la Nutrición Enteral (ICC de SEMICYUC número 54)

Componentes del indicador (aspectos a verificar diaria o semanalmente) (4)	Casos correctamente verificados (n = 386)	Valor de cumplimiento
Control diario de cantidad de dieta administrada	384	99,48%
Control diario de posición de la sonda enteral	386	100%
Control diario de la posición del paciente	329	85,23%
Control diario de glucemia	385	99,74%
Control diario del ionograma plasmático	378	97,93%
Control semanal de trigliceridemia	67	17,36%
Control semanal de colesterolemia	67	17,36%
Control semanal del proteinograma plasmático	117	30,31%
Valoración diaria del volumen de RG	362	93,78%
Valoración diaria de estreñimiento	316	81,86%
Valoración diaria de DANE	316	81,86%
Valoración diaria de distensión abdominal	298	77,20%
Valoración diaria de vómitos	386	100%
Valoración diaria de regurgitación	386	100%
Valoración diaria de broncoaspiración	386	100%

Esta tabla recoge el número de casos en que los distintos componentes que integran el ICC fueron correctamente verificados a lo largo de toda la NE del paciente. En la columna de la derecha se muestra, para cada componente del ICC, el valor de cumplimiento, en porcentaje, calculado a partir de la fórmula descrita. El estándar de cumplimiento propuesto por SEMICYUC es del 100%.

SEMICYUC: Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias; NE: nutrición enteral; ICC: indicador clínico de calidad; RG: residuo gástrico; DANE: diarrea asociada a la nutrición enteral.

Además de registrar una serie de datos básicos sobre todos los pacientes, se monitorizó diariamente la verificación de una serie de controles requeridos en NE, así como la ocurrencia, o no, de una serie de complicaciones características de la NE. Los ítems (controles y complicaciones) que fueron monitorizados se recogen en la tabla I.

La valoración del ICC Monitorización de la NE se realizó, para cada uno de los distintos aspectos que lo integran (Tabla I), según criterios de SEMICYUC, mediante la fórmula siguiente, siendo el estándar de cumplimiento propuesto del 100%. Para los cálculos estadísticos se utilizó SPSS *Statistics* versión 23.

$$\text{ICC 54 (Monitorización de la NE)} = \frac{\text{N.º de enfermos con NE correctamente monitorizados}}{\text{N.º total de enfermos ingresados con NE}} \times 100$$

RESULTADOS

Tal como aparece en la tabla I, el estándar del 100% tan solo fue alcanzado para el control de la posición de la sonda y la verificación sobre ocurrencia de vómitos, regurgitación y broncoaspiración. En el resto de aspectos considerados, los valores se aproximaron al estándar, a excepción del control semanal de trigliceridemia, colesterolemia y proteinograma plasmático, cuyo cumplimiento, referido al mismo denominador, fue muy bajo.

La presentación de complicaciones se recoge en la tabla II, siendo las más frecuentes estreñimiento (42,2%), distensión abdominal (22,5%) y volumen elevado de residuo gástrico (RG 17,9%). No hubo casos de broncoaspiración y solo nueve de regurgitación (2,3%).

Tabla II. Resultado de la ocurrencia de complicaciones asociadas a NE

Complicación	Casos (%) n = 386
Volumen de RG elevado	69 (19,06%)*
Estreñimiento	163 (42,2%)*
DANE	31 (9,81%)*
Vómitos	46 (11,9%)
Regurgitación	9 (2,3%)
Distensión abdominal	87 (29,2%)*
Broncoaspiración	0 (0%)

*Esta tabla muestra los resultados sobre la aparición de complicaciones características de la NE, a lo largo de toda la duración de la misma. *En los casos señalados no fue posible determinar la proporción sobre la totalidad de la muestra, debido a ausencia de datos en algunos pacientes: 24 en volumen de RG, 70 en estreñimiento y DANE, y 88 en distensión abdominal. NE: nutrición enteral; RG: residuo gástrico; DANE: diarrea asociada a nutrición enteral.*

DISCUSIÓN

El paciente crítico es particularmente susceptible a desnutrición (1,2,7) por estrés catabólico y déficit de aporte (8). Esta se asocia a deterioro clínico, disminución de calidad de vida, aumento de estancia y gasto sanitario (7), y es la principal causa de mortalidad y algunas complicaciones (9) como hiperglucemia, infecciones o fallo orgánico (10). Distintos aspectos relacionados con la prevención, detección y manejo (4) de desnutrición en un entorno determinado (*e.g.* UCI) ofrecen la posibilidad de establecer ICC. En consecuencia, SEMICYUC ha propuesto nueve ICC relativos a Nutrición y Metabolismo en el enfermo crítico.

El indicador objeto de nuestro estudio, si bien se presenta como un único ICC (número 54 de SEMICYUC Monitorización de la nutrición enteral), está integrado por diversos componentes y su numerador (número de enfermos con NE correctamente monitorizados) se presta a interpretaciones ambiguas. Por una parte, mide el cumplimiento en la verificación diaria de una serie de controles (cantidad de nutrientes administrada, posición de la sonda y del paciente, y parámetros analíticos), y además evalúa la monitorización, también diaria, sobre la ocurrencia, o no, de una serie de complicaciones gastrointestinales características de la NE. Por ello, la monitorización de este ICC comporta una multiplicidad de resultados difíciles de compilar, como ha ocurrido en nuestro estudio.

En cuanto a la verificación de controles del ICC 54, los resultados de esta evaluación pueden ser presentados como porcentajes independientes para cada control *(i.e.* cantidad de dieta en 24 h, posición de la sonda, posición del paciente, glucemias, ionograma, etc.). Así hemos llevado a cabo nuestro trabajo. Sin embargo, de este modo, el ICC se desdobla en múltiples indicadores con sus correspondientes resultados.

Por otra parte, el ICC 54 incluye la identificación de las complicaciones gastrointestinales características de la NE. Este punto no es fácil de definir y se presta a confusión. Entendemos que este aspecto del ICC persigue que, en todos los pacientes que reciben NE, todas y cada una de las complicaciones consideradas sean oportunamente detectadas, a base de verificar diariamente su ausencia o presencia. Sin embargo, la mera presentación de resultados (en porcentaje) de las complicaciones observadas entre los pacientes recibiendo NE, tal como hemos llevado a cabo en nuestro estudio, no garantiza el cumplimiento del indicador. Para medir adecuadamente este aspecto del indicador, habría que verificar diariamente, dejando constancia de ello, si todas y cada una de las complicaciones consideradas han aparecido o no en cada uno de los pacientes.

Vistos los múltiples aspectos del ICC, consideramos que no solo mide efectividad, sino también adecuación y seguridad del paciente. Para su adecuada monitorización, proponemos elaborar un listado de verificación diaria (Fig. 1), incluyendo todos los aspectos contemplados, para su puesta en común entre los estamentos médicos y de enfermería, para cada paciente recibiendo NE. De esta forma, se identificarían aisladamente oportunidades de mejora para las distintas verificaciones contempladas. Para evaluar el cumplimiento del indicador, se practicaría el recuento de cuestionarios correctamente cumplimentados, expresando el

Listado de verificación diaria para monitorización de nutrición enteral en UCI

Paciente:
Fecha:

	VERIFICACIÓN DE CONTROLES	Sí	No
1	Cantidad de dieta administrada	□	□
2	Posición de la sonda de alimentación	□	□
3	Posición del paciente (semisentado 45º)	□	□
4	Control de glucemia	□	□
5	Control de ionograma plasmático	□	□

	VERIFICACIÓN DE COMPLICACIONES	Sí	No
1	Volumen elevado de residuo gástrico (normal ≤ 500 mL)	□	□
2	Estreñimiento (si ≥ 5 días ininterrumpidos sin deposiciones)	□	□
3	Diarrea asociada a nutrición enteral (DANE si ≥ 5 deposiciones líquidas diarias, o ≥ 2 deposiciones con volumen superior a 1000 mL)	□	□
4	Distensión abdominal	□	□
5	Vómitos	□	□
6	Regurgitación	□	□
7	Broncoaspiración	□	□

INSTRUCCIONES: la cumplimentación del cuestionario se limitará a indicar, previo consenso entre el médico y la enfermera responsables del paciente, si han sido verificados, o no, cada uno de los 12 ítems que integran el listado de verificación

Enfermera/o responsable Medico intensivista

Figura 1.

Listado de verificación diaria para la monitorización de nutrición enteral en UCI. Para evaluar el cumplimiento del indicador clínico de calidad Monitorización de la Nutrición Enteral (número 54 de SEMICYUC), se practicará el recuento de cuestionarios correctamente cumplimentados (los 12 ítems) y se expresará en porcentaje sobre el total de cuestionarios debidos (uno por cada día de nutrición enteral y paciente).

resultado en porcentaje sobre el total de cuestionarios debidos (uno por cada día de nutrición enteral y paciente). Por otra parte, consideramos que un nivel de cumplimiento superior al 90% en la compleción de dichos listados sería compatible con una práctica de excelencia y podría establecerse como estándar, en lugar del 100% propuesto actualmente.

Finalmente, creemos que el control semanal de trigliceridemia, colesterolemia y proteinograma, dadas las reducidas estancias en UCI registradas actualmente, debería suprimirse. En caso de mantenerlo, el denominador debiera limitarse al número total de enfermos con NE, ingresados en UCI durante siete o más días. Alternativamente, el numerador debiera incluir como correctamente controlados a todos aquellos pacientes que no alcancen dicha estancia. Ello limitaría enormemente la utilización del ICC.

BIBLIOGRAFÍA

1. Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, et al. European Society for Parenteral and Enteral Nutrition (ESPEN). ESPEN Guidelines on Enteral Nutrition: Intensive care. Clin Nutr 2006;25(2):210-23.

2. Ridley E, Gantner D, Pellegrino V. Nutrition therapy in critically ill patients- a review of current evidence for clinicians. Clin Nutr 2015;34(4):565-571.
3. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 2016;40(2):159-211.
4. Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias (SEMICYUC). Indicadores de calidad en el enfermo crítico. Actualización 2011 [Internet]. Madrid, España; 2011. [Accedido 13 sep 2016]. Disponible en: http://www.semicyuc.org/temas/calidad/indicadores-de-calidad
5. Parra Hidalgo P, Calle Urra JE, Ramón Esparza T, Peiró Moreno S, Meneu de Guillerna R. Sociedad Española de Calidad Asistencial (SECA). Indicadores de calidad para hospitales del sistema nacional de salud [Internet]. Oviedo, España; 2011. [Accedido 3 may 2016]. Disponible en: www.calidadasistencial.es
6. De la Calle de la Rosa L, Bermejo de las Heras S, Blesa A, Giner M, Arias Díaz J. Evaluación del indicador clínico de calidad 'nutrición enteral precoz' en servicios de medicina intensiva. Nutr Hosp 2017;34(6):1288-91.
7. Llopis-Salvia P, Luna-Calatayud P, Avellana-Zaragoza JA, Bou-Monterde R. Organization and management of nutritional care process in hospitalized patients: the model implemented in the "Hospital Universitario de La Ribera". Nutr Hosp 2012;27(2):529-536.
8. Shankar B, Daphnee DK, Ramakrishnan N, Venkataraman R. Feasibility, safety, and outcome of very early enteral nutrition in critically ill patients: Results of an observational study. J Crit Care 2015;30(3):473-475.
9. Joffe A, Anton N, Lequier L, Vandermeer B, Tjosvold L, Larsen B, et al. Nutritional support for critically ill children. Cochrane Database Syst Rev 2016;(5):1-31.
10. Yi F, Ge L, Zhao J, Lei Y, Zhou F, Chen Z, et al. Meta-analysis: total parenteral nutrition versus total enteral nutrition in predicted severe acute pancreatitis. Intern Med 2012;(6):523-530.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

The presence of inorganic calcium in pediatric parenteral admixtures

Presencia de calcio inorgánico en las soluciones pediátricas de nutrición parenteral

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Abstract

Introduction: Newborn infants and small children require large amounts of calcium and phosphate in a low volume of solution which can increase the risk of precipitation of calcium phosphate. Calcium gluconate is the predominant calcium salt form employed in parenteral nutrition (PN) compounding due to its solubility profile with phosphate. Unfortunately, calcium gluconate contains higher levels of aluminum contamination than calcium chloride, resulting in an increased potential for aluminum toxicity in patients receiving traditional PN. The physicochemical stability of 30 total parenteral admixtures containing inorganic calcium salts was evaluated.

Methods: Parenteral admixtures were prepared in one-chamber ethylene vinyl acetate bags: amino acids, glucose, electrolytes including only inorganic calcium salt and 20% (w/w) lipid emulsions (SMOFlipid®, Omegaven® or Lipofundin MCT/LCT®) were placed together in a one chamber bag. Admixtures were stored at +4 °C for up to eight days after preparation. Visual observations, globule size distribution (using optical microscopy, laser diffraction and photon correlation spectroscopy methods), pH analysis and zeta potential measurements were performed.

Results: The physicochemical stability of 29 of parenteral admixtures in the presence of inorganic calcium salt was confirmed. One admixture was deemed unsuitable for use in clinical practice due to the coalescence of oil droplets.

Conclusion: Despite the presence of inorganic calcium salts, pediatric parenteral admixtures were stable up to eight days of storage. Due to presence of multiple components and a high risk of incompatibilities, physicochemical studies should be performed for each admixture before use in clinical practice.

Key words:

Pediatric parenteral nutrition. Physicochemical stability. Parenteral emulsion. Inorganic calcium. Home parenteral nutrition.

Resumen

Introducción: los recién nacidos y los lactantes precisan aportes elevados de calcio y fósforo en soluciones con pequeño volumen lo que aumenta el riesgo de formar precipitados de fosfato cálcico. La principal sal de calcio empleado en nutrición parenteral (NP) es el gluconato cálcico, debido a su perfil de solubilidad con el fosfato. Lamentablemente el gluconato cálcico contiene unas concentraciones elevadas de aluminio mayores que el cloruro cálcico, lo que resulta en riesgo potencial de toxicidad por aluminio en pacientes que reciben NP. En este trabajo se evalúa la estabilidad fisicoquímica de 30 mezclas de NP con sales de calcio inorgánico.

Métodos: las mezclas de NP se prepararon en bolsas de acetato de etilenvinilo. En una bolsa unicameral se mezclaron aminoácidos, glucosa, y electrolitos incluyendo una sal de calcio inorgánico y una emulsión lipídica al 20% (SMOFlipid®, Omegaven® o Lipofundin MCT/LCT®). Las mezclas se almacenaron a +4 ° C hasta 8 días tras la elaboración. Se realizó un examen visual, estudio de la distribución del tamaño de los glóbulos (mediante microscopía óptica, difracción por láser y espectroscopia fotónica), análisis de pH y medición del potencial zeta.

Resultados: se confirmó la estabilidad fisicoquímica de 29 mezclas de NP que contenían sales de calcio inorgánico. Sólo una de las preparaciones se consideró inválida para su uso clínico debido a la coalescencia de las gotas de grasa.

Conclusión: a pesar de la presencia de sales de calcio inorgánico, las mezclas de NP pediátrica fueron estables hasta 8 días de almacenamiento. La presencia de múltiples componentes y el riesgo elevados de incompatibilidades hace recomendable el estudio de estabilidad fisicoquímica de cada mezcla antes de su empleo en la clínica.

Palabras clave:

Nutrición parenteral pediátrica. Estabilidad fisicoquímica. Emulsión. Calcio inorgánico. Nutrición parenteral pediátrica.

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INTRODUCTION

Management of intestinal failure requires parenteral nutrition. For patients dependent on parenteral nutrition for longer than three months, home parenteral nutrition (HPN) is an opportunity for shortened hospital stays. The main indications for HPN in children include digestive tract diseases such as short bowel syndrome (59%), congenital enteropathies (10%), chronic pseudo-obstruction syndrome (9%) and inflammatory bowel diseases (5%) (1). In the vast majority of children, intestinal failure begins during the neonatal period and usually persists throughout the first years of life. The main aim of the complex treatment of children with intestinal failure is to achieve optimal growth and weight gain, and so the provision of macro- and micronutrients is crucial. The high energy and protein demand of dynamically growing and developing pediatric patients together with the possible loss of nutrients due to diarrhea, impaired motility or high stoma output, presents a significant challenge in preparing nutritional admixtures. In the early stages after surgical resection, anti-secretory drugs are useful to decrease both stoma output and stool volume (2). Total parenteral nutrition (PN) admixtures may be composed of different compounds which are mixed together, and so compatibility and stability must be considered (3). This is especially true for parenteral admixtures administered to premature infants, given the low final dose volume (4). The most critical parameters are the physical stability of these admixtures and the droplet size of the emulsions. If the droplet size exceeds the size of erythrocytes (6-8 μm), embolism can occur, which may have fatal consequences. The droplet size is influenced by many factors such as: the presence of electrolytes, especially those with a positive charge, can change the negative charge of the droplet surface of lipid emulsion (zeta potential), resulting in the coalescence of the droplets and even phase separation (5). All components, including vitamins, should mix together in order to avoid the requirement for patient manipulation in total parenteral nutrition (TPN) admixtures (6), and secondly, the presence of vitamins in PN protects lipid emulsions from oxidation (7). The second concern is the possibility of precipitation of calcium phosphate in pediatric parenteral admixtures. The most daunting problem for pharmaceutical preparation practices of PN is related to the day-to-day change of volume and formulation nutrients, due to changing clinical conditions and maturation. Considering the low dose volumes used in neonatology (as low as 1-2 ml), it is vital to ensure both physicochemical compatibility and adequate calcium and phosphorus supply (8). Further, newborn infants and small children require large amounts of calcium and phosphate in these low dose volumes which may increase the risk of precipitation of calcium phosphate (9,10). Precipitation can cause respiratory distress and pulmonary embolism (11). Inorganic phosphate in PN has the potential of forming precipitates with calcium, especially when using calcium chloride. As such, calcium gluconate is the predominant calcium salt form employed in PN compounding due to its solubility profile with phosphate. Unfortunately, calcium gluconate contains higher levels of aluminum contamination than calcium chloride, resulting in an increased potential for aluminum toxicity in patients receiving traditional PN. The risk of aluminum toxicity is especially present in the neonatal population, in whom higher per kilogram of bodyweight amounts of calcium and phosphates are administered. Organic sodium glycerophosphate (NaGP), with the divalent calcium ion, has a lower propensity towards precipitation than inorganic phosphate, thereby allowing for calcium chloride utilization. Data presented in this study demonstrating NaGP and calcium chloride compatibility provide a clinical option for limiting aluminum contamination while providing sufficient calcium and phosphate to meet the needs of neonatal patients. Although NaGP is approved for use in Europe, it lacks full American Food and Drug Administration approval except on a temporary basis during phosphate drug shortages.

The aim of the study was to determine the physicochemical stability of admixtures for PN, prepared in one-chamber bags, designed for pediatric patients who receive PN at home. The stability of 30 compositions of admixtures up to eight days of storage at +4 °C was evaluated. The admixtures characterized contained increasing amount of electrolytes, and the consequent value of CAN (critical aggregation number) parameter ranged from 300 to 1402. The admixtures were prepared in the one-chamber bags Exacta-Mix Eva (ethylene vinyl acetate) Bag Parenteral (Baxa Ltd., United Kingdom) at the Hospital Pharmacy. Vitamins were added just before analysis. Three types of lipid emulsions: SMOFlipid, Lipofundin MTC/LCT or Omegaven were used. All admixtures were composed only of inorganic calcium salt. The composition of the parenteral admixtures under test was designed by clinicians from the Children's Memorial Health Center Institute in Warsaw, Poland.

METHODS

COMPOUNDING OF ADMIXTURES FOR PARENTERAL NUTRITION IN HOSPITAL PHARMACY

Incomplete (without vitamins) TPN admixtures were prepared in the Pharmacy of the Children's Memorial Health Center in Warsaw, Poland, in compliance with pharmaceutical standards. Single-chamber bags, Exacta-Mix Eva Bag Parenteral, constituting the packaging of mixtures of the TPN were filled in a laminar flow system with sterile, air, purity class A. For this purpose, a Baxa 24 computer-controlled mixer was used, allowing for precise transfusion following base fluids, i.e., 40% dextrose solution (B. Braun Melsungen, Germany), amino acid solution (Aminoven® Infant 10%, Fresenius Kabi, Uppsala, Sweden or Vamin® 18 EF), water for injections, the lipid emulsion (Lipofundin® MCT/LCT, B. Braun Melsungen, Germany, Omegaven® or Smoflipid®, Fresenius Kabi, Austria), and preparation of organic phosphate (Glycophos®), sodium chloride (Natrium chloratum 10%, Polpharma, Starogard Gdanski, Poland), potassium chloride solution (Kalium chloratum 15%, WZF Polfa, Warsaw, Poland), magnesium sulphate solution (Magnesii sulfuricum 20%, Polpharma, Starogard Gdanski, Poland) and calcium chloride solution (Calcii chloratum 10%), trace elements (Addamel® or Peditrace®, Fresenius Kabi, Uppsala, Sweden).

TPN mixtures were protected from light. Following preparation, the mixtures were sent on the same day to Gdansk, where physicochemical analysis was performed. Vitamins (Soluvit® N dissolved in Vitalipid® N Infant, Fresenius Kabi, Uppsala, Sweden, or Cernevit®, Fresenius Kabi, Uppsala, Sweden) were added at the Department of Pharmaceutical Technology of GUMed injecting into the bag with the mixture just before each analysis. In Poland, and differently than other places in Europe, patients themselves add vitamins to PN admixtures prior to administration. The composition of the TPN admixtures are provided in table I.

STORAGE OF INCOMPLETE AND COMPLETE ADMIXTURES TPN

Parenteral admixtures were stored for up to eight days at refrigerated temperature (4 °C). Prior to analysis, mixtures were removed from the refrigerator, and stored for two hours at room temperature (21 ± 1 °C), the vitamins were added (t = 8 days) (Table I). After sampling, the mixtures were stored up to 24 hours at room temperature (21 ± 1 °C) in the dark, then analyzed (t = 8 days + 24h) (Fig. 1).

ADDITION OF VITAMINS

Parenteral admixtures were completed through the addition of vitamins (Table I). Vitamins were added under non-aseptic conditions, to better mimic the expected conditions of this stage, e.g. if a patient is at home. Vitamins were prepared by dissolving the freeze-dried water-soluble vitamins (Soluvit® N) in the fat emulsion comprising a vitamin soluble in the oil phase (Vitalipid® N) or Cernevit® in 0.9% sodium chloride injection (a mixture number: 25, 27, 30). For this purpose, each vial of Soluvit® N was added to 10 ml of Vitalipid® Infant and stirred to dissolve the Cernevit® vial in 10 ml of 0.9% sodium chloride solution for injection, and stirred until dissolved. Thus, dissolved vitamins were added using a syringe with a needle with filter in a prescribed amount to the TPN admixture.

Table I. Concentration of electrolytes (mmol/l), CAN and CaxP parameters of TPN admixtures

TPN	Na^+	K^+	Ca^{2+}	Mg^{2+}	CaxP	CAN
1	30.2	62.5	7.3	6.9	43.0	1000
2	26.3	15.4	6.6	2.6	43.4	632
3	14.6	16.6	5.1	3.6	7.7	589
4	18.1	13.8	5.6	5.5	21.7	747
5	20.6	32.6	5.9	1.8	35.3	545
6	66.0	27.3	4.9	4.4	14.0	690
7	47.3	22.7	4.3	4.5	32.0	633
8	15.9	13.1	7.9	1.8	26.0	647
9	22.7	34.5	4.7	4.1	4.7	616
10	39.9	18.9	9.1	10.8	24.7	1336
11	29.2	30.7	6.0	5.9	40.0	820
12	55.6	35.6	5.5	3.6	15.3	670
13	28.4	18.0	6.3	0.8	25.2	501
14	24.8	7.0	3.1	1.4	11.0	322
15	25.0	22.5	6.0	1.8	40.3	544
16	45.4	44.7	7.7	4.1	40.0	850
17	17.1	59.3	9.4	1.9	3.8	799
18	28.7	27.2	5.5	3.9	33.2	655
19	29.8	10.5	4.2	2.5	17.8	473
20	76.5	42.8	8.1	9.2	26.8	1229
21	10.9	46.3	4.6	6.0	25.1	735
22	37.7	39.9	7.5	3.5	0	783
23	28.5	14.5	3.3	0.7	8.8	297
24	30.3	35.3	8.3	5.1	46.7	926
25	54.3	58.4	6.0	9.0	6.0	1073
26	22.6	50.4	8.1	9.3	33.0	1189
27	11.3	14.9	6.9	8.3	17.3	1001
28	44.6	30.5	7.4	2.8	17.6	728
29	25.2	45.7	4.4	4.9	2.1	667
30	13.4	40.8	10.2	10.9	9.2	1402

PHYSICOCHEMICAL ANALYSIS OF COMPLETE PARENTERAL ADMIXTURES

The design of the physicochemical stability test is presented in figure 1. Analysis of the complete admixtures was carried out immediately after transportation (t = 24h) and after 24 hours of storage at room temperature, with light protection (t = 24h + 24h). Activation of pre-admixtures was at t = 24h or after eight days of storage. Completed parenteral admixtures were subjected to physicochemical stability analyses consisting of visual inspection, microscopic observation (biologic microscope with camera B1 223A Motic, Wetzlar, Germany), determination of oily globules size distribution - laser diffractometer (MasterSizer E Malvern Instruments, Malvern, UK) and photon correlation spectroscopy (Zetasizer, Malvern Instruments, Malvern, UK), zeta potential (Zetasizer, Malvern Instruments, Malvern, UK), pH measurement (pH meter Orion 350, Beverly, USA, with combination electrode). Before each pH measurement, a two point calibration of the pH meter was done, each with a buffer solution of pH 9.00 and pH 4.00, respectively. The pH 7.00 solution was used afterwards as a control. Between the calibration steps, the electrode was rinsed with distilled water and wiped dry. Each sample was measured after five minutes of equilibration.

The physical stability of parenteral admixtures was assessed by lipid droplet measuring in a light microscope with an upper droplet

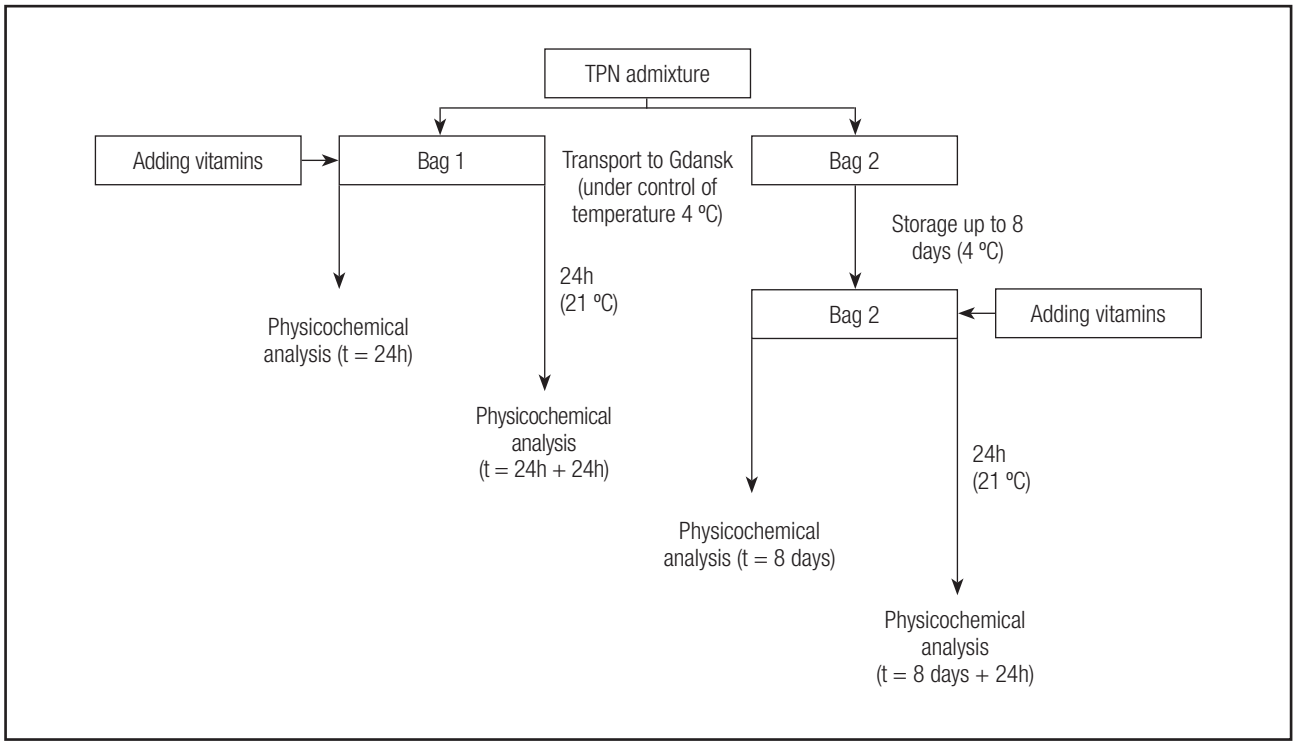

Figure 1.
Schedule of analysis of TPN admixtures.

size of ≥ 1 µm. Each microscopic sample (10 µl by a manual pipette) was analyzed with 40-fold magnification. Five individual visual fields were inspected per microscopic sample (15 total visual fields/aliquot): four in the corner and one in the middle of the preparation.

The size of the lipid droplets in the visual field was determined using an ocular micrometer (0.01 mm). The diameter of the largest lipid droplet was measured and counted in each of the 15 visual fields tested per aliquot. The diameter of the largest lipid droplet and the number of lipid droplets above 5 µm were measured and counted in each of the 15 visual fields tested per aliquot. The specifications of microscopic screening are shown in table II. Laser diffractometer method (LD) allows determining the median diameter ($d_{0.5}$ below this parameter is diameter of 50% of oily globules) and the maximum diameter of 90% of oily globules ($d_{0.9}$). Photon correlation spectroscopy method (PCS) was used to determine Z-average parameter.

RESULTS

VISUAL AND MICROSCOPIC OBSERVATIONS

Over eight days of storage, no visual changes were observed in the test samples stored at room temperature or in 4 °C. There was no creaming or discoloration. Neither precipitates nor flocculation were visible. A visual inspection was done for the assessment of large particle formation in the critical size 1-5 µm.

Under microscopic observation, the mean of the largest lipid droplet in µm out of 15 visual fields of 5 µm as the upper limit value for the emulsion stability was never reached by any sample, except one admixture (TPN 4). The mean value of the larger oily globules was about 2-3 µm (Table II and Fig. 2). There was no trend for the droplet size to increase or decrease over time of storage. In the unstable TPN 4 admixture, oil droplets in the range of 4-10 µm were detected.

OILY DROPLET SIZE DISTRIBUTION

Laser diffractometry method

Value of median ($d_{0.5}$) of oily droplets size in the complete admixtures was 310-390 nm and 90% of oily droplets ($d_{0.9}$) were under 570-680 nm. Despite the various composition and time of storage no oily globules lager than 1 µm were detected in any of all admixtures by using laser diffractometry method (Fig. 3).

Photon correlation spectroscopy

Z-average of oily droplets size was in range 252-372 nm, while the polydispersion index was 0.062-0.223, which indicates mo-

Table II. Microscopic observations of admixtures

TPN	t = 24h	t = 24h + 24h	t = 8 days	t = 8 days + 24h
1	Few 2 µm	Few 2 µm	Few 2 µm	< 1 µm
2	2 µm	< 1 µm	< 1 µm	< 1 µm
3	2 µm	2-3 µm	< 1 µm	2 µm
4	5-15 µm	10 µm	5-10 µm, agglomerates	Few 5-8 µm
5	2 µm	< 1 µm	Few 2 µm	2 µm
6	2 µm	Few 2 µm	< 1 µm	Few 2 µm
7	< 1 µm	2 µm	< 1 µm	< 1 µm
8	< 1 µm	< 1 µm	< 1 µm	< 1 µm
9	2 µm	< 1 µm	< 1 µm	< 1 µm
10	3-4 µm	2-3 µm	2-3 µm	Few 2 µm
11	< 1 µm	2-3 µm	Few 2 µm	2-3 µm
12	2-3 µm	2-3 µm	Few 2 µm	3-4 µm
13	2-3 µm	2-3 µm	Few 2 µm	2-3 µm
14	2 µm	2-3 µm	Few 2 µm	Few 2 µm
15	2 µm	< 1 µm	Few 2 µm	Few 2 µm
16	2 µm	2 µm	2-3 µm	Many 2-3 µm
17	< 1 µm	Few 2 µm	< 1 µm	Few 2 µm
18	2 µm	Few 2 µm	< 1 µm	Few 2 µm
19	2 µm	2 µm	2 µm	2 µm
20	2-3 µm	4-5 µm	2 µm	2-3 µm
21	2 µm	2 µm	2-3 µm	Few 2-3 µm
22	2-3 µm, few 4 µm	4-5 µm	2-3 µm	Many 4-5 µm
23	2-3 µm	4-5 µm	2 µm	2-3 µm
24	Few 2 µm	Few 2 µm	Few 2 µm	Few 2 µm
25	Few 2 µm	3-4 µm	2-3 µm	2-3 µm
26	2-3 µm	Few 3-4 µm	Few 2 µm	2-3 µm
27	Few 2 µm	Many 4-5 µm	Few 2 µm	Many 4-5 µm
28	2-3 µm	Few 2 µm	Few 2 µm	Few 2 µm
29	Many 2-3 µm	Few 2 µm	Few 2 µm	Few 2 µm
30	2-3 µm	2-3 µm	2-3 µm	2-3 µm

nodispersity studied systems (Fig. 4). The smallest oily droplets (Z-average approx. 250 nm) was recorded in admixtures 28, 29 and 30. No significant changes (± 30 nm) of oily droplets were noticed during storage TPN mixtures (Fig. 4). The TPN admixtures 2 and 10 have only at t = 24h larger oily droplets (Z-average about 550 nm), but in the others point of analysis Z-average was approximately 310 nm, so these admixtures were concluded as

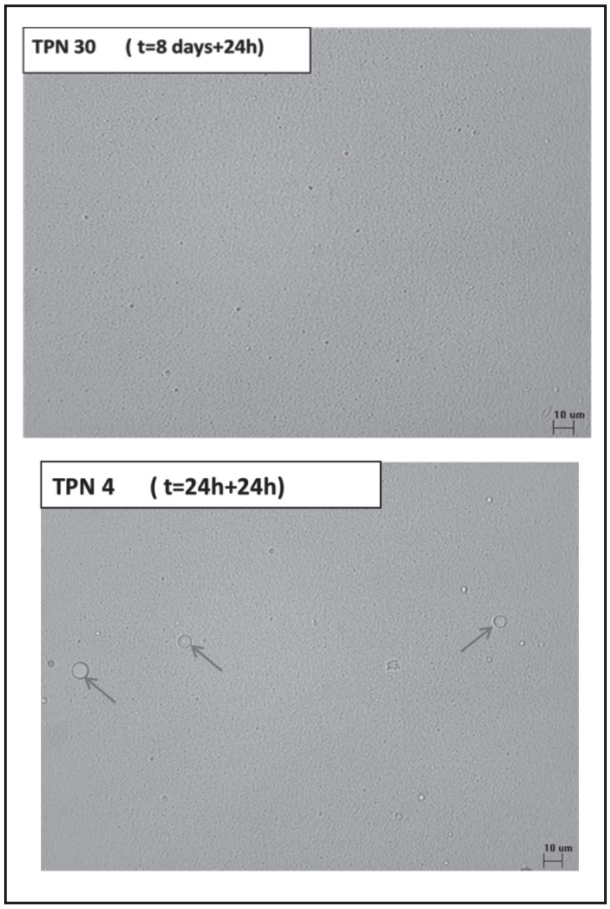

Figure 2.

Microscopic observation of admixtures (scale 10 µm).

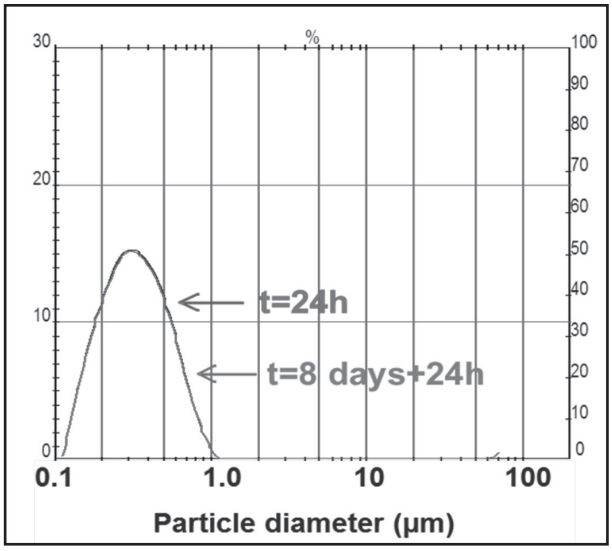

Figure 3.

Distribution of oily droplets of TPN 25 admixture during storage.

stable. Admixtures 7, 16, 22, 25 and 26 in a single time point reported a second peak in the range of 0.5 µm, indicating the presence of larger droplets of oil. However, the analysis in the other time points did not confirm these changes.

Zeta potential analysis

Zeta potential of all admixtures was in range -19 to -38 mV and did not change during the storage (± 4 mV) when compared with samples at t = 0 (Table III). The lowest recorded zeta potential of -40 mV was noted with TPN 23 while TPN 30 was seen to have a zeta potential of -21 mV (Table III).

pH measurement

The pH values in complete TPN admixtures were in range 5.29-6.29. Compared with samples at t = 24h, these values did not change (± 0.05 of units) during storage (Fig. 5). The smallest pH value (pH 5.3) of this parameter was observed in TPN 22, 25, 27, 30.

DISCUSSION

All TPN admixtures under investigation were prepared using standard procedures in the hospital Pharmacy. Due to clinical needs, admixtures contained a much higher than normal physiological concentration of electrolytes: calcium (3-10 mmol/l Ca^{2+}), magnesium (1-10 mmol/l Mg^{2+}) and potassium (7-60 mmol/l K^{+}) ions. CAN parameter of investigated admixtures was much higher than current in range 300-1400 mmol/l and CaxP (the products of multiplication of calcium and phosphate ions concentration) was in range 1-43 $mmol^2/l^2$. The highest CAN parameter was noticed in admixtures 30 (1402 mmol/l), whereas the smallest was found in admixtures 14 (322 mmol/l). All investigated admixtures were prepared using inorganic calcium salt to check if they are safe in PN for small children and if they can be used in clinical practice. Many authors suggest that calcium gluconate is preferred over calcium chloride when compounding PN because of its superior compatibility with inorganic phosphates. PN solutions containing calcium gluconate carry a higher aluminum load than equivalent solutions compounded with calcium chloride, leading to increased potential for aluminum toxicity (12). Premature infants are particularly at high risk of aluminum accumulation and toxicity as they often require days of PN support and have immature kidneys that are incapable of excreting aluminum efficiently. Calcium gluconate and phosphate salts are known to be especially high in aluminum content and are often administered to premature infants in substantial amounts to promote bone mineralization (13).

The analysis of physicochemical subjected to 30 TPN admixtures prepared in two bags in the Pharmacy of the Children's Memorial Institute in Warsaw. Incomplete (no vitamins) TPN admixtures were prepared in the single-chamber bags Exacta-Mix

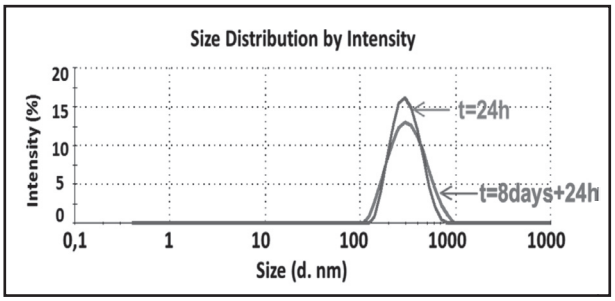

Figure 4.
Distribution of oily droplets of TPN 4 admixture during storage PCS method.

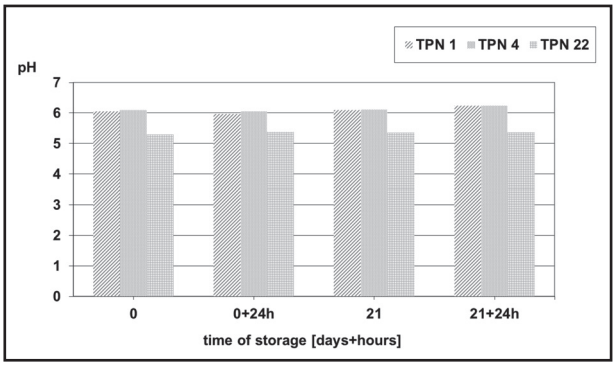

Figure 5.
pH values of the TPN admixtures, the effect of storage.

Eva bag Parenteral. Each composition of the TPN admixture was prepared in two bags, which allowed for analysis at four points: first bag, at t = 24, that is to say 24 hours after preparation (including transport), and after 24 hours of storage at room temperature (t = 24h + 24h); second bag, after eight days of storage at 4 °C (t = 8 days) and also after 24 hours storage at room temperature (t = 8 days + 24h).

The term physical stability of the TPN mixtures stored for a long time has practical application in parenteral nutrition at home: you can prepare the patient "inventory" of mixtures for a limited time. In the present study, the ability to store the mixtures tested to eight days was evaluated. The most important parameter to evaluate the physical stability of the mixtures is the presence of a drop of oil ≥ 5 µm, because they exceed the size of the diameter of capillaries and, consequently, if they are introduced into the bloodstream in large quantities, they can lead to embolism, necrosis of the surrounding tissues or have an effect on the functioning of the organ (14). It is believed that a small amount of oil with droplet sizes greater than 5 µm is not dangerous for the patients, since lipases are present in the endothelium of blood vessels. Lipases are responsible for the biodegradation of fatty acid esters. Among the test methods used, the most reliable, detecting drops of oil with increased size in mixtures TPN, turned out to be microscopic

Table III. Zeta potential (mV) of TPN admixtures

TPN	t = 24h	t = 24h + 24h	t = 8 days	t = 8 days + 24h
1	-28.5	-28.9	-30.7	-22.8
2	-32.2	-33.2	-34.3	-34.9
3	-29.2	-32.0	-37.5	-26.4
4	-30.6	-29.2	-35.2	-34.6
5	-32.0	-30.2	-39.2	-33.7
6	-32.1	-29.8	-33.3	-29.7
7	-31.6	-32.9	-33.5	-33.9
8	-28.0	-31.0	-31.6	-32.9
9	-28.6	-32.1	-32.2	-31.8
10	-24.8	-30.1	-24.4	-29.1
11	-32.0	-33.2	-31.6	-33.1
12	-30.8	-35.6	-30.6	-32.8
13	-33.9	-37.4	-36.9	-33.9
14	-36.6	-41.3	-37.7	-39.5
15	-34.4	-40.3	-34.6	-34.7
16	-33.7	-35.5	-32.8	-32.2
17	-31.2	-34.5	-34.2	-30.0
18	-32.5	-36.2	-32.0	-32.8
19	-32.3	-40.1	-36.1	-35.4
20	-32.2	-40.8	-31.3	-27.6
21	-31.6	-30.0	-34.0	-30.3
22	-28.5	-29.5	-35.1	-28.8
23	-38.2	-38.8	-43.9	-40.2
24	-32.3	-29.7	-31.5	-30.6
25	-28.3	-27.7	-29.6	-24.6
26	-22.9	-26.5	-29.4	-22.9
27	-27.5	-28.3	-28.1	-26.4
28	-28.1	-27.0	-28.5	-27.4
29	-28.5	-28.3	-30.2	-27.2
30	-22.5	-19.2	-23.3	-19.5

observation. The significance of this method to determine the durability of mixtures of the TPN also stress the authors of many publications. The light microscope method is highly sensitive and practicable, with a simple equipment and a conventional method validated by photon correlation spectroscopy (PCS) and the Coulter method (15). Using a microscope with a 40-fold magnification allows the detection of particles approximately 1 µm in size or enlarged emulsion particles up to 100 µm in size. Furthermore, other non-lipid globules (such as particulate matters or precipitations) can also be detected using this method. The method provides an easy, sensitive, cost-efficient, time-sparing, and convenient way to test the physical stability of a lipid emulsion in the critical droplet size to indicate destabilization (large fat droplet assessment ≥ 1-2 µm), and it is suitable for drug incompatibility testing in parenteral admixtures.

However, it is necessary to verify microscopic observation by other methods, so in this paper TPN admixtures were also analyzed using laser diffraction (LD) and photon correlation spectroscopy (PCS). Particle size measurement by means of a LD MasterSizer E enables the detection of particles from 0.05 to 80 µm, indicating size distribution. In turn, the use of ZetaSizer Nano ZS apparatus to measure the particle size using the method of dynamic light scattering allows the determination of particle size in the range of 0.6 nm-6 µm, taking advantage of the differences in the speed of the Brownian movement of particles in the medium in which they are suspended. The studies used both methods in view of the fact that, if the particles are too large, this method cannot determine the PCS size. An increase in oil droplet size by LD was not observed in any of the admixtures tested, despite their presence under microscopic observation. Some studies using PCS (no trends over time) detected the presence of a second peak and increased polydispersity index.

While mixtures 2 and 10 in the midpoint of the test (t = 24h) indicated an increased average droplet size of the oil phase (approximately 200 nm - by PCS), and mixtures 7, 20, 22, 25 and 26 showed the presence of a single time point of the second peak of about 5 mm, this change was not confirmed in the remaining time points. Although the results obtained by methods LD and PCS do not allow to detect irregularities at all the time points (the presence of larger oil droplets), yet on the basis of microscopic observations the mixture was physically unstable with composition 4. When the results obtained by the PCS and LD, it can be said that the median value of the oil droplets (Dv50; LD method) and an average oil droplet sizes (Z-Average, a method PCS) is slightly different. Z-average values were approximately 50 nm smaller. Measurement of zeta potential of TPN admixtures showed no significant changes during storage for 24h at room temperature (Table III). Zeta potential values were in the range denoted generally TPN admixtures. Another important factor indicating the stability of parenteral admixtures is pH, which decreases over time in PN admixtures because of the hydrolysis of fat triglycerides. Additional chemical reactions yielding base or acidic products also affect the pH. For the lipid stability and lecithin emulsifier, a pH range of 5-8 is necessary. The negatively charged surface (phosphate moiety) prevents the coalescence of the lipid globules. A pH below 5.0 favors lipid instabilities (16). In this study, no significant changes were noted in pH during storage of TPN admixtures (Fig. 5). Considerably lower pH of the mixtures 22, 25, 27 and 30 as compared to other systems is caused by using a different amino acid preparation (18 Vamin EF).

CONCLUSIONS

Based on the results of this study, and despite the increased concentration of electrolytes, the excess of CAN (297 to 1402)

and the presence of inorganic calcium salts, the physicochemical stability of the parenteral admixtures tested has been demonstrated. The exception was mixture 4, which was found to have coalescence of drops of oil visible during microscopic observations and at some point of time by the PCS, so the composition of TPN 4 should be modified. An important observation was that inorganic calcium salt in PN can achieve the same stability profile as the organic salt in use in the clinic today. To apply the above examined compositions in clinical practice is their preparation under the same conditions using the same ingredients and packaging. Changing any factor (packaging, manufacturer, or replacement of the inorganic salt to organic) can cause a lack of physical stability and requires reconsidering physical stability. The research of physical stability indicates that, except for admixture 4, the test compositions can be used in nutrition at home with prolonged stability of prepared TPN admixtures, provided that they are implemented in the same manner and using the same components.

REFERENCES

1. Petit LM, Girard D, Ganousse-Mazeron S, Talbotec C, Pigneur B, Elie C, et al. Weaning off prognosis factors of home parenteral nutrition for children with primary digestive disease. J Pediatr Gastroenterol Nutr 2016;62:462-8.
2. Nader EA, Lambe C, Talbotec C, Pigneur B, Lacaille F, Garnier-Lengliné H, et al. Outcome of home parenteral nutrition in 251 children over a 14-y period: Report of a single center. Am J Clin Nutr 2016;103:1327-36.
3. Ferguson TI, Emery S, Price-Davies R, Cosslett AG. A review of stability issues associated with vitamins in parenteral nutrition. e-SPEN J 2014;9:e49-e53.
4. Uccello-Barretta G, Balzano F, Aiello F, Falugiani N, Desideri I. Stability of hydrophilic vitamins mixtures in the presence of electrolytes and trace elements for parenteral nutrition: A nuclear magnetic resonance spectroscopy investigation. J Pharm Biomed Anal 2015;107:7-10.
5. Turmezei J, Javorszky E, Szabo E, Dredán J, Kállai-Szabó B, Zelkó R. Effect of storage temperature on the stability of total parenteral nutrition admixtures prepared for infants. Acta Pol Pharm 2015;72:843-9.
6. Wormleighton CV, Catling TB. Stability issues in home parenteral nutrition. Clin Nutr 1998;17:199-203.
7. Berger MM, Shenkin A. Vitamins and trace elements: Practical aspects of supplementation. Nutrition 2006;22:952-5.
8. Ribeiro D, Lobo B, Volpato NM, Veiga VF, Cabral LM, Sousa VP. Influence of the calcium concentration in the presence of organic phosphorus on the physicochemical compatibility and stability of all-in-one admixtures for neonatal use. Nutr J 2009;8:51-64.
9. Zenoni D, Loiacono S. Experience of compounding total parenteral nutrition admixtures for preterm infants in a hospital pharmacy: Evidence of calcium and phosphate compatibility problem. Eur J Hosp Pharm 2017. In press.
10. Watrobska-Swietlikowska D, Szlagatys-Sidorkiewicz A, Łuszkiewicz K. Evaluation of physical stability of all in one parenteral admixtures for pediatric home care with high electrolytes concentrations. Nutr Hosp 2014;31:236-43.
11. McKinnon BT. FDA safety alert: Hazards of precipitation associated with parenteral nutrition. Nutr Clin Practice 1996;11:59-65.
12. Anderson C, MacKey M. Physical compatibility of calcium chloride and sodium glycerophosphate in pediatric parenteral nutrition solutions. J Parenter Enteral Nutr 2016;40:1166-9.
13. Poole RL, Pieroni KP, Gaskari S, Dixon TK, Park KT, Kerner JA. Aluminum in pediatric parenteral nutrition products: Measured versus labeled content. J Pediatr Pharmacol Ther 2011;16:92-7.
14. Sobotka L. Stability and compatibility of parenteral nutrition (PN) admixtures. En: Basics in Clinical Nutrition. Czech Republic: Galén; 2011.
15. Aeberhard C, Steuer C, Saxer C, Huber A, Stanga Z, Mühlebach S. Physicochemical stability and compatibility testing of levetiracetam in all-in-one parenteral nutrition admixtures in daily practice. Eur J Pharm Sci 2017;96:449-55.
16. Driscoll DF, Thoma A, Franke R, Klütsch K, Nehne J, Bistrian BR. Lipid globule size in total nutrient admixtures prepared in three-chamber plastic bags. Am J Health-Syst Pharm 2009;66:649-56.

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Nutrición Hospitalaria

Trabajo Original

Paciente crítico

Resolution of control and monitoring instrument of nutritional therapy in the intensive care unit of a university hospital

Resolución del instrumento de control y monitorización de la terapia nutricional en la unidad de cuidados intensivos de un hospital universitario

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Abstract

Introduction: Patients in intensive care status are in nutritional threat and frequently present innutrition, therefore monitoring the nutritional offer becomes indispensable.

Aim: To purpose a control and monitoring form of enteral nutritional therapy and to evaluate its resoluteness.

Methods: Observational, analytical and retrospective study performed in intensive care patients receiving an enteral diet exclusively and/or associated with the oral/parenteral route, from January to April 2015 and from January to April 2016. An enteral nutritional therapy control form was purposed and applied in 2016 and the results were compared to those of the previous year. In both of these years, five quality indicators proposed by the task force of clinical nutrition from the International Life Sciences Institute (Brazil, 2008) were applied.

Results: Ninety-four patients, mostly aged, were included (47 per year) in the study. There was an increase in the number of patients that presented diarrhea ($p = 0.007$) and hyperglycemia ($p = 0.013$) as well as an increase in the occurrence of these episodes among patients ($p = 0.018$, $p = 0.032$, respectively). The frequency of diarrhea, fasting of more than 24 hours and hypoglycemia did not correspond to the goal established by the indicators. Energy and protein estimations were reported, as well as their compliance with the literature.

Conclusion: After using the form, a greater report of clinical intercurrences and information on caloric and protein estimates was observed, thus demonstrating its effectiveness with respect to data recording.

Key words:

Quality of health care. Critical care. Enteral nutrition. Indicators of quality in health care.

Resumen

Introducción: los pacientes en terapia intensiva presentan riesgo nutricional y frecuentemente se encuentran en estado de malnutrición, por lo que es fundamental la monitorización de la oferta nutricional.

Objetivo: proponer una forma de control y seguimiento de la terapia nutricional enteral y evaluar su efectividad.

Métodos: estudio de observación, analítico y retrospectivo, realizado en pacientes ingresados en una unidad de cuidados intensivos que reciben dieta por vía enteral exclusiva y/o asociada a vía oral/parenteral, en el periodo de enero a abril de 2015 y de enero a abril de 2016. En 2016 se propuso y aplicó un instrumento de control y monitorización de la terapia nutricional enteral en la unidad de cuidados intensivos y los resultados fueron comparados con los del año anterior. En ambos periodos se aplicaron cinco indicadores de calidad propuestos por el grupo especial de nutrición clínica del International Life Sciences Institute, de Brasil (2008).

Resultados: se incluyen 94 pacientes y se estudiaron 47 en cada año, la mayoría de ellos ancianos. Hubo un aumento del número de pacientes que desarrollaron diarrea ($p = 0,007$) e hiperglucemia ($p = 0,013$) y también de la cantidad de episodios de estas complicaciones ($p = 0,018$ y $p = 0,032$, respectivamente). La frecuencia de diarrea, ayuno superior a 24h e hipoglucemia no correspondía a la meta fijada por los indicadores. Se recogieron datos del aporte energético y proteico, así como su comparación con lo publicado.

Conclusión: después de la utilización del instrumento hubo un aumento en el registro de complicaciones clínicas y la información referente a la estimación calórica y proteica, lo que demuestra su efectividad en el registro de datos para el cual fue desarrollado.

Palabras clave:

Calidad de la asistencia sanitaria. Cuidados intensivos. Nutrición enteral. Indicadores de calidad en asistencia sanitaria.

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INTRODUCTION

Special attention must be paid to the nutritional status of critical patients, who due to the specific characteristics of several metabolic conditions are in nutritional threat and frequently present with caloric-protein innutrition (1). Among the hospitalized in Brazil, 48% present some degree of malnutrition and 12% of them are severely malnourished (2).

Hospital nutrition is associated with an increased rate of morbidity and mortality, length of hospital stay, hospitalization, and increased health costs (3). These patients are usually hypermetabolic, and present hyperglycemia, insulin resistance and marked lipolysis, as well as intense protein catabolism, which, together with immobilism and the difficulty of achieving nutritional goals, interfere with nutritional support, leading to an important muscular depletion and increased nutritional needs (4).

Enteral nutritional therapy (ENT) is seen as a therapeutic tool within Intensive Care (5,6). The use of quality indicators associated with the implementation of protocols is recommended to guarantee the quality of ENT and reduce costs for both the patient and the institution (6). In this context, the present study aimed to propose a form for the control and monitoring of enteral nutritional therapy and to evaluate its resolution.

MATERIALS AND METHODS

An analytical and retrospective study was performed through the collection of secondary data in medical records of patients admitted to an intensive care unit (ICU) of the University Hospital de Campo Grande (Mato Grosso do Sul, Brazil), previously approved by the Ethics in Research with Humans CEP/UFMS under the protocol number 1.328.152, with the consent of the responsible for the sector and signature of term of responsibility for use of medical records.

Individuals of both sexes, over 18 years of age, admitted to the ICU from January to April 2015 and from January to April 2016 and who received an enteral diet exclusively or associated with oral/parenteral administration were included in the sample. Children under 18 years of age and subjects whose nutrition was given orally and/or parenterally exclusively, indigenous, quilombolas and institutionalized were excluded from the study.

Data collection included the same period of 2015 and 2016. By 2015 there were no TN protocols validated in the industry. Patient records were the sources for data collection. In 2016, a form was proposed by the researcher, developed in partnership with the nutritionist of the sector, including dietary prescription control and notification of intercurrences related to ENT. The definitions of these intercurrences were standardized according to the European, American, Brazilian and Canadian guidelines (5,7-9). The data collection for 2016 was carried out in the proposed form.

In these two years, data were collected by the identification of individuals (date of birth, age and institution registration number), the main reason for hospitalization, comorbidities, length of staying in the ICU, nutritional diagnosis, dietary route of administration, type of diet, estimated time of needing of ENT after ICU admission, episodes and reasons for diet suspension, fasting time > 24 hours, clinical intercurrences, glycemia dysfunction, changes in physiological eliminations, and clinical outcome.

Five quality indicators of nutritional therapy (QINT) were applied. The indicators were chosen taking into account the characteristics of the sector. The analysis of the indicators was done according to the recommendations of the Clinical Nutrition Task Force - ILSI-Brazil (6).

The data were tabulated in spreadsheets of the program Microsoft Excel® 2013 and a statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) software, version 24.0 for Windows. Descriptive statistics were used for the characterization of the sample, with absolute and relative frequencies, medium and standard deviation. In order to compare proportions among the categorical variables, the Chi-squared test or Fisher's exact were used. The Mann-Whitney test was used for verification of the difference between the median values of the numerical variables, and the t test was used for the ranges after checking the distribution by the Shapiro Wilk normality test. The level of significance was 5%.

RESULTS

Among the patients admitted to the ICU during the study period, those who answered by the inclusion criteria were 47 in 2015 and 47 in 2016. In that last year, a specific form was adopted for the control of enteral and parenteral nutrition, what made it possible to record the calculation of energy needs for 93.6% of the patients.

There was no difference in the proportion of patients according to gender, age group, route of diet administration, ICU diet start time, ICU stay and patient outcome among the studied years. In 2015, the range age was 58.15 ± 19.30 years and in 2016, 58.87 ± 18.31 years ($p = 0.853$ t test). In 2015 and 2016, 97.9% and 95.7% of the patients, respectively, started the diet within 48 hours after admission. In 2015, the length of stay in the ICU was 14.87 ± 17.24 (range: 1-98) days, and in 2016 it was 18.11 ± 24.74 (range: 2-140) days ($p = 0.380$ Mann-Whitney test). The mortality rate during the period studied was 46.8% in 2015 and 29.8% in 2016 (Table I).

The main diagnoses on patient admission were pneumonia (40.4% in 2015 and 19.2% in 2016) and septic shock/sepsis (10.6% in 2015 and 29.8% in 2016). The frequency of cases of pneumonia was higher in 2015 ($p = 0.024$ Chi-squared test), and there was no difference in the proportion of septic shock/sepsis ($p = 0.1188$ Chi-squared test).

There was a greater percentage of patients with comorbidities in the year 2016 (93.6%) than in the year 2015 (78.7%) ($p = 0.036$ Chi-squared test). With respect to the type of comorbidities, there was no difference between the years studied (Chi-squared test). The most frequent were: systemic arterial hypertension (14.9% in 2015 and 25.5% in 2016, $p = 0.199$), acquired human immunodeficiency syndrome (21.3% in 2015 and 17.0% in 2016, $p = 0.600$) and chronic kidney disease (CKD) (12.8% in 2015 and 21.3% in 2016, $p = 0.272$).

Table I. Sample characterization according to study variables. Nutritional Therapy Unit, University Hospital Maria Aparecida Pedrossian, UFMS - 2015 and 2016

Variables	2015 (n = 47)		2016 (n = 47)		p
	No.	%	No.	%	
Sex					
Female	19	40.4	24	51.1	0.301[1]
Male	28	59.6	23	48.9	
Age					
18 to 30 years old	4	8.5	2	4.3	0.628[1]
31 to 60 years old	17	36.2	20	42.5	
> 60 years old	26	55.3	25	53.2	
Route of administration of the diet					
Enteral nutrition	47	100.0	46	97.9	1.000[2]
Parenteral and enteral nutrition	-	-	1	2.1	
Oral and enteral nutrition	-	-	-	-	
Beginning time of ENT[3]					
0 (in admittance)	36	76.6	38	80.8	0.614[1]
24 hours	6	12.8	5	10.6	0.748[1]
48 hours	4	8.5	2	4.3	0.677[2]
> 72 hours	1	2.1	2	4.3	1.000[2]
Permanence time at ICU[3]					
Until 3 days	9	19.1	4	8.5	0.135[1]
From 4 to 7 days	12	25.5	12	25.5	1.000[1]
From 8 to 15 days	11	23.4	14	29.8	0.484[1]
From 16 to 30 days	10	21.3	12	25.5	0.626[1]
Over 30 days	5	10.7	5	10.7	1.000[1]
Denouement					
Death	22	46.8	14	29.8	0.237[1]
Stay at ICU	3	6.4	4	8.5	
Transference	22	46.8	29	61.7	

[1]Chi-squared test. [2]Fisher's exact test. [3]The Chi-squared test was calculated in every category about this variable versus the most categories added.

In relation to clinical intercurrences (Table II), there was a higher percentage of patients who had diarrhea (70.2%) and hyperglycemia (68.1%) in 2016. In 2015, 17% of the patients presented anuria, whereas no case was observed in 2016. There was no difference in the proportion of patients who had constipation, hypoglycemia, stasis, melena and hematuria.

There was also a greater occurrence of diarrhea in 2016 (mean = 3.3 ± 4.1) compared to 2015 (mean = 1.8 ± 3.0). There were more episodes of hyperglycemia by one patient in 2016 (mean = 4.7 ± 5.5) compared to 2015 (mean = 3.5 ± 6.7). There was no difference in the number of episodes of hypoglycemia and stasis (Table III).

In addition, there was a higher proportion of patients (57.4%) submitted to fasting in 2016 in comparison to 2015 (36.2%). However, there was no difference in the number of fasting episodes per patient (Mann-Whitney test p = 0.718), 1.2 ± 0.4 in 2015 (n = 17) and 1.1 ± 0.3 in 2016 (n = 27). The most frequent causes of fasting were hemodynamic instability, stasis and medical procedures. There was a statistical difference between both years for the following causes: stasis, which was more frequent

Table II. Clinical intercorrences. Nutritional Therapy Unit. University Hospital Maria Aparecida Pedrossian, UFMS - 2015 and 2016

Clinical intercorrences[1]	2015 (n = 47)		2016 (n = 47)		p[2]
	No.	%	No.	%	
Diarrhea	20	42.6	33	70.2	*0.007*[3]
Hyperglycemia	20	42.6	32	68.1	*0.013*[3]
Anuria	8	17.0	-	-	*0.006*[4]
Constipation	15	31.9	19	41.3	0.347[3]
Hypoglycemia	15	31.9	14	29.8	0.823[3]
Stasis	10	21.3	17	36.2	0.111[3]
Melena	4	8.5	5	10.9	0.740[4]
Hematuria	3	6.4	-	-	0.242[4]

[1]One or more fasting causes by one patient. [2]Values of p in italic indicate statistically significant difference. [3]Chi-squared test. [4]Fisher's exact test.

Table III. Clinical intercorrences by one patient. Nutritional Therapy Unit, University Hospital Maria Aparecida Pedrossian, UFMS - 2015 and 2016

Clinical intercorrences	2015 (n = 47)		2016 (n = 47)		p
	Ranges	DP	Ranges	DP	
Diarrhea	1.8	3.0	3.3	4.1	*0.018*
Hyperglycemia	3.5	6.7	4.7	5.5	*0.032*
Hypoglycemia	1.3	2.5	1.0	2.1	0.803
Stasis	0.4	0.9	0.9	1.4	0.185

Mann-Whitney test.

Table IV. Fasting occurrence over 24 hours. Nutritional Therapy Unit, University Hospital Maria Aparecida Pedrossian, UFMS - 2015 and 2016

Variables	2015			2016			p[2]
	n	No.	%	n	No.	%	
Fasting Yes No	47	17 30	36.2 63.8	47	27 20	57.4 42.6	*0.039*[3]
Fasting causes[1]	17			27			
Stasis		1	5.9		11	40.7	*0.015*[4]
Exams		1	5.9		2	7.4	1.000[4]
Hemodynamic instability		12	70.6		10	37.0	*0.030* [3]
Abdominal distension		-	-		1	3.7	1.000[4]
Nursing procedures		-	-		1	3.7	1.000[4]
Medical procedures		6	35.3		5	18.5	0.289[4]
Sonda outlet		-	-		1	3.7	1.000[4]
Fasting time	17			27			
24 hours		5	29.4		12	44.4	0.503[3]
48 hours		5	29.4		8	29.6	
> 72 hours		7	41.2		7	26.0	

[1]One or more fasting causes by one patient. [2]Values of p in italic indicate statistically significant difference. [3]Chi-squared test. [4]Fisher's exact test.

Table V. Quality indicators in nutrition therapy. Intensive Care, University Hospital Maria Aparecida Pedrossian, UFMS - 2015 and 2016

Quality indicators in nutrition therapy	Meta*	2015	2016
I - Frequency of diarrhea in ENT patients	< 10%	42,6%	70,2%
II - Frequency of fasting > 24 h in patients in ENT	≤ 12%	34,0%	57,5%
III - Frequency of patients with glycemia dysfunction in ENT			
IIIa - Frequency of patients with hypoglycemia	5.1-6.9%	31.9%	29.8%
IIIb - Frequency of patients with hyperglycemia	70-80%	42.6%	68.1%
IV - Frequency of EP ** estimation in patients with ENT	> 80%	***	93.6%
V - Frequency of conformity of indication of ENT	< 13%	***	93.6%

**Clinical Nutrition Task Force - ILSI-Brazil (WAITZBERG, 2008). **Estimates of protein-energy expenditure. ***Data were not found.*

in 2016 (40.7%), and hemodynamic instability, more frequent in 2015 (70.6%). There was no difference between both periods in relation to the fasting time (Table IV).

QINT were applied in the two periods studied in order to monitor ENT quality in subsequent years, besides verifying the applicability of the proposed instrument according to table V.

DISCUSSION

Protocols for nutritional support provide greater control of nutrient receptions for patients and decrease the time to reach caloric and protein goals (10). Therefore, specific tools are necessary to facilitate the process of periodic evaluations, strategy establishment and assistance follow-up, using quality indicators to measure the effectiveness of the process. Furthermore, the use of protocols is cited as a differential framework in the care provided to patients in ENT when associated with continuing education and the participation of the multidisciplinary team (11,12).

The importance of the nutritionist in the ICU for the construction of these tools is emphasized, respecting the reality of the hospital to which they will be applied, as well as the human and material resources available for this purpose (13).

About the mean length of stay in the ICU, it was 14.87 ± 17.24 days in 2015 and 18.11 ± 24.74 days in 2016. A study conducted in the United States compared the clinical results of patients hospitalized in the ICU before and after the implementation of a nutritional protocol, finding an average time of intensive care hospitalization of 14.9 ± 18.0 days before the protocol and

14.1 ± 18.8 days post-protocol, and there was no impact on the length of stay (14).

In relation to mortality, the rate was 46.8% in 2015, similar to that of a cohort study conducted in Brazil, with a rate of 45% when correlating the caloric deficit in critically ill patients with mortality (15). In the present study there was no statistical difference in the mortality rate between the years studied, but a decrease of 17.0% from one year to another can be observed.

In addition to advanced age, the patients admitted to the ICU presented a serious clinical condition, mainly related to the specialties of pneumology and infectology, which resulted in an average hospitalization period of approximately 15 days. These also had comorbidities related to chronic diseases or immune suppression. Advanced age, clinical severity and the presence of comorbidities, which result in longer hospitalization periods, are characteristic of patients admitted to the ICU and also reinforce the need for strict control of nutritional prescription (16).

In the present study, the sample basically consisted of patients with an enteral diet, since only one of them used concomitant parenteral nutrition in 2016, and none in 2015. There was no oral enteral diet in neither of the years.

The early enteral nutrition (EEN) at ICU, until to 48 h after admission (8), helps to maintain intestinal mucosal integrity, reduces bacterial translocation and infection risks, and is associated with decreased mortality derived from high risk of complications caused by undernourishment and/or non-feeding (5,17). In the two-year study, more than 95% of the patients received EEN, in line with the American, Brazilian, Canadian and European guidelines (5,7-9), however, there was no relationship between the early onset of the diet and the time of hospitalization and mortality, as well as in the study by Pasinato et al. (18). The occurrence of EEN may be associated to the routine of the sector and the presence of a multidisciplinary team offering adequate ENT. In addition, these patients come from other services of the hospital, and often arrive at the ICU with the diet already started.

After all the efforts to offer adequate caloric-protein intake, there are barriers that prevent reaching nutritional goals in less time. The main causes of interruption of the diet are complications of the gastrointestinal tract: abdominal distension, stasis and diarrhea. Other commonly found causes are fasting for exams and procedures, inadvertent feeding tube probe and hemodynamic instability (19,20). These factors contribute significantly to the incidence of malnutrition in ICU patients and to their increased morbidity and mortality. Studies have also reported the lack of specific instruments and protocols as barriers impeding the success of ENT (5,11,21). The main clinical complications in the present study were gastrointestinal complications (diarrhea, constipation, stasis, melena) and glycemia dysfunctions (hyperglycemia and hypoglycemia).

Diarrhea was considered as the occurrence of three or more episodes of fluid evacuation in 24 hours; constipation, as absence for more than three days; stasis, as volume of gastric residue > 500 ml in 24 hours; hypoglycemia, < 70 mg/dl; and hyperglycemia, > 180 mg/dl (5,7,22).

In relation to the main intercurrences occurred in these two years, diarrhea and hyperglycemia are evident. The percentage of patients presenting these complications increased in this period, as well as the number of episodes per patient. In 2015, 42.6% of the patients presented diarrhea, and in 2016 this percentage increased to 70.2%. These values are above the desirable (< 10%) according to the indicators. Regarding hyperglycemia, even with the increase in patients presenting with this complication, the result of the indicator was satisfactory, taking into account the goal established for critical patients (70-80%). It may be explained by the greater report after the use of the instrument, and also the higher percentage of patients with comorbidities in 2016. However, hyperglycemia is not only related to ENT and is common in critically ill patients, being considered as a marker of severity of the disease (23).

There was a modest decrease in the number of patients presenting episodes of hypoglycemia, from 31.9% in 2015 to 29.8% in 2016. However, the result remains much higher than expected (5.1-6.9%). Hypoglycemia is associated with clinical complications and worse prognoses and should be avoided (7). In addition, Van Steen et al. (24) showed that insulin therapy continued in infusion pump is unnecessary due to lack of standardization of cut-off point of hyperglycemia in ICU patients increasing episodes of hypoglycemia, and the risk of mortality.

Other intercurrences in evidence in the study were anuria and hematuria, which did not appear in the reports of 2016 despite the hospitalization of patients with CKD, indicating a bias in the proposed tool, which has no specific field for this information.

Patients undergoing fasting for more than 24 hours totaled 36.2% in 2015, increasing to 57.4% in 2016. These percentages are not in line with the target (≤ 12%) established by Waitzberg et al. (6). Hemodynamic instability, with 70.6%, was the main cause of fasting > 24 hours in 2015, reflecting the severity of patients admitted to the ICU. In 2016, it decreased to 37.0% ($p = 0.030$). Stasis, which represented 5.9% of the causes of fasting in 2015, rose to 40.7% in 2016 ($p = 0.015$). Another variable indicates, possibly, the greater registration of these occurrences after adoption of the study tool.

Due to a lack of specific form, it was not possible to establish the frequency of calculation of energy and protein requirements, and it was not possible to assess the adequacy of the ENT indication in 2015. This measurement was possible after the use of the tool proposed in 2016, which evidenced the accomplishment of estimates of energy and protein requirements in 93.6% of the patients, taking into account the recommendations of the indicator. All these patients had ENT according to the main guidelines (5,7,9).

In view of the results obtained, the need to control the quality of patient care under ENT, which can be performed through QINT, was verified. Indicators are considered to be the most appropriate tool to assess nutritional assistance, besides being easy to apply, requiring only the training and commitment of the professionals involved (20).

In the first year of the study there were no forms or protocols of ENT validated in the sector dictating routines and nutritional processes, nor permanent multidisciplinary team working in the ICU. The sector counted on the care of residents from several areas, which

characterized the high turnover of caregivers. Therefore, there was a lack of care standardization, since the behaviors diversify according to the professional and reference used, causing treatment disparity. In the intermission between the years of research there were changes in the composition and performance of the multidisciplinary team, in addition to training collegiate in the institution and in the sector that started to charge the use of checklists, protocols and quality indicators. These factors may have interfered in the result of this study, because with the systematized assistance, a greater number of intercurrences are identified.

Thus, the information collected may serve as a theoretical reference for the Multiprofessional Nutritional Therapy Team of the referred hospital, which is in the implementation phase, in order to establish ENT system's effectiveness, as well as the basis for new studies, which can standardize and suggest nutritional assessment and diagnosis protocols, ENT choice algorithms, specific diet therapy for the clinical conditions and treatment of ENT related complications.

The present study evidenced the need for an instrument to control infusion of ENT, since after its use clinical intercurrences and information relative to caloric and protein estimates were systematically notified. Therefore, the instrument was effective regarding the data record that was developed.

Although the use of the monitoring instrument proposed in the present study did not affect the reduction of hospitalization time, occurrence of clinical intercurrences and mortality in the ICU, possibly due to the patients' severe clinical situation, it was an effective control tool, since there was adequate nutritional status for almost all patients, who were better monitored by professionals that alternate in shifts in the sector. There was also an increase in the quantity and quality of registered nutritional information, making it possible to identify the occurrence of individual nutritional assessment, calculation of nutritional needs, calories and proteins prescribed and administered, interruptions of the diets, and clinical intercurrences, among others. In addition, the need to include information in the instrument to avoid under-registration, such as a specific field for diuresis, was evidenced because in 2016 there was no report of anuria even with a significant number of patients with CRI (21.3%).

REFERENCES

1. Fontes D, Generoso SD, Correia MITD. Subjective global assessment: A reliable nutritional assessment tool to predict outcomes in critically ill patients. Clin Nutr 2014;33(2):291-5.
2. Waitzberg DL, Caiaffa WT, Correia MI. Hospital malnutrition: The Brazilian national survey (IBRANUTRI), a study of 4000 patients. Nutrition 2001;17(7):573-80. DOI: http://dx.doi.org/10.1016/S0899-9007(01)00573-1
3. Correia MI, Hegazi RA, Higashiguchi T, Michel JP, Reddy BR, Tappenden KA, et al. Evidence-based recommendations for addressing malnutrition in healthcare: An updated strategy from the feed. M.E. Global Study Group. JAMA 2014;15(8):544-50. DOI: http://dx.doi.org/10.1016/j.jamda.2014.05.011
4. WaitzbergDL, Ravacci GR, Raslan M. Desnutrición hospitalaria. Nutr Hosp 2011;26(2):254-64. DOI: https://dx.doi.org/10.3305/nh.2011.26.2.5070
5. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the Provision and Support Therapy in the Adult Critically Ill Patient Assessment of Nutrition: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). J Parenter Enteral Nutr 2016;40(2):159-211. DOI: https://dx.doi.org/10.1177/0148607115621863
6. Waitzberg DL. Indicadores de qualidade em terapia nutricional. São Paulo: ILSI Brasil; 2008.
7. Nunes ALB, Koterba E, Alves VGF, Abrahão V, Correia MITD. Terapia Nutricional no Paciente Grave. Projeto Diretrizes. 2011. p. 16. Available from: http://www.projetodiretrizes.org.br/9_volume/terapia_nutricional_no_paciente_grave.pdf. Accessed on: 12/11/2016.
8. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. J Parenter Enteral Nutr 2003;27(5):355-73. DOI: https://dx.doi.org/10.1177/0148607103027005355
9. Kreymann KG, Berger MM, Deutz NEP, Hiesmayr M, Jolliet P, Kazandjiev G, et al. ESPEN Guidelines on Enteral Nutrition: Intensive care. Clin Nutr 2006;25(2):210-23. DOI: https://dx.doi.org/10.1016/j.clnu.2006.01.021
10. Ventura AMC, Waitzberg DL. Enteral nutrition protocols for critically ill patients: Are they necessary? Nutr Clin Pract 2015;30(3):351-62. DOI: https://dx.doi.org/10.1177/0884533614547765
11. Heyland DK, Cahill NE, DhaliwaL R, Sun X, Day AG, McClave SA. Impact of enteral feeding protocols on enteral nutrition delivery: Results of a multicenter observational study. J Parenter Enteral Nutr 2010;34(6):675-84. DOI: https://dx.doi.org/10.1177/0148607110364843
12. Oliveira SM, Burgos MGPA, Santos EMC, Prado LVS, Petribú MMV, Bomfim FMTS. Complicações gastrointestinais e adequação calórico-protéica de pacientes em uso de nutrição enteral em uma unidade de terapia intensiva. Rev Bras Ter Intensiva 2010;22(3):270-3. DOI: http://dx.doi.org/10.1590/S0103-507X2010000300009
13. Ceniccola GD, Araújo WMC, Akutsu R. Development of a tool for quality control audits in hospital enteral nutrition. Nutr Hosp 2014;29(1):102-20. DOI: https://dx.doi.org/10.3305/nh.2014.29.1.7071
14. Barr J, Hecht M, Flavin KE, Khorana A, Gould MK. Outcomes in critically ill patients before and after the implementation of an evidence-based nutritional management protocol. Chest 2004;125(4):1446-57. DOI: http://dx.doi.org/10.1378/chest.125.4.1446
15. Siqueira-Paese MC, Dock-Nascimento DB, Aguilar-Nascimento JE. Critical energy deficit and mortality in critically ill patients. Nutr Hosp 2016;33(3):522-7. DOI: http://dx.doi.org/10.20960/nh.253
16. Mukhopadhyay A, Tai BC, See KC, Ng WY, Lim TK, Onsiong S, et al. Risk factors for hospital and long-term mortality of critically ill elderly patients admitted to an intensive care unit. Biomed Res Int 2014;ID960575:10. DOI: https://dx.doi.org/10.1155/2014/960575
17. Doig GS, Simpson F, Sweetman EA, Finfer SR, Cooper DJ, Heighes PT, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: A randomized controlled trial. JAMA 2013;309(20):2130-8. DOI: https://dx.doi.org/10.1001/jama.2013.5124
18. Pasinato VF, Berbigier MC, Rubin BA, Castro K, Moraes RB, Perry IDS. Enteral nutritional therapy in septic patients in the intensive care unit: Compliance with nutritional guidelines for critically ill patients. Ver Bras Ter Intensiva 2013;25(1):17-24. DOI: http://dx.doi.org/10.1590/S0103-507X2013000100005.
19. Agudelo GM, Giraldo NA, Aguilar N, Barbosa J, Castaño E, Gamboa S, et al. Incidencia de complicaciones del soporte nutricional en pacientes críticos: Estudio multicéntrico. Nutr Hosp 2011;26(3):537-45.
20. Filho RSO, Tamburrino AC, Trevisani VS, Rosa VM. Main barriers in control of energy-protein deficit in critical oncologic patient at nutritional risk. J Integr Oncol 2016;5(1):156-60. DOI: http://dx.doi.org/10.4172/2329-6771.1000156
21. Martins JR, Shiroma GM, Horie LM, Logullo L, Silva MLT, Waitzberg DL. Factors leading to discrepancies between prescription and intake of enteral nutrition therapy in hospitalized patients. Nutrition 2012;28(9):864-7. DOI: https://dx.doi.org/10.1016/j.nut.2011.07.025
22. Pancorbo-Hidalgo PL, García-Fernández FP, Ramírez-Pérez C. Complications associated with enteral nutrition by nasogastric tube in an internal medicine unit. J Clin Nurs 2001;10(4):482-90. DOI: https://dx.doi.org/10.1046/j.1365-2702.2001.00498.x
23. Marik PE, Bellomo R. Stress hyperglycemia: An essential survival response! Crit Care 2013;14(2):305-11. DOI: https://dx.doi.org/10.1097/CCM.0b013e318283d124.
24. Van Steen SCJ, Rijkenberg S, Limpens J, Van der Voort PHJ, Hermanides J, DeVries JH. The clinical benefits and accuracy of continuous glucose monitoring systems in critically ill patients - A systematic scoping review. Sensors (Basel) 2017;17(1):146-68. DOI: https://dx.doi.org/10.3390/s17010146

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Pediatría

Niveles de hierro en sangre según adherencia a la dieta libre de gluten en niños celiacos de edad escolar

Blood iron levels in accordance with adherence to a gluten-free diet in celiac school aged children

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Resumen

Introducción: la enfermedad celiaca (EC) provoca atrofia intestinal, trastornos en la absorción de nutrientes y desnutrición progresiva. La deficiencia de hierro es una carencia nutricional muy prevalente. Una alimentación estricta libre de gluten (LG) permite calidad de vida.

Objetivo: evaluar la situación nutricional del hierro de niños celiacos escolares mediante la determinación de parámetros bioquímicos, su relación con el consumo del mineral y la adherencia a la dieta LG en San Luis.

Métodos: estudio observacional, analítico y transversal. Fueron incluidos 44 niños con EC, de seis a diez años de edad, con diagnóstico de celiaquía y registrados en entidades públicas y privadas de San Luis (Argentina) durante 2011-2012. Mediante una encuesta cuali-cuantitativa se determinaron hábitos alimentarios y características sociodemográficas. Se evaluaron niveles de hierro y adherencia a una dieta LG. Se construyeron modelos de regresión lineal generalizados para verificar la asociación de ferritina con el consumo de hierro y adherencia a la dieta.

Resultados: la mayoría de las familias tenían nivel socioeconómico bajo y eran numerosas. La alimentación no previno la anemia ferropénica según biodisponibilidad. La mayoría de los niños presentaron un estado inmunológico, anticuerpos antiendomisio y antitransglutaminas normales. El 7% presentó bajos niveles de hierro. La ferritina en condiciones de consumo adecuado de hierro se relacionó con los anticuerpos predictores y la presencia de ambos padres en el hogar.

Conclusión: en condiciones de consumo adecuado de hierro, sus niveles en sangre se relacionan con adherencia al tratamiento libre de gluten.

Palabras clave:

Enfermedad celiaca. Adherencia. Niveles de hierro en sangre. Anticuerpos.

Abstract

Introduction: Celiac disease (CD) causes intestinal damage, inability to absorb nutrients, and progressive malnutrition. Iron deficiency is one of the predominant nutritional problems. A strict gluten-free diet (GF) allows for an optimal quality of life.

Objective: To assess the nutritional situation of iron in school-aged celiac children by determining biochemical parameters, their relation to the consumption of the mineral and adherence to gluten-free diets in San Luis.

Methods: Observational, analytical and cross-sectional study. We included 44 children with CD, from 6-10 years of age, with diagnosis of celiac disease and registered in public and private entities of San Luis (Argentina) during 2011-2012. A qualitative-quantitative survey was used to determine dietary habits and sociodemographic characteristics. Iron levels and adherence to a GF diet were evaluated. Generalized linear regression models were constructed to verify the association of ferritin with iron consumption and adherence to diet.

Results: Most families had low socioeconomic status and were large families. Current feeding did not prevent iron deficiency anemia. Most children had normal immune system, and normal antiendomysial and antitransglutaminase antibodies; 7% of the children showed low levels of iron. Under adequate iron consumption conditions, ferritin was associated to predictor antibodies and the presence of both parents in the home.

Conclusion: Under adequate conditions of iron consumption, the levels of iron in blood were related to adherence to gluten-free diets.

Key words:

Celiac disease. Adherence. Blood iron levels. Antibodies.

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INTRODUCCIÓN

La enfermedad celiaca (EC) afecta a numerosas personas mundialmente, aproximadamente el 1% de la población general, en cualquier etapa de la vida. La EC, además de ser una enteropatía inducida por gluten, es una condición que involucra factores inmunológicos, genéticos y ambientales en su desarrollo. Provoca un desorden sistémico mediado inmunológicamente en individuos genéticamente predispuestos, caracterizado por la presencia de una combinación variable de: a) manifestaciones clínicas dependientes del gluten; b) anticuerpos específicos de EC; c) perfil genético de riesgo (haplotipos HLA DQ2 y DQ8); y d) enteropatía (1).

La ingestión de las proteínas del gluten produce una lesión intestinal característica que provoca cambios estructurales en la mucosa del intestino delgado y trastornos de mala absorción de nutrientes, especialmente hierro y calcio (2). Existe un amplio rango de manifestaciones clínicas, desde astenia hasta síntomas intestinales como diarrea, distensión y dolor abdominal, además de cansancio y pérdida de peso y retraso de crecimiento en niños. No obstante, cada persona puede experimentar distintas manifestaciones según cómo se presente la intolerancia. En los pacientes con EC se ha observado anemia ferropénica acompañada de niveles bajos de otros micronutrientes (3). Si bien la intolerancia es de carácter permanente, existe evidencia de mejoría de los síntomas al suprimir el gluten de la dieta y reaparición del cuadro en caso contrario. El tratamiento de la dieta libre de prolaminas tóxicas es fácil de prescribir pero difícil de seguir, más aún si el niño no cuenta con apoyo familiar.

Estudios realizados por el Ministerio de Salud de Argentina a niños y adolescentes durante 2008-2009 indicaron celiaquía en 1:79 niños, representando una prevalencia del 1,26% (4). Por su parte, la Encuesta Nacional de Nutrición y Salud (ENNyS, 2006) mostró una prevalencia de anemia en niños pequeños elevada en el país, especialmente en la zona del noreste (8). Por consiguiente, su importancia en términos de frecuencia y de efectos en la salud compromete a una profunda revisión de la situación, aunque no existen estudios nacionales que informen acerca del estado del hierro en niños escolares.

En niños celiacos, las deficiencias nutricionales de micronutrientes más notables son la hipocalcemia y la deficiencia de hierro, que provocan daños irreversibles en su desarrollo psicomotor y conductual (5). La depleción del estado nutricional del hierro varía desde una disminución de sus depósitos hasta desarrollar anemia ferropénica.

La anemia por deficiencia de hierro es uno de los problemas nutricionales de mayor magnitud mundial (6). Es una carencia de nutriente específico que no afecta el crecimiento ponderal ni tiene manifestaciones clínicas de desnutrición; sin embargo, provoca un inadecuado desarrollo mental y motor en niños pequeños, independientemente del estrato socioeconómico de pertenencia (7).

Los niños de seis a diez años en edad escolar se encuentran en una etapa de estabilidad con respecto al metabolismo del mineral, ocurriendo en pocos casos una deficiencia marcada de hierro. Sin embargo, un consumo insuficiente del mineral, junto a otros acontecimientos que comprometan la absorción (parasitosis o algunas intolerancias como EC), puede generar un deficiente estado nutricional del hierro (2,6). Sin embargo, en niños celiacos en edad escolar, la anemia nutricional por deficiencia de hierro es una situación compleja y riesgosa, que compromete no solo su sistema inmunológico sino también su óptimo desarrollo físico e intelectual. No obstante, es importante considerar que una dieta libre de prolaminas tóxicas completa desde el punto de vista nutritivo no dará lugar a carencias nutricionales (2).

El presente trabajo evalúa la situación nutricional del hierro en el organismo de niños celiacos en edad escolar mediante la determinación de parámetros bioquímicos y su relación con el consumo del mineral y la adherencia a la dieta libre de gluten.

MATERIAL Y MÉTODOS

Se realizó un estudio observacional correlacional, de corte transversal. Se incluyeron 44 niños de ambos sexos entre seis y diez años de edad con diagnóstico confirmado por biopsia intestinal y anticuerpos antiendomisio y antitransglutaminasa positivos de EC, registrados en entidades públicas y privadas de la ciudad de San Luis (Argentina) durante 2011-2012. Los criterios de inclusión fueron: tener diagnóstico histopatológico de EC confirmado, estar en la etapa de mantenimiento (es decir, que hayan superado la etapa crítica) y de recuperación intestinal luego de seguir una dieta libre de gluten (2), tener entre seis y diez años y que sus padres hayan firmado el consentimiento informado de acuerdo a los recaudos éticos que establece la Declaración de Helsinki (9). Se visitaron 67 familias y se excluyó a 23 niños por no cumplir los criterios de inclusión.

VALORACIÓN BIOQUÍMICA

La anemia se valoró por medio de la concentración de hemoglobina (Hb) < 11 mg/dl (según la OMS), en una muestra de sangre venosa. Para diagnosticar deficiencia de hierro se determinaron en suero los niveles de *hierro* (método colorimétrico [Wiener, Argentina]; valor de Referencia [VR] en niños: 50-120 µg/dl) (10), *ferritina* (método inmunorradiométrico [IRMA] Coat-A-Count [DPC, Los Ángeles, CA, USA]; VR: 10-150 ng/m) y *transferrina* (método colorimétrico [Wiener, Argentina]; VR: 200-400 mg/dl). El *porcentaje de saturación de transferrina* se determinó según la expresión porcentual del cociente entre los niveles de hierro y de transferrina (VR: 20-50%). La presencia de parasitosis intestinal se evaluó mediante examen coproparasitológico.

ADHERENCIA AL TRATAMIENTO

La adherencia a la dieta libre de prolaminas tóxicas se midió según los marcadores serológicos de EC: limunoglobulina A (IgA; VR: 30-240 mg/dl), anticuerpos antitransglutaminasa tisular (tTG) y antiendomisio (EMA) por inmunofluorescencia indirecta y se informaron como positivo o negativo (11).

CONDICIONES SOCIOECONÓMICAS

Los determinantes socioeconómicos se estimaron por un cuestionario con preguntas abiertas y cerradas. El nivel socioeconómico (NSE) fue definido según el nivel de instrucción (NI) y la situación ocupacional del jefe del hogar (12). Las condiciones sociales se evaluaron a partir de la composición familiar, los trabajadores del hogar, los ingresos y la situación familiar (padres unidos o separados).

CONSUMO DE HIERRO ALIMENTARIO

La ingesta de hierro alimentario se midió usando un recordatorio de 24 horas a partir de pesos y medidas caseras combinado con Monsen (evalúa biodisponibilidad de absorción de hierro según la presencia de sinergistas de absorción del mineral). El recordatorio se realizó en visitas domiciliarias una vez por semana durante un mes, para conocer el consumo habitual del mineral (13).

La determinación de nutrientes se realizó utilizando tablas de la Organización de las Naciones Unidas para la Alimentación y la Agricultura (14), con otras fuentes de información nacional. Los resultados obtenidos, fueron comparados con las Recomendaciones Dietéticas Alimentarias (*Recomendad Dietary Allowances*, 2005) (15).

SUPLEMENTACIÓN CON HIERRO

El uso de suplemento con hierro se evaluó mediante preguntas anexadas al cuestionario de alimentación y analizado según consumo, dosis, duración y cumplimiento del tratamiento.

ANÁLISIS ESTADÍSTICO

Se empleó el programa SPSS versión 22.0 (SPSS, Chicago, IL). Se utilizó el test de Chi-cuadrado (χ^2) y se calcularon el coeficiente de correlación de Spearman (CS) y el estadístico ETA para indicar el grado de asociación entre variables. Posteriormente, se utilizó la prueba "*t*" para determinar diferencias de medias. Se diseñó un modelo de regresión lineal generalizado para conocer el grado de vinculación entre la variable dependiente e independientes con un $\alpha = 0,05$.

RESULTADOS

Durante 2011-2012 fueron estudiados 44 niños (28 mujeres y 16 varones) con diagnóstico histopatológico confirmado de celiaquía de la ciudad de San Luis, de entre seis y diez años de edad y provenientes de centros de salud pública y privada. Las principales características sociodemográficas del grupo estudiado se muestran en la tabla I, donde se destaca que el 45% de ellos pertenecía a un NSE bajo.

INFECCIÓN PARASITARIA EN LOS NIÑOS CELIACOS

Del total de niños estudiados, se observó que el 29,5% (13) presentaba parásitos intestinales; de estos, el 46% tenía *Oxiurius vermicularis* y el 38,5% mostró quistes de *Giardia lamblia.* No se relacionó el NI de los padres con la presencia de parásitos en sus hijos (instrucción paterna CS = 0,024 e instrucción materna CS r = 0,023).

CONSUMO, BIODISPONIBILIDAD Y ABSORCIÓN DE HIERRO EN LA ALIMENTACIÓN

Según la evaluación realizada respecto al consumo de hierro, se determinó que la mitad de los niños ingirieron el mineral en cantidades suficientes (Tabla I). Si bien las medias de consumo según grupo etario se hallaban por encima de las recomendaciones nutricionales (6-8 años = 10 mg; 9-10 años = 8 mg), la moda presentada fue muy baja para ambos grupos y la mitad de los niños más pequeños y el 25% de los niños de nueve a diez años no ingerían las cantidades diarias necesarias del mineral.

En base al origen de alimentos consumidos (vegetal y animal) y el tipo de hierro integrante en su composición química (hem y no hem), se analizó por el método de Monsen (13) la biodisponibilidad de las comidas y la absorción real del nutriente según la presencia de favorecedores de la absorción como son el factor cárneo y la vitamina C. Así, la absorción total promedio de hierro fue de entre 2,8 y 3,4 mg respectivo a cada grupo de alimentos. La absorción del hierro total (hem + no hem) alcanzó valores aceptables (10-15%). En general, los niños consumieron una dieta con biodisponibilidad media y baja (43,2% y 54,5%, respectivamente). El 90,9% de los niños no consumieron hierro con biodisponibilidad adecuada. Hubo correlación entre el consumo de hierro, la biodisponibilidad y el riesgo de padecer anemia ferropénica ($p < 0,05$). Se determinó que la mayoría de los niños con niveles de ferritina normales presentaron biodisponibilidad media y alta del hierro consumido y la mayoría de los niños que participaron del estudio (93%) no estaban suplementados con hierro.

EVALUACIÓN HEMATOLÓGICA DE LOS NIÑOS ESTUDIADOS

Los resultados obtenidos del hemograma determinaron que el 25% de los niños presentaron valores de hemoglobina cercanos al límite inferior del parámetro normal para la edad. El 13,6% presentó anemia y entre un 5 y un 7% presentó niveles de ferritina y ferremia por debajo de los valores de referencia (Tabla II).

Tabla I. Características socioeconómicas y familiares de los niños celiacos, San Luis 2012 (n = 44)

Características socioeconómicas y familiares	Categorías % (nº)		
Sexo	Varones 36,4 (16)	Mujeres 63,6 (28)	-
Edad	6-8 años 48 (21)	9-10 años 52 (23)	Media (DE) 8,3 (1,52)
Nivel socioeconómico	Alto 15,9 (7)	Medio 38,7 (17)	Bajo 45,4 (20)
Nivel de instrucción materna†	Primario Inc./Com. 15,9 (7)	Secundario Inc./Com. 52,3 (23)	Terciario/ Universitario 31,8 (14)
Nivel de instrucción paterna†	Primario Inc./Com. 29,5 (13)	Secundario Inc./Com. 54,6 (24)	Terciario/ Universitario 15,9 (7)
Obra social	Sí 72,7 (32)	No 27,3 (12)	-
Ingresos*	Diarios 9,1 (4)	Sem./Quin. 11,3 (5)	Mensual 79,5 (35)
Situación familiar**	Unidos 81,8 (36)	Separados 18,2 (8)	-
Trabajo de los padres	Ambos padres 50 (22)	1 solo padre 45,5 (20)	No trabajan 4,6 (2)
Responsable de gastos del hogar	Padre 70,5 (34)	Madre 22,7 (10)	Abuelos 6,8 (3)

*n: frecuencia absoluta; DE: desviación estándar. †Nivel de instrucción materna o paterna: Primario Inc. /Com. (Primaria incompleta o completa); Secundario Inc/ Com. (Secundaria incompleta o completa).*Ingresos: Sem. (semanales); Quin. (quincenales). **Situación familiar: unidos (padres que viven juntos); separados (padres que no viven juntos).*

Los valores de Hb se correlacionaron con el hematocrito (CP = 0,647; p < 0,0001) y los niveles de hierro sérico (ferremia), con el porcentaje de saturación de transferrina (CP = 0,652; p < 0,0001) (Tabla III). En cuanto a la ferremia y Hb, se observó una correlación significativa (CP = 0,389; p = 0,013). Sin embargo, no se demostró una correlación entre los indicadores del estado nutricional de hierro que determinan la depleción del mineral en el organismo. Los valores de Hb y los porcentajes de saturación de transferrina y ferritina de los niños estudiados no se asociaron entre ellos. Se evidenció, además, que la ingesta de hierro no se correlaciona con los niveles de ferritina determinados (CP = 0,261).

No hubo relación de las parasitosis con los valores de Hb, según el test estadístico del coeficiente de Omega^2 (Eta = 0,035), pero sí con la concentración de ferritina (valor de Eta = 0,88).

ADHERENCIA A LA DIETA SEGÚN INDICADORES SEROLÓGICOS

Para la determinación de IgA, se excluyeron tres (1,32%) casos debido a dificultades con la toma de la muestra, y solo dos niños (0,88%) mostraron valores menores del de referencia. La población estudiada presentó un estado inmunológico adecuado. En tabla IV se observa que los valores de IgA oscilaron entre 351,40 mg/dl y 18 mg/dl. Los anticuerpos predictores de adherencia al tratamiento, tTgA y EMA resultaron no reactivos en el 71,8% (n = 31) de los niños en estudio (Tabla V).

Al comparar el estado inmunológico a través de IgA de los niños según presentaron reacción inmunológica (EMA y tTgA), se observó que la media y mediana de la inmunoglobulina en ambos grupos (reactivos y no reactivos) estaban dentro de los valores de referencia, con valores superiores en el grupo de niños con anticuerpos positivos. No se encontraron diferencias significativas entre ambos grupos (prueba "*t*" para igualdad de medias

Tabla II. Descripción de la ingesta y absorción del hierro de la dieta habitual de los niños celíacos, San Luis 2012 (n = 44)

Descriptivos	Media (DE) a-b	Modo a-b	P 25 a-b	Mediana a-b	P 75 a-b
Hierro (mg)	12,52 (10,9) - 14,03 (7,5)	5,3-5,3	5,5-8,3	8,1-12,1	14,9-19,6
Absorción Hem (mg)	2,14 (1,3) - 2,7 (2,7)	0-1,2	0,6-1,3	1,2-1,9	2,2-3,4
Absorción No hem (mg)	0,75 (1,2) - 0,74 (0,9)	0,2-0,4	0,2-0,2	0,3-0,4	0,5-0,6
Absorción total	2,89 (2,5) - 3,44 (3,6)	0,2-1,6	0,8-1,5	1,5-2,1	2,7-4
Vit C	54,82 (20,7) - 66,14 (21,9)	44,2-33,7	39-46,4	49,3-68,9	70-80,3

Descriptivos según recomendaciones por edad de los niños. a: niños de 6-8 años (n = 21); b: niños de 9-10 años (n = 23). P: percentil; Vit C: vitamina C. Los resultados se expresan como la media ± DE.

Tabla III. Parámetros hematológicos de los niños celiacos, San Luis 2012 (n = 44)

Parámetros hematológicos	Por debajo del VR*	Mínimo	Máximo	Media (DE)	Mediana	Modo
Leucocitos (mm^3)	6	2.150	10.050	6.005 (1.836,54)	5.950	5.600
Hematíes (mm^3)	-	3.720.000	4.860.000	4.375.000 (345.903)	4.380.000	4510000
Hemoglobina g/dl	6	9,6	14	12,4 (1,035)	38,86	
Hematocrito %	3	32	45	38,6 (3,18%)	38,80	38
Ferritina ng/ml	2	3	207	57,09 (35,9)	49,94	3
Saturación de transferrina %	1	15	143	57,23 (26,54)	52,13	73
Ferremia ug/dl	3	54	195	104,05 (38,7)	97	54
Transferrina g/dl	19	90	327	190,28 (54,27)	178,9	121

**VR: valores de referencia; DE: desviación estándar; mm^3: milímetro cúbico.*

Tabla IV. Correlación entre los indicadores del estado nutricional del hierro en los niños celiacos, San Luis 2012 (n = 44)

Indicadores hematológicos	Test estadístico significación	Hb	Ferritina	% Saturación de transferrina	Hto	Ferremia
Hb	C. Pearson	1	0,116	0,095	0,647	0,389
	Sig. bilateral	-	0,457	0,561	0,000	0,013*
Ferritina	C. Pearson	-0,116	1	0,104	0,237	0,132
	Sig. bilateral	0,457	-	0,520	0,126	0,417
% Saturación de transferrina	C. Pearson	0,095	0,104	1	-0,042	0,652
	Sig. bilateral	0,561	0,520	-	0,796	0,000

**Correlación significativa en el nivel 0,05 (2 colas). Hb: hemoglobina; Hto: hematocrito.*

"Levene", p = 0,094), pero si al NC del 90%. La figura 1 muestra que no hay diferencias cuando se comparan las medias de los anticuerpos entre positivo y negativo con los valores de IgA dentro de los parámetros normales.

ANÁLISIS DE LAS RELACIONES ENTRE EL CONSUMO DE HIERRO, LA ADHERENCIA AL TRATAMIENTO Y LOS NIVELES DE HIERRO EN SANGRE

Al describir la situación nutricional del hierro, se observó que un pequeño número de niños presentaba niveles de hierro sérico por debajo de los parámetros considerados como normales, y los que padecían anemia no correspondían a deficiencia del mineral orgánico.

Al analizar los niveles de ferritina se evidenció que en condiciones adecuadas de consumo de hierro, la ferritina se asoció con los

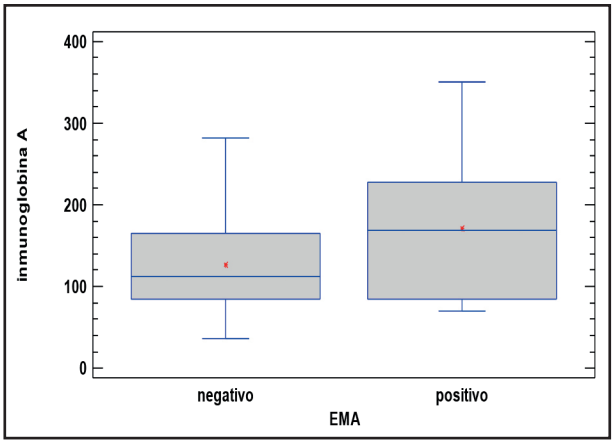

Figura 1.

Comparación de medias del anticuerpo predictor antiendomisio (EMA) con IgA normal en niños celíacos de San Luis, 2012 (n = 44).

Tabla V. Niveles de IgA, según los resultados de anticuerpos antiendomisio (EMA) y antitransglutaminasa (tTGS) en niños celiacos de San Luis, 2012 (n = 44)

EMA	tTGA	n	Media	Mínimo	Máximo	Mediana	Q_1	Q_3	DE
-	-	28	126,67	36,00	282,00	112,50	85,00	164,5	65,725
+	+	11	170,55	70,00	351,00	169,00	85,00	228,00	85,883

Q: quartil; n: número de individuos; DE: desviación estándar. Los resultados se expresan como la media ± DE.

anticuerpos predictores (valor de Eta = 0,618). A su vez, aplicando un modelo de regresión lineal generalizado se observó que las variables que explican los valores de ferritina son los anticuerpos predictores (p = 0,005) y la presencia de ambos padres en el hogar (p = 0,022).

En el caso de los niños con consumo insuficiente de hierro, solo se asoció con los niveles de ferritina la variable trabajo de los padres (si uno o ambos padres trabajan o reciben ayuda externa para el mantenimiento del hogar: p = 0,004).

DISCUSIÓN

El presente estudio analizó la relación entre el estado nutricional del hierro orgánico y la adherencia a la ingesta libre de prolaminas tóxicas, incluyendo un análisis multifactorial que consideró las condiciones de vida, la posición socio-ocupacional y el consumo de hierro en niños celiacos escolares.

El sexo femenino (63%) predominó, posiblemente porque las mujeres presentan con más frecuencia enfermedades autoinmunes (16).

Las condiciones sociales y familiares de "protección" en los niños celiacos contribuyen a comprender profundamente las necesidades de sus hijos en relación a una dieta de exclusión de por vida, como también de conseguir y utilizar correctamente los listados de alimentos aptos. Similares evidencias se reportaron en un estudio en adolescentes celiacos (17) donde el principal responsable de los gastos del hogar fueron los padres, quienes lograron finalizar el nivel secundario y se desempeñaban como empleados de fábricas, a diferencia del estudio realizado en España por Cabañero (2009) donde la mayoría de los padres continuó su formación más allá del nivel secundario y eran trabajadores independientes (18).

La presencia de hermanos en el hogar favorece el proceso de sociabilización de la enfermedad (19). Sin embargo, cuando la familia es numerosa o cuando ambos padres trabajan fuera del hogar, las condiciones internas y las posibilidades de atención se vuelven más riesgosas en relación a una alimentación segura libre de gluten.

El nivel socioeconómico bajo fue el más frecuente en las familias de los niños estudiados, representando un riesgo para acceder a alimentos libres de gluten por su costo excesivo (20). Así lo indica un estudio realizado en la ciudad de San Luis del costo de la Canasta Básica de Alimentos Libres de Gluten, un 54% superior al de la que contiene gluten (21). La situación de los celiacos chilenos es más difícil. Según Castillo y Rivas, el costo de la canasta chilena para celiacos es un 89% superior al de su canasta básica, posiblemente debido a la carente producción de harinas especiales en el país (21).

La alta incidencia de parasitosis en escolares puede ocasionar importantes problemas sanitarios y sociales debido a su sintomatología y complicaciones (22,23). En Valencia y México, se observó que un 30-50% de niños presentaban parasitosis, con predominio de escolares (24,25). La variabilidad porcentual refleja las diferencias de los hábitats y factores ambientales que marcan la mayor posibilidad de optimizar el ciclo de vida de esos individuos. Tanto la giardiasis como la oxiuriasis fueron consideradas como una de las siete parasitosis más prevalentes en el continente americano (24), presentes en el 30% de los niños estudiados.

Los niños con anemia no se asociaron con parasitosis intestinal. No obstante, los depósitos de hierro sí se vieron afectados, generando un potencial riesgo de padecer carencias nutricionales por déficit de absorción de nutrientes.

Posiblemente, las largas jornadas laborales y escolares, sumadas a la mayor incorporación femenina en el trabajo extradoméstico, han generado cambios en las comidas compartidas en el hogar, además de disminuir su número. Sumado a esto, las preparaciones caseras se han simplificado y la utilización del espacio culinario doméstico ha decrecido. Así, estos cambios se han asociado con una monotonía alimentaria y la reducción considerable de nutrientes en la dieta (26).

La anemia ferropénica en la EC se ha descrito como la manifestación extraintestinal más frecuente (27). Está relacionada fundamentalmente con el insuficiente consumo de hierro en la alimentación (28) o con dificultades en la absorción debido a una baja o nula adherencia al tratamiento (29). En los niños celiacos estudiados, la mayoría (75%) no alcanzaron valores de consumo adecuados de hierro. Así mismo, el 90% de ellos mostró riesgo de presentar anemia de acuerdo a la biodisponiblidad del mineral en la dieta habitual. Las evidencias encontradas en relación al consumo de hierro se asemejan a los resultados de un estudio realizado con niños de Madrid (30). No ocurrió lo mismo al comparar con un estudio realizado en Granada con niños menores de diez años, donde las ingestas recomendadas fueron superadas en un 115%, representando una dieta protectora de anemia ferropénica (31).

La correlación de la biodisponibilidad media y alta del hierro consumido con los niveles de ferritina alcanzados por los celiacos corroboró que la absorción del hierro es favorecida por la adecuada biosponibilidad del mineral, tal y como lo afirman Martínez Salgado y cols. en su estudio de anemia en niños mexicanos (32).

La alimentación del celiaco debe estar completamente adaptada a sus requerimientos particulares, a las condiciones de salud y al compromiso intestinal. Cualquier alteración en la alimentación afecta

directamente al proceso de absorción de nutrientes, lo que se traduce en carencias nutricionales. Se ha comprobado que a los diez años de tratamiento con la dieta sin gluten, el riesgo de enfermedades neoplásicas es similar al de la población general. En las no neoplásicas, reduce el riesgo de enfermedades de tipo autoinmune, alteraciones del metabolismo óseo y reproducción, neurológicas y psiquiátricas. Estas observaciones justifican la exclusión de por vida del gluten en la dieta del paciente celiaco (29,33).

El 71,8% (n = 31) de los niños en estudio resultaron no reactivos, según los anticuerpos EMA y tTgA con IgA normal, hecho que significa que aproximadamente dos tercios de la población estudiada se adherían al tratamiento sin gluten. Estos resultados se hallan dentro de los porcentajes estimados de adherencia, que fluctúan entre un mínimo del 45% y un máximo del 80% dependiendo de la edad. Los niños suelen tener mayor adherencia, considerando que la responsabilidad de cumplir con el tratamiento recae, en gran parte, en sus padres (34).

La anemia encontrada en los niños celiacos estudiados (13%) no respondía a una deficiencia orgánica del hierro. Los indicadores de deficiencia de hierro permitieron reconocer que un número reducido de niños presentaron valores por debajo de lo normal (5-7%). Los niños con anemia no se vincularon con anemia ferropénica, lo que significaría que la deficiencia del mineral no alcanzó en tiempo y carencia a permitir una desnutrición que evolucione hacia la anemia. Estos niños no pertenecen a un grupo de riesgo por sus necesidades de crecimiento y desarrollo, y las carencias observadas podrían deberse a una inadecuada absorción y/o ingreso de nutrientes al organismo.

En Argentina, la Encuesta Nacional de Nutrición y Salud (2006) halló que un 8,9% de niños preescolares presentaban anemia, el 3,5% en Cuyo. Estos datos son más bajos que los encontrados en presente estudio (13%) (37). En México (32), se encontró una prevalencia de niños escolares con anemia del 16,6% (2006), una diferencia importante en relación a niños de Medellín que presentaron anemia ferropénica en un 0,6% y deficiencia del mineral sin anemia en un 4,9%. Las prevalencias de anemia ferropénica y deficiencia de hierro encontradas fueron bajas, de acuerdo con los parámetros de hemoglobina y ferritina definidos por la OMS (10). Lo mismo se refleja en el grupo de niños celiacos de San Luis; los finos mecanismos de regulación del metabolismo del hierro pueden haber contribuido a estos resultados (36).

No se encontró asociación significativa entre la presencia de parásitos intestinales y la de anemia en ambos estudios (Medellín y celiacos San Luis), pero sí con respecto a la deficiencia del mineral.

El consumo promedio de hierro diario de niños de Medellín fue de 5,5 mg. Esto corresponde al 32% de la ingesta dietética recomendada para la edad del grupo estudiado. El aporte promedio de hierro hemático en la dieta fue de 0,7 mg (36). No se encontraron diferencias significativas en la cantidad y el tipo de hierro consumido entre los niños con y sin anemia, lo cual refleja resultados similares a los obtenidos en los niños celiacos del presente trabajo.

La asociación entre el hierro consumido y el depósito de hierro orgánico no resultó significativa. Lo mismo sucedió en un estudio llevado a cabo en España, mediante la valoración de niños provenientes del Sahara, donde se encontró que la adherencia al tratamiento sin gluten es determinante para los niveles de hierro en el organismo (37).

Para la población infantil que no padece de la condición de celiaquía es indudable que la deficiencia de hierro se puede prevenir mediante modificaciones de la dieta, fortificación de los alimentos y suplementación con hierro medicinal. Ninguna de estas estrategias es excluyente. La forma ideal de prevenir la carencia de hierro es mediante una dieta adecuada, lo que no siempre es posible de lograr por limitaciones económicas o hábitos muy arraigados. Se debería aumentar el consumo de alimentos ricos en sustancias que favorecen la absorción del hierro no hemínico (ácido ascórbico, carne), disminuir el consumo de inhibidores de la absorción (polifenoles, fitatos) y aumentar el consumo de hierro hemínico (carnes, morcilla, hígado) (38).

Si se tienen en cuenta estas consideraciones y se realiza una dieta estricta sin gluten, mejorará el estado de nutrición y el crecimiento en niños celiacos.

A partir de los análisis realizados en niños celiacos de seis a diez años de la ciudad de San Luis, se demostró que en condiciones de consumo adecuado de hierro, sus niveles orgánicos se relacionan con la adherencia al tratamiento libre de gluten. El estudio de la EC cobra interés fundamental en nuestro país y en el mundo, considerando el incremento dinámico de su prevalencia y el riesgo de las patologías graves para la salud, resultantes de un inadecuado diagnóstico y tratamiento.

Este estudio abordó de forma integral la intolerancia al gluten, las implicaciones en la adherencia al tratamiento y la relación con el hierro plasmático, usando protocolos estandarizados y patrones unificados para monitorizar la adherencia a la dieta sin gluten, así como para valorar los estadios de la depleción de hierro, el consumo y la biodisponibilidad del mineral, importante fortaleza que aporta al conocimiento científico en esta área de salud.

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BIBLIOGRAFÍA

1. Husby S, Koletzko S, Korponay-Szabo IR, Mearin ML, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012;54:136-60.
2. Torresani ME. Cuidado nutricional pediátrico. Buenos Aires, Argentina: Eudeba, Universidad de Buenos Aires; 2006. p. 435-64.
3. Borda G, Kriebaum A, Sánchez F, Nicoletti C. Enfermedad celiaca: aún subestimada y subdiagnosticada. Rev Posgrado VIta Cátedra Medicina 2006;159:26-30.
4. Ministerio de Salud de la Nación. Más información más derechos; 2013. Disponible en: http://www.msal.gob.ar/plan-reduccion-mortalidad/boletin/b04/b04_celiaquia_mas informacion mas derechos.html.VnBOa9Lh.

5. Lozoff B. Iron deficiency and child development. Food Nutr Bull 2007:28:S560-71.
6. Duran P. Anemia por deficiencia de hierro: estrategias disponibles y controversias por resolver. Arch Argent Pediatr 2007;105:6.
7. Batrouni L, Pirán Arce MF, Eandi M, Dasbul G, Toledo S. Parámetros bioquímicos de hierro e ingesta en niños de 12 a 24 meses de edad, Córdoba. Rev Chil Nutr 2004;31:16-3.
8. Kogan L, Abecé Galardón E, Biblieri A, Mangialavori G, Calvo E, Durán P. Anemia: la desnutrición oculta. Resultados de la iciavalaron el mismo (se adjunta copia de dicho aval).Encuesta Nacional de Nutrición y Salud 2008;1-73. Disponible en: http://www.msal.gov.ar.
9. Declaración de Helsinki de la AMM - Principios éticos para las investigaciones médicas en seres humanos. Asociación Médica Mundial 2016. Disponible en: http://www.wma.net/s/index.htm
10. UNICEF, UNU, WHO, MI. Preventing iron deficiency in women and children. Technical consensus on key issues. International Nutrition Foundation 1998;1-65. Disponible en: http://www.inffoundation.org/pdf/prevent_iron_def.pdf
11. Ribes Koninckx C. Utilidad diagnóstica de los marcadores serológicos. Mitos y realidades 2006. Disponible en: www.svnp.es/sites/default/files/celiaca.pdf
12. Andreatta MM, Muñoz SE, Lantieri MJ, Eynard AR, Navarro A. Artificial sweetener consumption and urinary tract tumors in Cordoba, Argentina. Prev Med 2008;47(1):136-9.
13. Olivares S, Andrade M, Zacarías I. Necesidades nutricionales y calidad de dieta. 1994. Santiago, Chile. Instituto de Nutrición y Tecnología de los Alimentos. Un 1994;III:73-82.
14. FAO/Latin Foods. Tabla de composición de alimentos de América Latina. FAO LATIN FOODS 2002. Disponible en: http://www.rlc.fao.org/es/bases/alimento/
15. Institute of Medicine of National Academy. Carbohidrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. 2005. Disponible en: http:// www.nap.edu/openbook.php?record_id=10490
16. Espino A, Castillo C, Guiraldes E, Santibáñez H, Miquel JF. Encuesta Nacional online aplicada en pacientes con enfermedad celíaca en Chile. Rev Med Chile 2011;139(7):841-7.
17. Krivozea C, Gracia E, Pirán Arce MF. Adherencia al tratamiento de la enfermedad celiaca y su relación con el bienestar de los adolescentes de la ciudad de San Luis en el año 2015. Trabajo final. Lic. en Nutrición, FCS, UNSL, Argentina 2015;(1):1-101.
18. Cabañero Pisa MA. Calidad de vida de los adolescentes afectos de enfermedad celíaca. Facultad de Medicina. Universidad de Murcia. España. 2010. Disponible en: http://hdl.handle.net/10201/10680.
19. Asociación Celiaca de Castilla y León. ¿Una enfermedad o un estilo de vida? Caja España. 2013. Disponible en: http://es.slideshare.net/EscuelaBicentenario/la-enfermedad-celaca-una-enfermedad-o-un-estilo-de-vida.
20. Bravo F, Muñoz M. Adherencia e impacto de la dieta sin gluten en niños con enfermedad celíaca. Rev Chil Pediatr 2011;82(3):191-7.
21. Guirín C. Disponibilidad y costo de la canasta básica de alimentos libres de gluten en los supermercados comprendidos dentro de las cuatro avenidas de la capital de la provincia de San Luis, Argentina. Trabajo final. Lic. en Nutrición. FCS, UNSL, Argentina 2014;(1):1-113.
22. Díaz Anciani I, Botero L, Ledesma F, Molero de Bracho, N, Cotech M, Jaoahari R, et al. Prevalencia de enteroparasitosis en individuos que acuden a la Unidad Docente Asistencial de Medicina Familiar "Luis Sergio Pérez". Kasmera 2000;28:45-62.
23. Guevara Y, De Haro I, Cabrera M, García de la Torre G, Salazar-Schettino PM. Enteroparasitosis en poblaciones indígenas y mestizas de la Sierra de Nayarit, México. Parasitol Latinoam 2003;58(1):30-4.
24. Rodríguez-Guzmán LM, Hernández-Jerónimo EJ, Rodríguez-García R. Parasitosis intestinal en niños seleccionados en una consulta ambulatoria de un hospital. Rev Mex Pediatr 2000;67(3):117-22.
25. Solano L, Acuña I, Barón MA, Morón de Salim A, Sánchez A. Influencia de las parasitosis intestinales y otros antecedentes infecciosos sobre el estado nutricional antropométrico de niños en situación de pobreza. Parasitol Latinoam 2008;63:12-9.
26. Piaggio L, Rolón M, Dupraz, S. Alimentación infantil en el ámbito escolar: entre patios, aulas y comedores. Salud Colectiva 2011;7(2):199-213.
27. Guevara Pacheco G, Chávez Cortés E, Castillo-Durán C. Deficiencia de micronutrientes y enfermedad celíaca en pediatría. Arch Argent Pediatr 2014;112(5):457-63.
28. Vásquez Garibay EM. La anemia en la infancia. Rev Panam Salud Publ 2003;13(6):349-51.
29. Ortiz M. Enfermedad celiaca. Características, avance y dietoterapia actuales. Trabajo final. Lic. de Nutrición. FCEN, Universidad de Belgrano, Argentina 2005;81:33.
30. Díez-Gañán L, Galán Labaca I, León Domínguez CM, Zorrilla Torras B. Encuesta de Nutrición Infantil de la Comunidad de Madrid. Madrid: Consejería de Sanidad de la Comunidad y Madrid 2008;1:1-305.
31. Velasco J, Mariscal-Arcas M, Rivas A, Caballero ML, Hernández-Elizondo J, Olea-serrano F. Valoración de la dieta de escolares granadinos e influencia de factores sociales. Nutr Hosp 2009;24(2):193-9.
32. Martínez Salgado H, Casanueva E, Rivera-Dommarco J, Viteri FE, Bourges-Rodríguez H. La deficiencia de hierro y la anemia en niños mexicanos: acciones para prevenirlas y corregirlas. Boletín Médico del Hospital Infantil de México 2008;65(2):86-99.
33. Ribes-Koninckx C. Enfermedad celíaca: presente y futuro. Rev Sdad Valencia Patol Dig 1998;17:23-31.
34. Mohaidle A, Mella JM, Pereyra L, Luna P, Fischer C, Cimmino DG, et al. Rol de los anticuerpos en la enfermedad celíaca luego de un año de tratamiento para predecir la adherencia a la dieta libre de gluten. Acta Gastroenterol Latinoam 2011;41:23-8.
35. Encuesta Nacional de Nutrición y Salud (ENNyS). Documento de Resultados. Ministerio de Salud de la Nación 2007;(1):1-170.
36. Agudelo GM, Cardona OL, Posada M, Montoya MN, Ocampo NE, Marín CM, et al. Prevalencia de anemia ferropénica en escolares y adolescentes, Medellín, Colombia. Rev Panam Salud Publ 2003;13(6):376-86.
37. Junquera CG, Lillo ML, Onsurbe Ramírez I. An Esp Pediatr 1999;51:575-6.
38. Olivares M, Walter T. Consequences of iron deficiency. Rev Chil Nutr 2003;30(3):226-33.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Pediatría

Stunting, wasting, and mid upper arm circumference status among children admitted to Nemazee Teaching Hospital

Desnutrición aguda y crónica, y circunferencia media del brazo en niños ingresados en el hospital universitario de Nemazee (Irán)

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Abstract

Introduction and aim: The aim of this study was to evaluate nutritional status in children without prior hospital admission or evidence of chronic disease.

Subjects and methods: The current study is a cross-sectional and observational study which was conducted for assessing the nutritional status of children. In this study, consecutive sampling was used, with a sample size about 400 children aged 6 months to 18 years at first hospital admission. All subjects were hospitalized consecutively in the Pediatric Emergency Department of the Nemazee Teaching Hospital of Shiraz University of Medical Sciences (Shiraz, Islamic Republic of Iran). All children with evidence or history of chronic diseases such as liver cirrhosis, microcephaly, macrocephaly due to congenital infection or abnormal skull shape, patients with muscular or neurological problem, with prolonged steroid usage, nephrotic syndrome, cardiac problem, and protein loosing enteropathy were excluded from the study. The duration of the study was six months, starting from January 2016.

Results: In the current study, 430 (225 boys and 175 girls) cases were included. Mean age was 5.39 (SEM 0.23) for boys and 5.78 (SEM 0.38) for girls. According to H/A criteria (current height/ideal height), 194 (48.5%) patients were stunted, 75 (18.8%) were mild, 49 (12.3%) were moderate and 70 (17.5%) were severe. According to W/A data (current weight/ideal weight), 188 (47%) of the patients studied were malnourished. Of these cases, 118 (29.5%) had mild malnutrition; 54 (13.5%), moderate; and 16 (4%), severe. According to body mass index (BMI), 40 (10%) patients were overweight, four (16%) were obese, and four (1%) were severe obese. In relation to middle upper arm circumference (MUAC), 56 (14%) patients were malnourished, 33 (8.3%) were at risk, 14 (3.5%) presented moderate malnutrition, and 9 (2.3%), severe malnutrition.

Conclusion: Prevalence of malnutrition among children without prior admission was 48.5% (according to H/A). According to W/A, 47% of children had different degrees of malnutrition.

Key words:

Malnutrition. Stunting. Wasting disease.

Resumen

Introducción y objetivo: el propósito de este estudio fue evaluar el estado nutricional de los niños ingresados por primera vez en el hospital y sin historia de enfermedad crónica.

Pacientes y métodos: se trata de un estudio transversal, observacional para valorar el estado nutricional al ingreso. La muestra estuvo constituida por algo más de 400 niños, de entre 6 meses y 18 años, ingresados por primera vez en el hospital. Se trataba de pacientes ingresados de forma consecutiva desde el servicio de Urgencias del hospital Nemazee de la Universidad Shiraz, en la República Islámica de Irán. Se excluyeron los pacientes con historia de enfermedad crónica como cirrosis hepática, microcefalia, macrocefalia por infección congénita o forma craneal anómala, pacientes con enfermedades musculares o neurológicas, con uso prologado de corticoides, síndrome nefrótico, cardiopatía o enteropatía pierde-proteínas. La duración del estudio fuere de seis meses, a partir de enero de 2016.

Resultados: se incluyeron 430 niños (225 varones y 175 niñas). La edad media fue de 5,39 años (SEM 0,23) para los varones y de 5,78 (SEM 0,38) en las niñas. De acuerdo al peso para la talla ideal, 194 (48,5%) tenían desnutrición crónica, 75 (18,8%) leve, 49 (12,3%) moderada y en 70 (17,5%) era grave. Según el porcentaje del peso ideal, 188 pacientes (47%) presentaban desnutrición aguda, de los cuales en 118 (29,5%) era leva, en 54 (13,5%) moderada y en 16 (4%), grave. Según el índice de masa corporal (IMC), 40 (10%) tenían sobrepeso, 16 (4%) eran obesos y cuatro (1%) presentaban obesidad mórbida. Según el perímetro del brazo (MUAC), 56 (14%) tenían desnutrición, 33 (8,3%) estaban en riesgo de desnutrición, 14 (3,5%) presentaban desnutrición moderada y 9 (2,3%) intensa.

Conclusión: la prevalencia de desnutrición en los niños ingresado por vez primera fue del 48,5%. De acuerdo al peso para la edad en 47% de los niños había algún grado de desnutrición.

Palabras clave:

Desnutrición. Enlentecimiento. Enfermedad debilitante.

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INTRODUCTION

Childhood malnutrition is a major public health problem among children in developing countries. It can affect physical and intellectual growth and is also considered as the main cause of child morbidity and mortality.

High degrees of malnutrition have been reported in our country (1). The rate of stunting, underweight, and wasting were 9.53, 9.66 and 8.19%, respectively (2). In another study from Spain, the rate of malnutrition at the moment of hospitalization was 8.2 (3). In a Brazilian study, 16.3% of children under five years of age presented malnutrition at admission (4). Most of this studies were carried out in apparently healthy school children. There are little published studies about nutritional assessment at hospital admission. The aim of this study is to evaluate the frequency of obesity and malnutrition among hospitalized children with no past medical history at the moment of hospital admission.

METHODS

This is a prospective, cross-sectional and observational study which was conducted for the assessment of children nutritional status. The study sample included 430 patients: 225 boys (56%) and 175 girls (44%), with a mean age of 5.39 (SEM 0.32) years for boys and 5.78 (SEM 0.38) years for girls. All subjects were hospitalized consecutively in the Pediatric Emergency Department of the Nemazee Teaching Hospital of the Shiraz University of Medical Sciences (Shiraz, Islamic Republic of Iran).

All children with evidence or history of chronic diseases such as liver cirrhosis, microcephaly, macrocephaly due to congenital infection or abnormal skull shape, and patients with muscular or neurological problems, with prolonged steroid usage, nephrotic syndrome, cardiac problems, and protein loosing enteropathy were excluded from the study. The duration of the study was six months starting from January 2016.

Parents or caregivers were informed about the aims of the study and verbal consent was obtained to take their children anthropometric measurements.

The instruments needed were a structured questionnaire and anthropometric measuring tools such as digital scale for weight with 0.1 kg accuracy and measuring tape with a 0.1 cm accuracy. The questionnaire included child age, sex, birth weight, height and head circumference (recorded from the child birth report card), which was completed by interviewing mothers or child caregivers.

Other required data were recorded through measuring height, weight, head circumference, and MUAC.

MEASURING WEIGHT

The child was weighed on a digital scale according to the standard way for the weight measurement. Evaluation of wasting was done according to the following formula: W/A: W/A: [observed weight/median weight (same age and sex)] x 100.

Classification of wasting was done as shown in table I.

MEASURING LENGTH

The height of children aged < 2 years was measured in supine position (top of the head to the bottom of the heel), and the rest of children were measured in standing position, with an accuracy of 0.10 cm.

Height measurement was taken on the flat floor and against a wall (flat surface). The measuring tape was placed 50 cm above the floor (and recorded height was gathered with that). The children stood with their feet flat, together, and against the wall. Legs were straight, arms were at sides, and shoulders were level. The child looked straight ahead, with the line of the sight parallel with the floor. Height was evaluated according to the following formula: H/A: [observed height/median height (same age and sex)] x 100.

Stunting was classified as shown in table II and the classification of body mass index is shown in table III.

Table I. Classification of wasting according to weight-to-age ratio (Gómez classification)

Nutritional status	W/A
No malnutrition	More than 90
Mild malnutrition	75-90
Moderate malnutrition	60-74
Severe malnutrition	Less than 60

Table II. Classification of stunting according to H/A ratio (Waterlow classification)

Nutritional status	H/A
No malnutrition	More than 95
Mild malnutrition	90-95
Moderate malnutrition	85-89
Severe malnutrition	Less than 85

Table III. Classification of nutritional status according to BMI

BMI	
< 5	Underweight
5-85th	Normal
85-95th	Overweight
95-99th	Obese
> 99th	Severe obese

BMI: body mass index.

MEASURING MUAC

First, the child's arms were relaxed and hanged down the sides of the body. The tip of the left shoulder (acromion) and the tip of the left elbow (olecranon) were located, and midpoint was marked. Then, the position of the tape was corrected for measuring arm circumference while ensuring that the tape neither pinched the arm nor was loose. Severity of malnutrition was calculated according to table IV.

MUAC has a high specificity and appears to be better predictor of childhood mortality than weight for height (5,6).

Gomez and Waterlow classifications were used for evaluation of weight for age and height for age ratio. World Health Organization (WHO) growth charts were used for weight, height, and BMI evaluation. Overweight, obesity, and severe obesity were defined according to BMI 85-95%, 95-99% and > 99%, respectively (Table III).

STATISTICAL ANALYSIS

Statistical analysis was performed with SPSS, version 16 (Chicago, IL, USA). Continuous variables were performed as mean and standard error of mean (SEM), while categorical variables were presented as number and percentage. The Chi-squared test was used to compare differences in categorical variables and the independent t test for continuous variables between boys and girls. p value less than 0.05 was considered to be statistically significant.

Table IV. Classification of nutritional status according to MUAC

MUAC (mm)	Nutritional status
Less than 110	Severe acute malnutrition
110-125	Moderate acute malnutrition
125-135	At risk of malnutrition
More than 135	Well nourished

MUAC: mid upper arm circumference.

RESULTS

The study sample included 430 patients: 225 boys (56%) and 175 girls (44%), with a mean age of 5.39 (SEM 0.32) for boys and 5.78 (SEM 0.38) for girls. Our patients were placed in four categories according to age: < 2 years (n = 124), 2-5 years (n = 120), 6-10 years (n = 78), and > 10 years (n = 78).

According to W/A data (current weight/ideal weight), 188 (47%) of the patients studied were malnourished: 118 (29.5%) presented mild malnutrition; 54 (13.5%), moderate; and 16 (4%), severe (Table V).

According to H/A data (current height/ideal height), 194 (48.5%) of the patients studied were stunted, 75 (18.8%) were mild, 49 (12.3%) were moderate, and 70 (17.5%) were severe (Table VI).

According to BMI, 40 (10%) patients from the sample were overweight, four (16%) were obese, and four (1%) were severe obese (Table VII). Regarding MUAC, 56 (14%) of the patients studied were malnourished, 33 (8.3%) were at risk, 14 (3.5%) presented moderate malnutrition, and nine (2.3%) were severely malnourished (Table VIII).

DISCUSSION AND CONCLUSION

In our study, we found that 47% of patients were underweight (low weight for age), 48.5% were stunted (low height for age),

Table V. Malnutrition among children admitted to the hospital according to W/A ratio (Gómez classification)

Sex	No malnutrition	Mild malnutrition	Moderate malnutrition	Severe malnutrition
Male (n = 255)	126 (56.0%)	64 (28.4%)	27 (12.0%)	8 (3.6%)
Female (n = 175)	86 (49.1%)	54 (30.9%)	27 (15.4%)	8 (4.6%)

Table VI. Nutritional status according to height-for-age criteria (Waterlow classification)

Sex	Normal	Mild	Moderate	Severe
Male (n = 255)	110 (48.9%)	49 (21.8%)	24 (10.7%)	42 (18.6%)
Female (n = 175)	96 (54.9%)	26 (14.9%)	25 (14.3%)	28 (16.0%)

Table VII. BMI among children admitted to the hospital

Sex	Underweight	Normal	Overweight	Obese	Severe obesity
Male	8 (3.6%)	186 (82.7%)	19 (8.4%)	10 (4.4%)	2 (0.9%)
Female	12 (6.9%)	134 (76.6%)	21 (12.0%)	6 (3.4%)	2 (1.1%)

Table VIII. MUAC among children admitted to the hospital

At risk	33 (8.3%)
Normal	344 (86%)
Moderate	14 (3.5%)
Severe	9 (2.3%)

and 14% were malnourished according to MUAC. In the study by Moreno Vilares et al. (7), prevalence of malnutrition was 7.1% for moderate and 0.7% for severe malnutrition, which is significantly lower than that of the current study. In the study by Durá Travé et al., prevalence of malnutrition at the moment of hospitalization was 8.2%, which was lower than in our study (8). In their study, children with congenital malformations were included. In our study, children with chronic disease or abnormal skull shape were excluded. In the study by Lee and Ahmad (9), the prevalence rates of acute and chronic undernutrition were 11% and 14% respectively, that is, lower than in our study. In another study from Brazil, the prevalence of malnutrition was 10%, 185%, 21% and 14.7% according to weight for height, weight for age, height for age and BMI, respectively (10). In this study, children with Down syndrome and children with bone deformity were excluded (10). Consistent with our study, Mahdavi et al., in a study carried out in Tabriz (Iran) covering 140 patients aged 2-12 years, found chronic malnutrition in 30.7% of cases according to H/A, and acute malnutrition in 48.6% of cases according to W/A results (11). In a study conducted in Turkey including 528 patients with a mean age of 5.8 years, Dogan et al. found chronic malnutrition in 27% of cases according to H/A and acute malnutrition in 52.4% of cases according to W/A (12). In another study which was done by Veghari and Vakili, the rate of underweight and stunting was estimated to be 3.20% and 4.93%, respectively (13). A study done by Nouri Saelidou et al. on children under five years in Azerbaijan, Iran, indicated that the rate of underweight and stunting was 2.3% and 7.3%, respectively (14). In another study, prevalence of underweight among Iranian children according to CDC percentiles was 13.9% (15). In the study by Moeeny et al., malnutrition was present in 25.2% of inpatient children (16).

In another study from Turkey, according to the Gomez classification, malnutrition was present in 46.8% of the cases (17). In this study, patients with recurrent hospitalizations, neurological sequelae, and neonates were excluded; these exclusion criteria are similar to those of the current study. In the study by Ogunlesi et al., carried out in Nigeria, 18.3% of children had severe acute malnutrition according the Wellcome classification (18).

In the current study, 10% of the cases were overweight, 4% obese, and 1% were severe obese. In the study by Veghari and Vakili, prevalence of overweight was 3.3-5.2% between 1998 and 2013 (13). In a study from Iran, prevalence of overweight was 10.4% (19). In line with our study, a study was done in Azerbaijan by Nouri et al. where the prevalence of obesity and overweight was 1.3% and 5.1%, respectively (14). In a multicenter study from Spain (20), overweight and obesity were seen in 37.9% of children, which is significantly higher than the percentage observed in the current study.

According to MUAC, 2.3% of the patients studied had severe malnutrition, 3.5% had moderate malnutrition and 8.3% were at risk of malnutrition. There are some differences between the results of these studies. These differences may be due to the different criteria which were used for the definition of malnutrition. In the current study, all children with a history of chronic disease or malformations were excluded. But in the study by Durá Travé et al., patients with congenital malformations were included (8).

CONCLUSION

In conclusion, our study demonstrates that the frequency of malnutrition among hospitalized children is relatively high. This higher prevalence of malnutrition needs more consideration because malnutrition has adverse effect on the outcome of the patients admitted in hospital.

The main limitation of the study was that it is a single center study.

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REFERENCES

1. Karimi B, Ghorbani R, Niaki MA. Malnutrition and some related factors in primary school children, Semnan, Iran. J Egypt Public Health Assoc 2016;91:174-8.
2. Kavosi E, Hassanzadeh Rostami Z, Kavosi Z, et al. Prevalence and determinants of under-nutrition among children under six: A cross-sectional survey in Fars province, Iran. Int J Health Policy Manag 2014;3:71-6.
3. Dura-Trave T, San Martín-García I, Gallinas-Victoriano F, et al. Prevalence of malnutrition in hospitalised children: Retrospective study in a Spanish tertiary-level hospital. JRSM Open 2016;7:2054270416643889.
4. Saccardo Sarni RO, Suano de Souza FI, Catherino P, et al. Treatment of severe malnourished children with WHO protocol: Experience of a referral center in Sao Paulo, Brazil. Arch Latinoam Nutr 2005;55:336-44.
5. Joseph B, Rebello A, Kullu P, et al. Prevalence of malnutrition in rural Karnataka, South India: A comparison of anthropometric indicators. J Health Popul Nutr 2002;20:239-44.
6. Briend A, Zimicki S. Validation of arm circumference as an indicator of risk of death in one to four year old children. Nutr Res 1986;6:249-61.
7. Moreno Villares JM, Varea Calderón V, Bousono García C. Malnutrition in children admitted to hospital. Results of a national survey. An Pediatr (Barc) 2017;86:270-6.

8. Dura Trave T, San Martín García I, González Benavides A, et al. Nutritional status at the time of admission among patients admitted to a tertiary-care paediatric hospital. Nutr Hosp 2015;31:2465-71.
9. Lee WS, Ahmad Z. The prevalence of undernutrition upon hospitalization in children in a developing country: A single hospital study from Malaysia. Pediatr Neonatol 2017.
10. De Moraes Silveira CR, De Mello ED, Antonacci Carvalho PR. Evolution of nutritional status of pediatric in patients of a tertiary care general hospital in Brazil. Nutr Hosp 2008;23:599-606.
11. Mahdavi AM, Ostadrahimi A, Safaiyan A. Nutritional status of children hospitalized in Tabriz Paediatric Hospital, Islamic Republic of Iran, 2008. East Mediterr Health J 2011;17:36-40.
12. Dogan Y, Erkan T, Yalvac S, et al. Nutritional status of patients hospitalized in pediatric clinic. Turk J Gastroenterol 2005;16:212-6.
13. Veghari G, Vakili M. Trend of stunting, overweight and obesity among children under five years in a rural area in Northern Iran, 1998-2013: Results of three cross-sectional studies. Arch Iran Med 2016;19:397-402.
14. Nouri Saeidlou S, Babaei F, Ayremlou P. Malnutrition, overweight, and obesity among urban and rural children in North of West Azerbijan, Iran. J Obes 2014;2014:541213.
15. Kelishadi R, Ardalan G, Gheiratmand R, et al. Thinness, overweight and obesity in a national sample of Iranian children and adolescents: CASPIAN Study. Child Care Health Dev 2008;34:44-54.
16. Moeeni V, Walls T, Day AS. Assessment of nutritional status and nutritional risk in hospitalized Iranian children. Acta Paediatr 2012;101:e446-51.
17. Kapci N, Akcam M, Koca T, et al. The nutritional status of hospitalized children: Has this subject been overlooked? Turk J Gastroenterol 2015;26:351-5.
18. Ogunlesi TA, Ayeni VA, Fetuga BM, et al. Severe acute malnutrition in a population of hospitalized under-five Nigerian children. Niger Postgrad Med J 2015;22:15-20.
19. Jafari S, Fouladgar M, Naeeni MM, et al. Body mass index, weight-for-age, and stature-for-age indices in Iranian school children in relation to weight and growth disorders: A population-based survey. Int J Prev Med 2014;5:S133-8.
20. Moreno Villares JM, Varea Calderón V, Bousono García C, et al. Nutrition status on pediatric admissions in Spanish hospitals; DHOSPE study. Nutr Hosp 2013;28:709-18.

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Trabajo Original

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Adolescents with high intellectual ability: differences in body composition and physical activity by sex

Adolescentes con alta capacidad intelectual: diferencias en su composición corporal y actividad física por sexo

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Abstract

Objectives: Physical activity (PA) has been shown to have multiple health and wellness benefits, but there is no such information for adolescents with high intellectual ability (HIA). Thus, the aim of this study is to assess body composition and PA in HIA Chilean adolescents.

Methods: Weight and body composition were measured by bioelectrical impedance in 73 adolescents (39 female) aged 14-18 years from the Valparaíso region of Chile. HIA was assessed via Raven's Progressive Matrices (> 75th percentile) and PA, via questionnaire. Obesity was defined as a body fat percentage (BF%) ≥ 25 (for boys) or ≥ 30 BF% (for girls).

Results: Obesity prevalence was 43.59% in females and 8.82% in males. A total of 69% of adolescents performed more than two hours of weekly exercise, with the amount being greater in males. BF% and fat mass index were significantly different ($p < 0.05$) in adolescents who engaged in fewer than two hours of weekly exercise. On the contrary, subjects who performed more than two hours of weekly exercise exhibited higher mass muscle percentages ($p < 0.01$). After controlling for socioeconomic status and PA, the obesity odds ratio (OR = 7.6; 95% CI: 1.9-30.9) was significantly higher in females ($p < 0.01$).

Conclusions: Adolescents with HIA reported elevated PA. However, obesity was more prevalent in females, who also reported less weekly PA than males.

Key words:

Physical activity.
Gifted and talented.
School-aged children.
Chile.

Resumen

Objetivos: la actividad física (AP) ha demostrado múltiples beneficios en salud, pero no hay información en adolescentes con altas capacidades intelectuales (ACI). El objetivo de este estudio es evaluar la composición corporal y AF en adolescentes chilenos con ACI.

Métodos: la composición corporal fue evaluada por bioimpedancia en 73 adolescentes (39 mujeres) de 14 a 18 años de la Región de Valparaíso, Chile. La ACI se evaluó a través del test de matrices progresivas de Raven y la AF, a través de un cuestionario. La obesidad se definió mediante el porcentaje de grasa corporal (%GC) ≥ 25 (hombres) y ≥ 30% (mujeres).

Resultados: la prevalencia de obesidad fue del 43,59% en mujeres y del 8,82% en hombres. Un 69% de los adolescentes realizan más de dos horas de ejercicio semanal, siendo mayor en hombres. El %GC y el índice de masa grasa fueron significativamente diferentes ($p < 0,05$) en adolescentes que realizan menos dos horas de ejercicio semanal. Por el contrario, los sujetos que realizan más de dos horas de ejercicio semanal presentaron mayores porcentajes de masa muscular ($p < 0,01$). Después de controlar por nivel socioeconómico y AF, el *odds ratio* para obesidad (OR = 7,6; IC del 95%: 1,9-30,9) fue significativamente asociado a las mujeres ($p < 0,01$).

Conclusiones: los adolescentes con ACI reportaron alta AF semanal. Sin embargo, la obesidad fue más prevalente en mujeres, que también informaron menor AF semanal.

Palabras clave:

Actividad física.
Dotado y talentoso.
Niños en edad escolar. Chile.

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INTRODUCTION

Children and adolescents who systematically engage in moderate or high-intensity physical activity (PA) reap multiple health and wellness benefits (1-3). Additionally, a positive influence on academic performance is observed because PA and aerobic fitness improve attention, favoring interactions between the learning environment and cognitive development (4-6). Moreover, cardiorespiratory exercise favors neuronal plasticity, neurocognitive function and cerebral activity (7). On the contrary, sedentary behavior is reported to contribute to energy imbalance, which can lead to health alterations, such as obesity or non-communicable chronic diseases (NCDs) (8,9).

According to data from the World Health Organization (WHO), in 2010, approximately 81% of students between 11 and 17 years old were sedentary (10). The trend in Chile is similar, and the prevalence of sedentary behavior in those aged 15 to 24 years is up to 75.9%. This percentage dramatically increases to 90.5% by adulthood according to the National Health Survey (11).

Adolescents of low socioeconomic status (SES) exhibit a high prevalence of sedentary behavior (12,13). In addition, a high prevalence of obesity has been reported among children and adolescents of low SES (14,15). Yet, school-aged children (approximately 5-17 years old) spend seven or more hours in school; because of reforms promoted by the Chilean Ministry of Education to improve the quality of learning, this time is spent mainly seated. However, the weekly time devoted to PA, which is approximately 90 minutes per week, has not changed, contributing to caloric retention (16). It is also observed that Chilean students who report high levels of PA perform better on standardized tests (17,18) and obtain health and wellness benefits. There is a group of students who regularly attend school and special academic programs due to their high intellectual ability (HIA). Reports show that almost 10% of the population is of HIA (19) and are characterized by greater intellectual skill and faster learning than their peers. They have also perfectionist, critical and creative tendencies (19-21), resulting in interrelations between opportunity, personality, psychosocial factors, individual effort and neurobiological base (21).

A relation between PA and HIA has not been reported yet; however, there are studies of adolescent students, although without a focus on HIA, supporting the positive influence of PA on academic performance. Thus, it is necessary to determine the PA of these students to identify a possible relation between HIA and PA. Therefore, our aim is to evaluate the body composition and PA of adolescents of HIA who attend an academic talent program.

METHODS

The target population was all students in grades 9 to 12 from different schools who regularly attended an academic talent program named "*Buenos Estudiantes con Talento Académico (Good Students with Academic Talent) de la Pontificia Universidad Católica de Valparaíso*" (BETA PUCV) (22) in the region of Valparaíso, Chile. Sampling was conducted from April to October 2014. To represent the student population of the BETA PUCV program (n = 169), obesity (as measured by body mass index [BMI]) was selected as the variable with the greatest variance for this age group (8.5% of adolescents from the region of Valparaíso have BMI values in the obese range (23). Sampling was performed with 95% reliability and a 5% sample error. The minimum sample size needed was n = 71. Seventy-nine students agreed to participate in the study (39 males). The final sample consisted of 73 students aged 14 to 18 years (46.48% males; 16 ± 1.19 years) who attend public schools, provided complete personal and SES data, completed the entire PA questionnaire and provided complete anthropometric measurements (bioelectric impedance could not be conducted in six students).

ANTHROPOMETRIC MEASUREMENTS

Weight was evaluated using a TANITA BC420SMA precision bascule (100 g sensitivity; Tanita, Tokyo, Japan) and height, using the SECA 217 stadiometer (0.1 cm precision; Seca, Hamburg, Germany). BMI (weight [kg]/height [m^2]) was classified as eutrophic or overweight (including obese) based on the references and z-scores for sex and age (24). Body fat percentage (BF%), muscle mass percentage (MM%) and fat mass index (FMI: fat mass [kg]/height [m^2]) were assessed via tetrapolar bioelectric impedance (TANITA BC420SMA). Measurements were conducted at room temperature under the following conditions: subjects did not wear metallic objects, did not drink alcohol at least 48 hours before the measurement, did not engage in intense exercise at least 12 hours before the measurement, did not eat or drink (especially caffeine) at least four hours before the measurement, had urinated 30 minutes before the measurement, and did not take diuretics before the measurement.

In this study, obesity was defined by BF%; subjects with body fat ≥ 25% in males and ≥ 30% in females were considered to be obese based on their relations with NCDs (25).

PHYSICAL ACTIVITY HABITS

Weekly PA was evaluated through a questionnaire designed for Chilean students (16) and validated via accelerometer measurements (26). A questionnaire was completed by each adolescent. The PA questionnaire comprises five items: a) daily hours spent lying down; b) minimum time spent on activities (classes, TV, homework or studying, and video games); c) time spent walking; d) time spent on recreation; and e) scheduled PA time (inside and outside of school). The questionnaire was administered under the supervision of a researcher (JE) to all students at the same time. The questionnaire scores range from 0 to 10 points and are classified by levels: low (0-3 points), regular (4-6 points) or high (7-10 points) (27).

The number of scheduled hours devoted to PA was obtained from item 5 in the questionnaire. Then, the amount of scheduled PA was classified as ≤ 2 hours or > 2 hours.

HIGH INTELLECTUAL ABILITY

HIA was evaluated using the Raven's progressive matrices general scale (28) by the BETA PUCV program psychologist (PC). This test contains 60 problems divided into five series (12 elements each) in order of increasing difficulty. The cohort distribution is determined by the talent program following the standards and percentiles determined by the Chilean Ministry of Education (MINEDUC) (29). To join the BETA PUCV program, students must test above the 75th percentile, that is, at level II (intellectually above average) or above with respect to the student cohort.

SOCIOECONOMIC STATUS

SES was determined through an ESOMAR questionnaire, which evaluates the occupation and educational level of the breadwinner (30). This questionnaire classified the sample into six socioeconomic groups: very high SES (A), high (B), medium-high (CA), medium (CB), medium-low (D) and low (E). In our analysis, we merged these six categories into four groups: 1) A+B; 2) CA; 3) CB; 4) D+E.

PUBERTAL DEVELOPMENT

Pubertal development was evaluated according to Tanner stages (31). Photographs of the five Tanner stages were shown to each adolescent, who was then asked to select the photo that best described their stage of development.

STATISTICAL ANALYSIS

A descriptive analysis was performed using frequencies, means, standard deviations and percentages. Data normality was evaluated separately for each variable using Shapiro-Wilk normality tests. Significant differences in PA by sex were evaluated based on a Mann-Whitney U test (non-parametric) and Student's t-test. For categorical variables, Chi-squared and Fisher's exact tests were used. Logistic regression was used to relate obesity (BF%; independent variable) to sex, adjusting for PA and SES. The data were processed using STATA 12.0 for Windows, and $p < 0.05$ was considered as significant.

ETHICAL ASPECTS

The processes of anthropometric measurement, bioelectric impedance analysis and questionnaire completion were orally explained to and authorized by the adolescents and their parents. Informed consent forms were signed by the adolescents and their parents. This study was approved by the Ethics Committee of the Pontificia Universidad Católica de Valparaíso in accordance with the Declaration of Helsinki (32).

RESULTS

After classifying the students and evaluating the body composition and PA of HIA adolescents, as a first approximation, we proceeded to evaluate the general characteristics of the sample by sex (Table I). Significant differences in mass and height were reported between males and females, with males having higher mass ($p < 0.05$) and height ($p < 0.001$) measurements. This sample also shows a high prevalence of eutrophic adolescents (94.12% in males and 76.92% in females), with only 6.65% of adolescents (two males, three females) classified as obese based on BMI. To obtain more accurate information about the body composition of the adolescents, their BF% was evaluated, observing that obesity is higher among females, with a prevalence of 43.59% and only 15.69% among males. Correspondingly, males show significantly higher MM% ($p < 0.001$), with values of approximately 80.06% for males and only 67.56% for females. Thus, significant differences were observed in FMI ($p < 0.001$). There were no significant differences in either scheduled PA hours or PA scores. No significant differences were observed in Tanner stage or SES by sex. In addition, in this sample, the A+B SES category was not observed.

After considering the general characteristics of the adolescents, body composition differences by weekly PA hours were evaluated (Table II). Most HIA students engage in more than two hours of scheduled PA, specifically 69.86% ($n = 51$), while only 30.14% ($n = 22$) engage in less than two hours. Additionally, students who engage in more than two hours of PA show lower FMI ($p < 0.05$) and BF% ($p < 0.05$) and higher MM% ($p < 0.05$). Significant differences in BMI were not observed. However, when variables of body composition were evaluated separately, significant differences appear.

After the adolescents were classified by amount of PA and sex based on the score obtained from the questionnaire (Fig. 1), 26.03% of students had low levels of PA, while 54.79% had regular and 19.18% had high levels. The association between sex and PA is not significant.

Finally, considering the higher prevalence of obesity in females than in males previously shown, a logistic regression was estimated, controlling for PA and SES (Table III), to determine the association between obesity and sex in HIA students. The results show that females have a high risk of obesity (OR = 7.63; 95% CI: 1.89-30.90).

DISCUSSION

The results of the current investigation indicate that HIA adolescents have a low prevalence of overweight and obesity. As evaluated through BMI, the obesity prevalence is lower than that reported for public schools by JUNAEB, which found that 12.5% of 9th grade students are obese, while only 6.85% of HIA students are obese using the same standards as in our investigation (23). However, in the current investigation, we also defined obesity using BF% because of its relation to NCDs (25). We observed

Table I. General characteristics by sex for the sample of 73 gifted adolescents in a talent program in Valparaíso, Chile from April to October 2014

	Male (n = 34)	Female (n = 39)	
	Mean ± SD	Mean ± SD	*p*-value
Age	16.21 ± 1.12	16.08 ± 1.26	0.649 [j]
Intellectual ability [a]	52.76 ± 3.46	51.72 ± 2.82	0.159 [j]
Mass (kg)	65.32 ± 11.77	60.19 ± 9.19	*0.032* [k]
Height (m)	1.72 ± 0.06	1.60 ± 0.06	*0.000* [j]
BMI (kg/m^2)	22.18 ± 4.14	23.71 ± 3.79	0.056 [k]
Nutritional status [b,c]			0.052 [l]
Eutrophic	32 (94.12)	30 (76.92)	
Overweight	2 (5.88)	9 (23.08)	
BF (%) [d]	15.69 ± 7.98	28.8 ± 6.30	*0.000* [k]
Obesity [e,c]			0.001 [l]
Non-obese	31 (91.18)	22 (56.41)	
Obese	3 (8.82)	17 (43.59)	
FMI (kg/m^2) [d]	3.77 ± 2.92	7.04 ± 2.67	*0.000* [k]
Muscle mass (%) [d]	80.06 ± 7.55	67.56 ± 5.96	*0.000* [k]
Physical activity score [f]	4.76 ± 1.91	4.87 ± 1.96	0.814 [j]
Scheduled exercise [g]	4.75 ± 4.53	3.48 ± 2.17	0.125 [k]
Physical activity [h,c]			0.164 [m]
≤ 2 hours	7 (20.59)	15 (38.46)	
> 2 hours	27 (79.41)	24 (61.54)	
Socioeconomic status [i]			0.507 [m]
Medium-high	6 (17. 65)	9 (23.08)	
Medium	6 (17.65)	10 (25.64)	
Medium-low and low	22 (64.71)	20 (51.28)	
Tanner (stage)			0.195 [l]
II	3 (8.82)	0 (0.00)	
III	9 (26.47)	11 (28.21)	
IV	16 (47.06)	16 (41.03)	
V	6 (17.65)	12 (30.77)	

BMI: body mass index; BF: body fat; FMI: fat mass index. [a]Intellectual ability was evaluated by means of the Raven's progressive matrices test. [b]Data were obtained using the OMS 2007 reference. [c]Data are shown as frequencies (%). [d]Assessed by bioelectrical impedance (TANITA). [e]Definition of obesity: ≥ 25 BF% in boys and ≥30 BF% girls. [f]Score of 0-10 points. [g]Weekly hours: school physical education time and sport extracurricular activities. [i]Obtained by the application of the European Survey (ESOMAR). [j]t-test. [k]Mann-Whitney test. [l]Fisher's exact test. [m]Chi-squared test (Pearson).

Table II. General characteristics by amount of physical activity for the sample of 73 gifted adolescents in a talent program in Valparaíso, Chile, from April to October 2014

	≤ 2 hours (n = 22)	> 2 hours (n = 51)	
	Mean ± S D	Mean ± SD	*p*-value
Total sample			
Age	16.32 ± 1.21	16.06 ± 1.19	0.398 [d]
Mass (kg)	63.73 ± 10.88	62.08 ± 10.70	0.424 [e]
Height (m)	1.64 ± 0.09	1.66 ± 0.08	0.353 [d]
BMI (kg/m^2) [a]	23.80 ± 3.98	22.65 ± 4.00	0.146 [e]
FMI (kg/m^2) [b]	6.48 ± 3.09	5.09 ± 3.21	*0.042* [e]
BF% [c]	26.14 ± 8.53	21.20 ± 9.83	*0.045* [d]
MM% [c]	70.09 ± 8.06	74.79 ± 9.34	*0.044* [d]
Male, n (%)	7 (20.59)	27 (79.41)	
HIA	54.57 ± 3.10	52.29 ± 3.45	0.170
Age	16.14 ± 1.46	16.22 ± 1.05	0.858
Mass (kg)	67.49 ± 11.39	64.77 ± 12.02	0.233
Height (m)	1.72 ± 0.07	1.72 ± 0.06	0.864
BMI (kg/m^2) [a]	22.67 ± 3.09	22.05 ± 4.41	0.259
FMI (kg/m^2) [b]	4.41 ± 1.99	3.60 ± 3.13	0.142
BF% [c]	18.83 ± 7.17	14.87 ± 8.10	0.100
MM% [c]	77.06 ± 6.73	80.83 ± 7.68	0.101
Female, n (%)	15 (38.46)	24 (61.54)	
HIA	51.47 ± 2.47	51.88 ± 3.05	0.672
Age	16.40 ± 1.12	15.88 ± 1.33	0.213
Mass (kg)	62.01 ± 10.58	59.05 ± 8.25	0.387
Height (m)	1.60 ± 0.07	1.59 ± 0.05	0.942
BMI (kg/m^2) [a]	24.33 ± 4.33	23.32 ± 3.46	0.583
FMI (kg/m^2) [b]	7.46 ± 3.09	6.78 ± 2.41	0.624
BF% [c]	29.55 ± 6.92	28.33 ± 5.99	0.697
MM% [c]	66.85 ± 6.53	68.01 ± 5.68	0.729

$p < 0.05$. [a]BMI: body mass index; [b]FMI: fat mass index calculated from bioelectrical impedance (TANITA). [c]Assessed by bioelectrical impedance (TANITA). [d]t-test. [e]Mann-Whitney test.

that females exhibit significant higher adiposity ($p < 0.001$) than males, which is consistent with the observations of Moreno et al. (33), Lizana et al. (34), Lizana et al. (35), Camaño Navarrete et al. (36) and Lizana et al. (14). However, male and female participants in the present study reported lower BF% than observed among Chilean adolescents of different SES (14). Thus, we observed sexual dimorphism, with higher adiposity among females, but at lower levels than in other Chilean reports (14).

The amount of PA performed by the HIA students who participated in this study is higher than the amount of PA reported for

Table III. Association between obesity and sex in adolescents with high intellectual ability, controlling for physical activity and socioeconomic status

	High body fat mass OR (95% CI)	
Female	*7.63 (1.89-30.90)*	*p = 0.004*
Physical activity	0.72 (0.21-2.40)	*p* = 0.589
High SES	1.74 (0.35-8.60)	*p* = 0.497
Low SES	0.39 (0.09-1.58)	*p* = 0.185
Observations	73	
Chi^2	17.14	
Hosmer-Lemeshow	0.2120	
Correctly classified	78.08%	

OR: odds ratio; 95% CI: 95% confidence interval; SES: socioeconomic status.

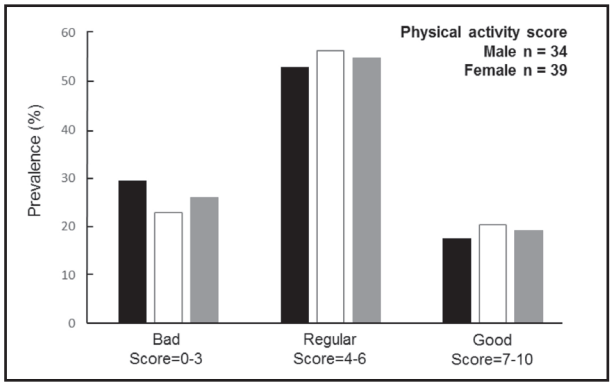

Figure 1.

Rank of physical activity according to sex (black bar = male; white = female and total sample gray bar) among high intellectual ability adolescents (aged 14-18 years) from region of Valparaíso, Chile. PA score derived from a questionnaire composed of five items (recumbent, seated, walking, school-based physical activity and sport extracurricular activities).

the general population of Chilean adolescents enrolled in school. In Santiago (Chile), 66% of students in 9th grade engage in less than two hours of PA per week (18). However, only 30.14% of HIA students engage in less than two hours of PA weekly, which means that these students perform more PA than the amount included in the curriculum and more than is reported by other investigations of students of similar age but who are not HIA students (16,17). This additional activity could be contributing to higher cognitive activity, improved attention and wellness and, hence, to better intellectual performance (4,5). Investigations have demonstrated that students who are physically active have better academic performance (4,5,17,18). Public education policies tend to emphasize the development of mathematical and linguistic abilities to the detriment of PA, despite not following the WHO recommendations for daily PA. Correa-Burrows et al. (18) found that students who engage in a high amount of PA perform better on standardized tests. Specifically, 19.18% of the students in our investigation fall into the high PA category, which is a higher percentage than that reported by Liberona et al. (27), where only 0.7% of students performed high levels of PA.

One limitation of this investigation is that, of the 15 regions in Chile, the students were only drawn from the region of Valparaíso; thus, these results may not be generalizable to the entire school-aged population. Future studies could be performed in other regions and for different age groups. However, all BETA PUCV (HIA) students are from the region of Valparaíso. Another limitation of this study is the use of questionnaires to report PA; moreover, the questionnaire did not include the intensity of exercise. Hence, it would be interesting to conduct this study using accelerometer measures. The findings also suggest that HIA students may be positively influencing their academic performance via their high amount of weekly PA and their high prevalence of normal body composition. With respect to this relation, additional longitudinal studies are required to establish the direction of causality.

Another limitation is that there are no previous data on body composition and PA for HIA students; discussions have focused on data obtained from Chilean student samples that were not necessarily classified by intellectual ability, so we must be cautious in comparing the results.

The results of this study have several implications for schools. Teachers possess scarce knowledge about HIA students and may be taken aback by exceptional students in their subjects, perhaps because most teachers start teaching without knowing about educating talented (gifted) children (37). This research shows that HIA students engage in more PA than their peers, and according to published reports, this could be associated with or foster their high performance. In Chile, public education policy has increased the work and content in subjects such as Maths and Spanish in the classroom, thus worsening sedentary lifestyles and decreasing hours of PA despite abundant international support for an association between PA and school performance. These results indicate the importance of PA among HIA students and suggest that PA has to be encouraged in educational institutions to develop their talents.

In summary, HIA students engage in more PA than their national counterparts, showing low obesity prevalence. However, obesity is higher in females. This study provides knowledge about the PA of HIA students, showing a possible relation between these two factors.

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REFERENCES

1. De Greeff JW, Hartman E, Mullender-Wijnsma MJ, Bosker RJ, Doolaard S, Visscher C. Long-term effects of physically active academic lessons on physical fitness and executive functions in primary school children. Health Educ Res 2016;31:185-94.
2. Penedo FJ, Dahn JR. Exercise and well-being: A review of mental and physical health benefits associated with physical activity. Curr Opin Psychiatry 2005;18:189-93.
3. WHO. Global recommendations on physical activity for health. Geneva: World Health Organization; 2010.
4. Chomitz VR, Slining MM, McGowan RJ, Mitchell SE, Dawson GF, Hacker KA. Is there a relationship between physical fitness and academic achievement? Positive results from public school children in the northeastern United States. J Sch Health 2009;79:30-7.
5. Janssen M, Chinapaw MJM, Rauh SP, Toussaint HM, Van Mechelen W, Verhagen EALM. A short physical activity break from cognitive tasks increases selective attention in primary school children aged 10-11. Ment Health Phys Act 2014;7:129-34.
6. Kalantari HA, Esmaeilzadeh S. Association between academic achievement and physical status including physical activity, aerobic and muscular fitness tests in adolescent boys. Environ Health Prev Med 2016;21:27-33.
7. Hötting K, Röder B. Beneficial effects of physical exercise on neuroplasticity and cognition. Neurosci Biobehav Rev 2013;37:2243-57.
8. Carson V, Hunter S, Kuzik N, Gray CE, Poitras VJ, Chaput JP, et al. Systematic review of sedentary behaviour and health indicators in school-aged children and youth: An update. Appl Physiol Nutr Metab 2016;41:S240-65.
9. Myer GD, Faigenbaum AD, Stracciolini A, Hewett TE, Micheli LJ, Best TM. Exercise deficit disorder in youth: A paradigm shift toward disease prevention and comprehensive care. Curr Sports Med Rep 2013;12:248-55.
10. World Health Organization. Prevalence of insufficient physical activity. Global Health Observatory (GHO) data; 2010. Accessed on 2011 May 20. Available from: http://www.who.int/gho/ncd/risk_factors/physical_activity_text/en/.
11. Ministry of Health. National Health Survey 2010. Santiago de Chile: Ministry of Health; 2010.
12. López RP, Hynes HP. Obesity, physical activity, and the urban environment: Public health research needs. Environ Health 2006;5:25;5:25.
13. Sallis JF, Glanz K. The role of built environments in physical activity, eating, and obesity in childhood. Future Child 2006;16:89-108.
14. Lizana PA, González S, Lera L, Leyton B. Association between body composition, somatotype and socioeconomic status in Chilean children and adolescents at different school levels. J Biosoc Sci 2018:50:53-69.
15. Lizana PA, Paula CV, Araya L, Aguilera F, Mora M. Obesity, body fat distribution, and physical activity in school-age children: An urban and rural comparison in Valparaíso, Chile. Biomed Environ Sci 2016;29:834-9.
16. Burrows AR, Díaz BE, Sciaraffia MV, Gattas ZV, Montoya CA, Lera ML. Dietary intake and physical activity in school age children. Rev Med Chil 2008;136:53-63.
17. Burrows R, Correa-Burrows P, Orellana Y, Almagiá A, Lizana P, Ivanovic D. Scheduled physical activity is associated with better academic performance in Chilean school-age children. J Phys Act Health 2014;11:1600-6.
18. Correa-Burrows P, Burrows R, Ibaceta C, Orellana Y, Ivanovic D. Physically active Chilean school kids perform better in language and mathematics. Health Promot Int 2017;32(2):241-9. DOI: 10.1093/heapro/dau010
19. Gagné F. Building gifts into talents: Brief overview of the DMGT 2.0. Gifted. 2009;152:5-9.
20. Sastre S, Pascual MT. Alta capacidad intelectual, resolución de problemas y creatividad. Rev Neurol 2013;56:67-76.
21. Sastre-Riba S. Alta capacidad intelectual: perfeccionismo y regulación metacognitiva. Rev Neurol 2012;54:21-9.
22. Programa BETA PUCV. ¿Qué es beta? 2015. Cited 2015 Jun 1. Available from: http://www.programabeta.cl/2013/04/que-es-beta/.
23. National Board of Student Aid and Scholarships (JUNAEB). Nutritional map report 2013. Santiago, Chile; 2014.
24. De Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ 2007;85:660-7.
25. Williams DP, Going SB, Lohman TG, Harsha DW, Srinivasan SR, Webber LS, et al. Body fatness and risk for elevated blood pressure, total cholesterol, and serum lipoprotein ratios in children and adolescents. Am J Public Health 1992;82:358-63.
26. Godard MC, Rodríguez N MP, Díaz N, Lera ML, Salazar RG, Burrows AR, et al. Value of a clinical test for assessing physical activity in children. Rev Med Chil 2008;136:1155-62.
27. Liberona Y, Castillo O, Engler V, Villarroel L, Rozowski J. Nutritional profile of schoolchildren from different socio-economic levels in Santiago, Chile. Public Health Nutr 2011;14:142-9.
28. Raven J. Test de matrices progresivas. Escala General. Buenos Aires: Paidós; 2007.
29. Ministerio de Educación de Chile. Aprueba bases para la postulación de becas para estudiantes con talento académico, de establecimientos educacionales municipales, que cursan entre el segundo ciclo de educación básica y 4° año de educación media, en el marco de ejecución de la asignación. Chile; 2014. p. 1-8.
30. European Society for Opinion and Marketing Research. A system of international socio-economic classification of respondents to survey research. Amsterdam; 1997.
31. Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child 1976;51:170-9.
32. The World Medical Association. Declaration of Helsinki - Ethical principles for medical research involving human subjects. Seoul, Korea: 59th WMA General Assembly; 2008.
33. Moreno LA, Mesana MI, González-Gross M, Gil CM, Fleta J, Wärnberg J, et al. Anthropometric body fat composition reference values in Spanish adolescents. The AVENA Study. Eur J Clin Nutr 2006;60:191-6.
34. Lizana P, Almagia A, Simpson M, Binvignat O, Ivanovic D. Berral F. Aproximación a la tendencia secular del estado nutricional y composición corporal en escolares de enseñanza secundaria, V región, Chile 1985-2010. Int J Morphol 2011;29:473-8.
35. Lizana PA, Almagiâ A, Simpson C, Ivanovic D, Binvignat O, Berral FJ. Changes of somatotype in high school students, V region, Chile; 1985-2010. Nutr Hosp 2012;27:270-5.
36. Caamaño Navarrete F, Delgado Floody P, Guzmán Guzmán IP, Jerez Mayorga D, Campos Jara C, Osorio Poblete A. La malnutrición por exceso en niños-adolescentes y su impacto en el desarrollo de riesgo cardiometabólico y bajos niveles de rendimiento físico. Nutr Hosp 2015;1:2576-83.
37. Winebrenner S. Teaching strategies for twice-exceptional students. Interv Sch Clin 2003;38:131-7.

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Trabajo Original

Pediatría

Physical fitness, cardiometabolic risk and heart rate recovery in Chilean children

Condición física, riesgo cardiometabólico y frecuencia cardiaca de recuperación en escolares chilenos

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Abstract

Objective: To evaluate the association of physical fitness (PF) and cardiometabolic risk (CMR) with heart rate recovery time (ΔHRR) in Chilean school aged children.

Methods: Cross-sectional study in 478 6-9 years old children participants. We measured weight, height and abdominal circumference. Fitness was measured using the 6MWT, grip strength and leap forward without impulse tests; PF z-scores were calculated. Heart rate (HR) was monitored and recorded during the 6MWT. ΔHRR was calculated as the difference between HR before and one minute after test; blood glucose, insulin, triglycerides and HDL-cholesterol were measured. Waist circumference, CMR-z and HOMA were calculated.

Results: Absolute ΔHRR and CMR-z measures in normal weight children were lower than in obese children ($p < 0.05$ and $p < 0.01$, respectively). In obese children, ΔHRR was also associated with grip strength/weight ($r = -0.6$, $p < 0.01$) and PF-z ($r = -0.6$, $p = 0.04$). Insulin and HOMA were significantly related to ΔHRR ($r = 0.3$, $p < 0.001$), especially in overweight and obese children. ΔHRR values were not associated with CMR-z.

Conclusions: A significant relationship between ΔHRR with fitness and insulin sensitivity in overweight and obese school children was found. We consider that these results support the need to measure these variables in overweight and obese children, in order to strengthen the need for early prevention.

Key words:

Fitness. Cardiometabolic risk. Heart rate recovery time. School children obesity.

Resumen

Objetivo: establecer la asociación entre la condición física (CF) y el riesgo cardiometabólico (RCM) con el tiempo de recuperación de la frecuencia cardiaca (ΔFCR) en escolares chilenos.

Métodos: estudio trasversal de 478 escolares de 6 a 9 años de ambos sexos. Se evaluó peso, talla y perímetro abdominal. Se midió CF global mediante T6M, fuerza de agarre y salto hacia adelante sin impulso; se calculó z-CF. Se midió frecuencia cardiaca (FC) con sensor durante el T6M. Calculamos ΔFCRecup como la diferencia entre la FC en reposo y la FC al minuto de finalizado el test, glicemia, insulinemia, trigliceridemia y colesterol-HD. Perímetro de cintura, z-RCM y HOMA fueron calculados.

Resultados: los escolares normopeso tuvieron menor ΔFCRecup y z-RCM que los obesos ($p < 0,05$ and $p < 0,01$ respectivamente). En niños obesos, el ΔFCRecup se asoció a fuerza de agarre/peso ($r = -0,6$, $p < 0,01$) y z-CF ($r = -0,6$, $p = 0,04$). Un menor ΔFCRecup se relacionó con menores niveles de insulinemia y HOMA ($r = 0,3$, $p < 0,001$), especialmente en el grupo de escolares con sobrepeso y obesidad. El ΔFCRecup no fue asociado a z-RCM.

Conclusión: existe asociación entre el ΔFCRecup y la condición física y sensibilidad insulínica en escolares con sobrepeso y/u obesidad, lo que refuerza la necesidad de la medición de esta variable en niños con sobrepeso y obesidad para una prevención temprana.

Palabras clave:

Condición física. Riesgo cardiometabólico. Frecuencia cardiaca de recuperación. Obesidad escolar.

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INTRODUCTION

The prevalence of sedentary life in adults and children continues to rise globally. At least 60% of the world population does not perform the necessary physical activity to prevent obesity and related non-communicable diseases (NCDs) (1). And Chile is not an exception. According to a 2012 report of physical fitness in schools, 70% of Chilean students in 8th grade had unsatisfactory aerobic fitness levels and lived predominantly sedentary lives (2), spending > 10 hours in activities of low energy expenditure and excessive time in front of a screen (television or computer) (3,4). Obesity and a sedentary lifestyle during childhood leads to poor physical fitness, increasing the risk for obesity, metabolic syndrome and cardiovascular disease in adulthood. These consequences have not been sufficiently studied in children. Thus we considered of interest to assess the association between physical fitness and cardiometabolic risk (CMR) to strengthen the call for more physical activity in children and adolescents. We further hypothesized that the evidence of prolonged heart rate recovery time in young children might motivate parents to act at an early stage, thus preventing further deterioration (5).

Heart rate recovery (ΔHRR) reflects the functional capacity of autonomic nervous system (6) and perhaps could be considered a measure autonomic dysfunction (7). Additionally, adults with high cardiorespiratory fitness recover faster than adults with lower level physical fitness (8). Metabolic risk factors are inversely associated with ΔHRR in healthy children and adolescents (9). The physiological mechanism underlying heart rate recovery after exercise in children operates faster than in adults; smaller heart size, relative muscle mass, perfusion distance and faster cardiorespiratory circulation time kinetics explain most of the difference (10). Simhaee et al. showed that children with high body mass index (BMI) have a longer heart rate recovery time and that those with faster recovery have more moderate to vigorous physical activity. Other studies show that there is a direct correlation between sedentary behavior and increased heart rate recovery (9). A cross-sectional study of 993 healthy adolescents of 12-19 years of age shows that heart rate recovery time was inversely related to metabolic risk factors (waist circumference, systolic blood pressure, plasma triglycerides, levels of C-reactive protein) and positively related to circulating HDL levels (11). Prolonged heart rate recovery time, which reflects a deteriorating physical condition, might be useful to detect children with elevated CMR. Thus, it is important to further investigate the link between heart rate recovery time and cardiovascular/metabolic risk in children (9). The aim of this cross-sectional study was to explore the association between physical fitness (6-minute walk test and muscle strength) and CMR, with heart rate recovery, in a group of Chilean schoolchildren aged 6-9 years.

MATERIALS AND METHODS

POPULATION

The study sample comprised 478 6-9 years-old children (n = 216 girls) participating in the Growth and Obesity Cohort Study (GOCS) conducted in Santiago, Chile. GOCS is a study of low-middle income Chilean children born in 2002-2003 (n = 1,196, ~ 50% girls), of normal gestation 37-42 weeks with birth weight ≥ 2,500 g (12). The study was approved by the Ethics Committee of the Institute of Nutrition and Food Technology, University of Chile. All parents/legal guardians agreed to the participation of their children by signing the free informed consent form.

ASSESSMENT OF PHYSICAL FITNESS (PF)

Muscle strength was evaluated testing upper body strength (arms, handgrip strength) using a (Baseline 12-0286®) digital force gauge (13) and lower body strength (legs) was assessed by the standing long jump (14). Aerobic fitness was evaluated with the submaximal six minute walk test (6MWT) (15). Heart rate (HR) was measured and recorded with a heart rate monitor (Polar model FS1C): at rest before the test, then every three minutes, and finally one minute after test completion. Test results were expressed in meters traveled divided by the height of each child. The results of grip strength and jump were expressed in relative values, as the fat-free mass and length of stride of participants significantly modify the absolute values. We created an overall z-score of physical fitness (6MWTz/height + grip strength Z/weight + jump Z/height/3), and categorized "low" physical fitness as < -1 SD; "intermediate", between 1 and -1 SD; and "high", as > 1 SD.

NUTRITIONAL ASSESSMENT

All children were measured in duplicate for weight (light clothing), standing at the center of a Tanita Body Composition Analyser BC-418, with 100 g precision and 220 kg capacity; height (Frankfurt methodology using a portable SECA, 222 stadiometer with upper range 200 cm and divisions of 1 mm) (16); and waist circumference, with an automatic locking tape (SECA) measured above the rim of the iliac crest, through the navel (17). Average height and weight measurements were used to determine BMI.

BODY COMPOSITION

In a sub-sample of 122 boys and 92 girls, fat-free mass was estimated by total body water with bioelectrical impedance using Tanita BC-418MA, eight-electrode, hand-to-foot system, manufactured by Tanita Corporation (Tokyo, Japan) (18). We observed a high correlation between body weight and fat free mass ($r = 0.95$, $p < 0.001$).

CMR-z

We evaluated CMR based on glucose, fasting insulin levels and lipid profile. CMR defined z ≥ 1.29 (90th percentile), from the score of the variables included in the equation (waist circumference-Z + glucose-Z + insulin-Z + triglycerides-Z – HDL-Z/5) (19). We used USA cut-offs for waist circumference (17) and plasma lipids (20),

and blood glucose and insulin based on Chilean data (21). Insulin and HOMA were classified based on the centile distribution of Chilean children 6-15 years (22). The 75th centile for Tanner 1 (HOMA: 2.1) was used as a cut-off to diagnose insulin resistance.

HEART RATE RECOVERY

We calculated a change in heart rate recovery (ΔHRR) as the difference between heart rate at the end of the 6MWT and after the one minute rest. Later, differences were classified in quartiles. The lowest quartile represented better recovery.

STATISTICAL ANALYSIS

After analyzing the distribution of variables, data were expressed with means ± SD. Continuous variables were compared by sex and age range. To study the association between heart rate recovery and overall physical fitness (PF-z), insulin and HOMA, either Pearson or Spearman correlation coefficients were used. The associations between physical condition (lower, middle, top) and heart rate recovery (in quartiles) were evaluated with Chi-squared tests. Finally, the Student's t-test was used to compare the ΔHRR, according to presence or absence of insulin resistance, and ANOVA was used to assess whether heart rate recovery varied by nutritional status and CMR. A p value < 0.05 was considered to be statistically significant.

RESULTS

The characteristics of the sample are summarized in table I. A total of 478 students (54.8% boys) of 8.3 ± 0.7 years were included in this study. When analyzing the results by sex, girls had lower resting HR, HR maximum and z-PF ($p < 0.001$), and the like ΔHRR (beats/minute) than boys. The prevalence of obesity was significantly higher in boys than in girls (15% and 7%, respectively; $p < 0.01$).

After calculating cut-offs for ΔHRR quartiles (< 41, 41-58, 58-80 and > 80), no differences were found by sex or age range, although we found a higher % of girls in the top two quartiles ΔHRR (60% girls *vs* 45% children). The ΔHRR was lower in schoolchildren with normal nutritional status compared with those who were obese ($p = 0.03$) (Fig. 1); no differences were found in analyzing the results by sex and age range.

The characteristics of the physical fitness tests are summarized in table II. In the jumping test, adjusted for height, boys jumped significantly more than girls (94 *vs* 84 cm, $p < 0.01$), a difference that was not maintained in tests of grip strength/weight and 6MWT/height. Studying the data by nutritional status, normal weight subjects scored better on tests of muscle strength and aerobic capacity than those who were overweight or obese ($p < 0.001$). In analyzing the results of physical fitness according to z-FP, 85% of schoolchildren had an intermediate fitness level (+/- 1 SD).

Table III shows the cardiovascular and metabolic profile and CMR score by sex and nutritional status. There were statistically significant differences in blood glucose and HDL-C by sex. Nutritional status, waist circumference, triglycerides, insulin and HOMA were also significantly different.

Thirteen and seventeen percent of schoolchildren had hyperinsulinemia and altered HOMA, respectively; 44% of them had high CMR scores (≥ z: 1.29); and no differences by sex or age were found. Children with overweight and obesity had higher CMR-z than normal children (Table III). However, no relationship between ΔHRR and CMR-z were observed, except for z value for insulin and HOMA, in this group. ($r = 0.4$; $p < 0.001$). When comparing schoolchildren with and without insulin resistance, we noted that this condition was associated with increased ΔHRR (72.4 *vs* 58.2 l/min; $p < 0.001$) (Fig. 2).

No statistical relationship was found between ΔHRR and -PF z (lower, middle or high). Instead, an association was observed if ΔHRR and strength grip/weight ($r = -0.3$; $p < 0.01$) were included, especially in 6-7 years old obese children ($r = -0.6$; $p < 0.01$). Finally, in the same group, higher ΔHRR was associated with a lower z-PF ($r = -0.6$, $p = 0.04$).

Table I. Basic characteristics of the sample

	Boys (n = 262)		Girls (n = 216)		*p*
	6-7 years (n = 84)	8-9 years (n = 178)	6-7 years (n = 78)	8-9 years (n = 138)	
Age (years)	7 .5 ± 0.3	8.7 ± 04	7.5 ± 0.3	8.5 ± 0.4	b,c
Weight (kg)	26.2 ± 4.7	33.0 ± 7.7	26.7 ± 6.6	31.9 ± 7.5	b,c
Height (m)	1.2 ± 0.07	1.3 ± 0.07	1.2 ± 0.7	1.3 ± 0.8	b,c
BMIz	0 .9 ± 1.1	1.1 ± 1.2	0.7 ± 1.0	0.8 ± 1.1	a
Resting heart rate (l/min)	80.4 ± 8.3	77.7 ± 7.8	81.6 ± 8.5	81.5 ± 9.7	a,b
Max heart rate (l/min)	162.7 ± 18.2	142.6 ± 18.8	166.1 ± 18.1	157.0 ± 20.0	a,b,c
ΔHRR (b/min)	42.4 ± 19.2	71.0 ± 23.6	45.5 ± 16.5	67.1 ± 26.4	b,c
Physical fitness-Z score	0.2 ± 0.7	0.1 ± 07	-0.16 ± 0.6	-0.09 ± 0.6	a
CMR-z score	1.2 ± 0.1	1.1 ± 0.09	1.2 ± 0.1	1.4 ± 0.1	NS

$p < 0.01$. BMI: body mass index; ΔHRR: change in heart rate recovery; a: differences by sex; b: differences by age range in boys; c: differences by age range in girls.

Table II. Physical fitness characteristics by sex and age range

	Boys (n = 262)		Girls (n = 216)		*p*
	6-7 years (n = 84)	8-9 years (n = 178)	6-7 years (n = 78)	8-9 years (n = 138)	
Jump (cm)	113.7 ± 16.4	124.3 ± 19.1	110.0 ±14.3	102.3 ± 17.2	a,b,c
Jump/height (cm)	93.0 ± 14.5	94.4 ± 15.1	83.5 ± 12.1	84.1 ± 13.8	a
Grip strength (kg)	11.3 ± 2.3	12.5 ± 2.3	10.6 ± 2.0	12.0 ± 2.6	a,b,c
Grip strength/weight (kg)	0.4 ± 0.1	0.3 ± 0.1	0.4 ± 0.08	0.3 ± 0.09	b, c
6MWT (m)	617.0 ± 50.0	624.3 ± 47.3	604.3 ± 49.7	625.5 ± 45.2	c
6MWT/height (m)	504.0 ± 44.1	474.0 ± 44.5	491.0 ± 47.1	477.0 ± 42.0	b,c *

*p < 0.01; *p 0.02. 6MWT: 6 minute walking test; a: differences by sex; b: differences by age range in boys; c: differences by age range in girls.*

Table III. Cardiometabolic profile, HOMA and CMR-z score by sex and nutritional status

	Boys (n = 262)				Girls (n = 216)			
	Normal (n = 122)	Overweight (n = 57)	Obese (n = 74)	*P*	Normal (n = 113)	Overweight (n = 61)	Obese (n = 35)	*p*
WC (cm)	57.3 ± 3.4	62.8 ± 3.9	73.4 ± 6.5	b,c*	56.9 ± 4.1	65.7 ± 4.6	72.5 ± 5.5	b,c
Triglycerides (mg/dl)	81.3 ± 37.5	88.2 ± 29.4	106.2 ± 52.5	b,c*	86.1 ± 32.6	93.2 ± 45.8	129.9 ± 65.9	b,c
Insulinemia (uUl/ml)	7.0 ± 2.3	7.2 ± 3.2	8.5 ± 3.6	b,c*	6.8 ± 2.4	7.7 ± 2.8	8.7 ± 3.1	b,d**
HDLc (mg/dl)	51.5 ± 13.3	50.0 ± 11.9	48.5 ± 10.7	d**	48.3 ± 12.3	44.5 ± 11.4	44.8 ± 10.6	d**
Glicemia (mg/dl)	90.5 ± 6.3	91.1 ± 6.3	92.3 ± 6.8	d**	86.8 ± 6.7	87.8 ± 6.8	89.9 ± 8.1	d**
HOMA	1.6 ± 0.6	1.6 ± 0.8	2.0 ± 0.9	b,c	1.5 ± 0.5	1.7 ± 0.7	2.0 ± 0.8	b**
CMR-z	0.6 ± 1.0	1.1 ± 0.8	2.1 ± 1.2	a,b,c	0.8 ± 0.8	1.7 ± 1.0	2.8 ± 1.1	a,b,c

*p < 0.01; *p = 0.04; **p < 0.001. WC: waist circumference; CMR-z: cardiometabolic risk score; a: differences between normal weight and overweight; b: differences between normal weight and obese; c: differences between overweight and obesity; d: differences by sex.*

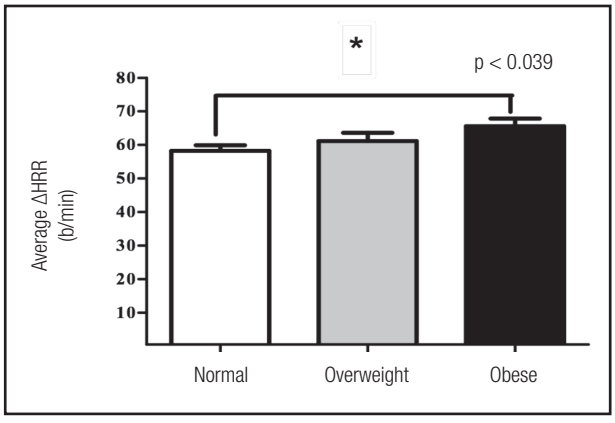

Figure 1.

Mean ΔHRR by nutritional status in schoolchildren aged 6-9 years. Anova, Bonferroni. p value represents trend between groups. Average ΔRHR: normal (58.2 ± 25.8 l/min), overweight (61.2 ± 26.8 l/min), obesity (66.0 ± 23.4).

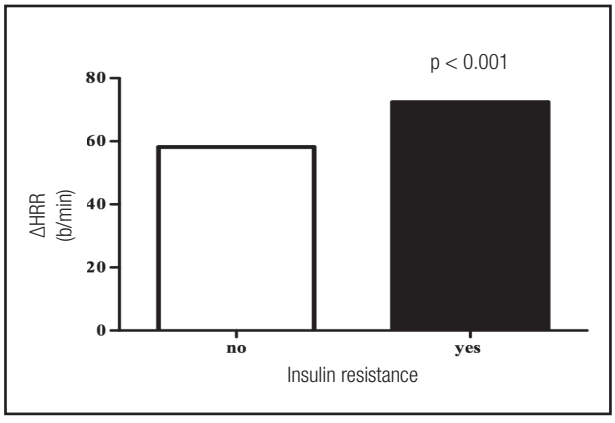

Figure 2.

ΔRHR and insulin resistance in schoolchildren aged 6 to 9 years. Student's t-test. *p* value represents trend between groups.

DISCUSSION

Our study showed that overall PF-z, grip strength, HOMA and insulinemia were significantly associated with ΔHRR in overweight and obese children.

An important point to consider when interpreting the results of this study is the large variability in HR by age. This variability is due to a progressive maturation of the autonomic nervous system between three and six years old children. During this period, there is a tendency to increase sympathicotonia (23-25). Over-activation of the sympathetic nervous system in obesity, hypertension and hyperinsulinism (26,27) could be explained by an increase in free radicals, a decrease in nitric oxide, and an increase in both tubular sodium reabsorption and arterial vasoconstriction (28). Our results showed fluctuations in heart rate at rest and after the 6MWT by sex and age range, and an association between insulin levels, HOMA and waist circumference with ΔHRR in children with overweight/obesity. Wilks et al. reported that lifestyle changes for four to six weeks in children and adolescents with overweight/obesity would produce a significant improvement in heart rate recovery, although this recovery would not be associated with an improvement in cardiometabolic risk factors (29).

We find that higher ΔHRR was associated with a lower overall physical fitness (z-PF) in obese children aged six to seven years, a difference that was not observed in other children. This could be possibly explained by the fact that this group is more susceptible to develop sympathicotonia due to the lower age range. Furthermore, the nutritional state of these children is associated with greater cardiovascular and metabolic risk (9). The association is not expressed in the same way when analyzing separately the ratio of heart rate recovery with different fitness tests. In our study, ΔHRR was associated only with better grip strength/weight. This result is consistent with the fact that a better physical fitness in children is usually associated with greater muscle strength. Artero et al. found, in a sample of 709 adolescents, that muscle strength was associated with better physical condition and lower cardiometabolic risk (30). In this regard, this finding and our work complement previous studies in which the results showed that heart rate recovery was a marker of aerobic fitness, not related with muscle strength (31). On the other hand, the lack of association with the 6MWT could be because the latter would have a low correlation with maximum oxygen consumption (VO_2max), assessing functional capacity and not fitness aerobic. Morinder et al. found a low correlation between the traveled distance by the 6MWT and VO_2max in 8-16 years obese children (32). Other authors obtained similar results in obese children and adolescents by comparing the correlation of 6MWT and Cooper tests with VO_2max (33).

In analyzing our results related to ΔHRR, nutritional status and cardiometabolic risk, it is important to consider that 23% of subjects were obese, similar to that reported by the Board of School Aid and Scholarships Chile (34). Nearly half (48%) of our sample had CMR, close to the prevalence of insulin resistance (53%) described in Chilean children and adolescents between four and 16 years (35). In our study, children with insulin resistance had significantly higher ΔHRR, results similar to those of KuoHsu-Ko et al. in a sample of adolescents and adults with insulin resistance (36).

The differences found in ΔHRR by nutritional status were similar to those described in American obese schoolchildren (9). Another study in healthy adolescents and adults between 12 and 49 years showed that those who had slower heart rate recovery had higher BMI (36).

A lack of association was found between ΔHRR and CMR, which is consistent with other studies. In a sample of US adolescents (NHANES III), Liny el al. found, after a test of aerobic submaximal fitness, that heart rate recovery per minute was not associated with overall CMR, even if it was associated with some components of the metabolic syndrome (11). This result could be explained because the low demand of the submaximal test does not generate an increase of maximum heart rate or a change in ΔHRR, so it cannot detect individuals with higher CMR. In a sample of 1,395 children of both sexes, aged 9-12 years old, evaluated with a maximal test of short duration (three minutes), Laguna M. et al. found a significant association between blood pressure and ΔHRR in younger subjects and no association with global CMR (37).

One limitation of this study was the choice of the 6MWT. Future research should consider using the Navette test, an instrument with strong evidence to determine aerobic capacity in children and adolescents (38). Further, the lack of previous data related to the physical fitness of Chilean children could have influenced the overall classification and analysis of PF-z, and thus the absence of an association with heart rate recovery. In addition, not having measured blood pressure could partly explain the lack of association between CMR and ΔHRR, which however was associated with levels of insulin and HOMA. These findings support the need to improve efforts to reduce the high prevalence of overweight and obesity in schoolchildren aged 6-7 years. We can conclude that in overweight and obese children, ΔHRR could be a sensitive method for evaluating physical fitness and metabolic risk.

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REFERENCES

1. Second National Health Survey in Chile 2009-2010. 2011. Cited August 2017. Available from: http://web.minsal.cl/portal/url/item/bcb03d7bc28b64dfe040010165012d23.pdf
2. Physical Education Results Report 8th basic 2012. System for Measuring the Quality of Education 2012. Cited August 2017. Available from: http://archivos.agenciaeducacion.cl/biblioteca_digital_historica/resultados/2013/result8b_edfisica_2013.pdf.
3. Kain J OS, Castillo M, Vio F. Validation and application of instruments to evaluate educational interventions in obesity of schoolchildren. Rev Chil Pediatr 2001;72(4):308-18.
4. Burrows AR, Diaz BE, Sciaraffia MV, Gattas ZV, Montoya CA, Lera ML. Dietary intake and physical activity in school age children. Rev Med Chil 2008;136(1):53-63.

5. Biro FM, Wien M. Childhood obesity and adult morbidities. Am J Clin Nutr 2010;91(5):1499s-505s.
6. Fernando RJ, Ravichandran K, Vaz M. Aerobic fitness, heart rate recovery and heart rate recovery time in Indian school children. Indian J Physiol Pharmacol 2015;59(4):407-13.
7. Prado DM, Silva AG, Trombetta IC, Ribeiro MM, Guazzelli IC, Matos LN, et al. Exercise training associated with diet improves heart rate recovery and cardiac autonomic nervous system activity in obese children. Int J Sports Med 2010;31(12):860-5.
8. Mahon AD, Anderson CS, Hipp MJ, Hunt KA. Heart rate recovery from submaximal exercise in boys and girls. Med Sci Sports Exerc 2003;35(12):2093-7.
9. Simhaee D, Corriveau N, Gurm R, Geiger Z, Kline-Rogers E, Goldberg C, et al. Recovery heart rate: An indicator of cardiovascular risk among middle school children. Pediatr Cardiol 2013;34(6):1431-7.
10. Falk B, Dotan R. Child-adult differences in the recovery from high-intensity exercise. Exerc Sport Sci Rev 2006;34(3):107-12.
11. Lin LY, Kuo HK, Lai LP, Lin JL, Tseng CD, Hwang JJ. Inverse correlation between heart rate recovery and metabolic risks in healthy children and adolescents: Insight from the National Health and Nutrition Examination Survey 1999-2002. Diabetes Care 2008;31(5):1015-20.
12. Corvalan C, Uauy R, Stein AD, Kain J, Martorell R. Effect of growth on cardiometabolic status at 4 y of age. Am J Clin Nutr 2009;90(3):547-55.
13. Milliken LA, Faigenbaum AD, Loud RL, Westcott WL. Correlates of upper and lower body muscular strength in children. J Strength Cond Res 2008;22(4):1339-46.
14. Castro-Pinero J, Ortega FB, Artero EG, Girela-Rejón MJ, Mora J, Sjostrom M, et al. Assessing muscular strength in youth: Usefulness of standing long jump as a general index of muscular fitness. J Strength Cond Res 2010;24(7):1810-7.
15. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166(1):111-7.
16. Lundstrom A, Lundstrom F. The Frankfort horizontal as a basis for cephalometric analysis. Am J Orthod Dentofacial Orthop 1995;107(5):537-40.
17. Fernández JR, Redden DT, Pietrobelli A, Allison DB. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. J Pediatr 2004;145(4):439-44.
18. Aguirre CA, Salazar GD, López de Romana DV, Kain JA, Corvalan CL, Uauy RE. Evaluation of simple body composition methods: Assessment of validity in prepubertal Chilean children. Eur J Clin Nutr 2015;69(2):269-73.
19. Brage S, Wedderkopp N, Ekelund U, Franks PW, Wareham NJ, Andersen LB, et al. Objectively measured physical activity correlates with indices of insulin resistance in Danish children. The European Youth Heart Study (EYHS). Int J Obes Relat Metab Disord 2004;28(11):1503-8.
20. Daniels SR, Greer FR. Lipid screening and cardiovascular health in childhood. Pediatrics 2008;122(1):198-208
21. Barja S, Arnaiz P, Domínguez A, Villarroel L, Cassis B, Castillo O, et al. Normal plasma insulin and HOMA values among Chilean children and adolescents. Rev Med Chil 2011;139(11):1435-43.
22. Burrows AR, Leiva BL, Burgueno AM, Maggi MA, Giadrosic RV, Díaz BE, et al. Insulin sensitivity in children aged 6 to 16 years: Association with nutritional status and pubertal development. Rev Med Chil 2006;134(11):1417-26.
23. Finley JP, Nugent ST. Heart rate variability in infants, children and young adults. J Auton Nerv Syst 1995;51(2):103-8.
24. Yeragani VK, Sobolewski E, Kay J, Jampala VC, Igel G. Effect of age on long-term heart rate variability. Cardiovasc Res 1997;35(1):35-42.
25. Goto M, Nagashima M, Baba R, Nagano Y, Yokota M, Nishibata K, et al. Analysis of heart rate variability demonstrates effects of development on vagal modulation of heart rate in healthy children. J Pediatr 1997;130(5):725-9.
26. Tentolouris N, Liatis S, Katsilambros N. Sympathetic system activity in obesity and metabolic syndrome. Ann NY Acad Sci 2006;1083:129-52.
27. Emdin M, Gastaldelli A, Muscelli E, Macerata A, Natali A, Camastra S, et al. Hyperinsulinemia and autonomic nervous system dysfunction in obesity: Effects of weight loss. Circulation 2003;103:513-9.
28. Moreira MC, Pinto IS, Mourao AA, Fajemiroye JO, Colombari E, Reis AA, et al. Does the sympathetic nervous system contribute to the pathophysiology of metabolic syndrome? Front Physiol 2015;6:234.
29. Wilks DC, Rank M, Christle J, Langhof H, Siegrist M, Halle M. An inpatient lifestyle-change programme improves heart rate recovery in overweight and obese children and adolescents (LOGIC Trial). Eur J Prev Cardiol 2014;21(7):876-83.
30. Artero EG, Ruiz JR, Ortega FB, España-Romero V, Vicente-Rodríguez G, Molnar D, et al. Muscular and cardiorespiratory fitness are independently associated with metabolic risk in adolescents: The HELENA study. Pediatr diabetes 2011;12(8):704-12.
31. Corte de Araujo AC, Roschel H, Picanco AR, Do Prado DM, Villares SM, De Sa Pinto AL, et al. Similar health benefits of endurance and high-intensity interval training in obese children. PloS One 2012;7(8):e42747.
32. Morinder G, Mattsson E, Sollander C, Marcus C, Larsson UE. Six-minute walk test in obese children and adolescents: Reproducibility and validity. Physiother Res Int 2009;14(2):91-104.
33. Calders P, Deforche B, Verschelde S, Bouckaert J, Chevalier F, Bassle E, et al. Predictors of 6-minute walk test and 12-minute walk/run test in obese children and adolescents. Eur J Pediatr 2008;167(5):563-8.
34. Chile SABaSo. Prevalence of obesity in Elementary School students. Nutrition Map 2013. Cited August 2017. Available from: www.junaeb.cl/wp-content/uploads/2013/03/Informe-Mapa-Nutricional-2013.pdf.
35. Burrows AR, Leiva BL, Weistaub G, Ceballos SX, Gattas ZV, Lera ML, et al. Prevalence of metabolic syndrome in a sample of Chilean children consulting in an obesity clinic. Rev Med Chil 2007;135(2):174-81.
36. Kuo HK, Gore JM. Relation of heart rate recovery after exercise to insulin resistance and chronic inflammation in otherwise healthy adolescents and adults: Results from the National Health and Nutrition Examination Survey (NHANES) 1999-2004. Clin Res Cardiol 2015;104(9):764-72.
37. Laguna M, Aznar S, Lara MT, Lucia A, Ruiz JR. Heart rate recovery is associated with obesity traits and related cardiometabolic risk factors in children and adolescents. Nutr Metab Cardiovasc Dis 2013;23(10):995-1001.
38. Castro-Pinero J, Artero EG, España-Romero V, Ortega FB, Sjostrom M, Suni J, et al. Criterion-related validity of field-based fitness tests in youth: A systematic review. Br J Sports Med 2010;44(13):934-43.

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ARÁN

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Trabajo Original

Pediatría

Impact of milk based micronutrient supplementation in school children in Quito-Ecuador

Impacto de la suplementación de micronutrientes con leche en niños escolares de Quito-Ecuador

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Abstract

Background: The most common micronutrient deficiencies in Ecuadorian schoolchildren are vitamin A (VA), zinc, and iron. The objective of the present study was to test the efficacy of cow's milk as a vehicle for VA, zinc, and iron supplementation.

Methods: Three hundred twenty-eight children aged 6-10 years were included in a randomized, double blind controlled study; 173 children received 480 mL of whole milk (300 Kcals; G1) daily and 155 children received fortified milk (300 Kcals; G2) daily for 23 weeks. Participants had a nutritional evaluation before and after supplementation. Both treatment groups were comparable for gender, age, weight and height at the beginning of the study.

Results: Both types of milk were well accepted by the participating children. Data showed that serum concentrations of VA, zinc, and iron significantly increased within both treatment groups. The increase in serum concentrations of the indicated micronutrients was significantly greater in children with deficiencies than in non-deficient ones. There were not significant differences in serum concentrations of VA, zinc, and iron between groups after supplementation. Data also showed that there was an increase in the percentage of children with normal BMI at the expense of a decrease of the percentage of children with excess weight at the end of the treatment period in G1 whereas in G2 it remained unchanged. Blood lipid profiles were normal before and after milk supplementation in both treatment groups.

Conclusions: These data indicated that fortified and non-fortified milk are excellent options to increase serum VA, zinc, and iron concentration in schoolchildren.

Key words:

Diet, food, and nutrition. Micronutrient. Milk. Vitamin A. Zinc. Iron.

Resumen

Introducción: las deficiencias de vitamina A (VA), zinc y hierro son las más comunes en escolares ecuatorianos. El objetivo del presente estudio fue estudiar la eficacia de la leche de vaca como vehículo para la suplementación de VA, zinc y hierro.

Métodos: trescientos veintiocho niños en edades entre 6 y 10 años fueron incluidos en un estudio aleatorizado controlado, doble ciego durante 23 semanas; 173 niños recibieron diariamente 480 mL de leche entera (300 Kcals; G1) y 155 niños recibieron leche entera fortificada (300 Kcals, G2). Los niños tuvieron una evaluación nutricional antes y después de la suplementación. Al inicio del estudio, G1 y G2 fueron similares en género, edad, peso, y talla. Los dos tipos de leche fueron bien aceptados.

Resultados: las concentraciones séricas de VA, zinc y hierro aumentaron significativamente en ambos grupos después del tratamiento. El aumento de estos micronutrientes fue significativamente mayor en los niños con deficiencias. No hubo diferencias significativas en las concentraciones de VA, zinc y hierro entre los grupos después de la suplementación. Además, hubo un incremento en el porcentaje de niños con IMC-normal dependiente de una disminución en el número de niños con exceso de peso al final del periodo de tratamiento en G1, mientras que en G2 no hubo cambios. Los perfiles lipídicos fueron normales antes y después de la suplementación con leche en los dos grupos.

Conclusiones: en resumen, tanto la leche fortificada como la no fortificada son excelentes opciones para aumentar las concentraciones de VA, zinc y hierro en escolares.

Palabras clave:

Nutrición, alimentación y dieta. Micronutriente. Leche. Vitamina A. Zinc. Hierro.

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INTRODUCTION

Current evidence shows the coexistence of under-nutrition and over nutrition within the same population as a worldwide phenomenon (1). Malnutrition occurs throughout the lifecycle affecting all socioeconomic groups. Malnutrition states are commonly accompanied with vitamin and mineral deficiencies (2). The World Health Organization estimates that 30% of the world population is deficient in iron, 21% in vitamin A (VA), and 17% in zinc. VA, zinc, and iron deficiencies are associated with low stature, increased susceptibility to infection, attention deficits, and low school performance (3).

Malnourishment is common among Ecuadorian schoolchildren. The last National Health and Nutrition Survey of Ecuador (ENSANUT) indicates that 15% of schoolchildren have chronic undernutrition and 29.9% have overweight or obesity which means that 45% are malnourished (1). Zinc and VA are the most common micronutrient deficiencies with a prevalence of 28.1% and 10.9%, respectively (1). In addition, the prevalence of iron-deficiency anemia is 3.5%. In summary, Ecuadorian schoolchildren present high prevalence of malnourishment characterized by under and over-nutrition accompanied by micronutrient deficiencies (1).

The high rates of malnutrition evidenced by the ENSANUT indicates that optimal strategies to correct these nutritional problems are needed (1). Food fortification is an important public health strategy to tackle malnutrition and micronutrient deficiencies due to its potential to reach large population groups without requiring important changes in food consumption patterns (4). To implement food fortification programs, it is important to consider the molecular structure of the supplement, the vehicle of delivery, potential interactions that could affect bioavailability between micro and macronutrients, acceptability to the population, and cost. Milk is a major source of dietary energy, protein, and micronutrients and has been shown to contribute to the nutritional improvement and growth of children (5). Cow's milk supplemented with iron, zinc, vitamin C, and copper administered for less than a year decreased the prevalence of anemia by 66% (6). Therefore, regular cow´s milk could be used as an optimal vehicle for micronutrient supplementation (6).

Combined micronutrient fortification is a good strategy to combat vitamin and mineral deficiencies (7). However, one potential problem is the observed competition among minerals for their absorption in the intestine (8,9).

Few studies have assessed the effect of multi-nutrient fortified milk on the nutritional status of normal and malnourished Ecuadorian schoolchildren with or without micronutrient deficiencies. Consequently, the objective of the present study was to test the efficacy of whole cow´s milk as a vehicle for VA, zinc, and iron supplementation. This work will contribute to clarify potential interactions between VA, zinc, and iron in fortified milk.

MATERIALS AND METHODS

PARTICIPANTS AND STUDY DESIGN

The study population consisted of 328 schoolchildren from middle-low or low socioeconomic strata from a semi-urban area in Quito (Ecuador). Children were included if they were 6 to 10 years of age of any gender who have attended the school regularly for the last 3 months prior to the study and signed along with their guardians an informed consent. Children were excluded if they had signs or symptoms of infection; were receiving micronutrient supplementation 30 days before the study or were planning to consume them; had history of lactose intolerance; present chronic diseases; congenital diseases, mal-absorption syndromes; cancer; or HIV infection (Fig. 1).

This was a randomized, double blind controlled study. In group 1 (G1) 173 children received 480 mL/day of whole milk (300 kcal; Zn = 1.96 mg, Fe = 0.14 mg, vit A = 136 µg), while in group 2 (G2) 155 children received 480 mL/day of fortified milk (300 kcal; Zn = 7.16 mg, Fe = 4.56 mg, VA = 360 µg) (Table I). Children received daily two glasses of 240 mL of milk; one in the morning and one in the afternoon, during 23 weeks, from January to June 2015. Milk supplementation for both groups was added to children's usual diets. All children had a full nutritional assessment before and after supplementation which included clinical examination, anthropometric measurements and laboratory analysis (Fig. 1).

A daily record of attendance to school, compliance to treatment, side effects attributed to milk consumption, and the presence and duration of acute respiratory and gastrointestinal diseases was recorded. Children did not receive other food supplementation during the study.

MILK SUPPLEMENTS

Milk preparation and distribution were done following high hygienic standards including safe water. Specially trained field

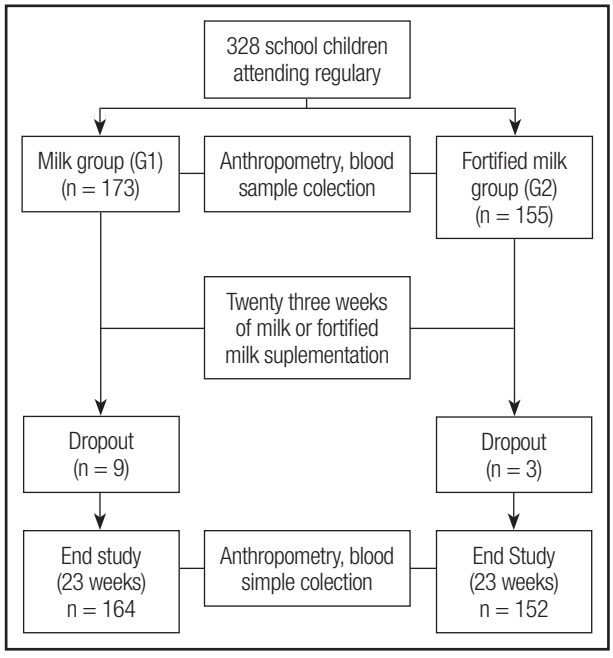

Figure 1.
Flowchart.

Table I. Macro and micronutrient content of fortified and non-fortified milk

Nutrients	Units	Content in milk (8 oz.)	% of RDA (in 2 servings)	Content in fortified milk (8 oz.)	% of RDA (in 2 servings)
Vitamin A	µg/31 g*	111.9	56	176.3	88
Vitamin C	mg/31 g	0.5	2.56	16.7	85.6
Vitamin D	UI/31 g	51.5	25.7	71.3	35.6
Iron	mg/31 g	0.9	18	2.3	46
Zinc	mg/31 g	1.9	47.5	3.6	90
Calcium	mg/31 g	292	53	390.6	71
Protein	g/31 g	5	29.4	5	29.4
Carbohydrate	g/31 g	14	21.5	14	21.5
Sodium	mg/31 g	95	4.2	95	4.2
Cholesterol	mg/31 g	28	32	28	32
Fat	g/31 g	8	45.7	8	45.7
Energy	kcal/31 g	150	16	150	16

**Indicates that 31 g of milk powder was reconstituted in 240 mL.*

personnel and parents prepared and administered milk supplements including weekends and holidays. Table I indicates macro- and micronutrient composition of fortified and unfortified milk and the estimated consumption of VA, zinc, and iron from both treatment groups relative to the Recommended Daily Allowance (RDA). Milk was fortified with dry vitamin A acetate 325 CWS containing 325000 IU of vitamin A per gram; powder ferric pyrophosphate retinyl acetate 20-22%; and zinc sulphate heptahydrate.

ANTHROPOMETRIC MEASUREMENTS

Weight and height were taken by trained personnel using standardized techniques and calibrated equipment. For weight measurement, an electronic SECA 213 scale was used. For height measurement, a SECA 213 stadiometer was mounted vertically on the wall above a hard, flat surface, following vendor instructions. Height was measured to the nearest 0.1 cm. During anthropometric measurements, children had minimal clothing without shoes. Anthropometric data was analyzed using Anthro Plus WHO growth charts for weight-, height- and BMI-for-age and sex (10).

Blood samples

Blood samples were obtained in the morning after approximately 10 hours of fasting. Samples were centrifuged within 2 hours and processed immediately (11).

COMPLETE BLOOD CELL COUNT

To determine the presence of infection at baseline, a complete blood cell count was performed. We did not use a marker of inflammation like C-reactive protein (CRP) because evidence indicates that consumption of healthy food reduces serum CRP concentrations, rendering this marker not ideal for milk supplementation studies (12).

VITAMIN A, ZINC, AND IRON DETERMINATIONS

We followed the same methodology for the determination and cut-off points for VA and zinc used in the ENSANUT-EC study (1). Serum VA < 20 µg/dL, zinc < 65 µg/dL, and iron <50 µg/dL were considered abnormal (11); plasma/serum ferritin concentrations < 15 µg/L were considered as depleted iron stores (1).

Vitamin A

All materials were prepared with distilled water and high purity water was used for solutions. Blood samples were collected in a vacuum tube containing lithium heparin as anti-coagulant (13). Blood was centrifuged and, plasma was stored at -80 °C protected from light. On the day of assay, samples were thawed at room temperature and homogenized. Vitamin A was extracted from plasma using Strata-XL 100u Polymeric Reversed Phase 60 mg/3 mL solid phase extraction cartridges (Phenomenex. Torrance, California). Briefly, plasma proteins were precipitated mixing 250 µl of sample and 750 µl of ethanol for 30 sec; samples were centrifuged at 10,000 rpm for 5 min at room temperature (RT) to obtain VA enriched supernatant. Subsequently, PRP cartridges were placed in a manifold and were conditioned with 1 mL of methanol and 1 mL of water. Sample supernatants were placed in the equilibrated PRP cartridges. Samples in cartridges were washed once with 1 mL 35% methanol and cartridges were vacuum dried for one minute. Vitamin A was eluted with 1.5 mL of mobile phase solution (75% acetonitrile and 25%

methanol). Finally, VA contained in eluded samples was measured by high-resolution liquid chromatography using a Synerfi 4u Hydro-RP 80A 250 x 4.6 mm 4 micron phenomenex ODS 100 x (3 mm), Agilent column with a wavelength of 326 nm as previously indicated. Controls of lyophilized human plasma of high 3.52 and low levels 1.38 µmol/L of VA were used (Chromesystems. Grafelfing, Germany). Limit of detection for VA was 4 µg/L (13).

Zinc

Equipment used for Zn measurements was treated with 10% v/v HNO3 solution for 12 hours to remove contaminants (14). Zinc was measured by atomic absorption spectroscopy with a flame atomization wavelength of 213.9nm, using a spectrophotometer Perkin-Elmer flame Analyst 400 model (Proinstra. Quito, Ecuador). Three hundred microliters of plasma were mixed with 2.7 mL of pure water and homogenized. Subsequently sample was directly measured in the spectrophotometer (14). Control samples (BCR 637 - 9; European Commission Joint Research Centre, Institute for Reference Materials and Measurements; Geel, Belgium) were run every 10 samples. Limit of detection for Zn was 1.5 µg/dL.

Iron, transferrin, and ferritin measurements

Iron was determined by the FerroZine ascorbate colorimetric method using a Roche Modular Analitics Evo P800 (Roche, USA). The limit of detection of the method was 5 µg/dL.

Transferrin was determined using inmunoturbimetry following the manufacturer's instructions (TRSF2, Roche, Indianapolis USA). The limit of detection of transferrin was 10 mg/dL. Transferrin saturation was calculated using the following formula: (serum iron x 100) / (serum transferrin x 1.27) (11).

Ferritin was measured by elechtrochemoluminiscence in a Ferritin kit (Roche. Indianapolis, USA). The limit of detection of ferritin was 0.50 µg/mL.

Glucose and lipid profile measurements

Glucose and lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides) were determined on a Roche Modular Evo P800 using standard reagents (Roche Diagnostics GmbH. Mannheim, Germany). Blood biochemistry analyses were carried out at NetLab laboratory that maintains an internal and external quality control system (15).

The study was approved by the IRB of "Universidad de Las Américas".

STATISTICS

A sample size of 318 was estimated with 95% confidence, 80% power, and a mean serum Hb concentration after intervention in G2 of 11.35 g/dL and in G1, 10.5 g/dL with a standard deviation of 2.7 g/dL for both groups. Descriptive statistics with its respective measures of dispersion were calculated for continuous variables; frequencies and percentages were calculated for categorical variables. Analyses were performed with intention to treat. Differences between groups were assessed with Chi Square and ANOVA or Kruskal Wallis. Differences within groups were assessed with paired t-test or the corresponding non-parametric statistics. Statistical analyses were performed with SPSS V. 21 software. A p value < 0.05 was considered significant.

RESULTS

Both types of milk were well accepted by participants. At baseline, treatment groups had similar demographic and anthropometric characteristics (Table II).

EFFICACY OF FORTIFIED MILK ON SERUM MICRONUTRIENT CONCENTRATIONS

Figure 2A compares mean serum VA concentrations in deficient and non-deficient children that received milk (G1) or fortified milk (G2) before and after supplementation. Data indicated there were not statistically significant differences in serum VA concentration in non-deficient children before and after milk or fortified milk consumption (Fig. 2A). In deficient children, basal serum VA concentrations in G1 and G2 were similar at baseline; consumption of milk or fortified milk significantly increased VA concentration in both treatment groups (Fig. 2A); serum VA concentrations were not different between G1 and G2 at the end of the study. Prevalence of VA deficiency in G1 went from 13/173 (7.5%) at baseline to 17/164 (10.4%) at the end-line, while in G2 went from 18/155 (11.6%) to 12/152 (7.9%), respectively.

Among zinc-sufficient children, there were not differences in zinc concentrations at baseline (Fig. 2B); however, milk or fortified milk supplementation significantly increased serum zinc concentrations in both treatment groups; at the end of the study period, serum zinc concentrations in zinc-sufficient children were similar

Table II. Base line characteristics of school children in the two treatment groups, milk (G1) and fortified milk (G2)

Demographic characteristics	Milk (n = 173)	Fortified Milk (n = 155)	p value
	X (SD)	X (SD)	
Male	51.4%	52.3%	0.86
Age (years)	8 (±2)	8 (±2)	1
Weight (kg)	21.93 (±6.46)	21.95 (±5.44)	1
Height (cm)	117.28 (±9.05)	118.09 (±7,83)	0.26
BMI (kg/m^2)	16.7 (±1.46)	16.4 (±2.08)	< 0.53

between both treatment groups. In zinc-deficient children, data showed that at base line G2 had significant higher concentrations than G1; milk or fortified-milk supplementation provoked a significantly increase in serum zinc concentrations in both treatment groups; at the end of the study period, there were not differences in zinc concentrations in G1 and G2 in zinc-deficient children. Prevalence of zinc deficiency in G1 went from 24/173 (13.9%) at baseline to 9/164 (5.5%) at the end of the study, while in G2 went from 20/155 (12.9%) to 6/152 (3.9%), respectively.

In relation to serum iron changes, in children without iron deficiency, base line serum iron concentrations were similar between G1 and G2; consumption of milk of fortified milk did not significantly modify serum iron concentrations in both groups (Fig. 2C). In iron-deficient children, basal serum concentrations were similar between G1 and G2; milk or fortified-milk consumption significantly increased serum iron concentrations after the supplementation; in addition, serum iron concentrations were similar between both treatment groups at the end of the study. Prevalence of iron deficiency in G1 went from 23/173 (13.3%) at baseline to 12/164 (7.3%) at the end of the study, while in G2 went from 20/155 (12.9%) to 11/152(7.2%), respectively.

EFFICACY OF FORTIFIED MILK ON IRON METABOLISM PARAMETERS

To better evaluate iron status on participating children, concentrations Hb, transferrin saturation index, and ferritin were evaluated. In Hb sufficient children, at baseline there were not significant differences in serum Hb concentrations between G1 and G2. Figure 3A shows a significant increase on Hb in both treatment groups upon consumption of milk or fortified milk; Hemoglobin concentrations were similar in both groups at the end of the study period. In Hemoglobin-deficient children, basal Hb concentrations were similar between G1 and G2; consumption of milk of fortified-milk significantly increased Hb concentrations in both treatment groups reaching similar values by the end of the study. The prevalence of Hb deficiency in G1 went from 27/173 (15.6%) at baseline to 15/164 (9.1%) at end-line, while in G2 went from 31/155 (20%) to 12/152(7.8%), respectively.

In children with normal transferrin saturation index, consumption of unfortified milk did not affect transferrin saturation; however, in children that consumed fortified milk there was a significant decrease in the saturation index although the changes were within the normal range (Fig. 3B). In children with abnormal transferrin saturation index, at base line the index was similar in G1 and G2; however, upon fortified milk consumption transferrin saturation significantly increased in both treatment groups; there were not differences in transferrin saturation between G1 and G2 after the supplementation.

Finally, iron reserves were determined by the measurement of serum ferritin. There were not children with deficient ferritin. Ferritin concentrations were similar at baseline in both groups (Fig. 3C). Opposite to the observed increment with other parameters of iron metabolism, serum ferritin concentrations significantly

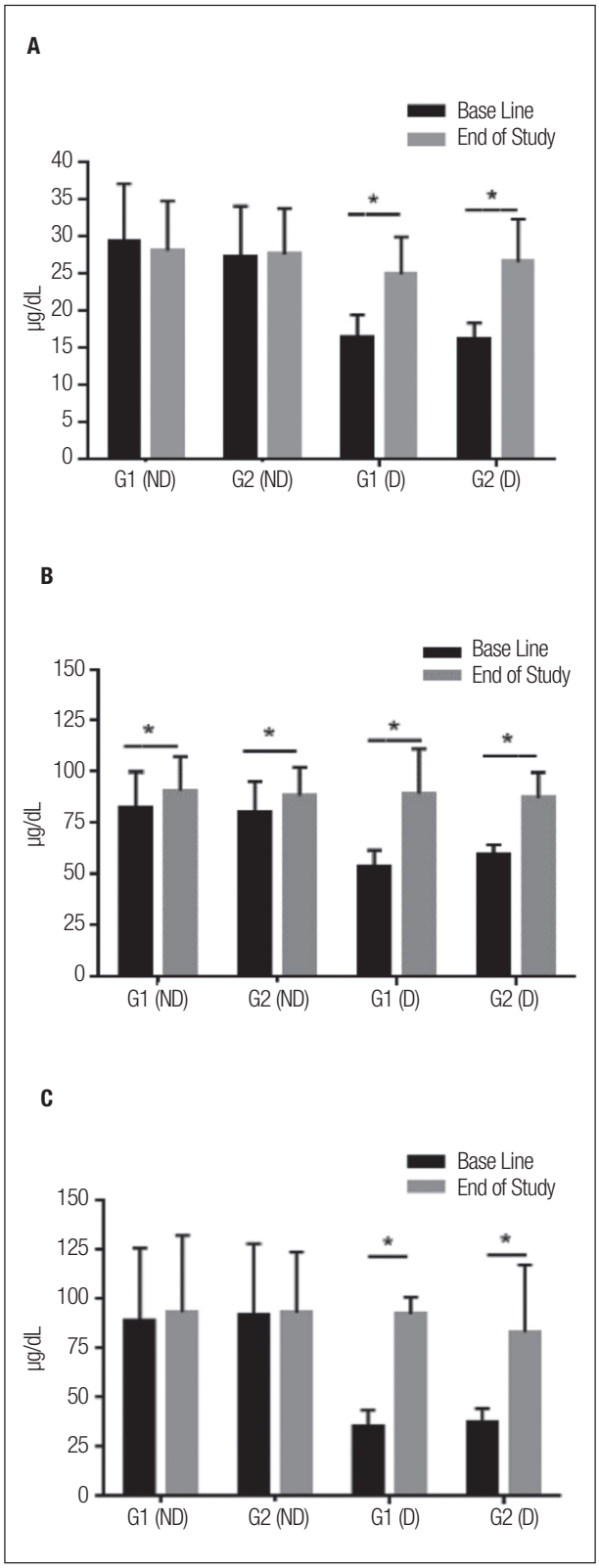

Figure 2.

Changes in mean serum concentration of vitamin A (A), zinc (B), and iron (C). $p < 0.05$; G1, milk; G2, fortified milk; ND: non deficient group; D: children with deficiency.

decreased by the end of the study in both treatment groups. Serum ferritin concentrations were similar between groups at the end of supplementation and values were within the normal range (Fig. 3C).

CHANGES ON ANTHROPOMETRIC PARAMETERS

Body mass index was used as an indicator of nutritional status. There were not undernourished children in both study groups. Considering all participating children, 71.0% (220/311) had BMI values within the normal range and 29% (91/311) had excess weight (overweight (22%) and obesity 7%) (Table III). In G1 72.0% (119/165) of children had normal BMI and 28% (46/165) had excess weight (overweight 22% and obesity 6%). In G2 69.2% (101/146) had normal weight and 30.8% (45/146) had excess weight (overweight 22.6% and obesity 8.2%). Table III also shows the changes in the number and percentages of children with normal BMI, overweight, and obesity in both treatment groups during the study period. In G1, there was an increase in the percentage of children with normal BMI at the expense of a decrease of the percentage of children with excess weight at the end of the treatment period. There were not important changes in BMI in G2 after milk supplementation.

It is important to point out that all participating children were within the normal range of height for age before and after the study period (not shown). However, children from both treatment groups grew approximately 3.2 cm during the study. There were not differences in height increments between groups, therefore, both groups ended with similar height at the end of the study.

CHANGES ON SERUM LIPID PROFILES

Prior to supplementation, all parameters of the lipid profile (total cholesterol, LDL, HDL, and TG) were within the normal range and were comparable in both study groups (Table IV). Upon supplementation, all lipid profile parameters significantly increased in G1. On the other hand, in G2, total cholesterol, LDL, and HDL significantly increase while TG decreased although not significantly (Table IV). All changes in lipid profile parameters were within the normal range for both treatment groups.

COMPLIANCE, SIDE EFFECTS, AND INCIDENCE OF ACUTE INFECTIONS

A daily registration of school attendance, milk consumption, potential side effects, and the presence of acute infections were recorded. Data showed that 12 children left the study, 9 (5.2%) from G1 and 3 (1.9%) from G2. The differences in the number of children that abandoned the study from both groups were not statistically significant ($p = 0.145$). In G1, 4 children moved from the school area and the remaining 5 left the study due to the presence of gastrointestinal symptomatology such as nausea, vomit, diarrhea, and abdominal pain. Similarly, the 3 children from G2 left the study due to gastrointestinal symptomatology.

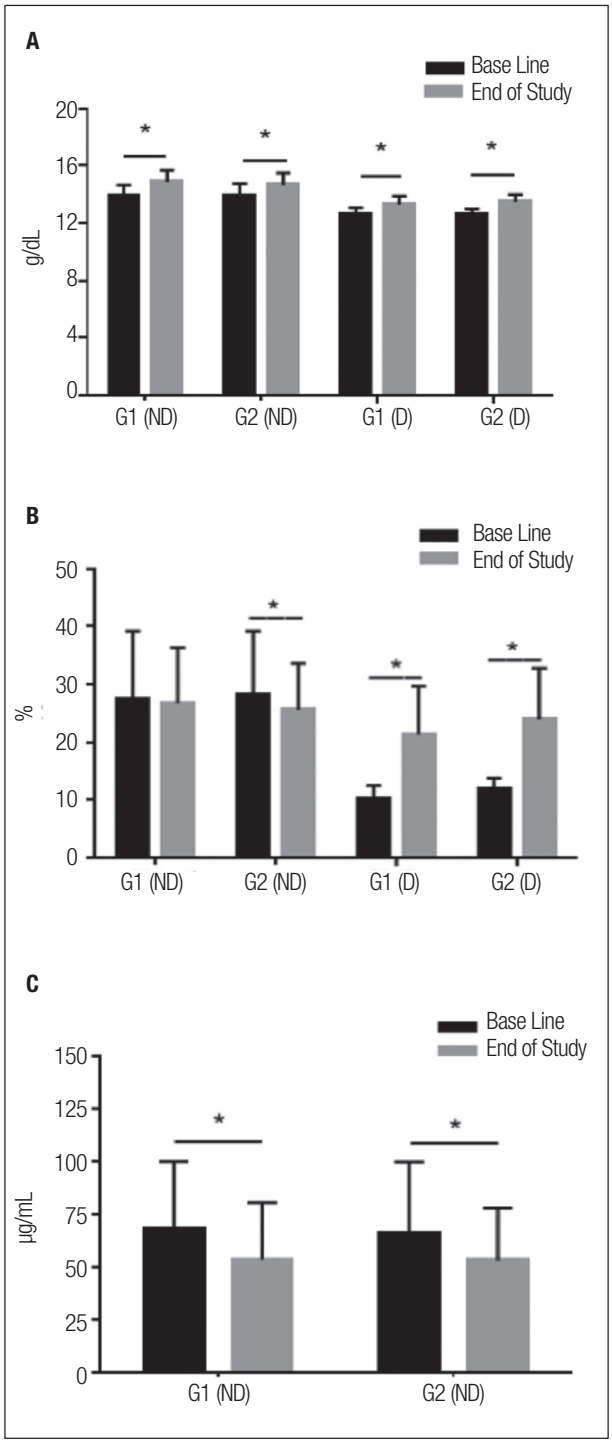

Figure 3.

Changes in mean serum concentration of hemoglobin (A), transferrin saturation index (B), and ferritin (C). $p < 0.05$; G1, milk; G2, fortified milk; ND: non deficient group; D: children with deficiency.

Table III. Changes in BMI within treatment groups in school children supplemented with milk or fortified-milk for 23 weeks

Basal (G1) milk n = 165				Final (G1) milk n = 158			
< -2 z-score Undernourishment	≥ -2/≤ 1 z-score Normal % (n)	> 1 /≤ 2 z-score Overweight % (n)	> 2 z-score Obesity % (n)	< -2 z-score Undernourishment	≥ -2/≤ 1 z-score Normal % (n)	> 1 /≤ 2 z-score Overweight % (n)	> 2 z-score Obesity % (n)
0	72% (119)	22% (36)	6% (10)	0	77.2% (122)	19.8% (31)	3% (5)
Basal (G2) fortified Milk n = 146				**Final (G2) fortified milk n = 145**			
< -2 z-score	≥ -2/≤ 1 z-score	> 1 /≤ 2 z-score	> 2 z-score	< -2 z-score	≥ -2/≤ 1 z-score	> 1 /≤ 2 z-score	> 2 z-score
0	69.2% (101)	22.6% (33)	8.2% (12)	0	69 % (100)	24.8% (36)	6.2% (9)

Table IV. Changes in lipid profile within treatment groups in school children supplemented with milk or fortified-milk for 23 week

	Milk (G1)			Fortified milk (G2)		
	Basal	Final	p value	Basal	Final	p value
Cholesterol	151.82 (±22.33)	158.59 (±23.70)	< 0.001	151.29 (±29.79)	157.34 (±31.87)	0.002
LDL	86.0 (±26.0)	88.00 (±27)	0.06	82.00 (±31.0)	86.00 (±24)	0.011
HDL	51,50 (±11.04)	53.76 (±12.79)	0.004	50.77 (±12.75)	52.46 (±12.25)	0.04
Triglycerides	66.00 (±37.8)	68.00 (±40)	0.05	65.50 (±40.3)	60.00 (±43)	0.747

There were not significant differences in the number of consumed servings between treatment groups, G1 89.2% (287/322 servings) and G2 86.7% (276/322 servings). None of the participating children reported severe side effects during the study. Eight percent of children from G1 and 9.6% from G2 had gastrointestinal symptoms. Approximately 9% of children in each treatment group presented acute infections (including cold and diarrhea) during the study.

DISCUSSION

Results showed that fortified and non-fortified milk are efficacious to improve serum VA, zinc, and iron concentration in schoolchildren with limited frequency of micronutrient deficiencies. Treatments were well accepted and did not cause severe side effects. Serum concentrations of VA, zinc, and iron significantly increased within both treatment groups. As expected, the beneficial effect of supplementation with both types of milk was greater in children with micronutrient deficiencies. After the supplementation period, there were not significant differences between treatment groups in serum concentrations of these micronutrients. Also, the percentage of children with excess weight decreased after milk intake in G1 while in G2 remained unchanged. In addition, lipid profiles remained normal upon milk supplementation in both groups. Consumption of fortified milk decreased the prevalence of VA, zinc, and iron deficiencies while un-fortified milk intake only decreased the prevalence of zinc and iron.

Food fortification is a common strategy to improve micronutrient deficiencies (16,17). Selection of vehicle-food for micronutrient fortification should consider the cost, frequency of consumption, amount of food used, shelf-live, and maintenance of organoleptic characteristics (18). Ideally, fortified foods should facilitate and not interfere with the bioavailability of micronutrients (19).

Cereal and cow's milk are the most common foods used for micronutrient fortification. Some cereals however, have the limitation to interfere with mineral absorption. Cow's milk has been successfully used as vehicle in micronutrient fortification in schoolchildren (20). Administration of fortified skim milk 200 mL with 20 mg of iron and 3 mg of cupper salts for 3-months significantly increased serum Hb concentrations without affecting iron, transferrin or ferritin concentrations of schoolchildren in Mexico (21). Data also show that in addition to the food vehicle for fortification, the form of the micronutrient salt is important for bioavailability. Evidence shows that ferrous sulfate, ferrous fumarate, and ferric pyrophosphate are efficacious to correct iron deficiencies (22,23). These studies show that milk is an excellent vehicle for iron supplementation in children.

Multi-micronutrient food fortification is an effective approach to control VA, zinc, and iron deficiencies. In meta-analyses that assessed the effects of VA, iron, and multi-micronutrient interventions on children growth indicate that individual interventions with VA, zinc, and iron have no significant effect on children linear growth while combined multi-micronutrient interventions have a positive effect (24,25). Pinkaew et al. evaluated the impact of

vitamin A- Zn- and Fe-fortified extruded rice in schoolchildren deficient in Zn from Thailand (26). Authors show that consumption of rice or fortified rice increases serum Zn concentrations. However, the increment in serum Zn concentrations was significantly greater in children that received fortified rice (26). In that study, there were not important changes in secondary end points, iron and VA status, since children were not deficient in these micronutrients (26). Present data showed that milk or fortified milk affected serum micronutrient status. Prevalence of VA deficiency increased (2.9%) while prevalence of Zn and Fe decreased 8.4% and 6% in G1, respectively; whereas prevalence of VA, Zn, and Fe decreased by 3.7%, 9%, and 5.7% in G2, respectively. Similar to the study by Pinkaew, our results showed that both fortified and non-fortified foods improved micronutrient status.

Although concentrations of VA, Zn, and Fe in our study were 1.5, 1.8, and 2.5 times greater in fortified milk than in non-fortified milk, the effects in children were similar at the end of the study. It is possible that the improvement in micronutrients in the non-fortified milk group was the result of adequate micronutrient intake, similar to the RDA. Here it is important to point out that milk treatments in the present study were added to the regular food intake of children. Addition of milk or fortified milk to children regular diets could have completed the required RDA for the micronutrients. The fact that serum VA, Zn, and iron concentrations were similar at the end of the study in children with and without deficiencies supports the contention that both groups of children consumed the required amounts of micronutrients. In addition, the low prevalence of undernourishment in both treatment groups at base line, could be an indication of a diet sufficient in macro- and micronutrients in most participating children that could have been complemented with the addition of either non-fortified or fortified-milk.

Studies of micronutrient supplementation indicate that individuals with deficiency respond better to supplementation than those without deficiencies (20). Present study also evidenced that non-fortified milk or fortified milk consumption had greater effect on micronutrient deficient children than in non-deficient ones. Increased serum concentrations could be the result of augmented gastrointestinal absorption, improved utilization, and greater internal turnover (27). In this study, milk or fortified-milk supplementation increased transferrin saturation index and decreased serum ferritin concentrations as a consequence of greater iron intake and potential enhanced absorption particularly in deficient children (28). With non-fortified milk and fortified-milk consumption, we observed variations on transferrin saturation that were within normal values. However, changes were more pronounced in fortified-milk supplemented group. These results are in agreement with other studies that have shown that iron supplementation increases transferrin saturation due to a greater availability of iron (29). In addition, it has been documented that iron overload also limits ferritin expression and synthesis (30).

Since over nutrition coexist within Ecuadorian schoolchildren, it was expected that a unique general nutritional intervention could result in different nutritional effects depending on children's initial nutritional status. The prevalence of children with excess weight decreased 6.3% in G1 whereas in G2 it remained unchanged. Present results also demonstrated that children from both treatment groups grew approximately 3.2 cm which corresponds to the maximum expected for schoolchildren (31). Increments of weight and height after milk administration in G1 and G2 agree with previous studies. Data show that administration of 190 mL of milk daily for approximately 22-months to schoolchildren resulted in greater weight and height gains compared with un-supplemented controls (32). In a similar way, administration of 250 mL of whole milk for three months significantly increased weight gain in schoolchildren compared with untreated controls (33). These studies indicate that administration of milk increases weight, height, and BMI. Food supplementation in schoolchildren, should consider the nutritional status of the population particularly those with excess weight or in the upper limit of normality for BMI.

The problem with multi-micronutrient food fortification is the potential interaction among minerals for their absorption in the intestine (34). Fortified milk used in this study had a Zn to iron ratio of 1.57, the important increments observed on serum Zn and iron and the positive effects on children growth, indicated that a potential negative interaction between these minerals for their absorption was not important.

A potential limitation of the present study is the lack of data on daily children's intake. However, since G1 and G2 groups were comparable at most baseline parameters, it is unlikely that children's intake would had been an important confounding factor.

To the best of our knowledge this is the first combined micronutrient intervention study carried out to correct the most common micronutrient deficiencies in Ecuadorian schoolchildren. These results warrant further research-intervention programs in other schoolchildren and other nutritional vulnerable populations.

REFERENCES

1. MSP, INEC. Encuesta Nacional de Salud y Nutrición 2012. Vol. Tomo 1, Ensanut-Ecu 2012. 2014. pp. 5-722.
2. Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, et al. Evidence-based interventions for improvement of maternal and child nutrition: What can be done and at what cost? Lancet 2013;382(9890):452-77.
3. Martínez R. Inseguridad alimentaria y nutricional en América Latina y el Caribe. Cepal [Internet] 2009;5(6):7-63. Available at: http://es.wfp.org/sites/default/files/Inseguridad_Alimentaria_ALC.pdf
4. Unicef. UNICEF ANNUAL Report 2011; 2012.
5. Michaelsen KF, Nielsen A-LH, Roos N, Friis H, Mølgaard C. Cow's Milk in Treatment of Moderate and Severe Undernutrition in Low-Income Countries. Nestlé Nutr Inst Work Ser Pediatr Progr 2011;67:99-111.
6. Olivares M, Hertrmpf E, Pizarro F, Walter T. El enriquecimiento con hierro de la leche: la experiencia chilena. Aliment Nutr Y Agric Nutr Agric 2003;32:69-75.
7. Eichler K, Wieser S, Rüthemann I, Brügger U. Effects of micronutrient fortified milk and cereal food for infants and children: a systematic review. BMC Public Health 2012;12(506).
8. Rashed AA. In Vitro Study to determine the effect of zinc on non-heme iron absorption. IJCRIMPH 2011;3(5):354-68.
9. Olivares M, Pizarro F, Ruz M, López de Romaña D. Acute inhibition of iron bioavailability by zinc: studies in humans. Biometals 2012;25(4):657-64.
10. World Health Organization. WHO AnthroPlus for Personal Computers Manual [Internet]. 2009 [cited 2017 Mar 8]. Available at: http://www.who.int/growthref/tools/who_anthroplus_manual.pdf
11. Fischbach FT, Dunning MB. A manual of laboratory and diagnostic tests. Lippincott Williams & Wilkins Publishers; 2015. pp. 1261.

12. Neale EP, Batterham MJ, Tapsell LC. Consumption of a healthy dietary pattern results in significant reductions in C-reactive protein levels in adults: a meta-analysis. Nutr Res 2016;36(5):391-401.
13. Márquez M, Yépez CE, Sútil-Naranjo Manuel Rincón R. Aspectos básicos y determinación de las vitaminas antioxidantes E y A. Invest Clin 2002; 43(3):191-204.
14. Herrero E. VA. Metodología recomendada para la medición del contenido de zinc en especímenes biológicos. Química Clínica 2003;22.
15. Baldeón ME, Castro J, Villacrés E, Narváez L, Fornasini M. Hypoglycemic effect of cooked Lupinus mutabilis and its purified alkaloids in subjects with type-2 diabetes. Nutr Hosp 2012;27(4):1261-6.
16. Dwyer JT, Wiemer KL, Dary O, Keen CL, King JC, Miller KB, et al. Fortification and Health : Challenges and Opportunities. Adv Nutr 2015;6(1):124-31.
17. Smith G. Micronutrient Fortification of Food: Issues for Asia. J Nutr Sci Vitaminol (Tokyo) 2015;61:S183-5.
18. Kyamuhangire W, Lubowa A, Kaaya A, Kikafunda J, Harvey P, Rambeloson Z, et al. The importance of using food and nutrient intake data to indentify appropriate veicles and estimate potential benefits of food fortification in Uganda. Nutrition News for Africa 2013;1-4.
19. Rosado JL, Diaz M, Gonzalez K, Griffin I, Abrams SA, Preciado R. The addition of milk or yogurt to a plant-based diet increases zinc bioavailability but does not affect iron bioavailability in women. J Nutr 2005;135(3):465-8.
20. Food and Agriculture Organization of the United Nations. Milk and dairy products in human nutrition [Internet]. Muehlhoff E, Bennett A MD, editor. Milk and Dairy Products in Human nutrition. 2013. 404 p. Available at: http://www.fao.org/docrep/018/i3396e/i3396e.pdf
21. Rivera R, Ruiz R, Hegenauer J, Saltman P, Green R. Bioavailability of iron- and copper-supplemented milk for Mexican school children. Am J Clin Nutr 1982;36(6):1162-9.
22. Randall P, Johnson Q, Verster A. Fortification of Wheat Flour and Maize Meal with Different Iron Compounds: Results of a Series of Baking Trials. Food Nutr Bull 2012;33:S344-59.
23. Hirve S, Bhave S, Bavdekar A, Naik S, Pandit A, Schauer C, et al. Low dose "Sprinkles" - an innovative approach to treat iron deficiency anemia in infants and young children. Indian Pediatr 2007;44(2):91-100.
24. Jiménez-Morán E, Bacardí-Gascón M, Jiménez-Cruz A. Efficacy of zinc on lineal growth on Latin American children younger than 5; systematic review. Nutr Hosp 2013;28(5):1574-9.
25. Pinkaew S, Winichagoon P, Hurrell RF, Wegmuller R. Extruded Rice Grains Fortified with Zinc, Iron, and Vitamin A Increase Zinc Status of Thai School Children When Incorporated into a School Lunch Program. J Nutr 2013;143(3):362-8.
26. Pinkaew S, Wegmuller R, Wasantwisut E, Winichagoon P, Hurrell RF, Tanumihardjo SA. Triple-Fortified Rice Containing Vitamin A Reduced Marginal Vitamin A Deficiency and Increased Vitamin A Liver Stores in School-Aged Thai Children. J Nutr 2014;144(4):519-24.
27. Fuqua BK, Vulpe CD, Anderson GJ. Intestinal iron absorption. J Trace Elem Med Biol 2012;26(2-3):115-9.
28. Roughead ZK, Hunt JR. Adaptation in iron absorption: iron supplementation reduces nonheme-iron but not heme-iron absorption from food. Am J Clin Nutr 2000;72(4):982-9.
29. Bartnikas TB. Known and potential roles of transferrin in iron biology. Biometals. 2012;25(4):677-86.
30. King M. Protein Synthesis -Translation and Regulation [Internet]. [cited 2017 Mar 9]. Available at: http://themedicalbiochemistrypage.org/protein-synthesis.php
31. Dimeglio A. Growth in pediatric orthopaedics. J Pediatr Orthop 21(4):549-55.
32. Baker IA, Elwood PC, Hughes J, Jones M, Moore F, Sweetnam PM. A randomised controlled trial of the effect of the provision of free school milk on the growth of children. J Epidemiol Community Health 1980;34:31-4.
33. Rahmani K, Djazayery A, Habibi MI, Heidari H, Dorosti-Motlagh AR, Pourshahriari M, et al. Effects of daily milk supplementation on improving the physical and mental function as well as school performance among children: results from a school feeding program. J Res Med Sci 2011; 16(4):469-76.
34. Lind T, Lönnerdal B, Stenlund H, Gamayanti IL, Ismail D, Seswandhana R, et al. A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: effects on growth and development. Am J Clin Nutr 2004;80(3):729-36.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Nutrición en el anciano

Micronutrient intake in elderly living in nursing homes

Ingesta de micronutrientes en ancianos residentes en instituciones de larga permanencia

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Abstract

Objective: The aim of this study was to evaluate the ingestion of micronutrients in elderly living in nursing homes.

Methods: This is a cross-sectional study, conducted with 216 individuals of both sexes, age equal or greater than 60 years, living in nursing homes for elderly in Salvador, Bahia, Brazil. Direct weighing of the food was used to get food intake, and prevalence of inadequacy was obtained using the software Multiple Source Method (MSM) and evaluated by estimated average requirement (EAR).

Results: A high prevalence of inadequate intake of micronutrients was observed, being over 90% for vitamins E, folate, pyridoxine and calcium, in both sexes and between 50 and 70% for selenium, retinol, riboflavin, cyanocobalamin and vitamin C.

Conclusion: The high prevalence of inadequate intake of micronutrients in elderly living on nursing homes observed in this study may be used for planning public health strategies aiming to improve the nutritional context of this population and their quality of life, reducing the costs of health care.

Key words:

Elderly. Nursing homes. Food intake. Micronutrients.

Resumen

Objetivo: el objetivo de este estudio fue evaluar la ingesta de micronutrientes en ancianos residentes en instituciones de larga permanencia.

Métodos: se trata de un estudio transversal, realizado con 216 individuos de ambos sexos, con edad igual o superior a 60 años y residentes en instituciones de larga permanencia en la ciudad de Salvador, Bahia, Brasil. Para la evaluación del consumo alimentario se utilizó el pesaje directo del alimento y la comparación con los valores de referencia del requerimiento promedio estimado (RPE). La prevalencia de ingesta inadecuada fue obtenida a través del software Multiple Source Method (MSM).

Resultados: se observó una alta prevalencia de ingesta inadecuada de micronutrientes por encima de 90% para las vitaminas E, folato, piridoxina y calcio, en ambos sexos, y entre el 50% y el 70% para selenio, retinol, riboflavina, cianocobalamina y vitamina C.

Conclusión: la elevada prevalencia de ingesta inadecuada de micronutrientes en los ancianos residentes en instituciones de larga permanencia observada en este estudio puede ser utilizada para la planificación de estrategias en salud pública, con el objetivo de mejorar la situación nutricional de esta población y su calidad de vida, reduciendo los costes derivados de la asistencia sanitaria.

Palabras clave:

Ancianos. Residencias para la tercera edad. Ingesta alimentaria. Micronutrientes.

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INTRODUCTION

Elderly living in nursing homes (NHs) seem to be more vulnerable to specific nutritional deficiencies, since these institutions may have many factors influencing over their alimentation. Namely, the process of institutionalization itself can influence dietary acceptance (1). Besides, the lack of individual nutritional recommendations, the lack of a team specialized in nutritional care and attention, as well as the inadequacy of a physical structure and human resources in many unities of food and nutrition of NHs may render those institutions into a proper environment for food insecurity on the resident population of elderly (2,3).

The concern with food insecurity in NHs is of importance, considering that the elderly, specially, constitute a population group more vulnerable to nutritional deficiencies of micronutrients by means of several variables, such as morphophysiological changes, presence of chronic diseases and psychosocial influences (4-6).

Investigations performed aiming to evaluate the ingestion of micronutrients in elderly and, mainly, on those living in NHs are scarce on the scientific literature. Risk of vitamins and minerals deficiencies, such as B vitamins, vitamins C and D and minerals such as calcium, zinc and magnesium, have been reported by few studies involving elderly on Brazilian ILPs (7-9). Deficiencies of micronutrients are associated with important health problems in elderly, such as the increase of risk for cardiovascular diseases (CVD), more predisposition to weight loss, especially the reduction of muscular mass and strength, and lower tolerance to support chronic or infectious pathological processes (10,11).

In face of the demographic context characterized by the increasing population aging and the new challenges that are being installed on the field of nutritional research coming from that reality, the need for studies in this area becomes relevant. Thus, the aim of this study was to evaluate the ingestion of micronutrients in elderly living in NHs on the city of Salvador-Bahia, Brazil.

METHODS

This is a cross-sectional study of population base, performed in the city of Salvador-BA, with individuals from both sexes aged 60 or more years and living in public and private NHs, at the urban part of the city.

SAMPLING

The ingestion of micronutrients by 216 institutionalized elderly was evaluated. They were randomly selected from 29 NHs located in ten sanitary districts on the city of Salvador/Ba. In order to perform the intrapersonal variance of consumption and adjustment of nutrients distribution, two dietary measurements were made with an interval of three months between them. The first dietary measurement was made considering all the elderly in the study. For performing the second measurement, the sample was determined considering 40% of the elderly that participated in the initial food intake (n = 216), with a margin of error of 5%. Elderly using enteral, parenteral nutrition and/or specific diet for some medical procedure were not included in the study.

DATA COLLECTION

Food intake data were collected by trainees of nutrition and nutritionist using the total direct food weighing method, with subsequent weighing of the remains. The collection of dietetic measurements was performed considering one day of food intake for each elderly randomly selected to take part in the study. The selected elderly had no previous knowledge about the evaluation. Thus, the collection covered all days of the week (from Monday until Friday) and, mandatorily, one day of the weekend. Food weighing was performed with a portable digital electronic scale Low Range-MBL 2000 BEL, with capacity for 2.0 kg and sensibility of 0.5 grams. Liquids were measured with measuring cylinders of polyethylene with capacities for 500 ml and 100 ml and graduation intervals of 5 ml and 1 ml.

ETHICAL ASPECTS

This project was approved by the Committee of Ethics of the School of Nutrition (CEPNUT) of the Universidade Federal da Bahia, recorded with number 11/2012. After authorization from the NHs by their respective directors or management responsible, the participation of the elderly was voluntary, by signature or fingerprint on the term of informed consent. All data were returned for the institutions by reports and the elderly identified in situations of severe health were forwarded for specialized clinics.

DATA ANALYSIS

Data of individual food intake obtained by the direct food weighing method were calculated with the DietPro version 4.0 software. Foods and preparations which were not in the program were added using nutritional information from the tables of nutritional composition of the aliments, specific for the Brazilian population (12). Without information about those preparations in the tables, standard recipes were used, besides using the labels of the food. Posteriorly, data were added to the program Statistical Package for the Social Science (SPSS), version 16.0 for statistical analyses. In order to estimate the distribution of the usual intake of the elderly and, subsequently, the prevalence of the inadequacy of micronutrients consumption, the software Multiple Source Method (MSM) was used, developed by the European Prospective Investigation Cancer and Nutrition (EPIC), due to its capacity in estimating the usual intake of nutrients, foods and groups of aliments, eliminating the intrapersonal variance of consumption. Besides, this method enables to estimate the usual intake both at the population and individual levels (13,14). The prevalence of

inadequacy of micronutrients was calculated as the percentage of individuals with intake under the estimated average requirement (EAR) value, in other words, with an intake below the estimated average need of the nutrient for each sex, allowing to estimate the percentage of population under risk of adverse health effects (15).

RESULTS

Figure 1 shows the prevalence of inadequacy of micronutrients intake of the elderly (≥ 60 years) living in NHs. High prevalences of inadequate intake of vitamin E (100%), folate (98.6%), pyridoxine (90.7%) and calcium (91.7%) are highlighted. Prevalence of inadequate intake near 80% was observed for ingestion of zinc. The elderly had inadequate ingestion of thiamine, around 66%. Inadequate intakes under 50% were observed for micronutrients selenium, retinol, riboflavin, cyanocobalamin and vitamin C.

Data of vitamin and mineral intake for male elderly are expressed in table I in values of means and percentages. High prevalences of inadequacy (over 90%) were observed for vitamin E, B vitamins such as folate and pyridoxine, as well as for calcium (only of elderly males over 70 years of age).

Elderly males with ages between 51 and 70 years had prevalence of inadequacy for calcium intake. Prevalences of inadequacy of intake under 50% were observed for micronutrients retinol (vitamin A), riboflavin (vitamin B2), vitamin C and cyanocobalamin (vitamin B12).

Values of vitamin and mineral intake for the population of female elderly are expressed in table II. High prevalences of inadequacy were observed, over 90% for vitamin E, folate, pyridoxine and calcium. Prevalences of inadequacy were between 50 and 75% when considering thiamine and zinc. Elderly still have inadequacy of selenium and riboflavin intake, with prevalence values near 50%. It is noteworthy that for nutrients retinal, vitamin C and cyanocobalamin prevalences of inadequacy between 25 and 50% were observed by means of the percentile values.

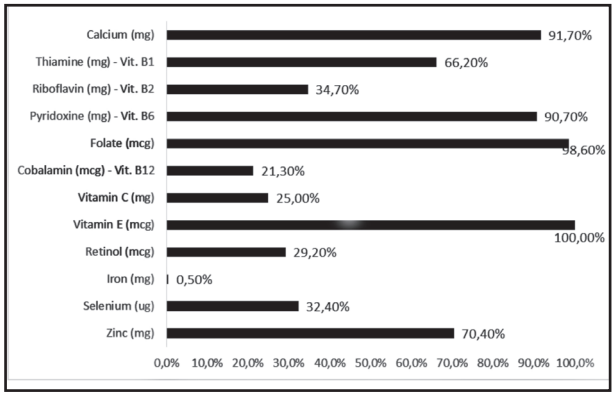

Figure 1.

Prevalence of inadequate intake of micronutrients from the general population of elderly living in nursing homes in Salvador, Bahia, Brazil (n = 216).

DISCUSSION

Nutritional deficiencies do not express clinical manifestations during their initial stages, thus individuals may have deficits of nutrient intake without, however, developing immediate manifestation of clinical signs. In this context, early knowledge of the deficits of micronutrients intake may contribute to preventing severe deficiencies.

A positive aspect of this work is the use of two dietary measurements of dietary survey, a criterion that allows to reduce the biases and effects of the variations of individual intake, bringing better results regarding the knowledge of the participants' usual intake. Besides, it is noteworthy that the method of food investigation used in this study, that is, direct food weighing, allows to know more safely the food being consumed by the public being studied. In addition, by means of the direct food weighing method food intake and remains can be recorded and the portion consumed by the individual can be estimated more accurately, thus improving the reliability of the investigation. It is worth considering that direct weighing has been recommended in the validation of other methods of food survey for epidemiological studies (16).

The high prevalence of dietary inadequacy and the risk of micronutrient deficiencies in institutionalized elderly population has been confirmed by some exploratory studies (2,6,7). This study showed high results of the prevalence of inadequacy of micronutrients intake, mainly for vitamins E, B6, B9 and for calcium, corroborating the trend found in the literature in other investigations where the ingestion of those, and also of other nutrients, was below the recommendation for age and sex in elderly living in NHs (6,7,17). In the study by Fisberg et al. (2013), based on data from the Research of Family Budget (RFB 2008-2009), the prevalence of inadequacy in the diet of non-institutionalized Brazilian elderly was similar to the one found in this study (more than 50% for vitamins A, D and E, calcium, magnesium and pyridoxine) (18).

Berner et al. (2002), evaluating a group of 50 elderly living in one NH, observed ingestion below the recommendation for calcium, magnesium, zinc, copper, vitamins D and E, thiamine, folic acid and vitamin B6 (17). Posteriorly, Wendland et al. (2003), who studied another group of elderly living in three NHs, found risk of deficiency for calcium, B vitamins, thiamine, riboflavin and niacin, using the 24-hour recall as the food survey method (2). Another cross-sectional study performed by De Lima et al. (2012) with 55 elderly living in one NH located in Belo Horizonte, Minas Gerais, revealed significantly insufficient ingestion of zinc (82.7%) and niacin (65.4%) (7). There are not many researches performed in a multicenter character; however, the result of a cross-sectional study recently performed by Iuliano et al. (2013) in 18 institutions found inadequate ingestion under the recommendation for calcium, zinc and folate for both sexes, such as the ones observed in our study (19).

Scientific literature, by means of clinical and experimental studies, shows that B vitamins perform important functions regarding energy metabolism, anabolism and cognitive function, being essential for maintaining the health of the elderly (20).

Table I. Means and percentiles of vitamin and mineral intakes in male elderly living in nursing homes in Salvador, Bahia, Brazil

Micronutrients	Nutritional recommendation	Mean	CI (95%)	p10	p25	p50	p75	p90	PI (%)
Retinol (UI)	625	974.45	(767.29-1,181.6)	335.82	464.44	827.49	1,230.3	1,726.8	27
Thiamine (mg)	1	1.04	(0.98-1.1)	0.81	0.87	1.03	1.16	1.36	44
Riboflavin (mg)	1.1	1.29	(0.16-1.42)	0.75	1.02	1.25	1.44	1.92	25
Pyridoxine (mg)	1.4	0.99	(0.92-1.07)	0.6	0.8	0.93	1.16	1.49	90
Folate (mcg)	320	153.66	(137.19-170.13)	66.9	99.83	158.88	199.57	242.08	98
Cobalamin (mcg)	2	3.19	(2.55-3.84)	1.66	2.19	2.7	3.95	4.85	17
Vitamin C (mg)	75	175.4	(113.58-237.21)	24.49	54.07	114.83	227.9	340.57	32
Vitamin E (mg)	12	5.29	(5.0-5.58)	3.84	4.7	5.31	6.02	6.49	100
Calcium (mg)**	800	728.92	(627.53-830.32)	444.83	532.9	734.75	824.35	1,104.4	65
Calcium (mg)***	1,000	705.41	(626.39-784.44)	396.75	544.15	726.7	840.44	960.07	97
Iron (mg)	6	12.52	(11.9-13.14)	9.87	11.14	12.29	13.68	15.27	0
Selenium (mcg)	45	70.59	(65.9-75.28)	41	59.65	73.36	84.48	91.95	12
Zinc (mg)	9.4	8.44	(7.9-8.99)	5.59	7.05	8.23	9.78	11.42	68

**According to the estimated average requirement (EAR) values, IOM (2000). **Ages reference value 51-70 years. ***Age reference value over 70 years. PI: inadequacy prevalence (%); CI: 95%; n = 59.*

Table II. Means and percentiles of vitamin and mineral intakes in female elderly living in nursing homes in Salvador, Bahia, Brazil

Micronutrients	Nutritional recommendation	Mean	CI (95%)	p10	p25	p50	p75	p90	PI (%)
Retinol (UI)	500	1,129.9	(992.8-1,266.9)	285.2	465	959.4	1,481	2,156	27
Thiamine (mg)	0.9	0.77	(0.74-0.81)	0.5	0.63	0.78	0.9	1.04	75
Riboflavin (mg)	1.1	1.05	(0.98-1.11)	0.57	0.79	1.02	1.26	1.54	38
Piridoxine (mg)	1.4	0.87	(0.82-0.91)	0.53	0.68	0.84	1.05	1.29	91
Folate (mcg)	320	80.4	(119.4-114.6)	55.6	78.6	114.4	168.5	227.9	98.7
Cobalamin (mcg)	2	3.12	(2.7-3.55)	1.47	2.07	2.61	3.42	4.36	23
Vitamina C (mg)	60	158.59	(132.42-185.35)	40.9	64.52	94.4	168.22	444.66	22
Vitamin E (mg)	12	4.04	(3.87-4.22)	2.75	3.27	3.8	4.75	5.43	100
Calcium (mg)	1,000	615.36	(578.8-651.9)	325.11	434.47	597.87	772.29	923.71	94
Iron (mg)	5	9.7	(9.33-10.06)	6.94	8.13	9.28	11.11	12.63	0.6
Selenium (mcg)	45	50.8	(47.95-53.64)	29.19	38.85	49.12	60.02	77.06	40
Zinc (mg)	6.8	6.16	(5.85-6.46)	3.98	4.86	5.81	7.19	8.78	72

**According to the estimated average requirement (EAR) values, IOM (2000). PI: inadequacy prevalence (%); CI: 95%; n = 157.*

Serum deficiencies of folic acid and cyanocobalamin are proven to be associated with the rise of homocysteine levels, a relevant marker of vascular lesion and predictor of cardiovascular diseases (21,22). Also, several studies on the elderly have shown the relationship between pyridoxine, folate and cyanocobalamin deficiencies with a high risk of neurodegenerative diseases, with Alzheimer's dementia and depression among them (23-25).

Several studies have evidenced the low ingestion of calcium on the elderly population and the repercussions of this deficit, which are associated with higher risks of falls and fractures, as well as diseases of inflammatory condition such as osteoporosis and osteopenia, relevant on the elderly population (26,27). The low consumption of calcium, associated with a low efficiency of its absorption, condition precipitated by achlorhydria, which is common on senile individuals, may contribute to the reduction

of the reserves of this mineral, precipitating bone diseases (28). Other metabolic factors are important for maintaining bone health. One of them has stood out during the last years due to its relevance: the normal circulating levels of 1.25 dihydroxy D vitamin, a hormone involved in the proper absorption and metabolism of calcium (29).

Calcium is a micronutrient of special relevance in the elderly, since it also has importance over the activation of cellular proteins, namely, troponin C (which regulates muscular contraction), protein kinase C (acting on the bonding of hormones with cellular proteins), as well as digestive enzymes, required for the digestion of carbohydrates, and lipids (alpha-amylase and lipase), being fundamental for the proper digestion in elderly, a factor already affected by the morphophysiological alterations common to the natural aging (30).

Corroborating the result found in this research, other studies reveal deficits in relation to the intake of antioxidant micronutrients in institutionalized elderly (3,7,8,17,19). Antioxidant micronutrients, such as vitamins A and C, zinc and selenium, are particularly important since individuals have a physiological condition at senescence characterized by an increase in the production of reactive species of the oxidative metabolism (RSOM), associated with a reduction of the antioxidant defense systems propitiating an environment of oxidative stress (10,31-33). This conditions seems to contribute to the occurrence of neurological damage, risk of dementia, depression and chronic diseases associated with aging, among them diabetes mellitus, hypertension, dyslipidemia and atherosclerosis (34).

Thus, in a special way, antioxidants have also been considered as possible mediators of sarcopenia given the catabolic effect that the oxidative stress exerts on the skeletal muscle (35). Few studies are available when the objective is to relate antioxidants consumption and sarcopenia. However, a study conducted by Samba et al. (2007), in a group of non-institutionalized elderly, showed that smaller plasma concentrations of carotenoids and vitamin E were associated with less force on hips and knees (11). Similarly, a cross-sectional study of more than 1,000 residents in the elderly community identified that the serum concentration of serum magnesium was significantly associated with improvement rates of muscle strength (36). In addition, another study aimed to verify the association between ingestion of micronutrients and muscle strength showed that nutrients with selenium, beta-carotene and vitamin C were positively associated with handgrip strength (37).

In this context, it is highlighted that other nutrients such as iron, magnesium, phosphorus and zinc are directly associated in the multifactorial dynamic of muscle anabolism, either by directly participating in the formation of muscle mass, or by contributing to the normal activity of anabolic hormones, ensuring muscle health (38-40).

It is worth to consider that this study has methodological characteristics that must be weighted. The method of analyzing the adequacy of micronutrients intake uses EAR, model based on the average need of nutrient estimated for populations. Besides, the lack of food composition tables estimating the intake of micronutrients such as magnesium and of microelements such as copper, chromium, manganese, boron, molybdenum and vanadium may mask more specific and equally important nutritional deficiencies, considering that such nutrients are fundamental on the homeostatic regulation.

CONCLUSION

In face of the information exposed, the conclusion is that there is a high prevalence of inadequacy regarding vitamin E, folate, pyridoxine and calcium intake in elderly population living in nursing homes. This emphasizes the importance of new studies with this population, considering that elderly, especially, are a group more vulnerable to nutritional deficiencies of micronutrients, by means of several variables, such as morphophysiological changes (on the processes of mastication, swallowing, digestion, absorption and utilization of nutrients), presence of chronic diseases and influences of social, psychological and emotional character.

Providing the adequate food intake for the elderly in NHs may contribute to ensure that those institutions may warrant quality of life as well as food and nutrition security for those elderly.

REFERENCES

1. Santelle O, Lefevre AMC, Cevato AM. Alimentação institucionalizada e suas representações sociais entre moradores de instituições de longa permanência para idosos em São Paulo, Brasil. Cad Saude Publica 2007;23:3061- 5.
2. Lengyel CO, Whiting SJ, Zello GA. Nutrient inadequacies among elderly residents of long-term care facilities. Can J Diet Pract Res 2008;69(2):82-8. DOI: 10.3148/69.2.2008.82.
3. Wendland BE, Greenwood CE, Weinberg I, Young KW. Malnutrition in institutionalized seniors: The iatrogenic component. J Am Geriatric Soc 2003;51:85-90. DOI: 10.1034/j.1601-5215.2002.51015.x.
4. Albers U, Palacios G, Pedrero-Chamizo R, Meléndez A, Pietrzik K, González-Gross M. La polimedicación en mayores institucionalizados; su efecto sobre los niveles de vitamina B12, folato y homocisteína. Nutr Hosp 2012;27(1):298-302. DOI: 10.3305/nh.2012.27.1.5639.
5. Linjakumpu T, Hartikainen S, Klaukka T, Veijola J, Kivelã SL, Isoaho R. Use of medications and polypharmacy are increasing among the elderly. J Clin Epidemiol 2002;55(8):809-17.
6. Nogués R. Factors that affect nutrient intake in the elderly and condition proper nutrition. Clin Nutr 1995;15(2):39-44.
7. De Andrade FB, Caldas Junior AF, Kitoko PM, Zandonade E. The relationship between nutrient intake, dental status and family cohesion among older Brazilians. Cad Saúde Pública 2011;27(1):113-22.
8. Costa BVL, Fonseca LM, Lopes ACS. Nutritional status and associated factors in institutionalized elderly. J Nutr Disorders Ther 2012;2(3):116. DOI: 10.4172/2161-0509.1000116.
9. Silva AGH, Cozzolino SMF. Cálcio In: Cozzolino SMF. Biodisponibilidade de nutrientes. 2nd ed. São Paulo: Manole; 2007.
10. Gano LB, Donato AJ, Pierce GL, Pasha HM, Magerko KA, Roeca C, et al. Increased proinflammatory and oxidant gene expression in circulating mononuclear cells in older adults: Amelioration by habitual exercise. Physiol Genomics 2011;43(14):895-902. DOI: 10.1152/physiolgenomics.00204.2010.
11. Semba RD, Lauretani F, Ferrucci L. Carotenoids as protection against sarcopenia in older adults. Arch Biochem Biophys 2007;458(2):141-5. DOI: 10.1016/j.abb.2006.11.025.
12. Philippi ST. Tabela de Composição de Alimentos: Suporte para Decisão Nutricional. 2nd ed. São Paulo: Coronário; 2002.
13. Harttig U, Haubrock J, Knüppel S, Boeing H, EFCOVAL Consortium. The MSM program: The web-based statistics package for estimating usual dietary

intake using the Multiple Source Method. Eur J Clin Nutr 2011;65(Suppl 1):S87-91. DOI: 10.1038/ejen.2011.92.
14. Haubrock J, Nöthlings U, Volatier JL, Dekkers A, Ocké M, Harttig U, et al. European Food Consumption Validation Consortium. Estimating usual food intake distributions by using the multiple source method in the EPIC-Potsdam Calibration Study. J Nutr 2011;141(5):914-20. DOI: 10.3945/jn.109.120394.
15. Institute of Medicine. Food and Nutrition Board. Dietary reference intakes: Energy, carbohydrates, fiber, fat, protein and amino acids (macronutrients). Washington, DC: National Academy; 2005.
16. Nelson M, Bingham SA. Assessment of food consumption and nutrient intake. In: Nelson M, Bingham SA. Design concepts in nutritional epidemiology. New York: Oxford University Press; 1997.
17. Berner YN, Stern F, Polyak Z, Dror Y. Dietary intake analysis in institutionalized elderly: A focus on nutrient density. J Nutr Health Aging 2002;6(4):237-42.
18. Fisberg RM, Marchioni DML, Castro MA, Verly EJ, Araujo MC, Bezerra IN, et al. Inadequate nutrient intake in the elderly population in Brazil: National Survey of Food 2008-2009. Rev Public Health 2013;47(Suppl 1);222S-30S. DOI: 10.1590/S0034-89102013000700008.
19. Iuliano S, Olden A, Woods J. Meeting the nutritional needs of elderly residents in aged care: Are we doing enough? J Nutr Health Aging 2013;17(6):503-8. DOI: 10.1007/s12603-013-0042-7.
20. Clarke R. B-vitamins and prevention of dementia. Proc Nutr Soc 2008;67(1):75-81. DOI: 10.1017/S0029665108006046.
21. Ganguly P, Alam SA. Role of homocysteine in the development of cardiovascular disease. Nutr J 2015;14:6. DOI: 10.1186/1475-2891-14-6.
22. Castro R, Rivera I, Blom HJ, Jakobs C, Tavares de Almeida I. Homocysteine metabolism, hyperhomocysteinemia and vascular disease: An overview. J Inherit Metab Dis 2006;29:3-20. DOI: 10.1007/s10545-006-0106-5.
23. Malouf R, Grimley Evans J. Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. Cochrane Database Syst Rev 2008;8(4):CD004514. DOI: 10.1002/14651858.CD004514.
24. Malouf R, Grimley Evans J. The effect of vitamin B6 on cognition. Cochrane Database Syst Rev 2009;(4):CD004393. DOI: 10.1002/14651858.CD004393
25. Clarke R, Birks J, Nexo E, Ueland PM, Schneede J, Scott J, et al. Low vitamin B-12 status and risk of cognitive decline in older adults. Am J Clin Nutr 2007;86(5):1384-91.
26. Iwamoto J, Sato Y, Takeda T, Matsumoto H. High-dose vitamin K supplementation reduces fracture incidence in postmenopausal women: A review of the literature. Nutr Res 2009;29(4):221-8. DOI: 10.1016/j.nutres.2009.03.012.
27. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: A meta-analysis. Lancet 2007;370(9588):657-66. DOI: 10.1016/S0140-6736(07)61342-7.
28. Gennari C. Calcium and vitamin D nutrition and bone disease of the elderly. Public Health Nutr 2001;4(2B):547-59.
29. Weaver C, Heaney R. Food sources, supplements, and bioavailability. In: Calcium in Human Health. Weaver C, Heaney R, eds. Totowa, NJ: Humana Press; 2006. pp. 129-44.
30. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, et al. Effect of vitamin D on falls: A meta-analysis. JAMA 2004;291(16):1999-2006. DOI: 10.1001/jama.291.16.1999.
31. Carafoli E, Penniston JT. The calcium signal. Sci Am 1985;253(5):70-8.
32. Mangge H, Becker K, Fuchs D, Gostner JM. Antioxidants, inflammation and cardiovascular disease. World J Cardiol 2014;6(6):462-77. DOI: 10.4330/wjc.v6.i6.462.
33. Liu H, Yang Y, Huang G, Tan S, Liu Y. Positive association of pro-inflammatory biomarkers and increased oxidative stress in the healthy elderly. Arch Gerontol Geriatr 2012;54(2)e8-e12. DOI: 10.1016/j.archger.2011.05.016.
34. Nakamura YK, Read MH, Elias JW, Omaye ST. Oxidation of serum low-density lipoprotein (LDL) and antioxidant status in young and elderly humans. Arch Gerontol Geriatr 2006;42(3):265-76. DOI: 10.1016/j.archger.2005.08.002.
35. Ferrari CK. Functional foods, herbs and nutraceuticals: Towards biochemical mechanisms of healthy aging. Biogerontology 2004;5(5):275-89. DOI: 10.1007/s10522-004-2566-z.
36. Scott D, Blizzard L, Fell J, Giles G, Jones G. Associations between dietary nutrient intake and muscle mass and strength in community-dwelling older adults: The Tasmanian Older Adult Cohort study. J Am Geriatr Soc 2010;58(11):2129-34. DOI: 10.1111/j.1532-5415.2010.03147.x.
37. Domínguez LJ, Barbagallo M, Lauretani F, Bandinelli S, Bos A, Corsi AM, et al. Magnesium and muscle performance in older persons: The InCHIANTI study. Am J Clin Nutr 2006;84(2):419-26.
38. Robinson SM, Jameson KA, Batelaan SF, Martin HJ, Syddall HE, Dennison EM, et al. Diet and its relationship with grip strength in community-dwelling older men and women: The Hertfordshire cohort study. J Am Geriatr Soc 2008;56(1):84-90. DOI: 10.1111/j.1532-5415.2007.01478.x.
39. Pannemans DL, Wagenmakers AJ, Westerterp KR, Shaafsma G, Halliday D. Effect of protein source and quantity on protein metabolism in elderly women. Am J Clin Nutr 1998;68(6):1228-35.
40. Roubenoff R, Castaneda C. Sarcopenia-understanding the dynamics of aging muscle. JAMA 2001;286(10):1230-1.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Nutrición en el anciano

Ingesta de proteína, lípidos séricos y fuerza muscular en ancianos

Protein intake, serum lipids and muscle strenght in the elderly

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Resumen

Introducción: la recomendación diaria de proteína para adultos es de 0,8 g/kg/día. Sin embargo, varios estudios argumentan que una ingesta de 1,0-1,5 g proteína/kg/día podría beneficiar la salud de los ancianos.

Objetivo: evaluamos la ingesta de proteína y los niveles de lípidos séricos en ancianos con fractura de cadera determinando su correlación con la fuerza de prensión en ambas manos.

Métodos: el estudio incluyó a 47 pacientes adultos de 65-85 años hospitalizados por reciente fractura de cadera. Se midió peso, talla, perfil de lípidos y fuerza muscular de ambas manos, y también se aplicó el Mini Nutritional Assessment (MNA) para evaluar el estado de nutrición.

Resultados: de acuerdo al MNA, el 93% de los ancianos estaban malnutridos o en riesgo de malnutrición. Los ancianos eran predominantemente mujeres y con una edad homogénea de 80 años. Los hombres consumieron significativamente más proteína que las mujeres. La fuerza muscular se asoció negativamente con los niveles de triglicéridos (TG) y el 36% de los ancianos tuvieron niveles de triglicéridos superiores a 150 mg/dl.

Conclusiones: los niveles de TG se asociaron inversamente con la fuerza muscular en ancianos con fractura de cadera. Estos resultados, que deberán validarse en otras poblaciones, consideran que los niveles elevados de TG son un factor de síndrome metabólico y se asocian a baja fuerza muscular en ancianos, esto es relevante debido a que la prevención de la obesidad y el síndrome metabólico son una prioridad a través de la promoción de estilos de vida más saludables y políticas de alimentación que podrían implementarse ampliamente.

Palabras clave:

Sarcopenia. Fragilidad. Nutrición del anciano. Ingesta de proteína. Triglicéridos.

Abstract

Introduction: The daily protein recommendation for adults is 0.8 g/kg/day; however, several studies argue that an intake of 1.0-1.5 g protein/kg/day could benefit the health of the elderly.

Objective: We evaluated the protein intake and serum lipid levels in elderly patients with hip fracture, determining their correlation with the grip strength in both hands.

Methods: The study included 47 adult patients aged 65-85 years hospitalized for recent hip fracture. Weight, height, lipid profile and muscle strength of both hands were measured, and MNA was also used to evaluate the nutritional status.

Results: The elderly, predominantly women and with a homogeneous age of 80 years on average, were malnourished or at risk of malnutrition in 93% of cases according to the MNA. Men consumed significantly more protein than women. Muscle strength negatively associated with triglyceride levels; 36% of the elderly had triglyceride levels above 150 mg/dl.

Conclusions: TG levels associated inversely with muscle strength in elderly patients with hip fracture. According to these results, which should be validated in other populations, elevated TG levels are a factor of metabolic syndrome and are associated with low muscle strength in the elderly. This is relevant because obesity prevention and metabolic syndrome are one priority through the promotion of healthier lifestyles and nutrition policies that could be widely implemented.

Key words:

Sarcopenia. Fragility. Elderly nutrition. Protein intake. Triglycerides.

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INTRODUCCIÓN

Durante el envejecimiento se pierde masa muscular de manera gradual y progresiva (1-3). Dependiendo de los criterios diagnósticos, esta disminución de masa muscular conocida como sarcopenia se estima que ocurre entre el 5% y el 45% de los ancianos (2,4,5). La sarcopenia es un síndrome geriátrico multifactorial que se asocia a fracturas, discapacidad física y otras comorbilidades (6,7). Su tratamiento combina actividad física y alimentación (8,9). La actividad física se asocia con mayor masa muscular, previniendo fragilidad y disfunción; la sarcopenia ha sido ampliamente observada en ancianos sedentarios (10-12). Además, se ha descrito disminución en la tasa metabólica secundaria a la disminución de actividad física y de la masa libre de grasa, incrementando la prevalencia de resistencia a la insulina, diabetes mellitus tipo 2, dislipidemia e hipertensión (13). Una alimentación adecuada en energía y, especialmente, en proteína ayuda a tratar la disminución de la masa muscular, fuerza y habilidades funcionales relacionadas con la edad (9). En ancianos, la malnutrición conduce a un balance negativo de nitrógeno y, finalmente, a fragilidad y sarcopenia, condiciones que resultan en discapacidad, y eventualmente en pérdida de independencia, caídas, fracturas y muerte (9,14).

Los ancianos, en general, necesitan más proteína en la dieta que los adultos jóvenes; sin embargo, los ancianos usualmente comen menos alimento, incluida menos proteína (14). Esto es relevante, ya que en mexicanos hospitalizados se ha identificado que un nivel de albúmina de 3,1 g/dl o mayor se asocia con una evolución satisfactoria intrahospitalaria (15). Aunque la cantidad diaria recomendada de proteína es de 0,8 g/kg/d para adultos de todas las edades (16), varios estudios (Protein Summit 2.0, PROT-AGE, New Nordic Nutrition Recommendations) argumentan que la ingesta de proteína de 1,0-1,5 g/kg/día podría beneficiar la salud de los ancianos (8,9,14,16). En general, la recomendación de proteína dietética sería del 15-20% de las calorías totales de la dieta para ancianos sanos. Se sabe que incrementar la proteína en la dieta mantiene músculos saludables en los ancianos, y por ello las recomendaciones para el consumo de proteína deberían estar bien dirigidas. Por ejemplo, se recomienda lograr un umbral de proteína de 25-30 g en cada una de las tres principales comidas (desayuno, comida, cena) (14). Por otro lado, muchos ancianos desayunan alimentos ricos en hidratos de carbono y bajos en proteína, lo que favorece aún más la dislipidemia en este grupo de edad (14). Otra recomendación está basada en el consumo de carne, y se sugiere consumir 113 g de carne (220 kcal; 30 g de proteínas) cinco veces a la semana (17). En este estudio evaluamos la ingesta de proteína y los niveles de lípidos séricos en ancianos con fractura de cadera y determinamos su correlación con la fuerza de prensión en ambas manos.

MATERIALES Y MÉTODOS

El estudio incluyó 47 pacientes adultos de 65-85 años hospitalizados en la Unidad Médica de Alta Especialidad No. 1 (UMAE1) por reciente fractura de cadera (menos de una semana y aún sin intervención quirúrgica), los cuales firmaron el consentimiento informado. Se determinó peso y talla de los pacientes, se midió la fuerza muscular de ambas manos, se aplicó el MNA (18) para evaluar el estado de nutrición y se recabó información del consumo de alimentos ricos en proteína. Además, se tomaron muestras sanguíneas por venopunción previo ayuno de ocho horas para determinar perfil de lípidos (colesterol total, triglicéridos, colesterol LDL, HDL y VLDL), biometría hemática y pruebas de función hepática.

Para la inferencia del peso corporal se utilizó la fórmula de Jung (19,20): peso en hombres (kg) = altura talón-rodilla x 1,10 + circunferencia de brazo (cm) x 3,07 - 75,81, y peso en mujeres (kg) = altura talón-rodilla x 1,09 + circunferencia de brazo (cm) x 2,68 – 65,51; predicción de la talla (cm) = 2 x media brazada (cm). La media brazada se determinó con el paciente con el brazo extendido y con cinta métrica se midió la distancia desde la punta del dedo medio hasta la parte central de la escotadura del esternón a la altura de la tráquea. Para la circunferencia de brazo se identificó el punto medio existente entre la saliente ósea del acromion y el olecranon, a lo largo de la lateral del brazo no dominante, con el codo flexionado a 90°. Una vez identificado el punto medio, se dejó caer el brazo de manera natural y se colocó la cinta horizontalmente alrededor del punto indicado. Después, para la obtención de la altura talón-rodilla, se midió la distancia entre el talón y la parte más alta de la articulación de la rodilla, por la parte lateral externa, con la pierna flexionada en el individuo acostado y formando un ángulo de 90° entre el muslo y la pantorrilla.

La fuerza muscular de prensión de ambas manos se evaluó con un dinamómetro marca TAKEI modelo SMEDLEY III T-18A. La prueba se efectuó manteniendo al paciente sentado y confortable con los hombros aducidos y sin rotaciones, el brazo y codo pegados al tronco, este último en flexión de 90° con antebrazo y muñeca en posición neutra, con la manilla del dinamómetro tomada con garra cilíndrica por parte del paciente y la pantalla del indicador digital mirando hacia el evaluador. Se le indicó a cada paciente que debía realizar una empuñadura con la máxima fuerza posible mediante un impulso rápido pero continuado hasta alcanzar la máxima potencia. De esta manera se realizaron dos medidas sucesivas para cada mano, esperando al menos 60 segundos entre dos mediciones sucesivas para la misma mano a fin de evitar la fatiga muscular, y se promediaron ambas lecturas para el valor de una mano. Posteriormente, también se promediaron los valores de ambas manos. La masa muscular fue estimada por la circunferencia de la pantorrilla (punto de corte 31 cm para ambos géneros).

RESULTADOS

Los ancianos estudiados son pacientes de un hospital público que habían ingresado por fractura de cadera, predominantemente mujeres y con una edad homogénea de 80 años en promedio. Los hombres consumían mayor cantidad de proteínas que las muje-

res, sin que se identificara diferencia en la fuerza muscular entre ellos (Tablas I y II). De acuerdo al MNA, el 93% de los participantes estaban malnutridos o en riesgo de malnutrición.

Los hombres consumieron significativamente más proteína que las mujeres (t45 = 2,021, p-valor = 0,049 para los gramos proteína por kg de peso; t45 = 3,41, p-valor = 0,001 para gramos de proteína totales) (Tabla II). Luego, buscamos asociación del consumo de proteína (gramos de proteína totales y gramos de proteína por kg de peso) y del perfil de lípidos con fuerza muscular, sin observar valores de correlación significativos, solo un valor limítrofe para VLDL colesterol y fuerza muscular (Tabla III). Sin embargo, la fuerza muscular asoció negativamente con los niveles de triglicéridos (r = -0,29, p-valor = 0,04) (Fig. 1). Diecisiete ancianos (36,1%) mostraron niveles de triglicéridos superiores a 150 mg/dl.

Considerando que en pacientes mexicanos hospitalizados se ha identificado que un nivel de albúmina de 3,1 g/dl o mayor se asocia con una evolución satisfactoria intrahospitalaria, se realizó comparación de la fuerza muscular entre estos grupos y se observó que 34 pacientes presentaron niveles de albúmina menor de 3,5 y 13 ≥ 3,1 g/dl, pero la fuerza muscular promedio no fue diferente entre los grupos (11,2 *vs.* 10,8 kg; p = 0,55).

De acuerdo a los grupos de MNA (estado nutricional), se efectuó ANOVA y no se identificó diferencia de la fuerza muscular entre los grupos (F = 0,28; p = 0,75) (Tabla IV).

DISCUSIÓN

La fuerza muscular se asoció negativamente a los niveles de triglicéridos en los ancianos hospitalizados con fractura de cadera. Aunque no evaluamos actividad física, esta podría estar representada en la fuerza muscular y, por tanto, podría explicar por qué quienes tienen menor fuerza muscular tienen mayores niveles de triglicéridos, ya que el ejercicio genera la depuración del colesterol muscular a través del mismo músculo esquelético que en el estado posprandial está repleto de VLDL del plasma (21). Por otra parte, los TG plasmáticos son hidrolizados en ácidos grasos vía lipoproteína lipasa (LPL). La disminución en los niveles

Tabla I. Estadísticas descriptivas de la muestra

Variables	n = 47
Sexo (H/M)	12/35
Edad (años)	80,2 ± 7,4
Peso (kg)	55,6 ± 7,2
Talla (m)	1,58 ± 0,07
IMC (kg/m^2)	22,0 ± 2,8
Estado nutricional normal	3 (6,4)
Riesgo de malnutrición	30 (63,8)
Malnutrición	14 (29,8)
Fuerza muscular izda. (kg)	11,2 ± 2,0
Fuerza muscular dcha. (kg)	12,1 ± 2,0
Promedio de fuerza muscular (kg)	11,6 ± 1,9
Albúmina (g/dl)	2,7 ± 0,59
Ingesta calórica (cal)	1.282 ± 411
Hidratos de carbono (%)	59,3 ± 9,8
Lípidos (%)	25,0 ± 8,9
Proteínas (%)	15,6 ± 3,4
Colesterol (mg)	133,1 (106,4-159,8)
Hb (g/dl)	10,2 ± 2,0
Hto (%)	31,4 ± 6,2
HDL-col (mg/dl)	35,1 (28,1-35,0)
LDL-col (mg/dl)	65,2 (56,7-73,7)
VLDL-col (mg/dl)	26,9 (24,1-29,6)
TG (mg/dl)	134 (120,4-147,7)

Los valores se muestran como medias ± SD o como medianas (rangos) de acuerdo a su distribución normal o sesgada.

Tabla II. Comparación entre hombres y mujeres con respecto a edad, consumo de proteína y fuerza muscular

Variables	Hombres	Mujeres	p
n	12	35	
Edad (años)	81 ± 6,7	79,9 ± 7,6	0,68
Proteína consumida por kg de peso (g/kg)	1,1 ± 0,2	0,8 ± 0,3	0,049
Consumo total de proteína (g)	66,7 ± 19,2	46,4 ± 17,3	0,001
Fuerza muscular (kg)	11,8 ± 1,4	11,6 ± 2,1	0,76

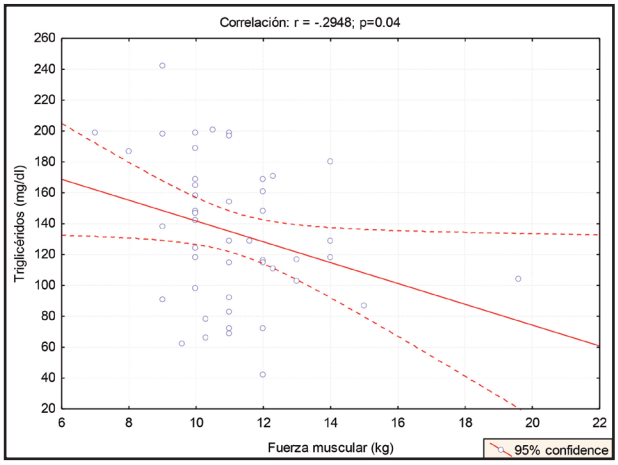

Figura 1.

Correlación de la fuerza muscular con los niveles séricos de triglicéridos.

de VLDL circulantes permite entonces menor competencia por la actividad de LPL, favoreciendo así el incremento en la hidrólisis de TG (21,22). La actividad de la LPL disminuye con la edad, pero el ejercicio puede incrementar esta actividad en el músculo esquelético y disminuir las concentraciones de TG (22).

Por otro lado, el contenido intrahepático de TG puede afectar adversamente la sensibilidad a la insulina aun en personas no diabéticas (23). Un estudio en ancianas japonesas, que implicó un programa de 12 semanas de caminata (120 min/semana), mostró que los cambios en los TG, ácido úrico y glutamiltransferasa (GGT) se asociaron significativamente con cambios en el HOMA-IR, e incluso se observó una asociación sinérgica entre la disminución de TG y ácido úrico y la disminución del HOMA-IR (24). Otro estudio en pacientes con enfermedad obstructiva crónica (EPOC) asoció fuerza muscular con resistencia a la insulina, y se observó que el HOMA2 IR fue mayor en personas con debilidad de cuádriceps que en aquellas sin debilidad. El análisis multivariado evidenció que una unidad de incremento de resistencia a la insulina se asoció con una disminución en la fuerza del cuádriceps y un incremento del riesgo en la debilidad del mismo de 4,2 veces (25).

Para los ancianos, el entrenamiento de fuerza y el consejo nutricional a largo plazo han mostrado efectos favorables en los lípidos séricos y lipoproteínas con disminución en los niveles de colesterol total, LDL-colesterol y triacilgliceroles, así como incremento en los niveles de HDL-colesterol. Asimismo, disminuyen las concentraciones de insulina y las cifras de presión arterial (26).

La Encuesta Nacional de Examen de Salud y Nutrición (NHANES) evaluó a más de 3.000 ancianos y los categorizó de acuerdo a los tertiles de la circunferencia de cintura y fuerza muscular en las piernas como sigue: a) sin dinapenia/sin obesidad abdominal (S-DIN/S-OA); b) con dinapenia/sin obesidad abdominal (C-DIN/S-OA); c) sin dinapenia/con obesidad abdominal (S-DIN/C-OA); y d) con dinapenia/con obesidad abdominal (C-DIN/C-OA). Se observó que el último grupo mostró niveles más bajos de HDL colesterol y más elevados de triglicéridos y glucosa que los grupos S-DIN/S-OA y C-DIN/S-OA. Mayores niveles de TG se observaron en el grupo C-DIN/C-OA comparado con el grupo S-DIN/C-OA. Las probabilidades de tener síndrome metabólico, enfermedades cardiovasculares y diabetes tipo 2 fueron mayores en el grupo C-DIN/C-OA comparado con C-DIN/S-OA y S-DIN/S-OA. Por lo tanto, los ancianos con dinapenia y obesidad abdominal parecen tener mayor riesgo de alteraciones metabólicas que los que muestran dinapenia exclusiva o que aquellos que no muestran ni obesidad abdominal ni dinapenia (27). También se ha demostrado que los ancianos con obesidad y dinapenia muestran menor función física objetiva y subjetiva que los que solo presentan dinapenia u obesidad por separado (28).

Otros marcadores se han asociado con la fuerza muscular y la resistencia a la insulina. En un estudio transversal en adolescentes, se encontró una asociación inversa entre el grado de fuerza muscular y los biomarcadores inflamatorios ajustados para edad, sexo, estado puberal, nivel socioeconómico, adherencia a la dieta mediterránea, función cardiorrespiratoria, grado de riesgo metabólico y grasa corporal. El análisis de covarianza mostró que los adolescentes con un perfil inflamatorio adverso y bajos niveles de fuerza muscular mostraron el más severo grado de factores de riesgo metabólicos (suma de Z-scores de presión arterial sistólica, TG, radio de colesterol total/HDL colesterol, HOMA-IR y circunferencia de cintura). Se considera pues que el estado inflamatorio explica una parte significativa del elevado grado de riesgo metabólico en adolescentes con baja fuerza muscular (29). También, un estudio efectuado en niños hispanos de escuelas de bajos ingresos demostró que niveles elevados de fuerza muscular y resistencia se relacionaron con bajos niveles de riesgo cardiometabólico (consistente de HDL colesterol, TG, circunferencia de cintura, glucosa sanguínea y presión arterial media) al comparar por tertiles de fuerza muscular; por ejemplo, para los tertiles medio y superior la fuerza muscular y la resistencia se asoció con menor score (más favorable) de riesgo metabólico, independientemente de la capacidad aeróbica (30).

Los mediadores biológicos relevantes del síndrome metabólico y el envejecimiento no saludable incluyen obesidad sarcopénica, resistencia a la insulina con acumulación de grasa ectópica, alteraciones del metabolismo del magnesio, inflamación sistémica e hipotalámica, acortamiento de la longitud de los telómeros, epigenética y alteraciones del ritmo circadiano. El síndrome metabólico se relaciona con una mayor acumulación de adiposidad central e

Tabla III. Correlación de la ingesta de proteínas y los niveles de lípidos séricos con la fuerza muscular

	Proteínas (g/kg)	Colesterol total (mg/dl)	HDL-col (mg/dl)	LDL-col (mg/dl)	VLDL-col (mg/dl)
Fuerza muscular (kg)	r = -0,19 p = 0,20	r = 0,18 p = 0,21	r = 0,18 p = 0,22	r = -0,01 p = 0,93	r = -0,27 p = 0,06

Tabla IV. Fuerza muscular en ancianos de acuerdo al estado nutricional

MNA	Estado nutricional normal n = 3	Riesgo de malnutrición n = 30	Malnutrición n = 14
Fuerza muscular (kg)	11,0 ± 2,0	11,8 ± 2,1	11,5 ± 1,6

infiltración de grasa ectópica en el músculo esquelético y el hígado, relacionada con la sobrealimentación y el sedentarismo, con consecuencias perjudiciales en la vida tardía. La obesidad puede complicarse con la sarcopenia, que se refiere a la pérdida de masa muscular, fuerza y calidad en las poblaciones mayores (31).

La dieta de los ancianos debe proporcionar al menos 1,0-1,2 g de proteína/kg de peso corporal/día y 1,2-1,5 g para ancianos con enfermedad. En nuestro estudio, nosotros hipotetizamos que los ancianos consumían menos de 1,0 g de proteína/kg de peso corporal/día y que la ingesta de proteínas se asociaba con la fuerza muscular. El consumo promedio de proteína fue de 0,9 g de proteína/kg de peso corporal/día y las mujeres consumieron significativamente menos proteína (0,8 g) que los hombres (1,1 g). Sin embargo, no encontramos asociación entre ingesta de proteína y la fuerza de presión de las manos. En este estudio no incluimos un grupo control sin fractura de cadera, pero de acuerdo a la literatura en adultos mayores tanto del área rural como del área urbana de bajos recursos en México, a las que pertenecían nuestros pacientes, tienen un consumo semejante del 15% de proteínas (32). Con respecto a parámetros comparativos de la fuerza muscular, no existen tablas de valores para nuestra población. Un estudio con escaso número de adultos mayores mexicanos reportó fuerza muscular de prensión de 24,3 kg, pero no se describe la metodología (33). Con respecto a tablas de población española (34) en población ≥ 80 años, el promedio de fuerza muscular es de 17,8 kg para los hombres y de 9,7 kg para las mujeres, lo que parece muy diferente para hombres pero no para mujeres en nuestro estudio.

Un objetivo de futuros estudios podría ser identificar el tipo y la cantidad óptima de proteína y/o aminoácidos específicos para ancianos ya que una amplia gama de factores pueden afectar la cantidad de proteína dietética necesaria. Existen varias razones por las cuales los ancianos no consumen suficiente proteína para satisfacer necesidades como la predisposición genética al bajo apetito, los cambios fisiológicos y las condiciones médicas que llevan a la anorexia asociada con la enfermedad, las discapacidades físicas y mentales que limitan la preparación de alimentos y la inseguridad alimentaria debido a limitaciones financieras y sociales.

Nosotros concluimos que los niveles de TG se asociaron de forma inversa con la fuerza muscular en ancianos con fractura de cadera y esto tiene relevancia debido a que los niveles de TG mayores de 150 mg son un factor del síndrome metabólico. Estos resultados, que deberán validarse en otras poblaciones, muestran que los niveles elevados de TG se asocian a baja fuerza muscular en ancianos, lo cual es relevante debido a que la prevención de la obesidad y el síndrome metabólico es una prioridad a través de la promoción de estilos de vida más saludables y políticas de alimentación que podrían implementarse ampliamente.

BIBLIOGRAFÍA

1. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol 1998;147(8):755-63.
2. Abellan van Kan G. Epidemiology and consequences of sarcopenia. J Nutr Health Aging 2009;13(8):708-12.
3. Chávez-Moreno DV, Infante-Sierra H, Serralde-Zuniga AE. Sarcopenia and functionality in elderly inpatient. Nutr Hosp 2015;31(4):1660-6.
4. Cesari M, Pahor M, Lauretani F, Zamboni V, Bandinelli S, Bernabei R, et al. Skeletal muscle and mortality results from the InCHIANTI Study. J Gerontol A Biol Sci Med Sci 2009;64(3):377-84.
5. Newman AB, Kupelian V, Visser M, Simonsick EM, Goodpaster BH, Kritchevsky SB, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. J Gerontol A Biol Sci Med Sci 2006;61(1):72-7.
6. Almeida Dos Santos AD, Sabino Pinho CP, Santos do Nascimento AC, Oliveira Costa AC. Sarcopenia en pacientes ancianos atendidos ambulatoriamente: prevalencia y factores asociados Nutr Hosp 2016;33(2):100.
7. Cuerda C, Álvarez J, Ramos P, Abanades JC, Garcia-de-Lorenzo A, Gil P, et al. Prevalencia de desnutrición en sujetos mayores de 65 años en la Comunidad de Madrid. Estudio DREAM + 65. Nutr Hosp 2016;33(2):101.
8. Palop Montoro MV, Parraga Montilla JA, Lozano Aguilera E, Arteaga Checa M. Sarcopenia intervention with progressive resistance training and protein nutritional supplements. Nutr Hosp 2015;31(4):1481-90.
9. Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, et al. Protein intake and exercise for optimal muscle function with aging: Recommendations from the ESPEN Expert Group. Clin Nutr (Edinburgh, Scotland) 2014;33(6):929-36.
10. Klee Oehlschlaeger MH, Alberici Pastore C, Schuler Cavalli A, González MC. Nutritional status, muscle mass and strength of elderly in southern Brazil. Nutr Hosp 2014;31(1):363-70.
11. Snead DB, Stubbs CC, Weltman JY, Evans WS, Veldhuis JD, Rogol AD, et al. Dietary patterns, eating behaviors, and bone mineral density in women runners. Am J Clin Nutr 1992;56(4):705-11.
12. Carrasco Poyatos M, Navarro Sánchez MD, Martínez González-Moro I, Reche Orenes D. Daily physical activity impact in old women bone density and grip strength. Nutr Hosp 2016;33(6):1305-11.
13. Karakelides H, Nair KS. Sarcopenia of aging and its metabolic impact. Curr Top Dev Biol 2005;68:123-48.
14. Paddon-Jones D, Campbell WW, Jacques PF, Kritchevsky SB, Moore LL, Rodríguez NR, et al. Protein and healthy aging. Am J Clin Nutr 2015;pii: ajcn084061.
15. García-Salcedo JJ, Recio-Vega R, Serrano-Gallardo LB, Calderón-Salinas V. Homeostasis model assessment in elderly adults without diabetes mellitus. J Am Geriatr Soc 2013;61(7):1228-9.
16. Nowson C, O'Connell S. Protein requirements and recommendations for older people: A review. Nutrients 2015;7(8):6874-99.
17. Rondanelli M, Perna S, Faliva MA, Peroni G, Infantino V, Pozzi R. Novel insights on intake of meat and prevention of sarcopenia: All reasons for an adequate consumption. Nutr Hosp 2015;32(5):2136-43.
18. Izaola O, De Luis Roman DA, Cabezas G, Rojo S, Cuellar L, Terroba MC, et al. Mini Nutritional Assessment (MNA) test as a tool of nutritional evaluation in hospitalized patients. An Med Interna 2005;22(7):313-6.
19. H Reyes-Morales SV, JJ García-González, A Espinosa-Aguilar, R Jiménez-Uribe, A Peña Valdovinos, VM Mendoza-Núñez. Guía para la evaluación gerontológica integral. Rev Med Inst Mex Seguro Soc 2009;47(3):291-306.
20. R Lee DN. Nutritional assessment. 4ª ed. Nueva York: McGraw-Hill; 2007.
21. Maraki MI, Sidossis LS. The latest on the effect of prior exercise on postprandial lipaemia. Sports Med (Auckland, NZ) 2013;43(6):463-81.
22. Katsanos CS. Prescribing aerobic exercise for the regulation of postprandial lipid metabolism: Current research and recommendations. Sports Med (Auckland, NZ) 2006;36(7):547-60.
23. Hwang JH, Stein DT, Barzilai N, Cui MH, Tonelli J, Kishore P, et al. Increased intrahepatic triglyceride is associated with peripheral insulin resistance: In vivo MR imaging and spectroscopy studies. Am J Physiol Endocrinol Metab 2007;293(6):E1663-9.
24. Kawamoto R, Katoh T, Ninomiya D, Kumagi T, Abe M, Kohara K. Synergistic association of changes in serum uric acid and triglycerides with changes in insulin resistance after walking exercise in community-dwelling older women. Endocr Res 2016;41(2):116-23.
25. Wells CE, Polkey MI, Baker EH. Insulin resistance is associated with skeletal muscle weakness in COPD. Respirology (Carlton, Vic) 2016;21(4):689-96.
26. Sallinen J, Fogelholm M, Pakarinen A, Juvonen T, Volek JS, Kraemer WJ, et al. Effects of strength training and nutritional counseling on metabolic health indicators in aging women. Can J Appl Physiol 2005;30(6):690-707.
27. Senechal M, Dionne IJ, Brochu M. Dynapenic abdominal obesity and metabolic risk factors in adults 50 years of age and older. J Aging Health 2012;24(5):812-26.

28. Bouchard DR, Janssen I. Dynapenic-obesity and physical function in older adults. J Gerontol A Biol Sci Med Sci 2010;65(1):71-7.
29. Agostinis-Sobrinho CA, Moreira C, Abreu S, Lopes L, Sardinha LB, Oliveira-Santos J, et al. Muscular fitness and metabolic and inflammatory biomarkers in adolescents: Results from LabMed Physical Activity Study. Scand J Med Sci Sports 2017;7(12):1873-80.
30. Burns RD, Brusseau TA. Muscular strength and endurance and cardio-metabolic health in disadvantaged Hispanic children from the U.S. Prev Med Rep 2017;5:21-6.
31. Domínguez LJ, Barbagallo M. The biology of the metabolic syndrome and aging. Curr Opin Clin Nutr Metab Care 2016;19(1):5-11.
32. Aguilar-Salinas CA, Lerman-Garber I, Pérez J, Villa AR, Martínez CL, Turrubiatez LC, et al. Lipids, apoprotein B, and associated coronary risk factors in urban and rural older Mexican populations. Metabolism 2001;50(3):311-8.
33. Carrazco-Peña KB, Tene CE, Del Rio-Valdivia J. Sarcopenia and functional disability in aged. Gac Med Mex 2016;152(4):444-51.
34. Mateo Lázaro ML, Penacho Lázaro MA, Berisa Losantos F, Plaza Bayo A. New tables on hand strength in the adult population from Teruel. Nutr Hosp 2008;23(1):35-40.

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Nutrición Hospitalaria

Trabajo Original

Obesidad y síndrome metabólico

Influence of a meal-replacement diet on quality of life in women with obesity and knee osteoarthritis before orthopedic surgery

Influencia de una dieta modificada en la calidad de vida en mujeres con obesidad y artrosis de rodilla antes de la cirugía ortopédica

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Abstract

Background: Knee osteoarthritis is a disease with a high prevalence in our environment, especially in women. Weight loss can improve the quality of life of these patients before surgery.

Objectives: To evaluate the effect of a meal-replacement diet on weight loss, body composition, and the improvement of the quality of life in obese women with knee osteoarthritis pending surgery.

Methods: One branch intervention study was performed over three months on 81 women with a body mass index greater than 30 kg/m^2 with knee osteoarthritis before surgery. Patients received a hyperproteic meal-replacement diet with two bottles of an oral nutrition supplement in lunch and dinner (1,035 kcal). Anthropometric parameters, and body composition were measured. The quality of life was assessed by WOMAC and SF-36 test.

Results: The mean age of the patients was 62.23 (8.50) years. The percentage of weight loss was 8.23% (4.04). An improvement in the SF-36 total score was observed (basal: 49.35 [20.41], three months: 58.71 [17.07], $p < 0.01$). There was an improvement in WOMAC test (basal: 49.24% [25.53], three months: 40.59% [21.76], $p < 0.01$). It was observed that a 10% improvement in the SF-36 test was independently related to weight loss (OR: 1.2 [1.03-1.36], $p < 0.02$) adjusted by age and changes in body composition.

Conclusions: In women with osteoarthritis of the knee treated with a meal-replacement diet, there is a significant decrease in weight and fat mass with a relative increase of the latter. There is an improvement in the quality of life according to SF-36 and WOMAC. There is an independent relationship between weight loss and SF-36 improvement.

Key words:

Knee osteoarthritis. Quality of life. Diet. Weight loss.

Resumen

Introducción: la artrosis de rodilla es una enfermedad con alta prevalencia en nuestro medio, especialmente en mujeres. La pérdida de peso puede mejorar la calidad de vida de estas pacientes antes de la cirugía.

Objetivos: evaluar el efecto de una dieta de sustitución de comidas en la pérdida de peso, la composición corporal y la mejora de la calidad de vida en mujeres obesas con artrosis de rodilla pendientes de cirugía ortopédica.

Métodos: se realizó un estudio de intervención de una rama durante tres meses en 81 mujeres con un índice de masa corporal superior a 30 kg/m^2 con artrosis de rodilla antes de la cirugía. Las pacientes recibieron una dieta de sustitución de comidas hiperproteica con dos botellas de un suplemento nutricional oral en almuerzo y cena (1.035 kcal). Se midieron los parámetros antropométricos y la composición corporal. La calidad de vida fue evaluada por WOMAC y la prueba SF-36.

Resultados: la edad media de las pacientes fue de 62,23 (8,50) años. El porcentaje de pérdida de peso fue de 8,23% (4,04). Se observó una mejora en la puntuación total del SF-36 (basal: 49,35% [20,41], tres meses: 58,71% [17,07], $p < 0,01$). Hubo una mejora en la prueba WOMAC (basal: 49,24% [25,53], tres meses: 40,59% [21,76], $p < 0,01$). Se observó que una mejora del 10% en la prueba SF-36 que se relacionó independientemente con la pérdida de peso (OR: 1,2 [1,03-1,36], $p < 0,02$) ajustada por edad y cambios en la composición corporal.

Conclusiones: en mujeres con osteoartritis de la rodilla tratada con una dieta de sustitución de comidas hay una disminución significativa en el peso y la masa grasa, con un aumento relativo de esta última. Se observa una mejora en la calidad de vida según SF-36 y WOMAC y existe una relación independiente entre la pérdida de peso y la mejora del SF-36.

Palabras clave:

Artrosis de rodilla. Calidad de vida. Dietas. Pérdida de peso.

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INTRODUCTION

Osteoarthritis is a joint disease that affects 12-15% of the population aged 25 to 74 years old. The prevalence of this disease increases significantly with age (1).

The most common site of osteoarthritis is the knee. In the United States, this entity represents 37% of the population over 60 years of age; 12% are symptomatic and have functional repercussions. Prevalence is higher in people with older age and higher body mass index (BMI). There is a predominance of females in both the prevalence of osteoarthritis of the knee (2) and the replacement surgery (3). In Spain, the prevalence of osteoarthritis in relation to overweight in 2006 was 32.16% (34.9% in men and 20.93% in women) (4). The prevalence of knee osteoarthritis in the general population in the 60-69 age group was 28.1% (18.1% in men and 37.2% in women) (5).

Overweight and obesity have been shown to be a predictive factor for the development of osteoarthritis. A BMI greater than 25 kg/m^2 over 40 years increases the risk of symptomatic knee osteoarthritis (6). The mechanisms that link osteoarthritis with obesity are related to the chronic joint load (7), the altered body composition (8), and the situation of subacute inflammation (8).

The basis of any treatment of obesity is the modification of the hygienic-dietary patterns. It has been estimated that if the prevalence of obesity were reverted to levels ten years ago, 111,206 complete knee arthroplasties would be prevented (9). Several studies have estimated that up to half of cases of knee osteoarthritis can be avoided if obesity is eliminated as a risk factor (10).

The improvement of pain and functional disability is the main objective of the patient when considering a surgical treatment of arthropathy. The weight loss through conventional diet therapy has a positive effect on knee arthropathy (11). However, due to physical limitation this weight loss is discrete and can impair muscle mass (12). An alternative to conventional dietary treatment in the surgical patient is the meal-replacement diets. The effectiveness of these diets in the short term (three months) is contrasted. A meta-analysis in 2003 showed an average weight loss of between 6.19-6.50 kg (7% of total weight) compared to the control group, where a loss of 3.23-3.99 kg (4% of initial weight) was observed (13). Even so, there is little evidence of the effect of meal-replacement diets on quality of life in patients with arthropathy.

For this reason, we carried out a study with a meal-replacement diet on women with obesity and knee arthropathy candidates for orthopedic surgery. The main objective was to investigate the weight loss and the modification of body composition secondary to this type of diet, to evaluate the modification of the quality of life after the dietary intervention and to value its relationship with the change of anthropometric parameters and body composition.

METHODS

STUDY DESIGN

An intervention study of one branch with a meal-replacement diet with an oral nutritional supplement (Vegestart®) for three months was carried out in women with obesity (BMI greater than 30 kg/m^2) and knee osteoarthritis pending orthopedic surgery. Patients with active oncologic disease and previous history of alcohol or toxic abuse were excluded.

The study was performed from January 2014 until July 2016. The study was carried out in patients belonging to the health area of Valladolid Este in Spain. These patients were referred from the Department of Traumatology to the Department of Endocrinology and Nutrition of the Hospital Clínico Universitario de Valladolid for weight loss prior to orthopedic knee surgery.

PROCEDURES

All participants provided informed consent to a protocol approved by the local ethical review boards. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving patients were approved by the Hospital Clínico Universitario de Valladolid (HCUVA) ethics committee on 31-1-2014 with the code PI 14-151 CINV 13-60. All patients signed the informed consent and were included in the study. Patients received nutritional education and a low-fat hyperproteic hypocaloric diet (Table I). The diet was structured in six meals (breakfast, mid-morning, lunch, snack, dinner and late night snack). The lunch and dinner was replaced by an oral nutritional supplement called VEGEStart Complete®, whose nutritional characteristics are described in table I.

The adherence of these diets was assessed each seven days with a phone call by a dietitian to improve compliment of the calorie restriction and macronutrient distribution. The diet compliance was verified with a 24-hour telephone dietary questionnaire every seven days and a 48-hour dietary survey of in face-to-face visits. All parameters were measured at baseline and these variables were repeated after three months.

STUDY VARIABLES

Anthropometry

The anthropometric evaluation of the subjects was performed by determination of weight, height and body mass index (BMI).

The weight was measured without clothing with an accuracy of ± 0.1 kg using a hand scale to the nearest 0.1 kg (Seca, Birmingham, UK). The height was measured with the patient standing up to the nearest centimeter using a stadiometer (Seca, Birmingham, UK). BMI was calculated using the formula: weight (kg)/height x height (m^2).

The percentage of weight loss (% WL) was used to assess the relative weight difference.

Bioelectrical impedance measurement

A bioelectrical impedance analysis (BIA) was performed in all subjects. These measurements were performed before the start of the dietary intervention and three months after the intervention.

The BIA was performed on all subjects after a fast of at least five hours. It may be influenced by the degree of hydration, so subjects were warned that they could not exercise or drink alcohol within 48 hours prior to the test.

It was determined by a four-point single-decubitus device. An alternating current of 0.8 mA at 50 kHz produced by a calibrated signal generator (EFG, Akern It) was used and applied to the skin by adhesive electrodes placed on the back of the hand and right foot. Body composition was estimated with the Bodygraff® software.

The parameters analyzed with the BIA were: fat free mass and fat mass. All of them are represented as weight (kg) and percentage with respect to the total weight.

Quality of life test

Two different tests were used to evaluate the impact of the dietary intervention on health status and quality of life. The Short Form Health Survey (SF-36) test was used to evaluate the patient's quality of life before and after treatment. It is an instrument developed from an extensive battery of questionnaires used in the Medical Outcome Study (MOS) (14). In our design, we used the Spanish-translated version (15). It consists of 36 themes, which explore eight dimensions of health status: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. The score is directly proportional to the state of health (score ranges from 0 to 100).

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (16) was used to assess the functional limitation and influence of diet therapy in patients with osteoarthritis of the knee and/or hip. We used the validated Spanish version (17). The test was performed face-to-face in front of the patient. This test is used to assess the functionality of the patient from three subscales with different scores: pain, stiffness, physical function, total (results from the sum of the three scores). The interpretation of the test is that the higher score means a worsening in any of the three areas (pain, stiffness and physical function) or in the total. To homogenize the data, the scores have been standardized from 0 to 100, where 0 means no alteration and 100 is the situation with the greatest alteration.

Table I. Macronutrient composition of diet and oral nutritional supplement Vegestart®

Macronutrients	Complete diet	Oral nutrition supplement (200 ml)
Caloric value (kcal)	1035	200
Proteins (g [%TCV])	64.4 (25%)	15.4 (31%)
Lipids (g [%TCV])	19.1 (17%)	5.2 (23%)
Cholesterol (mg)	21	0
Carbohydrates (g [%TCV])	151.6 (59%)	21(42%)
Fiber (g)	15.9	4.2

%TCV: total caloric value percentage.

STATISTICAL ANALYSIS

The data were analyzed using the SPSS statistical package (SPSS for Windows version 15.0, 2008 SPSS INC, Chicago, USA). An analysis of patients by intention to treat was performed. Sample size was calculated to detect a percentage of weight loss over 5%. The level of significance was conventionally set at $p \leq 0.05$.

RESULTS

DEVELOPMENT OF THE STUDY

Eighty-one women with obesity and knee osteoarthritis pending orthopedic surgery were recruited between January 2014 and July 2016.

After three months of intervention, 75 (92.6%) patients maintained complete therapeutic adherence while six (7.40%) patients started the diet but did not complete it for different reasons (Fig. 1).

INITIAL EVALUATION

The mean age of the individuals was 62.23 (8.50) years.

Anthropometry and body composition

The initial weight was 99.33 (14.61) kg, while BMI was 40.80 (4.40) kg/m^2.

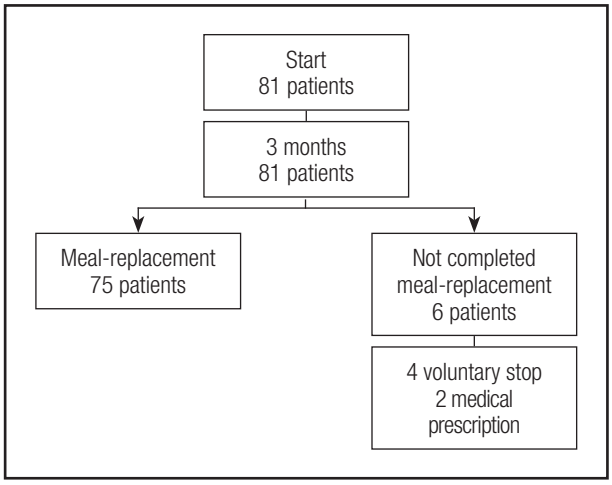

Figure 1.
Therapeutic intervention scheme.

In the analysis of body composition, fat mass and fat free mass were evaluated. A percentage of fat mass of 47.67% (5.19) with respect to the total weight and a percentage of fat free mass of 52.25% (5.24) were observed.

Quality of life

Test SF-36

To evaluate the patients' quality of life, the structured SF-36 test was performed in eight dimensions:

– Decreased values were observed in general health, physical functioning, role-physical, bodily pain and mental health. Decreased vitality values were also observed (Table II).
– In the areas of role emotional and social functioning, no decrease was observed (Table II).

WOMAC

This test was used for the assessment of pain and its implication in the functionality of the patient. All patients had altered values at all levels (pain: 52.94% [26.08]; stiffness: 50% [25-75]; functional capacity: 49.19% [27.01]); as well as in total index: 49.24% [25.53]).

Table II. Modification in quality of life test: SF-36 and WOMAC before and after three months of treatment

		Basal	3 months	p
SF-36	General health	41.49 (16.53)	48.79 (13.63)	< 0.01
	Physical functioning	25 (10-45)	35 (20-50)	< 0.01
	Role physical	25 (0-100)	75 (12.5-100)	< 0.01
	Role emotional	69.13 (42.74)	81.85 (36.59)	< 0.01
	Social functioning	75 (50-100)	87.5 (50-100)	0.10
	Bodily pain	43.95 (23.68)	54.23 (27.76)	< 0.01
	Vitality	44.22 (23.68)	57.71 (54.34)	0.03
	Mental health	59.80 (27.40)	68.49 (22.98)	< 0.01
WOMAC test	Pain	52.94 (26.08)	45.25 (23.57)	< 0.01
	Stiffness	50 (25-75)	25 (12.5-50)	0.02
	Functional capacity	49.19 (27.01)	40.16 (22.06-54.41)	< 0.01

EFFECT OF DIETARY TREATMENT

Anthropometry and body composition

A weight loss rate of 8.23% (4.04) was observed after a three-month meal-replacement hypocaloric diet. There was a decrease in all body components. When assessing the change in body composition at three months, there was a relative decrease in the percentage of fat mass 2.66% (0.53-3.92) and a relative increase in the percentage of fat-free mass 2.30% (3.72) (Table III).

Table III. Modification of parameters of anthropometry and body composition before and after three months of treatment

	Basal	3 months	p
Weight (kg)	99.33 (14.61)	91.02 (13.01)	< 0.01
BMI (kg/m^2)	40.80 (4.40)	37.02 (5.00)	< 0.01
Fat mass (kg)	46.60 (10.20)	40.19 (9.65)	< 0.01
Fat mass (%)	47.67 (5.19)	44.93 (6.43)	< 0.01
Fat free mass (kg)	55.49 (12.03)	52.87 (10.77)	< 0.01
Fat free mass (%)	52.25 (5.24)	54.51 (5.96)	< 0.01

BMI: body mass index.

Quality of life

SF-36 test

An improvement was observed in total score (basal time: 49.35 [20.41], at three months: 58.71 [17.07], $p < 0.01$). We obtained an improvement rate of 15.97% (28.08).

In the analysis of the different spheres (Table II) there was a significant improvement in all spheres except for social functioning (Fig. 2).

WOMAC

The total score of WOMAC showed a significant improvement (basal time: 49.24% [25.53], at three months: 40.59% [21.76], $p < 0.01$). The decrease proportion of this test after intervention was 13.64% (0-35.68). There was significant improvement in the three spheres (Table II and Fig. 2).

Relationship of anthropometry changes with improvement of the quality of life

The percentage of weight loss showed a positive correlation with the percentage of variation of SF-36 ($r = 0.23$; $p = 0.04$), with the WOMAC pain domain ($r = 0.34$; $p < 0.01$), with the functional capacity domain ($r = 0.31$; $p < 0.01$), and the percentage change in WOMAC total score ($r = 0.35$; $p < 0.01$).

A multivariate analysis was performed to determine the influence of anthropometric changes on the modification of the quality of life scores. Improvement in quality of life was observed to be related to weight loss regardless of changes in body composition and age (Table IV). There was no relationship between the WOMAC test, weight loss and body composition (Table IV).

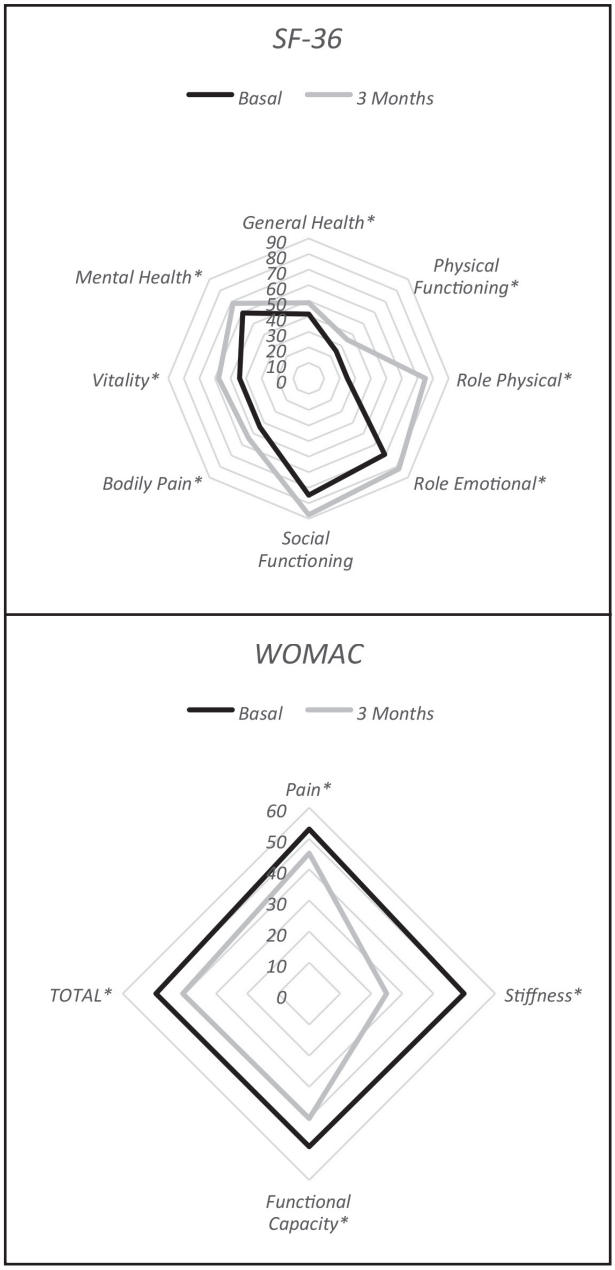

Figure 2.

Variation of the different areas of the SF-36 and WOMAC tests before the start of the intervention and three months later. *Significant difference ($p < 0.05$).

Table IV. Relation between improvement quality of life test (SF-36 and WOMAC) with anthropometry and body composition

Improvement 10% SF-36 test (Total) (Yes/No)			
	OR	**CI (95%)**	**p**
Age	0.96	(0.90-1.02)	0.16
Weight loss	1.20	(1.03-1.36)	0.02
Fat mass loss	1.03	(0.94-1.13)	0.49
Fat free mass gain	0.98	(0.89-1.09)	0.73
Improvement 10% WOMAC test (Total) (Yes/No)			
Age	0.98	(0.93-1.04)	0.61
Weight loss	1.01	(0.88-1.15)	0.92
Fat mass loss	1.05	(0.97-1.14)	0.23
Fat free mass gain	1.02	(0.92-1.12)	0.75

DISCUSSION

The effect of dietary treatment of obesity has shown several benefits on the complications associated with knee osteoarthritis. Even so, there are few studies that analyze the effect on quality of life in these patients when using a meal-replacement diet.

The SF-36 is a very useful test to evaluate the quality of life in a global way and in terms of different aspects affecting it. When comparing the score of the SF-36 test with the values of the test for the general Spanish population, a decrease in all values is observed except in the areas of role emotional, social functioning and mental health (18). This could be justified by habituation to chronic symptoms, or because of the difficulty of the test to assess these types of symptoms.

When comparing our data to those of similar populations (obese with degenerative arthropathy), quite a few similarities in the alteration of the different spheres of the SF-36 test are observed. When analyzing the excess weight, a previous study compared the obese *versus* non-obese population; in the age group between 55 and 64 years worse scores in the population with obesity in spheres of physical functioning, role physical, pain, general health and vitality were observed, while in other spheres the score was similar (19). Similar levels were also observed in populations with the same characteristics as ours in which different comorbidities are combined. In this way, it has been shown that the SF-36 physical spheres score worsens with the increase in the number of comorbidities, and particularly with the presence of obesity (20,21).

Given the special characteristics of these patients, a more specific test for arthropathy, such as WOMAC, was performed. When analyzing the WOMAC, a score of pain, stiffness, functional capacity and the total of the sum close to half were observed. The levels of pain and altered functional capacity in the WOMAC test are variable according to the study ranged from lower scores around 20% (22) till higher scores around 40-50% in populations with obesity (23). This data means that higher values

of BMI produce worse values of WOMAC (24). This would justify that the values obtained in our study were in a range of greater pain and disability. The pain and physical situation scores would resemble those of the other test performed (SF-36). This situation has been evaluated in other studies, with similar findings and improvement after arthroplasty replacement (25). The effect of dietary treatment on these parameters does not have such clear evidence in the literature.

The results on weight loss in our study are similar to those performed with the same intervention. In a study by De Luis et al. in a population of patients with arthropathy, a greater weight loss was observed in the treatment group with a commercial diet compared to dietary advice (26), with a mean weight loss of 7.7 kg compared to 3.92 kg in the control group. In another meta-analysis by Anderson, it was found that there was a greater percentage of weight loss, up to 9.3% in men and 8.6% in women, with an initial BMI ranged from 28 to 35 kg/m^2. These data were similar to what was done in our study (27).

When the change in body composition was analyzed, a decrease in the percentage of fat mass that was associated with a relative increase of fat-free mass was observed. This data shows that maintaining an adequate protein intake can help to reduce excess muscle loss, despite caloric restriction. This topic has been observed in different studies with hyperproteic meal-replacement diets of one or more meals (28,29).

The main symptoms that are usually evaluated in these patients are the improvement of pain and stiffness. In the WOMAC test, an improvement in the parameters of stiffness and physical function was observed. This change in functional capacity score is seen in multiple studies associated with weight loss in patients with arthropathy. In 2010, a meta-analysis on long-term weight loss in obese elderly patients showed that functional impairment and overall quality of life improved with weight loss in obese elderly patients (11).

We observed an improvement in all of the items of the SF-36 test after intervention except for social functioning. This situation could be due to two reasons: the baseline scores were close to the average of the general Spanish population, and the measurement of this sphere through a single question with three degrees makes it difficult to show differences.

In the SF-36 test, although there were no differences in social functioning, there was an improvement in mental health. This situation related to the decrease of pain and the improvement of the functional capacity in the evaluated tests relates the influence of these two characteristics to the psychic situation of the patients.

The reduction of weight in the context of the treatment of osteoarthritis of different locations, especially those of load (hip and knee), has a positive effect on pain. The effect starts to be effective with weight losses above 5% (30). This relationship has been analyzed in many studies of osteoarthritis of the knee using the WOMAC (31) with greater effect in those patients with greater weight loss. This effect is enhanced if there is a long-term maintenance of weight loss (32).

In our study, there were isolated correlations between the greater weight loss and the improvement of the WOMAC in its total score, in the field of pain and functional capacity. This approach has recently been observed in a study where the percentage of weight change was associated with the WOMAC score, both gain and weight loss (33). In the case of the analysis of the improvement of the articular functionality after the loss of weight the data are variable in the literature. In several cases, a functional improvement was observed in relation to weight loss in diet-only management (34), with intensive diet (35), or a combination of diet and exercise combined (36).

An independent relationship was observed in the weight loss with the intensity of the SF-36 test improvement. This relationship did not occur with the WOMAC test. The differences found between both tests in obese patients with arthropathy in relation to weight loss can be related to a partial improvement in pain and functional capacity, and with the positive effect that the weight loss had on the patient's well-being. It has been observed that this score improves more in obese patients than in non-obese patients after moderate weight control (37). Therefore, these results may be due to the influence of weight loss on quality of life in other aspects than mechanical ones, such as psychological and social factors.

The main limitation of our study was the absence of a control group with a different dietary intervention to be able to categorize the impact of the diet itself on the quality of life. Second, the inclusion of only women limits the extrapolation of study data, but this decision was made due to the higher prevalence of osteoarthritis of the knee in women. Finally, it would be interesting to carry out a long-term assessment of the maintenance of weight loss and the change of the quality of life of the patient.

CONCLUSIONS

A short term dietary treatment through a meal replacement diet in obese women with knee osteoarthritis pending surgery showed: a weight decrease between 5-10% with a relative decrease of fat mass and relative increase of fat-free mass; an improvement in the quality of life measured by the SF-36 test in all its spheres except for social functioning; and improvement in all dimensions of the WOMAC test. Adjusting for age and body composition weight loss showed an independent relationship with SF-36 improvement. Further studies are needed to evaluate this dietary intervention in patients with other arthropaty and during long term interventions.

TRANSPARENCY DECLARATION

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving patients were approved by the Hospital

Clínico Universitario de Valladolid (HCUVA) ethics committee on the 31-1-2014 with the code PI 14-151 CINV 13-60.

REFERENCES

1. Guilak F. Biomechanical factors in osteoarthritis. Best Pract Res Clin Rheumatol 2011;25(6):815-23.
2. Núñez M, Núñez E, Sastre S, Del-Val JL, Segur JM, Macule F. Prevalence of knee osteoarthritis and analysis of pain, rigidity and functional incapacity. Orthopedics 2008;31:753.
3. Kremers HM, Larson DR, Crowson CS, Kremers WK, Washington RE, Steiner CA, et al. Prevalence of total hip and knee replacement in the United States. J Bone Joint Surg Am 2015;97(17):1386-97.
4. Martín Ramiro JJ, Álvarez-Martín E, Gil-Prieto R. Discapacidad atribuible al exceso de peso en España. Med Clin (Barc) 2014;143(4):150-6.
5. Fernández-López JC, Laffon A, Blanco FJ, Carmona L, EPISER Study Group. Prevalence, risk factors, and impact of knee pain suggesting osteoarthritis in Spain. Clin Exp Rheumatol 2008;26(2):324-32.
6. Sridhar MS, Jarrett CD, Xerogeanes JW, Labib SA. Obesity and symptomatic osteoarthritis of the knee. J Bone Joint Surg Br 2012;94:433-40.
7. Felson DT, Goggins J, Niu K, Zhang Y, Hunter DJ. The effect of body weight on progression of knee osteoarthritis is dependent on alignment. Arthritis Rheum 2004;50:3904-09.
8. Wluka AE, Lombard CB, Cicuttini FM. Tackling obesity in knee osteoarthritis. Nat Rev Rheumatol 2013;9(4):225-35.
9. Messier SP. Obesity and osteoarthritis: Disease genesis and nonpharmacologic weight management. Rheum Dis Clin North Am 2008; 34(3):713-29.
10. Koonce RC, Bravman JT. Obesity and osteoarthritis: More than just wear and tear. J Am Acad Orthop Surg 2013;21:161-9.
11. Witham MD, Avenell A. Interventions to achieve long-term weight loss in obese older people. A systematic review and metaanalysis. Age Ageing 2010;39:176-84.
12. Henriksen M, Christensen R, Danneskiold-Samsoe B, Bliddal H. Changes in lower extremity muscle mass and muscle strength after weight loss in obese patients with knee osteoarthritis: A prospective cohort study. Arthritis Rheum 2012;64(2):438-42.
13. Heymsfield SB, Van Mierlo CA, Van der Knaap HC, Heo M, Frier HI. Weight management using a meal replacement strategy: Meta and pooling analysis from six studies. Int J Obes 2003;27:537-54.
14. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36) (I). Conceptual framework and item selection. Med Care 1992;30:473-83.
15. Alonso J, Prieto L, Antó JM. The Spanish version of the SF-36 Health Survey (the SF-36 health questionnaire): An instrument for measuring clinical results. Med Clin (Barc) 1995;104(20):771-6.
16. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15(12):1833-40.
17. Escobar A, Quintana JM, Bilbao A, Azkárate J, Güenaga JI. Validation of the Spanish version of the WOMAC questionnaire for patients with hip or knee osteoarthritis. Western Ontario and McMaster Universities Osteoarthritis Index. Clin Rheumatol 2002;21(6):466-71.
18. Alonso J, Regidor E, Barrio G, Prieto L, Rodríguez C, De la Fuente L. Population reference values of the Spanish version of the Health Questionnaire SF-36. Med Clin (Barc) 1998;111(11):410-6.
19. Anandacoomarasamy A, Caterson ID, Leibman, Smith GS, Sambrook PN, Fransen M. Influence of BMI on health-related quality of life: Comparison between an obese adult cohort and age-matched populations norms. Obesity (Silver Spring) 2009;17(11):2114-8.
20. Wesseling J, Welsing PM, Bierma-Zeinstra MA, Dekker J, Gorter KJ, Kloppenburg M, et al. Impact of self-reported comorbidity on physical and mental health status in early symptomatic osteoarthritis: The CHECK (Cohort Hip and Cohort knee) study. Rheumatology 2013;52:180-8.
21. Van Dijk GM, Veenhof C, Schellevis F, Hulsmans H, Bakker JP, Arwert H, et al. Comorbidity, limitations in activities and pain in patients with osteoarthritis of the hip or knee. BMC Musculoskelet Disord 2008;9:95.
22. Collins JE, Katz J, Dervan E, Losina E. Trajectories and risk profiles of pain in persons with radiographic, symptomatic knee osteoarthritis: Data from the osteoarthritis initiative. Osteoarthritis Cartilage 2014;22(5):622-30.
23. Garver MJ, Focht BC, Dials J, Rose M, Lucas AR, Devor ST, et al. Weight status and differences in mobility performance, pain symptoms, and physical activity in older, knee osteoarthritis patients. Arthritis 2014;375909.
24. Sanghi D, Srivastava RN, Singh A, Kumari R, Mishra R, Mishra A. The association of anthropometric measures and osteoarthritis knee in no-obese subjects: A cross sectional study. Clinics (Sao Paulo) 2011;66(2):275-9.
25. Núñez M, Lozano L, Núñez E, Segur JM, Sastre S, Maculé F, et al. Total knee replacement and health-related quality of life: Factors influencing long-term outcomes. Arthritis Rheum 2009;61(8):1062-9.
26. De Luis DA, Izaola O, García Alonso M, Aller R, Cabezas G, De la Fuente B. Randomized clinical trial between nutritional counseling and commercial hypocaloric diet in weight loss in obese patients with chronic arthropathy. Med Clin (Barc) 2009;132(19):735-9.
27. Anderson JW, Luan J, Hoie LH. Structured weight-loss programs: Meta-analysis of weight loss at 24 weeks and assessment of effects of intervention intensity. Adv Ther 2004;21:61-75.
28. Magrans-Courtney T, Wilborn C, Rasmussen C, Ferreira M, Greenwood L, Campbell B, et al. Effects of diet type and supplementation of glucosamine, chondroitin, and MSM on body composition, functional status, and markers of health in women with knee osteoarthritis initiating a resistance-based exercise and weight loss program. J Int Soc Sports Nutr 2011;8(1):8.
29. Treyzon L, Chen S, Hong K, Yan E, Carpenter CL, Thames G, et al. A controlled trial of protein enrichment of meal replacements for weight reduction with retention of lean body mass. Nutr J 2008;7:23.
30. Bliddal H, Leeds AR, Christensen R. Osteoarthritis, obesity and weight loss: Evidence, hypotheses and horizons - A scoping review. Obes Rev 2014;15:578-86.
31. Weiss E. Knee osteoarthritis, body mass index and pain: Data from the osteoarthritis initiative. Rheumatology (Oxford) 2014;53(11):2095-9.
32. Bliddal H, Leeds AR, Stigsgaard L, Astrup A, Christensen R. Weight loss as treatment for knee osteoarthritis symptoms in obese patients: 1-year results from a randomized controlled trial. Ann Rheum Dis 2011;70(10):1798-803.
33. Teichtahl AJ, Wluka AE, Tanamas SK, Wang Y, Strauss BJ, Proietto J, et al. Weight and change in tibial cartilage volumen and symptoms in obese adults. Ann Rheum Dis 2015;74(6):1024-9.
34. Riddle DL, Stratford PW. Body weight changes and corresponding changes in pain and function in persons with symptomatic knee osteoarthritis. A cohort study. Arthritis Care Res (Hoboken) 2013;65(1):15-22.
35. Foy CG, Lewis CE, Hairston KG, Miller GD, Lang W, Jakicic JM, et al. Intensive lifestyle intervention improves physical function among obese adults with knee pain: Findings from the look AHEAD trial. Obesity (Silver Spring) 2011;19(1):83-93.
36. Messier P, Mihalko SL, Legault C, Miller GD, Nicklas BJ, De Vita P, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis. JAMA 2013;310(12):1263-73.
37. Dowsey MM, Liew D, Stoney JD, Choong PF. The impact of obesity on weight change and outcomes at 12 months in patients undergoing total hip arthroplasty. Med J Aust 2010;193(1):17-21.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Obesidad y síndrome metabólico

Inflammatory cytokines and non-alcoholic fatty liver disease (NAFLD) in obese children and adolescents

Citocinas inflamatorias y enfermedades hepáticas grasas no alcohólicas (EHGNA) en niños y adolescentes obesos

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Abstract

Introduction: Non-alcoholic fatty liver disease is characterized by the intrahepatic deposition of fat. It is the most prevalent liver disease in the world, affecting obese children and adolescents. Its pathophysiology is not fully understood, although it is often related to insulin resistance. This in turn would be due to an inflammatory condition common to obesity. Thus, the objective of this study was to describe the behavior of proinflammatory cytokines in obese children and adolescents, with and without non-alcoholic fatty liver disease.

Method: A fasting venous blood sample was obtained of consecutive 90 obese individuals aged 8-18 years, of both sexes, for laboratory determinations of glycaemia, basal insulin and homeostasis model assessment insulin-resistance index, and the inflammatory markers tumor necrosis factor-alpha (TNF-α), interleukins 2 and 6 (IL-2 and IL-6), interferon-gamma and high sensitive C-reactive protein. The clinical evaluation included weight, height and waist circumference. We used the body mass index/age indicator for the severity of overweight assessment. The degrees of steatosis were determined by ultrasonography. Quantitative and qualitative variables were respectively expressed by measures of central tendency/dispersion and simple/relative frequency, using Statistical Program for Social Sciences, version 20.0. A p-value < 0.05 was considered as significant.

Results: A total of 90 individuals were studied, with a mean age of 11.98 (2.72) years, of which 48 (53%) were male. The body mass index (BMI) for age (BMI/i) and sex (z-score) classified 38 (42.2%) participants as obese and 52 (57.7%) as severe obese; Hepatic steatosis was identified in 56 (62.2%) participants and approximately 90% of them presented grade I steatosis. The inflammatory markers TNF-α, and C-reactive protein were increased in the studied sample and correlated in a positive and statistically significant way with the index of body mass/age and sex.

Conclusion: Hepatic steatosis was prevalent in the group of children and adolescents studied, but was not related to obesity degrees.

Key words:

Non-alcoholic fatty liver disease. Obesity. Fatty liver. Children. Adolescents.

Resumen

Introducción: la enfermedad hepática grasa no alcohólica se caracteriza por la deposición intrahepática de grasa. Es la enfermedad hepática más prevalente en el mundo y afecta a niños y adolescentes obesos. Su fisiopatología no se entiende completamente, aunque a menudo se relaciona con la resistencia a la insulina. Esto, a su vez, sería debido a una condición inflamatoria común a la obesidad. Así, el objetivo de este estudio fue describir el comportamiento de las citocinas proinflamatorias en niños y adolescentes obesos, con y sin enfermedad hepática grasa no alcohólica.

Método: se obtuvo una muestra de sangre venosa en ayuno de 90 individuos obesos consecutivos, de 8 a 18 años, de ambos sexos, para las determinaciones de laboratorio de glucosa, insulina basal, resistencia a la insulina *(homeostasis model assessment insulin-resistance index)* y marcadores inflamatorios como TNF-alfa, interleucinas 2 y 6, interferón-gamma y proteína C-reactiva ultrasensible. La evaluación clínica incluyó peso, altura y circunferencia de la cintura. El indicador del índice de masa corporal para la edad (IMC/e) y sexo *(z-score)* evaluó la gravedad del exceso de peso. Los grados de esteatosis se determinaron por ecografía. Las variables cuantitativas y cualitativas se expresaron respectivamente mediante tendencia/dispersión central y frecuencia simple/relativa, utilizando el Programa Estadístico para Ciencias Sociales, versión 20.0. Se consideró significativo un valor $p < 0,05$.

Resultados: fueron estudiados 90 pacientes con una media de edad de 11,98 (2,72) años, de los cuales 48 (53%) eran varones. Según IMC/e y sexo, 38 (42.2%) participantes fueron clasificados como obesos y 52 (57,7%), como obesos graves. La esteatosis hepática fue identificada en 56 (62,2%) participantes y aproximadamente el 90% de ellos presentaron esteatosis grado I. Los marcadores inflamatorios TNF-alfa y proteína C-reactiva estaban aumentados en la muestra estudiada y se correlacionaron de forma positiva y estadísticamente significativa con el IMC/e y sexo.

Conclusión: la esteatosis hepática fue predominante en el grupo de niños y adolescentes estudiados, pero no se relacionó con los grados de obesidad.

Palabras clave:

Enfermedad del hígado graso no alcohólico. Obesidad. Hígado graso. Niño. Adolescente.

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INTRODUCTION

Obesity is a chronic disease that affects the population throughout the world, being more prevalent than malnutrition and infectious diseases (1). Studies reveal that obesity affects not only adults but is also verified in children and adolescents (2,3), when related metabolic alterations may have its onset (4). Adipose tissue is characterized, in particular, by its complexity. It would originally be related to energy source and thermogenesis, depending on its differentiation in white adipose tissue (WAT) or brown adipose tissue (BAT), respectively. However, other functions have been attributed to adipose tissue, resulting from its active involvement in immune, hormonal and metabolic processes through the synthesis and release of substances called adipokines (5). Adipose tissue is recognized as an endocrine organ for its secretory and synthesizing function of leptin, estrogens, angiotensinogen and adiponectin, by the ability to establish connections with the central nervous system, in addition to the release of acute-phase proteins and pro-inflammatory cytokines such as tumor necrosis factor--alpha (TNF-α), interleukin-6 (IL-6) and insulin-like growth factor 1 (IGF-1) (6). TNF-α and IL-6 cytokines are related to obesity and reduced insulin sensitivity (7). Insulin resistance would lead to increased synthesis and storage of triglycerides in hepatocytes, and thus play an important role in the pathogenesis of non-alcoholic fatty liver disease (NAFLD), a disease with a high potential for cirrhosis and/or hepatocellular carcinoma (8). As a consequence, this population could develop other metabolic alterations such as dyslipidemias, hypertension and type 2 diabetes mellitus (T2DM), secondary to a supposed inflammatory state intrinsic to obesity that would respond by the expression of these comorbidities, according to studies described in adults (9). Considering these aspects, the purpose of this study was to describe the behavior of proinflammatory cytokines in obese children and adolescents with and without non-alcoholic fatty liver disease (NAFLD).

METHODS

A cross-sectional study involving 90 obese children and adolescents of both sexes, aged between eight and 18 years, consecutively evaluated at the Pediatric Nutrology Service of the Federal University of Bahia from January to December 2015, was carried out, featuring a convenience sample. Patients with conditions predisposing to overweight such as Cushing's syndrome, growth hormone deficiency, hypothyroidism, and syndromic obesity were excluded. There was no report of consumption of alcoholic beverages among participants. The body mass index (BMI) was calculated by dividing the weight (kg) by the square of the height (m) (kg/m^2). The z-score of the BMI indicator/age and gender was used to classify the participants' anthropometric status as obese (BMI/i > +2) and severe obese (BMI/i > +3) (10). Waist circumference was obtained with a soft and inelastic tape, at the midpoint between the last rib and the anterior iliac crest (11). GE LOGIC P6 ultrasound with a convex transducer of 2 to 5 MHz was used for the diagnosis and classification of steatosis in grades I, II and III, according to the alteration of echogenicity, and the identification of intrahepatic vessels and diaphragm, according to Hamaguchi et al. (12). The imaging examinations were performed at the research institution and by the same professional. This study was approved by the Ethics Committee from the Federal University of Bahia, Brazil. A children verbal assent and a written consent for participation were obtained through their legal representatives.

LABORATORY ANALYSES

A fasting venous blood sample was taken of all participants for laboratory determinations. The enzymes alanine transaminase (ALT), aspartate transaminase (AST) and gamma-glutamyl transpeptidase (gamma-GT) were measured by the calorimetric kinetic method and expressed in U/l. Altered fasting plasma glucose ≥ 100 mg/dl was assessed by the hexokinase method (Wiener lab.) (13). Insulin levels were evaluated by enzyme linked immunoenzymatic assay (ELISA). Any values greater than 15.0 µUI/ml were considered as abnormal (14). The homeostasis model assessment-insulin resistance (HOMA-IR) index = fasting glucose (mg/dl) x fasting insulin (µIU ml^{-1})/405 was used to identify insulin resistance (15). We used the cut-offs adjusted by gender and age according to Almeida et al., summing the mean value to two standard deviations (16). The high sensitivity C-reactive protein (hsCRP) was determined by immunoturbidimetric method. The interleukin-2 (IL-2), interleukin-6 (IL-6), interferon-gamma (IFN-γ) and tumor necrosis factor-α (TNF-α) were determined by ELISA DuoSet R&D Systems.

STATISTICAL ANALYSES

The Statistical Program for Social Sciences (SPSS), version 20.0, was used for statistical analyses. Quantitative and qualitative data were respectively expressed by measures of central tendency/dispersion and simple/relative frequency. Continuous variables were tested for normality of distribution by Kolmogorov-Smirnov test. The differences for these variables were analyzed using the Mann-Whitney U-test or Student's t-test, according to the distribution. The Chi-squared test compared the frequency of individuals in each category. A p-value < 0.05 was considered to be significant.

RESULTS

Ninety individuals were studied, with a mean age of 11.98 (2.72) years, of which 48 (53%) were male. The BMI for age (BMI/i) and sex (z-score) classified 38 (42.2%) participants as obese and 52 (57.7%) as severe obese, being 3.14 (0.86) years the mean (SD) and 2.02 and 8.52 the minimum and maximum values of BMI/i, respectively. Hepatic steatosis was identified in 56 (62.2%) participants, being more frequent in boys than in girls (58.9 *versus* 41.1%, $p > 0.05$). Among these, 50 (89.2%) pre-

sented grade I steatosis, five (8.92%) presented grade II and only one (1.78%), grade III steatosis. No case of steatohepatitis (NASH) was identified, considering that the levels of transaminases were within the reference values. Blood pressure levels were measured and found within normal limits. Table I shows the biochemical parameters and the inflammatory markers analyzed considering the presence of NAFLD.

The inflammatory profile of all study participants considering obesity degrees is shown in table II. Table III shows the clinical and laboratory characteristics of obese and severe obese patients, considering the presence of NAFLD. Table IV shows that there was a positive and statistically significant correlation between HOMA--IR, insulin and CRP, different from that of IFN-γ, IL-6, and IL-2. BMI/age also influenced the behavior of TNF-α and CRP.

Table I. Clinical and laboratory characteristics of 90 children and adolescents studied according to the presence of non-alcoholic fatty liver disease

	NAFDL Yes (n = 56)	NAFDL No (n = 34)	p value
Age (years)**	12.00 (10-14)	11.00 (10-14)	0.687
Male gender (%)	58.9	44.1	0.172
BMI/age (z-score)*	3.15 (0.61)	3.13 (1.18)	0.884
Severe obese	20 (35.7%)	18 (52.9%)	0.109
Waist circumference (cm)*	96.56 (12.67)	92.82 (14.54)	0.203
ALT (UI)*	26.09 (10.97)	22.50 (6.17)	0.084
AST (UI)**	23.00 (15.00-28.00)	20.00 (12.00-28.00)	0.237
GGT (UI)**	25.00 (20.00-35.00)	22.00 (17.00-28.00)	0.106
Cholesterol (mg/dl)*	166.82 (34.79)	163.01 (34.58)	0.617
LDL (mg/dl)*	97.50 (31.61)	93.30 (33.80)	0.563
HDL (mg/dl)*	42.32 (7.17)	43.63 (9.69)	0.468
Triglycerides (mg/dl)**	117 (82.23-144.50)	95.35 (72.50-172.25)	0.659
Glycemia (mg/dl)*	91.39 (9.96)	87.64 (9.06)	0.077
HOMA-IR**	2.54 (1.55-3.26)	2.18 (1.36-3.89)	0.600
Insulin (mUI)**	11.63 (7.37-15.22)	10.12 (6.94-17.84)	0.623
hs-CRP (mg/l)**	4.05 (1.97-7.28)	3.88 (1.88-13.67)	0.519
Interleukin-2 (pg/ml)**	0.240 (0.097-0.425)	0.192 (0.069-0.351)	0.265
Interleukin-6 (pg/ml)**	0.287 (0.121-0.770)	0.206 (0.058-0.658)	0.222
TNF-α (pg/ml)**	0.269 (0.119-0.642)	0.235 (0.101-0.453)	0.268
IFN γ (pg/ml)**	0.352 (0.103-0.721)	0.213 (0.075-0.535)	0.144

*BMI: body mass index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transpeptidase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HOMA-IR: homeostasis model assessment-insulin resistance; hs-CRP: high sensitivity C reactive protein; TNF-α: tumor necrosis factor-α; IFN-γ: interferon gamma. *Values express as mean (SD). ** Values express as median and interquartile.*

DISCUSSION

The relevance of this study is due to the fact that the altered findings were from a sample of 90 clinically asymptomatic obese individuals. Hepatic steatosis was prevalent, confirming literature data indicating NAFLD as one of the adverse consequences of obesity, in addition to hyperlipidemia, hypertension and type 2 diabetes mellitus (T2DM) (17). Grade I steatosis was identified in approximately 90% of the 56 children and adolescents diagnosed with NAFLD, reflecting a process of early and incipient installation of the spectrum involving the disease.

In table I, groups with and without liver disease are compared. We observed that individuals with NAFLD did not present significant differences in the analyzed parameters. However, in table II, inflammatory markers such as adipokine TNF-α were elevated in severe obese individuals, whereas CRP, an acute phase protein of inflammation secreted by the liver when stimulated by IL-6, was increased in obese individuals, suggesting the presence of an inflammatory state underlying obesity.

In addition, in table III, the 56 individuals diagnosed with hepatic steatosis were analyzed considering the obesity degree, and statistically significant changes were found. In severe obese patients, waist circumference was higher, probably due to the central

Table II. Behavior of inflammatory markers of 90 children and adolescents studied, according to obesity degrees

	Severe obese	Obese	p value
hs-CRP (mg/l)*	2.52 (1.16-5.37)	5.16 (2.94-9.07)	*0.009*
Interleukin-2 (pg/ml)*	0.222 (0.104-0.456)	0.208 (0.085-0.400)	0.520
Interleukin-6 (pg/ml)*	0.515 (0.116-0.865)	0.212 (0.091-0.559)	0.088
TNF-α (pg/ml)*	0.315 (0.190-0.667)	0.204 (0.084-0.428)	*0.024*
IFN-γ (pg/ml)*	0.230 (0.072-0.693)	0.281 (0.084-0.609)	0.750

*hs-CRP: high sensitivity C reactive protein; TNF-α: tumor necrosis factor-α; IFN-γ: interferon gamma. *Values express as median and interquartiles.*

Table III. Clinical and laboratory characteristics of 56 children and adolescents with non-alcoholic fatty liver disease according to the obesity degree

	Severe obese (n = 20)	Obese (n = 36)	p value
Age (years)*	13.30 (2.55)	11.36 (2.58)	*0.009*
Gender (%)	58.9%	41.1%	0.909
BMI/age (z-score)*	3.60 (0.87)	2.52 (0.25)	*0.007*
Degrees of steatosis:* Grade I Grade II Grade III	 18 (90.0%) 2 (10.0%) 0	 32 (88.9%) 3 (8.3%) 1 (2.8%)	0.597
Waist circumference (cm)*	98.01 (13.63)	93.67 (10.04)	*0.049*
ALT (UI)*	26.60 (12.17)	25.80 (10.40)	0.800
AST (UI)**	21.00 (16.00-33.00)	18.50 (12.00-28.00)	0.782
GGT (UI)**	26.00 (22.00-38.00)	20.00 (17.00-28.00)	*0.002*
Cholesterol (mg/dl)*	173.42 (32.50)	155.80 (36.47)	0.069
LDL (mg/dl)*	103.55 (31.96)	87.20 (33.96)	0.066
HDL (mg/dl)*	47.97 (10.48)	40.84 (9.67)	0.220
Triglycerides (mg/dl)*	147.56 (86.75)	129.99 (78.18)	0.464
Glycemia (mg/dl)*	97.90 (9.45)	88.09 (10.51)	0.450
HOMA-IR**	2.56 (1.69-5.11)	2.03 (1.20-2.87)	*0.009*
Insulin (mUI)**	14.01 (8.89-21.90)	8.66 (6.22-11.72)	*0.001*
hs-CRP (mg/l)**	1.94 (0.80-2.28)	1.30 (0.71-2.00)	0.484
Interleukin-2 (pg/ml)**	0.279 (0.101-0.345)	0.231 (0.094-0.365)	0.430
Interleukin-6 (pg/ml)**	0.490 (0.109-0.754)	0.320 (0.085-0.487)	0.059
TNF-α (pg/ml)**	0.390 (0.187-0.695)	0.301 (0.074-0.328)	*0.032*
IFN-γ (pg/ml)**	0.340 (0.091-0.609)	0.233 (0.098-0.687)	0.670

*BMI: body mass index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transpeptidase; LDL: low-density lipoprotein; HDL: high-density lipoprotein; HOMA-IR: homeostasis model assessment-insulin resistance; hs-CRP: high sensitivity C reactive protein; TNF-α: tumor necrosis factor-α; IFN-γ: interferon gamma. * Values express as mean (SD). ** Values express as median and interquartiles.*

distribution pattern of adiposity secondary to insulin resistance. Likewise, severe obese individuals presented the highest rates of GGT. In their study, Fishbein et al. (18) examined the relationship of transaminases with the severity of steatosis and concluded that major changes are expected in severe cases of fatty liver, as opposed to our findings, given the prevalence of steatosis in the early stage has been similar between obese and severe obese. No association between the inflammatory profile and serum GGT values was observed.

As previously mentioned, insulin resistance (IR) is the main determinant of the pathophysiology of NAFDL (8). We observed that the IR indicators (HOMA-IR and serum insulin) were higher in obese patients with NAFLD, but did not differ between patients with and without liver disease. In parallel, TNF-α, an inflammatory cytokine associated with obesity and insulin resistance, showed similar behavior. TNF-α plays a crucial role in the determination of insulin resistance (19), stimulates the synthesis of other cytokines and has direct action in the liver by the increase of lipogenesis by upregulating catalyzing enzymes (20). In addition, it suppresses the expression of genes involved in the uptake of glucose and fatty acid metabolism favoring its accumulation (21). Finally, the inflammatory cascade triggered by TNF-α would be related to the progression of NAFL to NASH (22). Thus, it can be pointed out that these children and adolescents with NAFLD and severe obesity should be monitored more frequently in the future, since at the time of this study, from the laboratory point of view, there were no indications of hepatitis.

Jovinge et al. (23) report an increase in TNF-α in male subjects related to atherosclerotic disease, although this has not been verified in relation to insulin resistance. However, other studies (24,25) performed in adults describe a significant correlation between TNF-α, serum insulin and body mass index. In this regard, we evaluated the behavior of TNF-α in cases where HOMA-IR and serum insulin were normal or altered and no statistically significant differences were detected, although this behavior was confirmed when the BMI/age was considered. In addition, a correlation analysis involving the 56 children and adolescents diagnosed with NAFLD was performed. A positive and statistically significant correlation was found between HOMA-IR and serum insulin and CRP, an acute phase protein of inflammation, which has serum levels directly proportional to body mass index and therefore associated with obesity (26). Inversely, the IL-6, an inflammatory cytokine associated with obesity and insulin resistance, secreted by T and B lymphocytes, endothelium, fibroblasts and macrophages, showed a negative and significant correlation with IL2, a cytokine that participates in the immune response, secreted by T lymphocytes, suggesting a modulatory effect between cytokines (27). Thus, in our study we may suggest that changes in inflammatory markers may have influenced glycemic metabolic indicators with respect to insulin resistance and NAFLD in subjects with severe obesity.

Most likely, limitations of the study refer to its cross-sectional design, which because of its characteristics does not make it possible to establish a cause and effect relationship. Likewise, individual immune variations, the complexity involving the characterization of the inflammatory status and the verification of the

Table IV. Correlation analysis of inflammatory markers and clinical and laboratory parameters of 56 children and adolescents with non-alcoholic fatty liver disease

	IL2	IL6	TNF-α	IFN-γ	High sensitivity PCR
Age (years)	0.066; 0.631	-0.127; 0.072	-0.095; 0.485	-0.112; 0.410	-0.182; 0.457
Waist circumference (cm)	0.061; 0.656	-0.124; 0.362	0.073; 0.595	-0.072; 0.600	-0.134; 0.584
BMI	-0.119; 0.264	-0.078; 0.465	0.122; 0.251	0.011; 0.921	0.183; 0.084
BMI/age	-0.131; 0.219	-0.111; 0.297	0.272; *0.009*	0.062; 0.562	0.285; *0.006*
ALT (UI)	-0.029; 0.834	-0.058; 0.674	0.126; 0.359	0.012; 0.929	0.076; 0.756
AST (UI)	-0.029; 0.832	0.016; 0.905	0.016; 0.905	0.235; 0.084	-0.183; 0.454
GGT (UI)	-0.029; 0.832	-0.181; 0.186	-0.094; 0.510	0.156; 0.273	0.090; 0.613
Glycemia (mg/dl)	-0.237; 0.079	-0.090; 0.512	-0.134; 0.325	0.251; 0.062	-0.275; 0.254
HOMA-IR	0.005; 0.969	0.045; 0.741	-0.055; 0.685	0.109; 0.424	0.407; *0.034*
Insulin (mUI)	-0.083; 0.542	0.020; 0.886	-0.036; 0.795	0.086; 0.527	0.484; *0.036*
hs-CRP (mg/l)	0.078; 0.750	-0.452; 0.050	0.356; 0.135	-0.257; 0.295	1
Interleukin-2 (pg/ml)	1	-0.305; 0.022	-0.163; 0.230	-0.377; *0.004*	0.078; 0.750
Interleukin-6 (pg/ml)	-0.305; *0.022*	1	-0.113; 0.407	0.128; 0.349	-0.452; 0.052
TNF-α (pg/ml)	-0.163; 0.230	-0.113; 0.407	1	-0.260; *0.053*	0.356; 0.135
IFN-γ (pg/ml)	-0.377; *0.004*	0.128; 0.349	-0.260; *0.053*	1	-0.254; 0.295

BMI: body mass index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transpeptidase; HOMA-IR: homeostasis model assessment-insulin resistance; hs-CRP: C reactive protein-high sensitivity; TNF-α: tumor necrosis factor-α; IFN-γ: interferon gamma.

cytokine dosages in a single moment probably may have compromised the verification of the inflammatory framework intrinsic to obesity. We also emphasize limitations involving the imaging method (ultrasound) used for the diagnosis of NAFLD, which does not allow determining the severity of the inflammation with respect to the presence of steatohepatitis or fibrosis, which would only be allowed through liver biopsy, considered as gold standard.

Studies (28,29) are carried out in an attempt to elucidate an alleged low-grade inflammatory process underlying obesity, which would account for the expression of associated comorbidities, such as type 2 diabetes mellitus, systemic arterial hypertension, dyslipidemias and fatty liver. However, understanding is neither complete nor sufficient to define whether obesity will lead to an inflammatory picture or whether inflammation will lead to obesity. In our study, no differences in the profile of inflammatory cytokines between patients with and without NALFD were observed. However, the severely obese had higher median levels of TNF-α and IL-6, although the latter was not significant ($p = 0.059$), showing, however, a tendency for association. Although not statistically significant, the proportion of serious obese children and adolescents without NALFD was significantly higher than those with this change (52.9 *vs* 35.7%), suggesting that obesity severity is a confounder of this relationship. In fact, we found that, only among patients with DHGNA, the TNF-α profile was higher and significant among the severe obese when compared to obese patients. A possible explanation for this finding corresponds to the greater mass of adipocytes among the severe obese, confirmed by the larger waist circumferences presented by this group. In fact, abdominal adiposity is associated with increased insulin resistance and hyperinsulinism. Thus, these patients would carry a greater amount of pro-inflammatory cytokines. In addition, considering only the severely obese, we observed that this condition was associated with the most suggestive parameter of NAFLD, which is insulin resistance, variable related to the entire spectrum of the disease, from the emerging steatosis to the progression of the disease to cirrhosis and hepatocarcinoma (30).

Thus, our study suggests that obesity is an inflammatory condition in isolation. In some cases, comorbidities such as NAFLD can be expressed. Thus, we suggest the investigation of this population in view of the presumption of an incipient inflammatory condition since the onset of obesity.

Finally, this study intends to establish a theoretical reference, considering that the search in the literature resulted in a greater number of articles of revision when compared to the original articles.

REFERENCES

1. WHO. Obesity preventing and managing the global epidemic. Report of WHO Consultation on Obesity. Geneva: World Health Organization; 1998.
2. Ogden CL, Flegal KM, Carroll MID, Johnson CL. Prevalence and trends in obesity among US children and adolescents 1999-2000. JAMA 2002;288:1728-32.3.
3. Costa RF, Cintra IP, Fisberg M. Prevalence of overweight and obesity in school children of Santos city, Brazil. Arq Bras Endocrinol Metab 2006;50(1):60-7.
4. Harrell JS, Jessup A, Greene N. Changing our future: Obesity and the metabolic syndrome in children and adolescents. J Cardiovasc Nurs 2006;21:322-30.

5. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004;89(6):2548-56.
6. Wajchenberg BL. Tecido adiposo como glândula endócrina. Arq Bras Endocrinol Metab 2000;44/1:1320.
7. Fonseca-Alaniz MH, Takada J, Alonso-Vale MI, Lima FB. The adipose tissue as a regulatory center of the metabolism. Arq Bras Endocrinol Metab 2006;50:216-29.
8. Carvalheira JBC, Saad MJA. Insulin resistance/hyperinsulinemia associated diseases not included in the metabolic syndrome. Arq Bras Endocrinol Metab 2006;50(2):360-7.
9. Codoner-Franch P, Valls-Belles V, Arilla-Codoner A, Alonso-Iglesias E. Oxidant mechanisms in childhood obesity: The link between inflammation and oxidative stress. Transl Res 2011;158(6):369-84.
10. Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference of school aged children and adolescents. Bulletin of the WHO 2007;660-7.
11. WHO. Obesity: Preventing and managing the global epidemic. Geneva: World Health Organization; 2000.
12. Hamaguchi M, Kojima T, Itoh Y, Harano Y, Fujii K, Nakajima T, et al. The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. Am J Gastroenterol 2007;102(2):2708-15.
13. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37(Suppl 1)36:S81-90.
14. Obesidade na infância e na adolescência - Manual de Orientação/Sociedade Brasileira de Pediatria. Departamento Científico de Nutrologia. 2nd ed. São Paulo: SBP; 2012. p. 142.
15. Geloneze B, Tambascia MA. Laboratorial evaluation and diagnosis of insulin resistance. Arq Bras Endocrinol Metab 2006;50(2):208-15.
16. Almeida CAN, Pinho AP, Ricco RG, Pepato MT, Brunetti IL. Determination of glycemia and insulinemia and the homeostasis model assessment (HOMA) in schoolchildren and adolescents with normal body index. J Pediatr (Rio J) 2008;84:136-40.
17. Roberts EA. Pediatric nonalcoholic fatty liver disease (NAFDL): A "growing" problem? J Hepatol 2007;46:1133-42.
18. Fishbein MH, Miner M, Mogren C, Chalekson J. The spectrum of fatty liver in obese children and the relationship of serum aminotransferases to severity of steatosis. J Pediatr Gastroenterol Nutr 2003;36(1):54-61.
19. Fain JN, Madan AK, Hiler ML, Cheema P, Bahouth SW. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. Endocrinology 2004;145:2273-82.
20. Chitturi S, Abeygunasekera S, Farrell GC, Holmes-Walker J, Hui JM, Fung C, et al. NASH and insulin resistance: Insulin hypersecretion and specific association with the insulin resistance syndrome. Hepatology 2002;35:373-9.
21. Ruan H, Miles PDG, Ladd CM, Ross K, Golub TR, Olefsky JM, et al. Profiling gene transcription in vivo reveals adipose tissue as an immediate target tumor necrosis factor-α: Implications for insulin resistance. Diabetes 2002;51:3176-88.
22. Peverill W, Powell LW, Skoien R. Evolving concepts in the pathogenesis of NASH: Beyond steatosis and inflammation. Int J Mol Sci 2014;15:8591-638.
23. Jovinge S, Hamsten A, Tornvall P, Proudler A, Bävenhoim P, Ericsson C-G, et al. Evidence for a role of tumor necrosis factor-alpha in disturbance of triglyceride and glucose metabolism predisposing to coronary heart disease. Metabolism 1998;47:113-8.
24. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest 1995;95:2409-15.
25. Kern PA, Sagnizadeh M, Ong JM, Bosch RJ, Deem R, Simsolo RB. The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. Clin Invest 1995;95:2111-29.
26. Trayhurn P, Wood IS. Adipokines: Inflammation and the pleiotropic role of white adipose tissue. Br J Nutr 2004;92(3):347-55.
27. Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, et al. IL-23 pathogenic T-cell population induces autoimmune inflammation. J Exp Med 200;201(2):233-40.
28. Caballero B. The global epidemic of obesity: An overview. Epidemiol Rev 2007;29:1-5.
29. Spielgeman BM, Flier JS. Obesity and the regulation of energy balance. Cell 2001;104:531-43.
30. Duvnjak M, Lerotic I, Barsic N, Tomasic V, Jukie LV, Velagie V. Pathogenesis and management issues for non-alcoholic fatty liver disease. World J Gastroenterol 2007;13:4539-50.

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ARÁN

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Trabajo Original

Obesidad y síndrome metabólico

Prevalence of childhood overweight/obesity in Spain 1993-2011 and associated risk factors in 2011

Prevalencia de sobrepeso y obesidad infantil en España (1993-2011) y factores asociados en 2011

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Abstract

Introduction: Childhood obesity is a recognized public health problem. The present work reports the changing prevalence of childhood overweight/obesity in Spanish boys and girls over the period 1993-2011, and examines the risk factors apparent in 2011.

Methods: Children with a body mass index (BMI) of ≥ 25 were deemed overweight, and those with a BMI of ≥ 30 were deemed obese. Overweight and obesity was consistently more common among boys than among girls.

Results: The prevalence of overweight and obesity in Spain increased over the study period.

Conclusions: According to the 2011 data, children who undertook no physical activity, or whose parents/guardians had a low level of education, showed the highest prevalence of obesity.

Key words:

Overweight. Pediatric obesity. Prevalence. Risk factors.

Resumen

Introducción: la obesidad infantil es un problema de salud pública a nivel mundial. El objetivo de este trabajo es describir la evolución de la prevalencia de sobrepeso/obesidad infantil en niños y niñas durante el periodo 1993-2011 y analizar cuáles son los factores de riesgo asociados, utilizando la Encuesta Nacional de Salud (ENS) de 2011.

Métodos: los niños con índice de masa corporal (IMC) ≥ 25 se consideraron con sobrepeso y aquellos con IMC ≥ 30, como obesos. Se hizo uso de la ENS desde 1993 a 2011.

Resultados: la prevalencia de sobrepeso y obesidad en España aumentó durante el periodo de estudio. La prevalencia de sobrepeso y obesidad fue más elevada en niños que en niñas.

Conclusiones: según los datos de 2011, los niños que no realizaban ningún tipo de actividad física o cuyos padres tenían un nivel de educación bajo mostraron la mayor prevalencia de obesidad.

Palabras clave:

Obesidad. Sobrepeso. Pediatría. Prevalencia. Factores de riesgo.

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INTRODUCTION

The prevalence of childhood obesity has increased across Europe (1) and it is now a recognized public health problem. According to the World Health Organization (WHO), obesity is a chronic disease that has reached epidemic proportions; in some parts of the world, 17.6% of children under five years of age are obese (2). Recent studies in different countries have shown 10% of all school-age children to have excess body fat, increasing their risk of developing chronic diseases (3). Indeed, overweight/obesity has become one of the most common nutritional problems among children of developed countries, though it is by no means limited to them (3,4).

Obesity is increasingly affecting all age groups and is associated with increased morbidity and mortality (5,6). The complications of obesity most commonly appear during adulthood, although nowadays they are also being detected in childhood. Many factors are associated with its appearance; genetic, sociodemographic (including sex and level of parental education) and lifestyle factors are all involved, including the duration of breastfeeding, the daily taking of breakfast, getting enough sleep, time spent in front of monitors (7) and the amount of physical activity undertaken (6,8). Tackling obesity is commonly one of the best set out objectives in healthcare strategies (9), but understanding the factors that encourage its appearance is vital if it is to be prevented (10,11).

The aim of the present work was to describe the prevalence of overweight and obesity in Spanish children (boys and girls) using data provided by the National Health Surveys (*Encuestas Nacionales de Salud*) of 1993-2011, and to determine the main socioeconomic and lifestyle factors influencing the appearance of these problems in 2011.

METHODS

DESIGN

This descriptive, cross-sectional study examined data provided by the 1993-2011 Spanish National Health Surveys (Ministerio de Sanidad, 1993; 1995; 1997; 2001; 2003; 2006; 2011). These surveys question members of the public regarding their health status and provide information on perceived morbidity, risk factors, the use of health services, and the following of preventive practices.

SUBJECTS

The data examined were those of children aged 2-15 years, chosen by stratified multi-stage sampling. Entries for children of this age were stratified by region, then by province (as conglomerates), then by "habitat" (urban or rural area). Schools were then chosen at random within these "habitats", then classes by age group between 2 and 15 years, followed by random sampling of the children in these age groups. The final sample size (which included data from only fully completed survey questionnaires) was n = 23,237 (11,663 girls and 11,574 boys). The children's heights and weights (as recorded by their parents/guardians) were used to calculate their body mass indices (BMI). Children with a BMI ≥ 25 were deemed overweight, and those with a BMI ≥ 30 were deemed obese.

STATISTICS

The prevalence (with 95% confidence intervals) of overweight and obesity was analyzed for each survey year separately.

The association of overweight and obesity with each independent variable as measured in 2011, i.e., sex, age at the time of the survey, recommended number of hours of sleep (3-4 years 12 h, 4-5 years 11 h, 5-11 years 10 h and 11+ years 9 h) (10,13), physical activity (measured as yes/no), hours spent watching TV or using other monitors (< 2 or ≥ 2 h per day) (14), having been breast-fed for the first three or six months (yes/no for each), taking breakfast daily (yes/no), level of education of head of family (no education or obligatory schooling, school baccalaureate or technical award, higher education) (15,16), was examined using the Chi-squared test. Significance was set at $p \leq 0.05$. Adjusted odds ratios (OR) were obtained by bivariate and consequent multivariate regression analysis. All calculations were performed using SPSS v.21.0 for Windows.

ETHICS

Since all data used were rendered anonymous and were in the public domain (www.ine.es), no ethical approval was required.

RESULTS

Table I shows the prevalence of childhood overweight and obesity for girls and boys over the study period. In 1993, 7.0% of boys were overweight, but in 2011 this figure had risen to 13.2%; for girls, the figures were 6.0% and 10.2% respectively. In 1993, 13.8% of boys and 8.7% of girls were obese, while in 2011, 13.6% of boys and 9.9% of girls were obese. Overweight and obesity was consistently more common among boys than in girls.

Table II reveals that, in 2011 (note that 2011 health survey data were used to determine all risk factor associations), those children who belonged to a family whose head had no or only low-level studies showed a higher prevalence of overweight (boys 13.2%, girls 7.4%) compared to those who had higher education (boys 19.1%, girls 9.0%) ($p < 0.05$ in all cases). Similar results were seen for obesity (boys 16.3% and girls 5.5% compared to 10.7 and 8.1%; $p < 0.05$ for the comparison between boys).

Those children who did not sleep the recommended number of hours were more commonly obese (boys 16.3%, girls 12.6%)

Table I. Prevalence of overweight/obesity in boys and girls, as recorded in different National Health Surveys (1993-2011)

		Both sexes			Boys			Girls		
		n	%	(95% CI)	n	%	(95% CI)	n	%	(95% CI)
Normal-weight	1993	3,926	82.3	(81.1-83.5)	1,937	79.3	(77.5-81.1)	1,989	85.4	(83.8-87)
	1995	1,517	83.9	(82.1-85.7)	764	82.3	(79.6-85)	753	85.5	(83.0-88.0)
	1997	1,452	81.7	(79.7-83.7)	718	79.1	(76.1-82.1)	734	84.5	(81.9-87.1)
	2001	3,663	80.6	(79.3-81.9)	1,826	78.2	(76.3-80.1)	1,837	83	(81.3-84.7)
	2003	4,258	78.9	(77.7-80.1)	2,125	76.6	(74.8-78.4)	2,133	81.3	(79.6-83.0)
	2006	4,640	77.4	(76.2-78.6)	2,286	74.2	(72.4-76.0)	2,354	80.7	(79.1-82.3)
	2011	2,864	76.3	(74.7-77.9)	1,470	73.2	(70.9-75.5)	1,394	79.9	(77.8-82.0)
Overweight	1993	309	6.5	(5.9-7.0)	170	7	(3.2-10.8)	139	6	(2.1-9.9)
	1995	131	7.2	(2.8-11.6)	65	7	(0.8-13.2)	66	7.5	(1.1-13.9)
	1997	138	7.8	(3.3-12.3)	73	8	(1.4-14.2)	65	7.5	(1.1-13.9)
	2001	362	8	(5.2-10.8)	203	8.7	(4.8-12.6)	159	7.2	(3.2-11.2)
	2003	598	11.1	(8.6-13.6)	309	11.1	(7.6-14.6)	289	11	(7.4-14.6)
	2006	677	11.3	(8.9-13.7)	366	11.9	(8.6-15.2)	311	10.7	(7.3-14.1)
	2011	443	11.8	(8.8-14.8)	265	13.2	(9.1-17.3)	178	10.2	(5.8-14.6)
Obese	1993	538	11.3	(8.6-14)	336	13.8	(10.1-17.5)	202	8.7	(4.8-12.6)
	1995	161	8.9	(4.5-13.3)	99	10.7	(4.6-16.8)	62	7	(0.6-1.4)
	1997	187	10.5	(6.1-14.9)	117	12.9	(6.8-19)	70	8.1	(1.7-14.5)
	2001	522	11.5	(8.8-14.2)	305	13.1	(9.3-16.9)	217	9.8	(5.8-13.8)
	2003	544	10.1	(7.6-12.6)	341	12.3	(8.8-15.8)	203	7.7	(4.0-11.4)
	2006	680	11.3	(8.9-13.7)	427	13.9	(10.6-17.2)	253	8.7	(5.2-12.2)
	2011	445	11.9	(8.9-14.9)	272	13.6	(9.5-17.7)	173	9.9	(5.4-14.4)

n: sample size; CI: confidence intervals.

Table II. Distribution of normal-weight, overweight and obesity with respect to sex and lifestyle variables according to the 2011 National Health Survey results

		Boys n (%)			Girls n (%)		
		Normal-weight	**Overweight**	**Obese**	**Normal-weight**	**Overweight**	**Obese**
Education level of family head	No studies or just obligatory schooling	670 (70.5)	125 (13.2)*	155 (16.3)*	458 (87.1)	39 (7.4)*	29 (5.5)
	Baccalaureate or technical training	521 (74.7)	90 (13.0)*	86 (12.3)*	197 (83.1)	17 (7.2)	23 (9.7)
	Higher education	275 (77.2)	50 (12.1)*	31 (10.7)*	92 (82.9)	10 (9.0)*	9 (8.1)
Hours of sleep	Recommended no. of hours not slept	842 (70.9)	152 (12.8)*	193 (16.3)*	778 (78.0)	94 (9.4)*	126 (12.6)*
	Recommended no. of hours slept	628 (76.6)	113 (13.8)	79 (9.6)*	616 (82.5)	84 (11.2)	47 (6.3)*
Physical activity	No	170 (62.0)	38 (13.9)	66 (24.1)	276 (74.4)	43 (11.6)	52 (14.0)
	Yes	1,300 (75.1)	227 (13.1)*	205 (11.8)*	1,116 (81.3)	135 (9.8)*	121 (8.8)
Time spent at a monitor (TV, computer, video-gaming)	≤ 2 h	101 (76.5)	15 (11.4)	16 (12.1)	83 (80.6)	11 (10.7)	9 (8.7)
	> 2 h	832 (71.5)	165 (14.2)	166 (14.3)	729 (77.6)	112 (11.9)	99 (10.5)
Breast-fed until 3 months old	No	1,278 (73.9)	241 (13.9)*	210 (12.1)*	1,221 (81.1)	157 (10.4)*	127 (8.4)
	Yes	192 (69.1)	24 (8.6)*	62 (22.3)	173 (72.1)	21 (8.8)*	46 (19.2)
Breast-fed until 6 months old	No	1,332 (73.6)	248 (13.7)	230 (12.7)	1,273 (80.7)	165 (10.5)	140 (8.9)*
	Yes	138 (70.1)	17 (8.6)	42 (21.3)	121 (72.5)	13 (7.8)	33 (19.8)
Took daily breakfast	No	7 (36.8)	5 (26.3)	7 (36.8)	14 (82.4)	2 (11.8)	1 (5.9)
	Yes	1,463 (73.6)	260 (13.1)	265 (13.3)*	1,380 (79.9)	176 (10.2)	172 (10.0)

*n: Sample size. *p < 0.05.*

than those who slept the recommended amount (boys 9.6%, girls 6.3%) ($p < 0.05$ both sexes). Those children who undertook some kind of physical activity were less commonly overweight (boys 13.1%, girls 9.8%) than those who undertook none (boys 13.9%, girls 11.6%) ($p < 0.05$ for both sexes); they were also less commonly obese (boys 11.8%, girls 8.8%) than those who undertook no physical activity (boys 24.1%, girls 14%) ($p < 0.05$ for the comparison between boys). No significant differences were seen between children who used monitors (TV, playing videogames, etc.) more than two hours per day compared to those who used them for less time, either in terms of overweight (boys 14.2%, girls 11.9% *vs* boys 11.4%, girls 10.7%) or obesity (boys 14.3%, girls 10.5% *vs* boys 12.1%, girls 8.7%).

Those children exclusively breast-fed for their first three months of life were less commonly overweight (boys 8.6%, girls 8.8%) than those who were not so fed (boys 13.9%, girls 10.4%) ($p < 0.05$ for boys and girls). No significant differences were seen between children who were exclusively breast-fed for the first six months of life and those who were not in terms of overweight (boys 8.6%, girls 7.8% *vs* boys 13.7%, girls 10.5%). No comparisons were made for obesity given the small sample size available, neither was any significant difference seen in terms of overweight between children who ate or did not eat breakfast (boys 26.3%, girls 11.8% *vs* boys 13.1% girls 10.2%).

Table III shows the results of the multivariate analysis. Age, male sex, being breast-fed until three months, not undertaking physical activity, and the level of education of the head of the family were independently and significantly associated with being overweight. The same variables were independently and significantly associated with being obese.

DISCUSSION

The present results show that the prevalence of overweight and obesity increased over the study period in both boys and girls. In addition, overweight and obesity was consistently more common among boys.

The present prevalence data for 1997 were compared to those of the enKid study (16) which was performed in 1997-1998. The prevalence of overweight was higher in this latter study (boys 14.3%, girls 15.6%) than in the present work (boys 8.0%, girls 7.5%). In addition, the present prevalence data for 2011 were compared to those reported by the Aladino 2011 (17). This latter study reported a higher prevalence of overweight (boys 22.9%, girls 17.4% *vs* the present boys 13.2%, girls 10.2%), but a lower prevalence of obesity (boys 7.7%, girls 4.7% *vs* the present boys 13.6%, girls 9.9%). These discrepancies might be due to differences in the methodologies employed.

According to the 2011 health survey results (used for all associations with lifestyle factors), the prevalence of overweight and obesity was higher among children of families whose heads were the least well educated. The enKid study reported similar results for obesity (15.6% *vs* 10.9% in families with the head in the highest education bracket) (16). Similarly, the Aladino 2011 study reported that, among normal-weight children, 58.5% of their mothers and 59.4% of their fathers had university studies, while among obese children only 14.6% of their mothers and 14.7% of their fathers had university studies. This might reflect a limitation of economic resources faced by families with low education levels, or their more limited knowledge of what makes a healthy diet, or perhaps a different aesthetic outlook (17).

Table III. Multivariate analysis of factors associated with overweight/obesity according to the data collected by the 2011 National Health Survey

		Overweight		Obesity	
		OR	(CI 95%)	OR	(CI 95%)
Sex	Boys	1.22***	(1.15-1.30)	1.4***	(1.29-1.51)
	Girls	1		1	
Age	Years	1.03***	(1.02-1.04)	0.88***	(0.87-0.89)
Breast-fed until 3 months old	Yes	1		1	
	No	1.24**	(1.07-1.43)	1.24**	(1.07-1.42)
Physical activity	Yes	1		1	
	No	1.03**	(1.01-1.06)	1.22***	(1.11-1.35)
Education level of family head	No studies or just obligatory schooling	1.21***	(1.17-1.26)	1.36***	(1.21-1.52)
	Baccalaureate or technical training	1.10***	(1.06-1.13)	1.22**	(1.09-1.39)
	Higher education	1		1	

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Those children who slept the recommended number of hours for their age were less commonly obese than those who did not get enough sleep. Very few studies performed in Spain have examined the link between the number of hours spent sleeping and overweight/obesity. The Aladino 2011 study did report, however, results very similar to those of the present work: 10.7% of those who slept sufficient hours were obese, rising to 15.2% among those who did not, whereas in the present study these figures were boys 9.6% *vs* 16.3%, and girls 6.3% *vs* 12.6% (17).

No differences were seen in overweight or obesity between those children who spent under or over two hours per day using monitors. This is in contrast to that reported in other studies. For example, in Sweden, children who had a television in their bedrooms, or who watched television for more than two hours per day, were more likely to be overweight/obese (OR 1.26 and 1.55 respectively) (7). This discrepancy might be due to the small numbers of children in the present study who actually spent < 2 h per day in this activity.

The prevalence of obesity was lowest among those children who undertook physical activity (boys 11.8%, girls 8.8%), and highest among those who undertook none (boys 24.1%, girls 14.0%). Another paper reported similar results, with obesity more prevalent among those who undertook no physical activity (boys 21.7%, girls 9.8% *vs* boys 9.7%, girls 4.3% in those who did) (9). Other authors also report children who played sport to be less commonly obese than those who did not (10.3% *vs* 22.7%) (16). In the present work, children who spent more time in physical activity spent less time using monitors.

Overweight was less common among children who had been breast-fed until three months of age than in those not so fed. Similar results have been reported from Korea (18), and in an earlier systematic review of 300 articles from around the world (19). No significant differences were found for children who were/were not breast-fed until six months of age, perhaps due to the small sample size available for comparison.

Overweight was no less prevalent among children who ate breakfast (no result is available for obesity given the small numbers involved). In contrast, the AVENA study (20) reported that the habit of not taking breakfast was more common among children who were overweight or obese (normal weight children 5.9%, overweight children 11.6%, obese children 13.3%, $p < 0.05$). The Aladino 2011 study also reported similar results, with 3.1% of normal weight children and 4.2% of obese children not eating breakfast. Not taking breakfast might reflect a wider range of poor food habits, or might leave children hungry later in the day, leading to their eating with poorer control. The discrepancy with the present results is probably due to the low sample size available for those who took no breakfast (17).

CONCLUSIONS

The prevalence of obesity increased in Spain between 1993 and 2011, and was more common among boys than in girls over this study period. Child overweight/obesity was found to be more prevalent in families in which the head of the family had a low level of education. Breastfeeding for three months appears to reduce the prevalence of overweight, while undertaking physical activity reduces the prevalence of obesity.

REFERENCES

1. Kipping RR, Jago R LD. Obesity in children. Part 1: Epidemiology, measurement, risk factors, and screening. BMJ 2008;15:33-1824.
2. Organization WH. Health Impact Assessment Methods and Strategies. Copenhagen: World Health Organization Regional Office for Europe. Cited 2016 Apr 1. Available from: http://www.euro.who.int/healthimpact
3. Kosti RI, Panagiotakos DB, Kosti RI, Panagiotakos DB. The epidemic of obesity in children and adolescents in the world. Cent Eur J Public Health 2015;14:151-9.
4. Tadesse Y, Derso T, Alene KA, Wassie MM. Prevalence and factors associated with overweight and obesity among private kindergarten school children in Bahirdar Town, Northwest Ethiopia: Cross-sectional study. BMC Res Notes 2017;10(1):22.
5. Jelastopulu E, Kallianezos P, Merekoulias G, Alexopoulos EC, Sapountzi-Krepia D. Prevalence and risk factors of excess weight in schoolchildren in West Greece. Nurs Heal Sci 2012;14:372-80.
6. Wu H, Zong X, Li H. The prevalence of overweight, obesity and stunting in school children aged 6-19 years in Beijing, China. Ann Hum Biol 2016;43(6).
7. Garmy P, Clausson EK, Nyberg P, Jakobsson U. Overweight and television and computer habits in Swedish school-age children and adolescents: A cross-sectional study. Nurs Heal Sci 2014;16(2):143-8.
8. Thasanasuwan W SW. Low sleeping time, high TV viewing time, and physical inactivity in school are risk factors for obesity in pre-adolescent Thai children. J Med Assoc Thai 2016;99(3):314-21.
9. Bartrina J, Rodrigo C. Epidemiología y factores determinantes de la obesidad infantil y juvenil en España. Rev Pediatr 2005;VII:13-47.
10. Vázquez IA, Zapico RB, Díez JH, Rodríguez CF. Actividad física, ocio sedentario, falta de sueño y sobrepeso infantil. Psicothema 2008;20(4):516-20.
11. Carriere C, Cabaussel C, Bader C, Barberger-Gateau P, Barat P TH. Multidisciplinary care management has a positive effect on paediatric obesity and social and individual factors are associated with better outcomes. Acta Paediatr 2016;105(11).
12. Ministerio de Sanidad Servicios Sociales e Igualdad. Encuesta Nacional de Salud 2011. Available from: http://pestadistico.inteligenciadegestion.msssi.es/publicoSNS/comun/ArbolNodos.aspx
13. Anton-Paduraru D, Teslariu O, Mocanu V. Influence of sleep on obesity in children. Rev Med Chir Soc Med Nat Iasi 2016;120(2):239-43.
14. Zapico RB, Vázquez IA, Díez JH, Rodríguez CF. La relación entre la falta de sueño, el ocio sedentario y el sobrepeso infantil. Análisis Modif Conduct 2006;32:391-401.
15. Vázquez IA, Zapico RB. La obesidad infantil como resultado de un estilo de vida obesogénico. Endocrnol Nutr 2007;54(10):530-4.
16. Serra L, Ribas L, Aranceta J. Obesidad infantil y juvenil en España. Resultados del estudio EnKid (1998-2000). Med Clin 2003;121(19):725-32.
17. Ortega RM, López AM, Perea JM, González L. Estudio Aladino, estudio de vigilancia del crecimiento, alimentación, actividad física, desarrollo infantil y obesidad en España. 2011. Available from: http://www.naos.aesan.msssi.gob.es/en/naos/ficheros/investigacion/Articulo_ALADINO.pdf
18. Park J, Chu HS, Chu SH, Jekal YS, Lee JY. The effect of predominant breast-feeding on the risk ofobesity in Korean preschool children. Nurs Heal Sci 2015;17:77-83.
19. Lefebvre CM, John RM. The effect of breastfeeding on childhood overweight and obesity: A systematic review of the literature. J Am Assoc Nurse Pract 2014;26(7):386-401.
20. Wärnberg J, Ruiz JR, Ortega FB, Romeo J, González Gross M, Moreno LA, et al. Grupo AVENA. Estudio AVENA (Alimentación y valoración del estado nutricional en adolescentes). Available from: http://www.estudioavena.es/downloads/Publicaciones/WarnbergJ_2006PediatrInt.pdf

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Trabajo Original

Obesidad y síndrome metabólico

Behavioral patterns that increase or decrease risk of abdominal adiposity in adults

Patrones de comportamiento que aumentan o disminuyen el riesgo de adiposidad abdominal en adultos

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Abstract

Introduction: The identification of risk or protective behavioral patterns associated with abdominal adiposity may aid in prevention and health promotion measures.

Objective: To identify and to associate behavioral patterns of risk and protection to abdominal adiposity in adults in a Brazilian city.

Material and methods: A population-based cross-sectional study was carried out in Viçosa, Brazil, with 1,226 adults of both sexes. Information on social-demographic characteristics, food intake, level of physical activity, alcohol consumption and smoking were collected by using a questionnaire. The anthropometric measurement of waist circumference and anthropometric indices waist/hip ratio and waist/height ratio were indicators of abdominal adiposity. To identify behavioral patterns, exploratory factor analysis was applied for the variables considered as risk or protective factors. The association of the identified patterns with abdominal adiposity was estimated by multiple linear regression, adjusted for gender, age and social economical class.

Results: Two patterns were obtained, "healthy" and "risk". The "healthy" pattern, comprised of the clustering of the variables food consumption, fruits, fresh fruit juices, raw and cooked vegetables and the appropriate level of physical activity, was negatively associated with abdominal adiposity identified by waist circumference ($p = 0.048$), waist/hip ($p = 0.013$) and waist/height ($p = 0.018$) indices. The "risk" pattern, composed of smoking, alcohol beverage abuse and habit of consuming visible fat in fat-rich red meat or poultry skin, was positively associated with abdominal adiposity identified by waist circumference ($p = 0.002$) and waist/hip ($p = 0.007$) and waist/height indices ($p = 0.006$).

Conclusions: Two behavioral patterns were identified, a risk pattern and a protective pattern for abdominal adiposity in the assessed population. The study shows the importance of conducting clustering of multiple risk and protective factors to better explain the health conditions of a group.

Key words:

Abdominal obesity. Factorial analysis. Protective factors. Risk factors.

Resumen

Introducción: la identificación de los riesgos o los patrones de comportamiento de protección asociados con la adiposidad abdominal puede ayudar en las medidas de prevención y promoción de la salud.

Objetivo: identificar y establecer la asociación entre los patrones de comportamiento de riesgo y de protección y la adiposidad abdominal en adultos en una ciudad brasileña.

Material y métodos: se llevó a cabo un estudio transversal basado en la población en Viçosa, Brasil, con 1.226 adultos de ambos sexos. Se recogió información sobre las características sociodemográficas, la ingesta de alimentos, el nivel de actividad física, el consumo de bebidas alcohólicas y el hábito tabáquico mediante un cuestionario. La medición antropométrica de la circunferencia de la cintura y de los índices antropométricos cintura/cadera y cintura/altura fueron los indicadores de adiposidad abdominal. Para identificar los patrones de comportamiento, se aplicó un análisis factorial exploratorio de las variables de riesgo o factores de protección considerados. La asociación de los patrones identificados con la adiposidad abdominal se estimó por regresión lineal múltiple, ajustada por género, edad y nivel socioeconómico.

Resultados: se establecieron dos patrones, "sano" y "riesgo". El patrón "sano", compuesto por la agrupación de las variables consumo de alimentos, frutas, zumos de fruta fresca, verdura cruda y cocida y el nivel apropiado de actividad física, se asoció negativamente con la adiposidad abdominal identificada por la circunferencia de la cintura ($p = 0,048$) y los índices cintura/cadera ($p = 0,013$) y cintura/altura ($p = 0,018$). El patrón de "riesgo", compuesto por hábito tabáquico, abuso de alcohol y consumo de grasa visible en carnes rojas ricas en grasa o piel de las aves, se asoció positivamente con la adiposidad abdominal identificada por la circunferencia de la cintura ($p = 0,002$) y las ratios cintura/cadera ($p = 0,007$) y cintura/altura ($p = 0,006$).

Conclusiones: fueron identificados dos patrones de comportamiento, el patrón de riesgo y el patrón de protección, relacionados con la adiposidad abdominal en la población estudiada. El estudio muestra la importancia de agrupar múltiples factores de riesgo y de protección para explicar mejor las condiciones de salud de un grupo.

Palabras clave:

Obesidad abdominal. Análisis factorial. Factores de protección. Factores de riesgo.

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INTRODUCTION

Obesity is characterized by excessive accumulation of body fat (1) and represents a serious public health issue due to its trend of increasing prevalence and the impact it has on society (2). Body mass index (BMI) has been the most frequently used method to define excess body weight; however, it is unable to differentiate between lean mass and fat mass (3) and so central obesity measures have been recently recommended due to a strong association with morbidity and mortality (4-6).

Abdominal adiposity is defined as the accumulation of intra-abdominal fat and it has been considered as an important risk factor for major chronic non-communicable diseases (NCDs) (7). Although there are sophisticated methods for evaluating abdominal fat, from an epidemiological point of view, the anthropometric indicators are considered for being used in population studies due to their low cost and ease of use (8). Waist circumference, waist-to-hip ratio and waist-to-height ratio are alternative proposals for the detection of abdominal obesity and have been strongly associated with cardiometabolic risk (5). However, even though there is consensus about the importance of measuring such anthropometric measures, epidemiological studies have not been able to demonstrate the measure or index that shows a better association with unhealthy behavioral patterns (7,9,10), making it necessary to carry out further studies that compare these indices to verify which one is more associated with behavioral patterns.

Studies in some countries have shown that abdominal adiposity in adults has increased over the past few years (11-13). This increase is attributed to changes in eating patterns and physical activity, increased stress and endocrine disruptors (14), and socioeconomic factors such as education level, income and occupation (8). Adequate dietary intake of fruits and vegetables and level of leisure physical activity, no smoking and no alcohol consumption has been associated to a lower risk of abdominal obesity (15-17).

The exploratory factor analysis has been increasingly used since this technique allows to identify the clustering of variables, showing the interrelations among them (18,19).

However, in nutritional epidemiology, most of the published papers that used this technique have focused on the clustering of foods/nutrients in the definition of dietary patterns (20,21), rather than on identifying abdominal adiposity risk or protection patterns by clustering behavioral and dietary variables. In addition, some unhealthy behaviors may interact, producing an even greater risk than the individual ones (22).

However, studies that make associations between abdominal adiposity risk or protection factors are rare and inconclusive (23,24). Therefore, it is of great importance to identify behavioral risk and protection patterns in predicting abdominal obesity so that intervention strategies to prevent and to control this type of worsening may be better targeted, with actions that promote health.

MATERIAL AND METHODS

This work is an epidemiological cross-sectional designed study conducted in the urban area of the city of Viçosa, Brazil, from September 2012 to April 2014. It was carried out by the health and nutrition study group of Viçosa (ESA/Viçosa). Data collection involved two steps: visits to the subjects' residences with the application of a structured questionnaire and anthropometric measurements on the university facilities. The fieldwork flow and all instruments used in the data collection were previously calibrated and tested in a pilot study (25,26).

The study sample was made up of adults of both sexes; 50.8% were women, from 20 to 59 years old. For sample calculation, the formula for prevalence estimates was used, considering the total number of individuals between 20 and 59 years old living in the urban area of Viçosa, totaling 43,431 people (27), an estimated prevalence of 50% (since this study is part of a thematic research project where other outcomes were analyzed), confidence level of 95%, sampling error of 4.1 percentage points and estimated *deff* (design effect sampling per cluster) of 1.55. An increase of 20% occurred for losses and refusals, and 10% for control of confusion factors. By using Epi-Info, version 3.5.2® (28), calculations evidenced a minimal sample size (n) of 1,137 participants.

The following were considered as exclusion criteria: pregnant women, postpartum women, bedridden individuals or those unable to be measured, and individuals with cognitive/intellectual difficulty or who were not able to answer the questionnaire. Individuals who reported having a previous diagnosis of diabetes or cardiovascular disease were not excluded from this study because the prevalence of these outcomes was considered to be low.

Two-stage cluster sampling was carried out. First, census sectors were randomly selected. After that, a block and a corner were selected, from which fieldwork was started in a clockwise direction. Thirty census sectors were randomly selected from 99 census sectors existing in Viçosa by simple random sampling with no replacement.

The information collected from the questionnaire consisted of social-demographic characteristics, food intake, physical activity level, alcohol consumption and smoking. The questions used in this survey were based on the Surveillance System of Risk and Protective Factors for Non Communicable Diseases through Telephone Interviews (*Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico,* VIGITEL) (26), held annually in Brazil. The anthropometric measurements used in this study were performed by measuring the height and the circumferences of waist and hip (29).

The social demographic variables were as follows: age (completed years), education degree in completed years of study (defined as 0-3, 4-7, and ≥ 8 years of schooling) and socioeconomic status, determined by tools of the Brazilian Association of Research Companies (30) and classified into A and B, C and D and E.

The risk behavior indicators for abdominal adiposity included in this study were: smoking, abusive consumption of alcoholic beverages, excessive screen time, consumption of sugar-sweetened beverages at least five times a week, considered regular, and habit of consuming saturated fat source food, such as whole milk, red meat with visible fat and poultry skin.

Smoking was categorized into smokers, former smokers and non-smokers, regardless of the frequency and intensity of using tobacco (31). The abusive consumption of alcohol was considered

as present when the intake of at least five shots in a single sitting occurred, based on the reference of the past 30 days for men and at least four for women. The standard was considered as the consumption of half a bottle or a can of beer, a glass of wine or a shot of distilled drink (32). The screen time was evaluated by summing the time the individual spent watching television or using the computer on weekdays and weekends. The cut-off point, indicator of a sedentary behavior, was the sum of the time longer than or equal to four hours a day watching TV or using the computer (33).

Among the behavioral indicators related to protective factors for abdominal adiposity, the following were included: the appropriate level of physical activity in leisure time and regular consumption of fruits, fresh fruit juices, raw salads, cooked vegetables and beans.

The level of physical activity during leisure time was assessed by the specific section of the long version of the International Physical Activity Questionnaire. The cut-off for physical activity practice time longer than or equal to 150 minutes per week to classify individuals as physically active (34) was used. Dietary intake associated with protection for abdominal adiposity was regarded from the report of intake of fruits, fresh fruit juices, vegetables and beans for at least five days a week, which was considered as regular consumption.

Abdominal adiposity was evaluated by means of anthropometric parameters of waist circumference (WC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHER). Waist circumference was measured by using an nonelastic 2-m long measuring tape (Sanny®, São Paulo, SP, Brazil), the measurement being made at the midpoint between the iliac crest and the last rib. Hip circumference was measured at the most protuberant area of the buttocks, and height was measured by a fixed rod stadiometer (Welmy®, in wall, Santa Bárbara D'Oeste, SP, Brazil), with a length of 2.5 m and resolution of 0.1 cm.

The cut-offs used were those proposed by Grundy et al. (35) to determine the prevalence of abdominal adiposity based on the evaluation of waist circumference, which considers that men with a WC ≥ 90 cm and women with a WC ≥ 80 cm have central obesity. WHR was determined by the following equation: [WHR = WC/hip circumference (cm)], and the cut-offs used were men with a ratio ≥ 1 and women ≥ 0.85 were considered as having central obesity (36). The cut-offs proposed by Ashwell and Hsieh (37), which consider that values ≥ 0.5 for men and women indicate abdominal adiposity, were used to determine adiposity prevalence from the evaluation of the waist-to-height ratio. Measurements were performed in triplicate by a single evaluator, using the average of the measurements in the analysis.

For the identification of behavioral patterns, the methodology of exploratory factor analysis was applied to the answers obtained from the structured questionnaire. Prior to the calculation of the principal component analysis (PCA), the coefficient of Kaiser-Mayer-Olkin (KMO) and Bartlett's sphericity test were estimated to assess the quality of the correlations among the variables. After that, the factors were extracted by the principal components analysis method, rotated by an orthogonal transformation (varimax), retaining those with eigenvalues > 1.3, defined according to the scree plot graph of the variance for the number of components. The exploratory factor structure was obtained from the indicators that presented factor loadings larger than 0.3, a score was determined for each behavioral pattern using principal components factor analysis, and the patterns were named according to the retained indicators.

The association among the patterns and abdominal obesity anthropometric indicators was analyzed using linear regression models. The WC, WHR and WHER variables presented a symmetric distribution ($p > 0.05$; Shapiro-Wilk test). The main independent variable was the score of the patterns, those which had a $p < 0.20$ in the linear regression analysis. The models were adjusted by confounding variables such as gender, age and social economical class. A significance level of 5% was considered in the study.

Quality control of this study was performed by applying, at random, questions of the questionnaire to 10% of the sample by phone calls and double data input. After checking data consistency, analyses were performed in the STATA statistical package, version 13.1, by taking into account the effect of sample design by the "svy" command group, which considered the complex sample design (sampling by clustering in two steps and prior stratification through census sectors). Sample weights, considering gender, age and education, were calculated in order to equalize differences in the social-demographic composition of the sample in relation to the composition of the adult population of the city, according to the 2010 census distribution (27).

The project was submitted and approved by the Ethics Committee, under protocol number 008/12. Participants of the study were requested to sign the terms of free consent, which was explained to them before data collection.

RESULTS

In this study 1,226 interviews were conducted, of which 50.8% were answered by women, 32.7% of the interviewees were 20 to 29 years old, 71.7% reported to have been at school for more than eight years and 64.6% were in middle C social economical class.

The frequencies of variables used as of risk or protection indicators for abdominal adiposity in the principal component analysis are presented in table I.

For protection indicators, regular consumption of raw salads (53.5%) and regular consumption of beans (86.2%) were reported by the interviewees.

In relation to risk indicators, the habit of consuming whole milk and red meat with visible fat and/or poultry skin was reported by 59.0% and 55.3% of the respondents, respectively.

The values presented in the tests for evaluation of the correlation between the indicators of protection or risk of abdominal adiposity and the adjustment for using factor analysis to identify behavioral patterns were satisfactory for the PCA (KMO = 0.60 and Bartlett's sphericity = 0.000). By means of the exploratory factor analysis, five components were found, two of which had eigenvalues larger than 1.3, explaining 23.78% of the components variation. After orthogonal rotation, two components remained in the correlation matrix, representing a behavioral pattern of risk and one of pro-

tection. Of the 12 variables regarded as risk or protection factors for the tested abdominal obesity, those considered to be valid to remain in each component were the indicators with saturation higher than 0.3 (indicated in italics), shown in table II.

The means of waist circumference, waist-to-hip ratio and waist-to-height ratio among men were 87.4 cm (95% CI 85.3-89.5), 0.91 (95% CI 0.89-0.92) and 0.51 (95% CI 0.50-0.53), respectively. Abdominal adiposity evaluated by waist circumference was present in 12.8% (95% CI 9.4-17.1) of the male participants, by means of the waist-to-hip ratio in 25.3% (95% CI 21.0-30.2) and waist-to-height ratio in 44.7% (95% CI 39.4-50.1).

For women, the average of waist circumference was 80.6 cm (95% CI 78.5-82.6), the mean of waist-to-hip ratio was 0.82 (95% CI 0.85-0.88) and the average of waist-to-height ratio was 0.55 (95% CI 0.35-0.56). Abdominal adiposity evaluated by measurement of waist circumference was present in 23.9% of women (95% CI 19.6-28.7), by waist-to-hip ratio in 55.3% (95% CI 49.8-60.5) and by waist-to-height ratio in 29.1% (95% CI 24.6-34.0).

The first behavioral pattern found in the study was termed "Healthy Pattern". It explained 12.58% of the variance and included the regular consumption of fruits, fresh fruit juices, raw and cooked vegetables and the appropriate level of physical activity.

The second behavioral pattern was characterized by the habit of smoking, and by the consumption of alcohol and fat-rich meats (red meat with visible fat and/or poultry skin). This pattern was identified as "Risk Pattern" and presented a variance of 11.20%.

Table I. Frequency of risk and protective factor for abdominal adiposity in the population, Viçosa, Brazil, 2012-2014

Indicator	Proportion* (%)	Confidence interval (95% CI)
Regular consumption of fruits†	34.8	(30.3-39.5)
Regular consumption of fresh fruit juice†	16.6	(13.1 -20.8)
Regular consumption of raw salads†	52.5	(44.1-60.7)
Regular consumption of cooked vegetables†	30.0	(26.7-33.5)
Regular consumption of beans†	86.7	(83.9-89.5)
Regular consumption of sugar-sweetened beverages†	27.6	(23.0-32.6)
Habit of consuming whole milk	59.3	(54.5-63.9)
Habit of consuming fat-rich meat‡	57.4	(52.2-62.5)
Smoking habit	17.9	(14.1-22.4)
Over consumption of alcohol§	42.6	(37.6-47.7)
Physically active‖	20.9	(15.4-27.8)
Excessive screen time¶	17.8	(13.8-22.5)

**Proportion weighed by gender, age and schooling. †Consumption of fruit, fresh fruit juice, raw salads and cooked vegetables, beans and sugar-sweetened beverages five or more days a week. ‡Consumption of red meat without removing visible fat or poultry skin from the food. §Consumption of > 5 shots (man) and > 4 shots (woman) in ≥ 1 day in the last 30 days. ‖Time of physical activity practice longer than or equal to 150 minutes per week. ¶Time spent in front of TV or computer longer than or equal to four hours a day.*

Table II. Rotated factor loadings for the first two factors of principal component analysis of the population, Viçosa, Brazil, 2012-2014

Indicators	"Pattern 1" Healthy Pattern	"Pattern 2" Risk Pattern	Communality
Regular consumption of fruits†	*0.39*	-0.27	0.42
Regular consumption of fresh fruit juice†	*0.35*	-0.15	0.48
Regular consumption of raw salads†	*0.71*	-0.01	0.55
Regular consumption of cooked vegetables†	*0.64*	-0.10	0.46
Regular consumption of beans†	0.23	0.02	0.41
Regular consumption of sugar-sweetened beverages†	0.01	0.21	0.51
Habit of consuming whole milk	-0.01	-0.06	0.61
Habit of consuming fat-rich meat‡	-0.16	*0.57*	0.45
Smoking habit	-0.11	*0.33*	0.60
Over consumption of alcohol drinks§	0.01	*0.77*	0.63
Physically active‖	*0.43*	0.28	0.49
Excessive screen time¶	-0.02	-0.03	0.77
Eigenvalues	1.51	1.34	
Percentage of explained variance	12.58	11.20	
Percentage of explained cumulative variance	12.58	23.78	

Observation: indicators with factor loading larger than or equal to 0.3 are in italics. †Consumption of fruit, fresh fruit juice, raw salads and cooked vegetables, beans and sugar-sweetened beverages five or more days a week. ‡Consumption of red meat without removing visible fat or poultry skin from the food. §Consumption of > 5 shots (man) and > 4 shots (woman) in ≥ 1 day in the last 30 days. ‖Time of physical activity practice longer than or equal to 150 minutes per week. ¶Time spent in front of TV or computer longer than or equal to four hours a day.

Table III shows the association between the two behavioral patterns found in abdominal adiposity, determined by waist circumference and by the indices of waist-to-hip ratio and waist-to-height ratio.

Negative associations among the "healthy" protection pattern and waist circumference, wait-to-hip ratio and waist-to-height ratio were found, showing that the increment in the consumption of fruits, fresh fruit juices, raw or cooked vegetables and the appropriate level of physical activity were associated with the reduction in abdominal adiposity in this population. Contrary to that, the pattern termed "risk" was positively associated with abdominal adiposity. In addition, the multiple linear regression analysis showed that the association between risk and protection patterns and the parameters of abdominal adiposity were better explained by the waist-to-height ratio and waist circumference since they presented 36.5% and 32.9% of the variability explained for the "healthy" pattern and 36.5% and 36.9% of the variability explained for the "risk" pattern.

DISCUSSION

This study investigated the clustering of risk factors and the association between risk and protection behavioral patterns with abdominal adiposity indicators among adult individuals of Viçosa, using the method of exploratory factor analysis. Two patterns were established, one of which is considered as a protection factor for abdominal adiposity, where variables of healthy food consumption, such as raw salads or cooked vegetables, fruits, fresh fruit juices and physical activity, were included. The second pattern identified was considered as risky because it grouped variables considered to be risk factors such as smoking, abusive alcohol consumption and the habit of consuming fat-rich meats.

Physical inactivity, smoking, alcohol drinking and inappropriate diet, regarded as the main risk factors, have been analyzed each in several studies. However, this way of analyzing may be inefficient, since, according to Hofstetter et al. (6), risk behaviors do not occur in isolation. Furthermore, populations simultaneously presenting risk behavior factors are more likely to present major non-communicable chronic diseases than individuals with only one risk factor (38). Therefore, using statistical techniques to reduce variables into clusters with similar profiles is recommended to assist in obtaining knowledge of possible associations of risk behaviors or health protection among them.

Once the analyses were adjusted, the "healthy" pattern was found to be negatively associated with abdominal adiposity. Similar to what was found in this study, McNaughton et al. (39), when using the exploratory factor analysis, found that the dietary pattern characterized by high consumption of fruits and vegetables was inversely associated with body mass index, blood pressure and waist circumference. Neumann et al. (40), when using the same statistical technique, found that the termed "modern" dietary pattern, made up of fat-free dairy products, seafood, fresh fruit juices and fruit was inversely associated with risk factors for cardiovascular diseases, and the waist-to-hip ratio measure was among these evaluated variables. Ribeiro et al. (41), when describing the frequency of fruit and vegetable consumption of adults living in the city of São Paulo, São Paulo state, found a positive correlation between the consumption of these foods and physical activity during leisure time.

Our findings can be explained by the positive and healthy actions of eating habits and lifestyle. The effects of fruits and vegetables on general and central obesity are believed to relate to their soluble fiber content, which is associated with increased satiety, delayed gastric emptying and enhanced insulin sensitivity (42). In relation to the practice of physical activity, the energy expenditure independent of intensity reduces abdominal fat (43).

When evaluating the aggregation of behavioral patterns of British university students, identified by means of cluster analysis, Dodd et al. (44) identified three subgroups, characterized by high prevalence of physical inactivity (70%), inadequacy in the regular consumption of fruits and vegetables (66%) and abusive alcohol consumption (56%). By using the same technique, Costa et al. (22) found the simultaneity of health protective behaviors, such as the occurrence of a proper consumption of fruit and the practice of physical activity during leisure time in 35.5% of men and 33.3% of adult women living in the city of Florianópolis, state of Santa Catarina, Brazil.

The data previously shown illustrate the limitation regarding the comparison of this study with other studies due to variations in the methodology used for determining a standard or a variable clustering, since the identification of standards involving behavioral or anthropometric variables has been frequently carried out by the statistical technique of clustering, which, according to Hofstetter et al. (6), place individuals with similar interrelationships in the same clusters.

Table III. Associations of risk and protection behavioral patterns with abdominal adiposity, Viçosa, Brazil, 2012-2014

Indicators	Waist circumference (cm)			Waist/hip ratio			Waist/height ratio		
	Regression coefficient β	Value p*	R^2	Regression coefficient β	Value p*	R^2	Regression coefficient β	Value p*	R^2
Pattern 1 "Healthy"	-0.991	0.048	32.9	-0.003	0.013	25.0	-0.007	0.018	36.5
Pattern 2 "Risk"	1.219	0.002	36.9	0.007	0.003	25.6	0.007	0.006	36.5

$p \leq 0.05$. Models adjusted according to gender, age and social economical class.

The second pattern found in the study, termed "risk", was positively associated with abdominal adiposity. Schuit et al. (45), in a cross-sectional study with European adult subjects, showed that the associations between the consumption of alcohol and smoking are strong especially among individuals with low education degree and income. Furthermore, the influence of smoking and consumption of alcoholic drinks on abdominal fat has been shown in other studies (46,47) by measurement of the waist circumference as well as waist-to-hip ratio.

A transversal study carried out by Faria et al. (47) with men living in Cuiabá, state of Mato Grosso do Sul, Brazil, found that the means of waist-to-hip ratio indices were higher among smokers and the means of waist circumference and waist-to-height ratio were higher among those who reported higher consumption of alcoholic drinks. Studies have shown a higher prevalence of abdominal obesity in former smokers, a result from the increment in the caloric intake and a reduction in the basal metabolic rate after quitting the addiction (48). Despite being evident, the literature has not been able to determine a relationship between cause and effect in relation to the association between consumption of alcohol drinks and abdominal fat due to the large methodological variation in the frequency analysis and the amount consumed (8).

Smoking, abusive alcohol consumption and the habit of consuming fatty meats (red meat with visible fat and/or chicken with skin) are considered as important risk factors for chronic non-communicable diseases and have been associated with abdominal adiposity. The relation between cigarette smoking and body fat distribution is complex and incompletely understood. Biological mechanisms involving higher levels of cortisol increase lipogenesis, differentiation of adipocytes and deposition of abdominal fat (47). As for the consumption of alcohol, its metabolism may trigger endocrine changes, such as increased cortisol, predisposing to changes in fat distribution. The habit of consuming fat-rich meats is associated with abdominal adiposity because this food group provides excess calories to individuals.

The combination of risk factors such as smoking, alcoholism and inadequate food intake has been investigated in studies in Brazil (22,31) and worldwide (44,45). The prevalence of those three risk factors, evaluated by the cluster statistical technique in a Brazilian study, showed that 4.9% of men and 1.9% of women had the occurrence of those factors at the same time (20). The same methodological work proposal in European countries presented prevalence data higher than these, which were 15.3% for men and 14.4% for women.

The identification of risk or protection behavioral patterns for non-communicable chronic diseases was carried out by using the PCA technique in a sample with 108,706 Brazilian adults, participants of the VIGITEL. That investigation showed results similar to those of this present study, where it was found that the behavioral pattern considered risk was defined by smoking, excessive alcohol consumption and regular intake of meat with visible fat (31). Therefore, strategies to control the increase in the prevalence of such risk factors in the population may be directed to these three factors, which have a tendency to aggregate.

The population-based transversal study with 2,732 adults, conducted in Pelotas, state of Rio Grande do Sul, Brazil, to evaluate the prevalence of the combination of behavioral risk factors, showed that the combination of physical inactivity factors and regular consumption of visible meat fat was present in 18.2% of the men and 17.0% of the women in the study. Vilela et al. (21), when evaluating the dietary pattern of adults in Cuiabá, state of Mato Grosso do Sul, Brazil, found a positive association between "Western" eating pattern, characterized by high intake of pasta, fatty meats, sugar-sweetened beverages and sweets, and the increase in the waist circumference and wait-to-hip ratio among women.

The parameters of abdominal adiposity, waist-to-height ratio and waist circumference presented a higher capacity for explaining the behavioral patterns than did waist-to-hip ratio, this is observed since of different found regression coefficients, that can show the superiority tool for discriminating the behavioral patterns. Waist-to-height ratio has a direct regulation with growth and waist circumference, so it minimizes erroneous assessment of health risk in individuals with different heights, which is the greatest advantage of this measure. In addition, this indicator has been considered as a good marker of abdominal obesity related to cardiovascular risk factors. Waist circumference is already recognized as an important and simple indicator of central adiposity and risk for chronic diseases (35).

This is the first population-based study conducted in Viçosa and one of the few works that identifies and explores risk and protection factors by using the statistical technique of principal components and makes associations with abdominal adiposity. Lam et al. (3) mentioned that the measures of central adiposity are more closely associated with cardiovascular risk factors and metabolic diseases than BMI. Furthermore, the body mass index does not consider body fat distribution, which is a limitation since there are suggestions that the metabolic complications of obesity are more closely related to visceral adiposity than to overall adiposity. However, some limitations should be considered. It is noteworthy that this is a cross-sectional study, which prevents the establishment of temporality of associations. Self-reports of risk behaviors tend to be underestimated because of being socially undesirable. In addition, menopausal women were not excluded because they presented lower sample representativity.

CONCLUSION

This study may have important implications for public policies because it was found that by clustering risk or protection factors, health conditions of a population can be better explained. In addition, multiple interventions may be more effective and efficient in promoting health.

AUTHOR'S CONTRIBUTION

Danielle Cristina Guimarães da Silva, Kelly Aparecida da Cunha, Wellington Segheto, Vanessa Guimarães Reis, France Araújo Coelho and Sílvia Helena O. Morais, post-graduate students in Science

of Nutrition, contributed to the data collection and analyses of this study, wrote the initial draft of the manuscript and assembled the final version.

Milene Cristine Pessoa, professor, contributed to the study design, data analyses and participated in the approval of the final version of the manuscript.

Giana Zarbato Longo, professor, supervised this study, contributed to the study design, and developed analyses and data analyses.

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REFERENCES

1. Friedman JM. Obesity: Causes and control of excess body fat. Nature 2009;459(7245):340-2.
2. World Health Organization**.** Obesity and overweight. Fact Sheet Number 311. Geneva (CH): WHO (2012). Available from: http://www.who.int/mediacentre/factsheets/fs311/en/index.html
3. Lam BCC, Koh GCH, Chen C, Wong MTK, Fallows SJ. Comparison of body mass index (BMI), body adiposity index (BAI), waist circumference (WC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) as predictors of cardiovascular disease risk factors in an adult population in Singapore. PLoS ONE 2015;10(4):e0122985.
4. Lanas F, Serón P, Muñoz S, Margozzini P, Puig T. Central obesity measurements better identified risk factors for coronary heart disease risk in the Chilean National Health Survey (2009-2010). J Clin Epidemiol 2017;86:111-6.
5. Lim LL, Seubsman S, Sleigh A, Bain C. Validity of self-reported abdominal obesity in Thai adults: A comparison of waist circumference, waist-to-hip ratio and waist-to-stature ratio. Nutr Metab Cardiovasc Dis 2012;22(1):42-9.
6. Hofstetter H, Dusseldorp E, Van Empelen P, Paulussen TW. A primer on the use of cluster analysis or factor analysis to assess co-occurrence of risk behaviors. Prev Med 2014;67:141-6.
7. Vasques ACJ, Priori SE, Rosado LEFPL, Franceschini SCC. The use of anthropometric measures to assess visceral fat accumulation. Rev Nutr 2010;23(1):107-18.
8. Pinho CPS, Diniz AS, Arruda IKG, Batista Filho M, Coelho PC, Sequeira LAS, et al. Prevalence of abdominal obesity and associated factors among individuals 25 to 59 years of age in Pernambuco State, Brazil. Cad. Saúde Pública 2013;29(2):313-24.
9. Park SH, Choi SJ, Lee KS, Park HY. Waist circumference and waist-to-height ratio as predictors of cardiovascular disease risk in Korean adults. Circ J 2009;73(9):1643-50.
10. Bevilacqua MR, Gimeno SGA. Abdominal obesity in Japanese-Brazilians: Which measure is best for predicting all-cause and cardiovascular mortality? Cad. Saúde Pública 2011;27(10):1986-96.
11. Ford ES, Maynard LM, Li C. Trends in mean waist circumference and abdominal obesity among US adults, 1999-2012. JAMA 2014;312(11):1151-3.
12. Walls HL, Stevenson CE, Mannan HR, Abdullah A, Reid CM, McNeil JJ, et al. Comparing trends in BMI and waist circumference. Obesity 2011;19(1):216-9.
13. Linhares RS, Horta BL, Gigante DP, Dias-da-Costa JS, Olinto MT. Distribution of general and abdominal obesity in adults in a city in southern Brazil. Cad. Saúde Pública 2012;28(3):438-47.
14. Friedman DS, Ford ES. Are the recent secular increases in the waist circumference of adults independent of changes in BMI? Am J Clin Nutr 2015;101(3):425-31.
15. Castanho GKF, Marsola FC, Mclellan KCP, Nicola M, Moreto F, Burini RC. Consumption of fruit and vegetables associated with the metabolic syndrome and its components in an adult population sample. Cien Saúde Colet 2013;18(2):385-92.
16. Chau JY, Chau JY, Grunseit AC, Stamatakis E, Brown WJ, Matthews CE, et al. Daily sitting time and all-cause mortality: A meta-analysis. PLoS One 2013;13(8):e80000.
17. Mielke GI, Hallal PC, Malta DC, Lee IM. Time trends of physical activity and television viewing time in Brazil: 2006-2012. Int J Behav Nutr Phys Act 2014;15(11):101.
18. Marchioni DML, Latorre MRDO, Eluf-Neto, Wünsch-Filho V, Fisberg RM. Identification of dietary patterns using factor analysis in an epidemiological study in São Paulo. São Paulo Med J 2005;123(3):124-7.
19. Sato RC, Zouain DM. Factor analysis for the adoption of nuclear technology in diagnosis and treatment of chronic diseases. Einstein 2012;10(1):62-6.
20. Olinto MTA, Willett WC, Gigante DP, Victora CG. Sociodemographic and lifestyle characteristic in relation to dietary patterns among young Brazilian adults. Public Health Nutr 2011;14(1):150-9.
21. Vilela AAF, Sichieri R, Pereira RA, Cunha DB, Rodrigues PRM, Gonçalves-Silva RMV, et al. Dietary patterns associated with anthropometric indicators of abdominal fat in adults. Cad. Saúde P*ública* 2014;30(3):502-10.
22. Costa FF, Benedet J, Leal DB, Altenburg de Assis MA. Clustering of risk factors for non-communicable diseases in adults from Florianopolis, SC. Rev Bras Epidemiol 2013;16(2):398-408.
23. Romaguera D, Ängquist L, Du H, Jakobsen MU, Forouhi NG, Halkjær J, et al. Food composition of the diet in relation to changes in waist circumference adjusted for body mass index. PLoS One 2011;6(8):e23384.
24. Funtikova AN, Subirana I, Gómez SF, Fitó M, Elosua R, Benítez-Arciniega AA, et al. Soft drink consumption is positively associated with increased waist circumference and 10-year incidence of abdominal obesity in Spanish adults. J Nutr 2015;145(2):328-34.
25. Segheto W, Silva DCG, Coelho FA, Reis VG, Morais SHO, Marins JCB, et al. Body adiposity index and associated factors in adults: Method and logistics of a population-based study. Nutr Hosp 2015;32(1):101-9.
26. Brazil Ministry of Health. VIGITEL Brasil 201. Vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico. Brasília: Ministério da Saúde; 2012.
27. Brazilian Institute of Geography and Statistics. Censo Demográfico 2010. Rio de Janeiro: Brazilian Institute of Geography and Statistics; 2010.
28. Dean AG, Dean JA, Colombier, Brendel KA, SmithDC, Burton AH, et al. Epi Info, version 6: A word processing, database, and statistics program for epidemiology on microcomputers. Atlanta, Georgia: Centers for Disease Control and Prevention; 1994.
29. Stewart A, Marfell-Jones M, Olds T, Carter L. International standards for anthropometric assessment. New Zealand: Lower Hutt; 2011.
30. Brazilian Association of Research Companies (ABEP). Critério de classificação econômica Brasil, 2011. Available from: www.abep.com.br. Accessed 25 February 2015.
31. Steele EM, Claro RM, Monteiro C. Behavioural patterns of protective and risk factors for non-communicable diseases in Brazil. Public Health Nutr 2014;17(2):369-75**.**
32. Furlan-Viebig R, Pastor-Valero M. Development of a food frequency questionnaire to study diet and non-communicable diseases in adult population. Rev Saúde Públ 2004;38(4):581-4.
33. Viner RM, Cole TJ. Who changes body mass between adolescence and adulthood? Factors predicting change in BMI between 16 year and 30 years in the 1970 British Birth Cohort. Int J Obes 2006;30:1368-74.
34. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: Updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 2007;39:1423-34.
35. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. American Heart Association; National Heart, Lung, and Blood Institute.

Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Published corrections appear in Circulation 2005;112:e297 and Circulation 2005;112:e298. Circ J 2005;112(e297):2735-52.
36. World Health Organization. Obesity: Preventing and managing the global epidemic - Report of a WHO Consultation (TRS894). Geneva: World Health Organization; 2000.
37. Ashwell M, Hsieh SD. Six reasons why the waist-to-height ratio is a rapid and effective global indicator for health risks of obesity and how its use could simplify the international public health message on obesity. Int J Food Sci Nutr 2005;56(5):303-7.
38. Lippke S, Nigg CR, Maddock JE. Health-promoting and health-risk behaviors: Theory-driven analyses of multiple health behavior change in three international samples. Int J Behav Med 2012;19(1):1-13.
39. McNaughton SA, Mishra GD, Stephen AM, Wadsworth ME. Dietary patterns throughout adult life are associated with body mass index, waist circumference, blood pressure and red cell folate. J Nutr 2007;137(1):99-105.
40. Neumann AICP, Martins IS, Marcopito LF, Araujo EA. Dietary patterns associated with risk factors for cardiovascular disease in a Brazilian city. Rev Panam Salud Public 2007;22(5):329-39.
41. Ribeiro AG, Cotta RMM, Ribeiro SMR. The promotion of health and integrated prevention of risk factors for cardiovascular diseases. Cien Saúde Colet 2012;17(1):7-17.
42. Rolls BJ, Ello-Martin JA, Tohill BC. What can intervention studies tell us about the relationship between fruit and vegetable consumption and weight management? Nutr Rev 2004;62(1):1-17.
43. Kay SJ, Fiatarone Singh MA. The influence of physical activity on abdominal fat: A systematic review of the literature. Obes Rev 2006;7(2):183-200.
44. Dodd LJ, Al-Nakeeb Y, Nevill A, Forshaw MJ. Lifestyle risk factors of students: A cluster analytical approach. Prev Med 2010;51(1):73-7.
45. Schuit AJ, Van Loon AJ, Tijhuis M, Ocké M. Clustering of lifestyle risk factors in a general adult population. Prev Med 2002;35(3):219-24.
46. Rouillier P, Bertrais S, Daudin JJ, Bacro JN, Hercberg S, Boutron-Ruault MC. Drinking patterns are associated with variations in atherosclerotic risk factors in French men. Eur J Nutr 2006;45(2):79-87.
47. Faria CS, Botelho C, Silva RMVG, Ferreira MG. Smoking and abdominal fat in blood donors. J Bras Pneumol 2012;38(3):356-63.
48. Chatkin R, Chatkin JM. Smoking and changes in body weight: Can physiopathology and genetics explain this association? J Bras Pneumol 2007;33(6):712-19.

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Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Normative reference values for hand grip dynamometry in Spain. Association with lean mass

Valores de normalidad de dinamometría de mano en España. Relación con la masa magra

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Abstract

Background and objectives: The objective of this study was to establish reference values for hand grip strength, compare the results obtained with Collin and Jamar type dynamometers and determine their association with anthropometric and lean mass measurements.

Material and methods: This cross-sectional population-based study was undertaken in Pizarra (Málaga, Spain). The grip strength of the dominant hand was measured using Collin and Jamar dynamometers. Skinfolds (triceps, abdominal, biceps of dominant arm and subscapular) were measured, and body composition was estimated. Eight hundred seventeen adults randomly selected from the census were recruited. Dynamometry reference values are presented for the dominant hand, by gender and age groups.

Results: No determinations could be made with the Collin dynamometer in 69 women due to the difficulty in grasping the dynamometer. We found significant positive correlations between the measurements with Jamar and Collin dynamometers ($r = 0.782$; $p < 0.001$) and between grip strength and lean mass index (LMI), determined by both dynamometers ($r = 0.538$, $p < 0.001$ and $r = 0.462$, $p < 0.001$, respectively). Malnourished patients according to LMI had significantly lower grip strength than normally nourished patients ($p < 0.001$ for Jamar; $p < 0.02$ for Collin).

Conclusions: Dynamometry reference values in the Spanish population are presented. We recommend the use of the Jamar type dynamometer *versus* the Collin type dynamometer. Hand grip dynamometry is associated with lean mass, which confirms its usefulness in nutritional assessment.

Key words:

Hand strength. Reference values. Hand grip. Dynamometry. Nutritional status.

Resumen

Antecedentes y objetivos: no existen valores de normalidad en España con el dinamómetro Jamar. El objetivo fue determinar valores de normalidad de fuerza muscular, comparar los resultados obtenidos con los dinamómetros tipo Collin y tipo Jamar entre sí, y determinar su asociación con medidas antropométricas y de masa magra.

Material y métodos: estudio transversal de base poblacional en Pizarra (Málaga). Se determinó la fuerza de prensión de la mano dominante mediante dinamómetros Collin y Jamar. Se midieron los pliegues cutáneos (tricipital, abdominal, bicipital del brazo dominante y subescapular) y se estimó la composición corporal. Se reclutaron 817 adultos seleccionados aleatoriamente del censo. Se presentan valores de referencia de dinamometría para la mano dominante, por género y grupos de edad.

Resultados: no se pudieron realizar determinaciones con el dinamómetro Collin en 69 mujeres debido a la dificultad para agarrar el dinamómetro. Encontramos correlaciones positivas significativas entre las medidas de los dinamómetros Jamar y Collin ($r = 0{,}782$; $p < 0{,}001$) y entre la fuerza muscular determinada mediante ambos dinamómetros y el índice de masa magra (IMM) ($r = 0{,}538$, $p < 0{,}001$ y $r = 0{,}462$, $p < 0{,}001$, respectivamente). Los pacientes desnutridos según IMM presentaron una fuerza muscular significativamente menor a la de los pacientes normonutridos ($p < 0{,}001$ para Jamar y $p < 0{,}02$ para Collin).

Conclusiones: se presentan valores de referencia de dinamometría en población española. Recomendamos el uso del dinamómetro tipo Jamar frente al dinamómetro tipo Collin. La dinamometría de mano se asocia con la masa magra, lo que avala su utilidad en la valoración nutricional.

Palabras clave:

Fuerza muscular. Valores de normalidad. Prensión de la mano. Dinamometría. Estado nutricional.

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INTRODUCTION

There is a great variety of techniques to evaluate the nutritional status of a patient, although there is no single parameter available. Malnutrition implies a decrease in muscle mass, which is reflected in poorer performance on functional tests and alterations in body composition (1-3). This decrease in muscle strength appears before changes in anthropometric measurements and laboratory parameters are observed. Accordingly, the measurement of muscle strength may be a useful tool in screening and assessing malnutrition (4). The American Society for Parenteral and Enteral Nutrition has included the assessment of grip strength by dynamometer as one of the six criteria to define malnutrition (5), encouraging the use of cut-off points in each population by age and gender (6).

There are numerous clinical studies in hospitalized individuals or outpatients (surgical, elderly, oncological, etc.) that demonstrate that decreased grip strength, measured by hand dynamometry, is associated with increased stays, mortality and complications (3,7,8). Similarly, in epidemiological studies performed in different age groups, decreased grip strength is also associated with higher mortality and impaired functionality (3). Some body composition measures, like lean mass, seem to have a close relationship with hand strength as well as with physical function (9).

The hand dynamometer evaluates the isometric force of the hand and the forearm providing a quick, easy to use, and inexpensive method to assess the grip strength and, thus, the nutritional status of patients (10). Currently, the Jamar dynamometer is the most commonly used in clinical practice (4,11-13). Over the last few years, dynamometry reference values have been published in different countries, usually for the Jamar-type dynamometer (4,11,14,15), including a meta-analysis (16).

In Spain, the normative data are from another type of dynamometer (17-19) with no studies using the Jamar dynamometer. Likewise, there are no data comparing the results of the two different types of dynamometers, so it remains unknown if the measurements of both dynamometers are comparable in clinical practice. There are only a few studies relating dynamometry results to body composition (15,20). The objective of this study was to contribute reference values in a sample of subjects belonging to the general population in Spain using the Jamar dynamometer, to compare them with the Collin dynamometer, and to assess the relationship between dynamometry and anthropometric parameters, especially lean mass.

MATERIAL AND METHODS

Our sample comprised a total of 817 healthy adults recruited from the population-based Pizarra study (Malaga) (21). These individuals, aged between 18 and 65 years, were randomly selected from the municipal census. Individuals who were institutionalized, pregnant, or who had severe physical or psychiatric conditions were excluded as were morbidly obese subjects (body mass index [BMI] > 40 kg/m^2). All subjects gave their written consent, and the study was approved by the Ethics and Clinical Research Committee of the Regional University Hospital of Malaga.

Anthropometric measurements included weight, obtained with a scale adjusted to 0.1 kg (SECA 665, Seca, Germany), and height, using a stadiometer adjusted to 0.01 m (Holtain Ltd., Croswell, UK), to calculate BMI. Skinfold thicknesses (subscapular, triceps, biceps, abdominal) were measured at standard sites (22) by a single investigator using a plicometer (Holtain Ltd., Croswell, UK) with the precision of 0.2 mm. Three measurements were taken and the mean was calculated. Arm circumference was measured using a flexible measuring tape to the nearest 0.1 cm at the midpoint of the arm. Lean mass and fat mass percentages were estimated using the Durnin (23) and Siri (24) equations. Hand dynamometry was performed using a Collin dynamometer (Medizintechnik AS, Germany) and a Jamar dynamometer (Asimow Engineering Co., Los Angeles, CA).

In the case of the Jamar dynamometer, the subjects were instructed to adjust the device so that the grip would be comfortable for their hand to obtain the best performance (25), although most chose to use the second position (3.8 cm). The subjects were instructed to squeeze the dynamometer with the maximum force they could apply after receiving a verbal command (26).

The measurements were taken with the patients sitting in a straight back chair with both feet on the ground, shoulders close to the body in a neutral position, and the elbow flexed at 90° without rotation (27).

Three measurements were obtained in the dominant hand with a rest period of at least one minute between trial (28). There was a minimum ten minute break between Collin and Jamar measurements, in that order.

The mean was calculated and the highest value was used to represent hand grip strength.

STATISTICAL ANALYSIS

Data analysis was performed using SPSS Statistics software v22. Descriptive data are shown as means and standard deviations. The Kolmogorov-Smirnov test was used to establish whether the variables followed a normal distribution.

In the hypothesis testing for continuous variables between groups, the Student's t test was used in the variables that followed a normal distribution and a non-parametric test (Mann-Whitney) was used for variables that were not normally distributed. We rejected the null hypothesis with an alpha of 0.05 for two tails. The degree of association between hand dynamometry, BMI and body composition measurements was analyzed using the Pearson's correlation coefficient.

RESULTS

A total of 817 adults, 364 men and 453 women, were studied (Table I).

Table I. General and anthropometric characteristics of the study population

Variables	Total n = 817 Mean ± SD	Men n = 364 Mean ± SD	Women n = 453 Mean ± SD
BMI (kg/m^2)	28.8 (± 4.4)	29.3 (± 4.1)	28.4 (± 4.6)
Age (years)	49.7 (± 9.6)	50.9 (± 9.59)	48.8 (± 9.6)
Weight (kg)	76.3 (± 13.9)	84.2 (± 12.7)	70 (± 11.5)
Height (cm)	162.7 (± 4.4)	169.7 (± 7.1)	157.1 (± 5.9)
Arm circumference (cm)	30.2 (± 3.5)	31.1 (± 3.3)	29.6 (± 3.5)
Triceps skinfold (mm)	16.8 (± 7.5)	11.3 (± 5)	21.1(± 6.3)
Biceps skinfold (mm)	11.4 (± 5.8)	8.4 (± 3.9)	13.8 (± 5.9)
Subscapular skinfold (mm)	23.1 (± 7.3)	20.1 (± 6.9)	24.8 (± 7.2)
Abdominal skinfold (mm)	25.8 (± 8.2)	26.1 (± 8.5)	25.5 (± 7.9)
Arm muscle circumference (cm)	24.9 (± 3.7)	27.6 (± 3.2)	22.9 (± 2.7)
Fat mass percentage	34.1 (± 6.5)	29.1 (± 5.2)	38.1 (± 4.4)
Lean mass (kg)	50 (± 10.4)	59.1 (± 7.5)	42.6 (± 5.5)
Lean mass index (kg/m^2)	18.7 (± 2.7)	20.5 (± 2.3)	17.2 (± 2)

n: number. BMI: body mass index.

The measurements were valid for the Jamar dynamometer in all subjects studied, but only in 748 cases for the Collin dynamometer (364 men and 384 women), due to the difficulty for grasping the dynamometer. A total of 69 women could not apply the necessary force. Their mean age was 54.6 (± 9.2) years, significantly higher ($p < 0.001$) than in the group of women who were able to perform the test (47.8 ± 9.2 years). Tables II and III show the grip strength values for the two dynamometers used, grouped by gender and distributed by age, together with their corresponding percentiles.

A high correlation was found between the data obtained with the Jamar and Collin dynamometers ($r = 0.782$; $p < 0.001$) (Fig. 1). Mean strength was higher in men than in women with both instruments and in all age groups ($p < 0.001$). There was a tendency towards a negative correlation between age and grip strength with the Jamar dynamometer ($r = -0.67$; $p = 0.58$), which was significant with the Collin dynamometer ($r = -0.143$; $p < 0.001$). This significant correlation was observed with the Collin dynamometer in the subjects between the ages of 45 and 60 ($r = -0.1$; $p = 0.04$), and those above 60 years ($r = -0.22$; $p = 0.02$), which was not the case in those under age 45 ($r = 0.02$; $p = 0.74$). With the Jamar type dynamometer, this correlation was significant in the group of subjects under age 45 ($r = 0.12$; $p = 0.04$), in those between the ages of 45 and 60 ($r = -0.12$; $p = 0.023$) and in subjects over 60 years of age ($r = -0.2$; $p = 0.02$).

A positive correlation was found between grip strength using the Jamar dynamometer and BMI ($r = 0.086$; $p = 0.014$). This relationship increased when subjects were classified as normal weight ($r = 0.268$; $p < 0.001$) or overweight ($r = 0.146$; $p = 0.006$). No association was found between BMI and grip strength in obese patients.

The values obtained using the Jamar dynamometer showed a positive correlation with weight ($r = 0.514$; $p < 0.001$), height ($r = 0.714$; $p < 0.001$), and arm circumference ($r = 0.249$; $p < 0.001$), and a negative correlation with fat mass in kg: ($r = -0.597$; $p < 0.001$), triceps skinfold ($r = -0.497$; $p < 0.001$), biceps skinfold ($r = -0.404$; $p < 0.001$) and subscapular skinfold ($r = -0.209$; $p < 0.001$). There was also a significantly positive correlation between muscle strength and lean mass in kg ($r = 0.774$; $p < 0.001$) and lean mass index (LMI) ($r = 0.538$; $p < 0.001$) (Figs. 2 and 3).

Mean values obtained using the Collin dynamometer showed a positive correlation with weight ($r = 0.434$; $p < 0.001$), height ($r = 0.663$; $p < 0.001$) and arm circumference ($r = 0.206$; $p < 0.001$), and a negative correlation with fat mass (kg): ($r = -0.569$; $p < 0.001$), triceps skinfold ($r = -0.518$; $p < 0.001$), biceps skinfold ($r = -0.404$; $p < 0.001$) and subscapular skinfold ($r = -0.214$; $p < 0.001$). There was also a significantly positive correlation between grip strength and lean mass (kg) ($r = 0.683$; $p < 0.001$) and LMI ($r = 0.462$; $p < 0.001$).

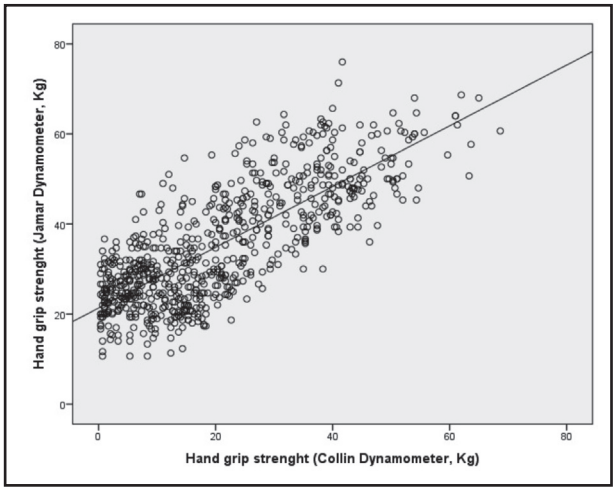

Figure 1.

Relationship between hand grip strength measured by Collin dynamometer and Jamar dynamometer.

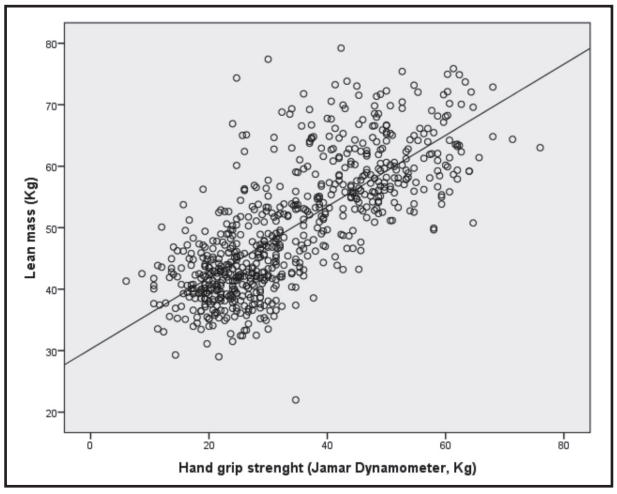

Figure 2.
Relationship between hand grip strength (Jamar) and lean mass.

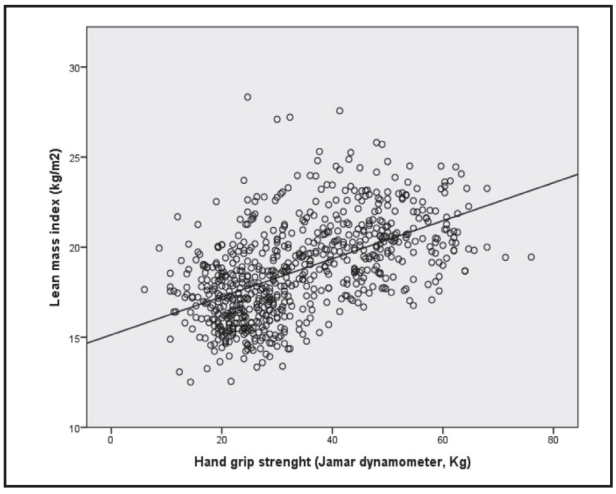

Figure 3.
Relationship between hand grip strength (Jamar) and lean mass index.

Table II. Strength of the dominant hand by gender and age, measured with a Collin dynamometer

Age group (years)	Grip strength (kg)								
	Mean ± SD	Maximum ± SD	P5	P10	P25	P50	P75	P90	P95
Men									
Total n = 364	31.4 ± 13.6	34 ± 14	8	15	25	35	43.8	52	56
Under 45 years n = 125	35.8 ± 12.6	38.3 ± 12.9	15	20.2	33	40	45	55	56.7
From 45 to 60 years n = 164	32.2 ± 13	35 ± 13.4	11.3	15.5	26.3	36	43	50.5	55.8
Over 60 years n = 71	22 ± 12.3	24.4 ± 12.9	6.6	8	16	24	30	45	50.8
Women									
Total n = 384	10.3 ± 7.4	12 ± 7.6	2	3	6	11	17	22	25
Under 45 years n = 161	12.6 ± 7	14.3 ± 7	3	5	8	15	20	24	26.9
From 45 to 60 years n = 181	8.6 ± 7.3	10.5 ± 7.8	1.1	2	4.5	9	15	20	23.9
Over 60 years n = 38	8.4 ± 7	10 ± 7.2	1	1.9	3	9.5	16.3	20.1	23.2

SD: standard deviation.

Table III. Strength of the dominant hand by gender and age, measured with a Jamar dynamometer

Age group (years)	Grip strength (kg)								
	Mean ± SD	Maximum ± SD	P5	P10	P25	P50	P75	P90	P95
Men									
Total n = 364	45.7 ± 9.9	47.8 ± 10.3	30	34	40	48	54	62	64.8
Under 45 years n = 125	47.2 ± 10	49.5 ± 10.4	32.6	37.6	42	48	57.5	64	64.7
From 45 to 60 years n = 164	47.2 ± 9.2	49.5 ± 9.5	34.5	37.5	44	50	55.8	62	66
Over 60 years n = 71	39.5 ± 9.3	40.9 ± 9.6	26.6	29.2	34	40	47	54	58.2
Women									
Total n = 453	24.2 ± 6.2	26 ± 6.3	16	18	22	26	30	34	36
Under 45 years n = 175	24.7 ± 5.4	26.4 ± 5.4	18	20	23	26	30	33.4	36.4
From 45 to 60 years n = 216	24.7 ± 6.6	26.4 ± 6.7	15	18	22	26	30	34	38
Over 60 years n = 58	21.3 ± 6.4	22.5 ± 6.7	12.8	14	18	22	28	31.1	34

SD: standard deviation.

Stratifying our population by European Society of Clinical Nutrition and Metabolism criteria (LMI of 17 kg/m^2 for men and 15 kg/m^2 for women [29]), patients considered as malnourished due to low lean mass had significantly lower mean grip strength than normally nourished patients, both with the Jamar dynamometer and with the Collin dynamometer (Table IV).

Table IV. Hand grip strength for both dynamometers according to lean mass index as malnutrition criteria

	Low LMI	Normal LMI	p value
Total			
Collin n = 649	14.3 ± 9 (n = 52)	21.1 ± 15.4 (n = 597)	0.002
Jamar n =709	26.6 ± 8.3 (n = 57)	34.6 ± 13.7 (n = 652)	< 0.001

LMI: lean mass index. Low LMI interpreted as LMI < 17 kg/m^2 in men and LMI < 15 kg/m^2 in women.

DISCUSSION

In this study, we present normative reference values for the Spanish population using a Jamar hand dynamometer, a dynamometer for which there were no previous references in Spain, providing cut-off points to define malnutrition. Our results are similar to those of other studies that have published reference values for the Jamar-type dynamometer in Caucasian populations (14,20,30).

In the total sample, the cut-off points to define malnutrition (5th percentile) were 29 kg in men and 14 kg in women for the Jamar dynamometer, although this varied depending on age (Table III). These values are similar to those of other studies (15,20) and may be related to poorer functionality, as some authors suggest (31,32).

Similar to other studies (4,20,27), our values were significantly higher in men than in women for all age groups and negative correlations with age were observed, finding a decrease in grip strength (4). This has been attributed to age-related sarcopenia, since the weight loss that occurs with aging is primarily due to the loss of lean mass, thus leading to loss of grip strength (17). In our sample, no significant differences between the groups of individuals under 45 years and between 45 and 60 years were found, possibly because age-related sarcopenia appears especially in subjects aged 60 and older (4).

As in other studies, a positive association was found between grip strength and anthropometric measures such as weight, BMI, arm circumference, and height (11,33), although the association is weak (14).

A close correlation between dynamometry values and lean mass was also observed. Patients who met criteria for malnutrition according to LMI (29) presented lower hand grip strength. Since malnutrition due to low lean mass is primarily associated with increased morbidity and mortality related to malnutrition (29), dynamometry becomes a measure that provides a clear added value to nutritional assessment.

In subjects with acute or chronic disease, numerous factors may influence decreased muscle strength, including immobilization, decreased intake, inflammation, oxidative stress, electrolyte disturbances, use of drugs (corticosteroids, muscle relaxants, etc.). In this respect, grip strength is an excellent marker of functionality as, unlike weight, it can discriminate between malnourished individuals and those who are simply underweight and share the same BMI (10).

Furthermore, nutritional intervention studies have demonstrated significant improvement in muscle strength in the short and medium term, which also supports hand grip usefulness in patient follow-up (3,34).

We found good correlations between grip strength measured with both dynamometers. Although the Collin dynamometer is significantly more economical, we believe its use may be less suitable than that of the Jamar dynamometer because some people (especially older women) have some difficulty in correctly grasping the device and applying force, so the measurement may not be valid. This may be of special relevance in the hospital setting, where the mean inpatients age is high.

STRENGTHS AND WEAKNESSES

Our work was carried out in the context of a population-based epidemiological study with an adequate sample size. Moreover, we measured anthropometric parameters enabling us to relate muscle strength to body composition, especially to lean mass.

Nonetheless, this was a cross-sectional study in which other parameters of functionality were not evaluated, nor was the long-term effect on morbidity and mortality verified. Measurements were only taken in the dominant hand, although some studies suggest that dominance does not affect grip strength (15,33,35). Finally, there was a large percentage of subjects with obesity, which could have partially conditioned the results.

CONCLUSIONS

We present reference values for hand dynamometry using a Jamar hand dynamometer for a Spanish population, providing cut-off points to define malnutrition. We recommend using the Jamar dynamometer as opposed to the Collin dynamometer in clinical practice. Hand dynamometry is associated with lean mass, which supports its usefulness in nutritional assessment.

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REFERENCES

1. Hornby ST, Nunes QM, Hillman TE, Stanga Z, Neal KR, Rowlands BJ, et al. Relationships between structural and functional measures of nutritional status in a normally nourished population. Clin Nutr 2005;24(3):421-6.
2. Norman K, Schütz T, Kemps M, Lübke HJ, Lochs H, Pirlich M. The Subjective Global Assessment reliably identifies malnutrition-related muscle dysfunction. Clin Nutr 2005;24(1):143-50.
3. Norman K, Stobäus N, González MC, Schulzke J-D, Pirlich M, Symreng T, et al. Hand grip strength: Outcome predictor and marker of nutritional status. Clin Nutr 2011;30(2):135-42.
4. Budziareck MB, Pureza Duarte RR, Barbosa-Silva MCG. Reference values and determinants for handgrip strength in healthy subjects. Clin Nutr 2008;27(3):357-62.
5. White JV, Guenter P, Jensen G, Malone A, Schofield M, Academy of Nutrition and Dietetics Malnutrition Work Group, et al. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: Characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). J Acad Nutr Diet 2012;112(5):730-8.
6. Malone A, Hamilton C. The Academy of Nutrition and Dietetics/The American Society for Parenteral and Enteral Nutrition Consensus Malnutrition Characteristics: Application in Practice. Nutr Clin Pract 2013;28(6):639-50.
7. Gale CR, Martyn CN, Cooper C, Sayer AA. Grip strength, body composition, and mortality. Int J Epidemiol 2007;36(1):228-35.
8. Rantanen T, Volpato S, Ferrucci L, Heikkinen E, Fried LP, Guralnik JM. Handgrip strength and cause-specific and total mortality in older disabled women: Exploring the mechanism. J Am Geriatr Soc 2003;51(5):636-41.
9. Araujo AB, Chiu GR, Kupelian V, Hall SA, Williams RE, Clark R V, et al. Lean mass, muscle strength, and physical function in a diverse population of men: A population-based cross-sectional study. BMC Public Health 2010;10(1):508.
10. Vaz M, Thangam S, Prabhu A, Shetty PS. Maximal voluntary contraction as a functional indicator of adult chronic undernutrition. Br J Nutr 1996;76:9-15.
11. Mitsionis G, Pakos EE, Stafilas KS, Paschos N, Papakostas T, Beris AE. Normative data on hand grip strength in a Greek adult population. Int Orthop 2009;33(3):713-7.
12. Schlüssel MM, Dos Anjos LA, De Vasconcellos MTL, Kac G. Reference values of handgrip dynamometry of healthy adults: A population-based study. Clin Nutr 2008;27(4):601-7.
13. Werle S, Goldhahn J, Drerup S, Simmen BR, Sprott H, Herren DB. Age- and gender-specific normative data of grip and pinch strength in a healthy adult Swiss population. J Hand Surg Eur Vol 2009;34(1):76-84.
14. Massy-Westropp NM, Gill TK, Taylor AW, Bohannon RW, Hill CL. Hand grip strength: Age and gender stratified normative data in a population-based study. BMC Res Notes 2011;4:127.
15. Peters MJH, Van Nes SI, Vanhoutte EK, Bakkers M, Van Doorn PA, Merkies ISJ, et al. Revised normative values for grip strength with the Jamar dynamometer. J Peripher Nerv Syst 2011;16(1):47-50.
16. Bohannon RW, Peolsson A, Massy-Westropp N, Desrosiers J, Bear-Lehman J, Rothstein JM, et al. Reference values for adult grip strength measured with a Jamar dynamometer: A descriptive meta-analysis. Physiotherapy 2006;92(1):11-5.
17. Lázaro MLM, Penacho Lázaro MA, Losantos FB, Plaza Bayo A. Nuevas tablas de fuerza de la mano para población adulta de Teruel. Nutr Hosp 2008;23(1):35-40.
18. Luna-Heredia E, Martín-Peña G, Ruiz-Galiana J. Handgrip dynamometry in healthy adults. Clin Nutr 2005;24(2):250-8.
19. Marrodán Serrano MD, Romero Collazos JF, Moreno Romero S, Mesa Santurino MS, Cabañas Armesilla MD, Pacheco Del Cerro JL, et al. Handgrip strength in children and teenagers aged from 6 to 18 years: Reference values and relationship with size and body composition. An Pediatr 2009;70(4):340-8.
20. Dodds RM, Syddall HE, Cooper R, Benzeval M, Deary IJ, Dennison EM, et al. Grip strength across the life course: Normative data from twelve British studies. PLoS One 2014;9(12):e113637.
21. Soriguer F, Gutiérrez-Repiso C, Rubio-Martín E, García-Fuentes E, Almaraz MC, Colomo N, et al. Metabolically healthy but obese, a matter of time? Findings from the prospective Pizarra study. J Clin Endocrinol Metab 2013;98(6):2318-25.
22. Olveira G. Manual de nutrición clínica y dietética. 3rd ed. Olveira G, ed. Madrid: Díaz de Santos; 2007. p. 188-9.
23. Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: Measurements on 481 men and women aged from 16 to 72 years. Br J Nutr 1974;32(1):77-97.
24. Siri WE. Body composition from fluid spaces and density: Analysis of methods. 1961. Nutrition 1993;9(5):480-92.
25. Boadella JM, Kuijer PP, Sluiter JK, Frings-Dresen MH. Effect of self-selected handgrip position on maximal handgrip strength. Arch Phys Med Rehabil 2005;86(2):328-31.
26. Johansson CA, Kent BE, Shepard KF. Relationship between verbal command volume and magnitude of muscle contraction. Phys Ther 1983;63(8):1260-5.
27. Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S. Grip and pinch strength: Normative data for adults. Arch Phys Med Rehabil 1985;66(2):69-74.
28. Watanabe T, Owashi K, Kanauchi Y, Mura N, Takahara M, Ogino T. The short-term reliability of grip strength measurement and the effects of posture and grip span. J Hand Surg Am 2005;30(3):603-9.
29. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. Clin Nutr 2015;34(3):335-40.
30. Mendes J, Alves P, Amaral TF. Comparison of nutritional status assessment parameters in predicting length of hospital stay in cancer patients. Clin Nutr 2014;33(3):466-70.
31. Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di Iorio A, et al. Age-associated changes in skeletal muscles and their effect on mobility: An operational diagnosis of sarcopenia. J Appl Physiol 2003;95(5):1851-60.
32. Sallinen J, Stenholm S, Rantanen T, Heliövaara M, Sainio P, Koskinen S. Handgrip strength cut points to screen older persons at risk for mobility limitation. J Am Geriatr Soc 2010;58(9):1721-6.
33. Günther CM, Bürger A, Rickert M, Crispin A, Schulz CU. Grip strength in healthy Caucasian adults: Reference values. J Hand Surg Am 2008;33(4):558-65.
34. Olveira G, Olveira C, Doña E, Palenque FJ, Porras N, Dorado A, et al. Oral supplement enriched in HMB combined with pulmonary rehabilitation improves body composition and health related quality of life in patients with bronchiectasis (Prospective, Randomised Study). Clin Nutr 2016;35(5):1015-22.
35. Bohannon RW. Grip strength: A summary of studies comparing dominant and nondominant limb measurements. Percept Mot Skills 2003;96(3 Pt 1):728-30.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Influence of liver transplantation in the nutritional profile of severe cirrhotic patients

La influencia del trasplante de hígado en el perfil nutricional de pacientes cirróticos graves

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Abstract

Objective: The aim of this study was to analyze the influence of liver transplantation in food intake and nutritional status of severe cirrhotic patients.

Methods: The sample consisted of 23 patients who underwent liver transplantation. Three 24-hour dietary recall were applied and anthropometric measurements were collected before and three months after transplantation. The consumption of macronutrients and fat soluble vitamins were also evaluated. The anthropometric data evaluated were body mass index, abdominal circumference, percentage of adequacy of arm circumference, triceps skinfold thickness and arm muscle circumference. Related mean comparison tests, comparison of changes in the proportions of categorical variables and correlation of quantitative variables were used in the statistical analysis. Data were considered to be significant when $p < 0.05$.

Results: Most patients were female and aged between 40 and 65 years. The average consumption of calories, proteins, lipids, cholesterol and monounsaturated fatty acids was significantly higher after liver transplantation ($p < 0.05$). The average of anthropometric parameters did not differ significantly between the evaluated times. There was no significant change in nutrient intake or anthropometric classification after transplantation. Most patients were classified as malnourished or overweight after transplantation, according to some anthropometric parameters.

Conclusion: Food consumption changed after transplantation. There was no change in the nutritional status from pre- to post-transplant but, in general, most patients had altered nutritional status in both evaluation moments.

Key words:

Food consumption.
Liver transplantation.
Liver cirrhosis.
Nutritional status.

Resumen

Objetivo: el objetivo de este estudio fue hacer un análisis de las influencias del trasplante de hígado en el consumo alimentario y estado nutricional de pacientes cirróticos graves.

Métodos: la muestra fue de 23 pacientes a los que se hizo trasplante de hígado. Se recopilan los datos antropométricos, además de tres recordatorios alimentarios de 24 horas antes y tres meses tras el trasplante. El consumo de macronutrientes y vitaminas liposolubles también fue evaluado. Los datos antropométricos evaluados fueron: índice de masa corporal, circunferencia abdominal, porcentual de adecuación del contorno de cintura, los pliegues cutáneos tricipital y de la circunferencia muscular del brazo. En el análisis estadístico se utilizaron tests de comparación de medias relacionadas, comparación de los cambios en las proporciones de las variables categóricas y la correlación de las variables cuantitativas. Los datos fueron considerados significativos cuando $p < 0,05$.

Resultados: la mayoría de los pacientes estudiados eran del sexo femenino y con edad entre 40 y 65 años. El consumo medio de calorías, proteínas, lípidos, colesterol y ácido graso monoinsaturado fue significativamente mayor después del trasplante hepático ($p < 0,05$). La media de los parámetros antropométricos no difirió significativamente entre los momentos evaluados. No hubo cambio significativo en la ingestión de nutrientes y en la clasificación antropométrica después del trasplante. La mayoría de los pacientes fueron clasificados como desnutridos o con exceso de peso tras el trasplante, de acuerdo con algunos parámetros antropométricos.

Conclusión: el consumo alimentario fue modificado después del trasplante. No hubo alteración del estado nutricional del preoperatorio comparado con el postoperatorio, pero de una forma general, la mayoría de los pacientes presentaron alteraciones de su estado nutricional en los dos momentos de la evaluación.

Palabras clave:

Consumo alimentario.
Trasplante de hígado.
Cirrosis hepática.
Estado nutricional.

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INTRODUCTION

Liver transplantation is the treatment of choice for patients with end-stage liver disease with the purpose of improving survival and quality of life. Data of the Brazilian Association of Organ Transplantation (1) have shown an increase in the performance of liver transplantation in Brazil. Only during the months from January to September of 2015, 1,326 transplants were performed.

Nutritional changes may influence on the process of liver transplantation, appearing as an independent risk factor for the patient's stay in the intensive treatment unit and total days of hospitalization, and increasing the complications and mortality in these patients. Adequate nutritional status and food intake are very important both to improve the general condition of the patient candidate for liver transplantation and for a good recovery after surgical trauma (2).

Insufficient or excessive consumption of foods causes widely described damage; however, there is evidence that diet quality characteristics are important in defining health status, particularly with regard to chronic degenerative diseases of adulthood (3).

Thus, better research is necessary in this context, since knowledge of dietary habits and nutritional risk factors associated with this disease are essential for therapeutic strategies aimed at improving the quality of life of this population. The aim of this study was to investigate the influence of liver transplantation in the anthropometric profile and consumption of nutrients in cirrhotic patients.

METHODS

STUDY CHARACTERIZATION

The study is a clinical uncontrolled trial type and was held at the ambulatory of nutrition, Liver Transplant Center, of the Hospital Walter Cantídio Complex in Fortaleza in the period from July 2013 to September 2015. The sample consisted of 23 patients, aged 18 to 65, who were assessed before and three months after liver transplantation in relation to nutritional and anthropometric aspects. The sample size was based on the number of patients in whom tracking was possible. The sample size was calculated considering the following criteria: number of patients who underwent liver transplant in 2012, which was equal to 127, proportion that is expected to be found of individuals with inadequate nutrient intake (50%), and sampling error of 15% and 90% of confidence level. Thus, it was determined that the sample size of this study should be 24 participants. This study was approved by the Ethical Committee of the State University of Ceará (CAAE No 15503213.2.0000.5534) and written consent was obtained from all participants.

DATA COLLECTION

The sociodemographic and clinical data of patients were collected from their charts, including age, sex, origin, ethnicity, schooling, family income, clinical diagnosis, associated pathologies, history of family diseases, blood type, model for end-stage liver disease (MELD) score and Child-Pugh classification. Nutritional and anthropometric data were obtained through interviews and evaluation of individuals in the two periods of work.

ANTHROPOMETRY

Weight, height, arm circumference (AC), abdominal circumference (AbC), triceps skinfold (TSF), biceps skinfold (BSF), subscapularis skinfold (SSSF) and suprailiac skinfold (SISF) were measured in triplicate. Body weight was measured by a scale (Filizola® Digital Scale, São Paulo, Brazil) with capacity of 150 kg and precision of 0.1 kg. Height was determined using a stadiometer (1 mm precision) attached to the scale, according to previously described procedures (4). Patients with edema or ascites had their weight discounted according to James (5) and Duarte and Castellani (6). Body mass index (BMI) was calculated and classified according to the World Health Organization criteria (WHO) (7,8).

The skinfolds were measured on the right side of the body using a Lange® adipometer (0.5 mm precision) according to previously described procedures (4). AbC and AC were measured with an unstretched tape measure. AbC was determined at umbilical scar level at the end of normal expiration. AC was measured at the midpoint between the acromial process of the scapula and the olecranon, with the arms loose along the trunk and the hands facing the thigh. The muscle arm circumference (MAC) was calculated according to the following formula: MAC (cm) = AC (cm) - 3.14 x (TSF (mm)/10).

The percentages of adequacy of AC, TSF and MAC were also calculated comparing the results found with the reference values proposed by the National Health and Nutrition Examination Survey using percentile tables (9). Adequacy percentages were classified according to Blackburn and Thorton (10). The percentage of body fat was obtained through the formula proposed by Siri (11), which considers body density estimated from the sum of TSF, BSF, SSSF and SISF. This measure was classified according to Lohman et al. (12). The values obtained from AbC were classified based on the International Diabetes Federation criteria (13).

ASSESSMENT OF FOOD INTAKE

The food intake evaluation was carried out by collecting three food 24-hour recalls of three non-consecutive days, including one weekend day. The energy needs of each individual were calculated based on the estimated energy requirement (EER), proposed by the Institute of Medicine (11). Macronutrients and fat-soluble vitamins were qualitatively evaluated considering the consumption above, within or below the recommended according to the cut-off values recommended by the Institute of Medicine (14-17).

STATISTICAL ANALYSIS

The statistical analysis of this study was performed using SPSS version 17.0. Data were expressed as frequencies, percentages, means and standard deviations. Data normality was tested using

the Kolmogorov-Smirnov test and homogeneity of data, using the Levene's test. The paired Student's t-test was used to compare the means of food consumption and anthropometric variables before and after transplantation. The McNemar and McNemar-Bowker tests were used to compare the proportions of individuals categorized according to the food consumption and anthropometric classifications before and after the transplantation, when the categories were dichotomic and polytomic, respectively. To investigate correlations among variables, a Pearson's correlation test was conducted. Data were considered as significant with p values below 0.05.

RESULTS

Most participants were female (52.2%), aged 40 to 65 years, from northeastern Brazil (where the survey was conducted), brown race or mulatto mainly (65.21%), with High School completed and household income of about one to five minimum wages (Table I). The blood type 0 prevailed among most patients (47.9%), with Child-Pugh B score between 7 and 9 (47.8%) and MELD score between 20 and 24 (78.3%). Viral hepatitis was the most frequent underlying disease, including hepatitis C, which was present in 34.78%, and hepatitis B, in 8.6% of the study population. Hypertension was the disease associated with clinical diagnosis of cirrhosis that affected more patients (17.4%) and was more prevalent in family history (73.9%) (Table II).

Although the anthropometric parameters showed no statistically significant difference between pre- and post-transplant (Table III), in the proportion comparison analysis a high prevalence of obesity before transplantation (52.17%) and eutrophic after transplantation (56.5%) was observed according to BMI. According to the AC, 52.17% and 56.53% of the participants were malnourished before and after transplantation, respectively. The classification did not changed between the periods in relation to the MAC for most participants, but 82.61% and 56.53% were normal before and after transplantation, respectively. According to the TSF classification, 47.82% of the participants were malnourished before and 52.17% were overweight after transplantation.

The largest proportion of the study participants had body fat percentage above average both before (66.66%) and after transplantation (60%). According to the evaluation of abdominal circumference, 92.85% of patients were at risk for cardiovascular disease due to the accumulation of abdominal fat above ideal on pre-transplant, and this number was reduced to 71.4% after transplantation. There was no significant change between the proportions of classifications of anthropometric parameters before and after transplantation ($p > 0.05$).

Among nutrients, it was observed that the average consumption of calories, proteins, lipids, cholesterol and monounsaturated fatty acids was significantly higher in post-transplantation than in pre-transplantation ($p < 0.05$) (Table IV).

Calorie and fiber consumption was classified as below the recommended, both before (65.22% and 91.30%) and after (91.3% and 82.6%) transplantation for most of the study participants. Regarding the consumption of carbohydrates, proteins and lipids, most of the participants were classified as within the recommended levels both in the pre- (69.57%, 95.70% and 82.60%, respectively) and post-transplant (78.53%, 100 00% and 82.60%, respectively) periods.

Regarding the consumption of lipid fractions, 78% of patients were rated with cholesterol consumption within the recommended values in pre-transplant, but this percentage was reduced in post-transplantation to 47.8%. For saturated and polyunsaturated fatty acids, most participants consumed according to recommended values both before (95.70% and 78.30%, respectively) and after (87.00% and 87.00%, respectively) transplantation. The consumption of monounsaturated fatty acids was lower than recommended for all participants in both periods.

The consumption of vitamins A, D, E and K was lower than recommended for most participants in pre- (95.70%, 60.87%, 95.70% and 100.00%, respectively) and post-transplantation (100.00%, 78.30%, 95.70% and 100.00%, respectively).

Table I. Sociodemographic characteristics of the study population (n = 23) of severe cirrhotic patients submitted to liver transplant

Characteristic	n	(%)
Gender:		
Male	11	47.8
Female	12	52.2
Age (years):		
20-40	2	8,7
40-65	22	91.3
Origin (region):		
Northeast	16	69.6
North	4	17.4
Other	3	13
Ethnicity:		
White	8	34.79
Brown/mixed race	15	65.21
Level of education:		
Incomplete Elementary School	1	4.3
Complete Elementary School	4	17.4
Incomplete High School	2	8.7
Complete High School	7	30.4
Incomplete higher education	6	26.1
Complete higher education	2	8.7
Postgraduate	1	4.3
Family income (minimum monthly salaries):*		
1 to 5	19	82.7
5 to 10	3	13
> 10	1	4.3

**Value of R$880.00 in 2016, which is equivalent to approximately US$272.00.*

Table II. Clinical and pathological characteristics of the study population (n = 23) of severe cirrhotic patients submitted to liver transplant

Characteristic	n	(%)
Blood type:		
A	7	30.4
AB	2	8.7
B	3	13
0	11	47.9
Child-Pugh classification:		
A	8	34.8
B	11	47.8
C	4	17.4
Model for end-stage liver disease score:		
10-19	5	21.7
20-24	18	78.3
Underlying disease:		
Viral hepatitis	9	39.1
Alcoholic hepatitis	6	26.1
Viral hepatitis type C and alcoholic hepatitis	1	4.4
Others	7	30.4
Associated diseases:		
Diabetes mellitus	3	13
Hypertension	4	17.4
Smoking	3	13
Family history:		
Obesity	3	13
Diabetes mellitus	16	69.6
Hypertension	17	73.9
Cardiovascular diseases	8	34.8
Cancer	11	47.8

Table III. Anthropometric characteristics of the study population (n = 23) of severe cirrhotic patients submitted to liver transplant

Variable	Pre-transplant		Post-transplant		p value*
	Mean	SD	Mean	SD	
Weight (kg)	64.92	17.36	64.17	16.1	0.612
Height (m)	1.6	0.1	1.6	0.1	-
BMI (kg/m²)	24.94	4.88	24.51	4.3	0.469
AC (cm)	27.81	4.81	27.48	4.49	0.624
AC adequacy (%)	90.11	14.68	89.32	13.28	0.708
TSF (cm)	16.54	5.73	17.16	6.39	0.632
TSF adequacy (%)	101.13	46.64	107.56	51.01	0.445
MAC (cm)	24.73	5.58	23.97	4.87	0.258
MAC adequacy (%)	99.09	15.66	96.57	15.48	0.34
AbC (cm)	95.36	10.95	92.43	10.78	0.23
Total body fat (%)	25.89	7.7	26.54	6.54	0.745

*SD: standard deviation; BMI: body mass index; AC: arm circumference; TSF: triceps skinfold; MAC: muscle arm circumference; AbC: abdominal circumference. *Student's t-test for related samples: level of significance set at $p \leq 0.05$.*

There was no significant change between the consumer ratings of the evaluated nutrients in the two periods of work ($p > 0.05$). There was no significant correlation between energy consumption and anthropometric parameters after transplantation ($p > 0.05$).

DISCUSSION

The aim of this study was to investigate the influence of liver transplantation on the nutritional status of cirrhotic patients. Although no significant changes in anthropometric ratings or adequacy of nutrients were observed between the periods studied, it was observed that some anthropometric parameters classified most participants as malnourished or overweight after transplantation and that the average consumption of calories, proteins, lipids, cholesterol and monounsaturated fatty acids increased significantly after transplantation.

Most of the participants in this study were between 40 and 65 years old and male. Similar to the study by Boin et al. (18), the most frequent cause of the liver diseases leading to transplantation was hepatitis C virus.

Before liver transplantation, most of the patients in this study had a B score and a score between 20 and 24 according to the Child-Pugh and MELD indices, respectively, which may refer to survival of less than 24 months in 43% of patients and a mortality rate of 76% (19). Tandon et al. (20) observed that severe muscle depletion (more prevalent in males, in patients classified as Child-Pugh class C, and in those with low BMI) is associated with increased mortality of patients on the waiting list for liver transplantation. Testing the association between the anthropometric indicators and the gender or the Child-Pugh and MELD indices with the data of this research was not possible because the sample data did not meet the requirements for association analysis.

Regarding the variations in the classifications of the participants by the anthropometric parameters, there are divergences between the different methodologies, which was also shown in the work of Alves, Mendes and Kruel (21), who found many of their participants in the post-liver transplantation with normal weight

Table IV. Energy and macronutrient intake of the study population (n = 23) of severe cirrhotic patients submitted to liver transplant

Variable	Pre-transplant		Post-transplant		p value*
	Mean	SD	Mean	SD	
Energy (kcal)	1774.26	537.86	2239.8	784.82	0.008
Carbohydrates (g)	234.52	81.6	283.18	122.16	0.063
Carbohydrates (%)	52.98	9.28	49.95	7.19	0.15
Proteins (g)	93.61	43.68	127.11	45.22	0.001
Proteins (%)	20.96	5.93	22.67	4.67	0.16
Lipids (g)	53.87	20.55	69.14	24.44	0.008
Lipids (%)	26.65	5.54	27.83	5.25	0.398
Fibers (g)	18.04	9.16	20.59	10.07	0.134
Cholesterol (mg)	245.00	137.47	350.12	165.02	0.031
SFA (g)	6.96	2.1	6.83	2.29	0.813
MUFA (g)	7.83	2.31	9.22	2.84	0.034
PUFA (g)	8.48	2.43	8.09	1.63	0.489
Vitamin A	724.79	834.56	517.35	448.51	0.146
Vitamin D	31.54	47.73	12.04	23.23	0.096
Vitamin E	8.57	4.32	9.96	5.17	0.081
Vitamin K	10.70	15.30	15.50	17.92	0.081

*SD: standard deviation; SFA: saturated fat acids; MUFA: monounsaturated fat acids; PUFA: polyunsaturated fatty acids. *Student's t-test for related samples: level of significance set at $p \leq 0.05$.*

according to BMI (41.70%), AC (38.90%) and MAC (69.80%), while malnutrition was more prevalent according to TSF (38.9%).

The study of the prevalence of abdominal obesity in patients undergoing liver transplantation is observed in few studies. Anastácio et al. (22) and Ribeiro et al. (23) showed that 88% and 53.7% of participants, respectively, had some degree of abdominal obesity. These studies reinforce our results, in which patients undergoing transplantation have a body fat percentage and abdominal circumference above the recommended, which may be due to increased energy consumption after transplantation. However, a significant correlation between energy consumption and anthropometric parameters was not seen, probably due to the number of participants.

In relation to food intake, it is assumed that the increase in caloric intake after transplantation is mainly due to improved health and appetite of the patient; return to the diet without restrictions due to the absence of hepatic encephalopathy, edema and ascites; decreased level of physical activity; and the use of immunosuppressants. As this work, Merli et al. (2) proved a significant increase in energy consumption after transplantation.

The consumption of macronutrients was within the recommended values in most patients during the two study periods. The average protein increase is probably due to the increased consumption of meat, milk and its derivatives as seen in the analysis of 24-hour dietary recalls. These foods constitute an excellent source of high quality protein as they contain all the essential amino acids in proportions similar to those required for the synthesis of human tissue proteins. The increase of vegetable oil consumption during food preparation, as well as increased appetite and unrestricted diets, may have also interfered with lipid consumption.

The opposite result was observed by Ferreira et al. (24) in relation to the consumption of proteins, which was inadequate in 72% of patients of their work. However, the percentage of participants with consumption of carbohydrates and lipids was also high.

Fiber consumption below the recommended by the participants of this study can be attributed to low consumption of whole grains, fruits and vegetables, which can influence the cholesterol control, the development of constipation and increased food intake (25).

The consumption of lipid fractions was in line with the recommended for saturated and polyunsaturated fatty acids at the two moments of intervention. Conversely, monounsaturated fatty acids and cholesterol showed a decrease in the proportion of participants with consumption according to the recommended after transplant. However, the average consumption of the latter two was significantly higher after transplantation. Ferreira et al. (24) found similar results in relation to the consumption of saturated and monounsaturated fatty acids, but differ in relation to cholesterol, which was consumed in excess by most participants, and polyunsaturated fatty acids, with consumption below the recommended.

The increase in consumed cholesterol is probably due to increased consumption of foods rich in protein and fat, as observed in the 24-hour recalls, because these foods are similar sources. In the 24-hour recalls the absence of consumption of vegetable oils of good quality, such as olive oil, and other sources such as oleaginous seeds has been observed as well, which may have contributed to the fact that consumption of monounsaturated fatty acids was suboptimal.

The consumption of fat-soluble vitamins below the recommended in the two moments of the study can be explained by the low consumption of fruits and vegetables, which is supported by data of the Family Budget Research (26) that showed low consumption of such foods by the Brazilian population. In addition, participants are advised not to consume raw vegetables after surgery, in order to avoid the risk of contamination.

The liver has an important role in the transport and storage of fat soluble vitamins (A, D, E, K). Insufficient quantities of these vitamins can be related to hepatic dysfunction, and hence changes in the nutritional status (27). It has been reported that vitamin A deficiency is related to hepatitis C and alcoholic cirrhosis (28,29). Studies have shown that very low concentrations of vitamin D in serum are associated with increased mortality of patients with chronic liver disease and an impaired immune function due to a deficiency of this vitamin has been suggested. Low Vitamin D levels are also associated with worse survival, the degree of hepatic dysfunction and disease severity assessed according to the Child-Pugh score (30,31).

Vitamin E deficiency has been well documented in alcoholic liver disease. However, the beneficial effect of vitamin E supplementation on liver diseases is dependent on the nature of the disorder (32).

In cholestatic liver diseases or lack of biliary secretion which prevents the formation of chylomicrons, menaquinone and phytoquinones, vitamin K deficiency can be observed, particularly by defect in the absorptive process (33).

As a study limitation, it must be highlighted that three months might not be enough time to observe some metabolic post-transplantation disorders. Therefore, it is suggested that the study be continued, since some studies have reported a year as a time for major changes in nutritional status. In addition, it was not possible to use electrical bioimpedance to evaluate body composition due to the high incidence of ascites and edema in this patients, mainly before transplantation. However, it should be pointed out that the skinfolds evaluation methods used in this research, performed by qualified professionals, are valid and reliable, allowing the analysis of lean mass and fat mass and showing a clear view of the body fat distribution (34).

CONCLUSION

The average consumption of some nutrients was higher after transplantation. There were no changes in nutritional status from the pre to the post-transplant period but, in general, most patients had changes in nutritional status in the two stages, indicating that good guidance and nutrition monitoring is of paramount importance to avoid nutritional risks in order to ensure the success of transplantation and improve survival and quality of life of these patients.

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AUTHORSHIP

All authors were involved in the conception and development of the research, data analysis and writing of the manuscript.

REFERENCES

1. Associação Brasileira de Transplante de Órgãos. Registro Brasileiro de Transplantes. Ano XVIII, 2015; n. 4. Available from: http://www.abto.org.br/
2. Merli M, Giusto M, Giannelli V, et al. Nutritional status and liver transplantation. J Clin Exp Hepatol 2011;1(3):190-8.
3. Monteiro CA, Mondinib L, Costa RBL, et al. Mudanças na composição e adequação nutricional da dieta familiar nas áreas metropolitanas do Brasil (1988-1996). Rev Saúde Pública 2000;34(3):251-8.
4. Anthropometric standardization reference manual. Lohman TG, Roche AF, Martorell R, eds. Champaign: Human Kinetics Books; 1988.
5. James R. Nutritional support in alcoholic liver disease: A review. J Hum Nutr 1989;2:315-23.
6. Duarte AC, Castellani FR. Semiologia Nutricional. Rio de Janeiro: Ed. Axcel Books do Brasil Ltda; 2002.
7. World Health Organization. Physical status: The use and interpretation of anthropometry. WHO Technical report series n. 854. Geneva: WHO; 1995.
8. World Health Organization. Obesity: Preventing and managing the global epidemic. WHO Technical report series. Geneva: WHO; 1998.
9. Frisancho AR. Anthropometric standards for the assessment of growth and nutritional status. Ann Arbor: The University of Michigan Press; 1990.
10. Blackburn GL, Thornton PA. Nutritional assessment of the hospitalized patient. Med Clin North Am 1979;63(5):11103-15.
11. Siri WS. Body composition from fluid spaces and density: Analysis of methods. En: Brozek J, Henschel A, eds. Techniques for measuring body composition. Washington: National Academy of Science - National Research Council; 1961.
12. Lohman TG. Advances in body composition assessment. Current issues in exercise science series. Champaign: Human Kinetics Books; 1992.
13. The IDF consensus worldwide definition of the metabolic syndrome. International Diabetes Federation; 2005.
14. Institute of Medicine (IOM). Dietary reference intakes (DRI) for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. Washington: National Academy Press; 2005. Available from: http://www.nap.edu
15. Institute of Medicine (IOM). Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington: National Academy Press; 2000. Available from: http://www.nap.edu
16. Institute of Medicine (IOM). Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington: National Academy Press; 2001. Available from: http://www.nap.edu
17. Institute of Medicine (IOM). Dietary reference intakes (DRI) for calcium and vitamin D. Washington: National Academy Press; 2011. Available from: http://www.nap.edu
18. Boin IFSF, Leonardi MI, Udo EY, et al. Aplicação do escore MELD em pacientes submetidos a transplante de fígado: análise retrospectiva da sobrevida e dos fatores preditivos a curto e longo prazo. Arq Gastroenterol 2008;45(4):275-83.
19. MCavoy N, Wilson TES. Hepatic failure. Anaesth Intensive Care 2012;13(4):161-5.
20. Tandon P, Ney M, Irwin I, et al. Severe muscle depletion in patients on the liver transplant wait list: Its prevalence and independent prognostic value. Liver Transpl 2012;18:1209-16.
21. Alves VS, Mendes RH, Kruel CDP. Nutritional status, lipid profile and HOMA-IR in post-liver transplant patients. Nutr Hosp 2014;29(5):1154-62.
22. Anastacio LR, Ferreira LG, De Sena RH, et al. Body composition and overweight of liver transplant recipients. Transplantation 2011;92(8):947-51.
23. Ribeiro AHS, Ribeiro HS, Anastácio BLR, et al. Energy expenditure and balance among long term liver recipients. Clin Nutr 2014;33(6):1147-52.
24. Ferreira LG, Anastácio LR, Lima AS, et al. Resting energy expenditure, body composition, and dietary intake: A longitudinal study before and after liver transplantation. Transplantation 2013;96(6):579-85.
25. Gavanski DS, Baratto I, Gatti RR, et al. Avaliação do hábito intestinal e ingestão de fibras alimentares em uma população de idosos. RBONE 2015;9(49):3-11.
26. Instituto Brasileiro de Geografia e Estatística. Pesquisa de orçamentos familiares 2008-2009: análise do consumo alimentar pessoal no Brasil. Rio de Janeiro: IBGE; 2011. Available from: http://biblioteca.ibge.gov.br/visualizacao/livros/liv50063.pdf
27. Giammanco A, Cefalù AB, Noto D, et al. The pathophysiology of intestinal lipoprotein production. Front Physiol 2015;20(6):61.
28. Peres WA, Chaves GV, Gonçalves JC, et al. Vitamin A deficiency in patients with hepatitis C virus-related chronic liver disease. Br J Nutr 2011;106(11):1724-31.
29. Bitetto D, Bortolotti N, Falleti E, et al. Vitamin A deficiency is associated with hepatitis C virus chronic infection and with unresponsiveness to interferon-based antiviral therapy. Hepatology 2013;57(3):925-33.
30. Malham M, Jùrgensen SP, Ott P, et al. Vitamin D deficiency in cirrhosis relates to liver dysfunction rather than an etiology. World J Gastroenterol 2011;17(7):922-5.
31. Salzl P, Wagner D, Keonig V, et al. Vitamin D3 levels predict survival but not portal hypertension in patients with liver cirrhosis. Hepatology 2012;56:925.
32. Arteel G, Marsano L, Mendez C, et al. Advances in alcoholic liver disease. Best Pract Res Clin Gastroenterol 2003;17(4):625-47.
33. Senzolo M, Burra P, Cholongitas E, et al. New insights into the coagulopathy of liver disease and liver transplantation. World J Gastroenterol 2006;12(48):7725-36.
34. Cyrino ES, Okano AH, Glaner MF, et al. Impacto da utilização de diferentes comzpassos de dobras cutâneas para a análise da composição corporal. Rev Bras Med Esporte 2003;9(3):145-9.

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Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Looking for optimum ECG electrodes for bioelectrical impedance analysis (BIA). The need for evaluation

En búsqueda de electrodos óptimos para el uso de la bioimpedancia eléctrica. Una evaluación necesaria

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Key words:

Electrocardiogram (ECG) electrodes. Bioelectrical impedance analysis. Body composition. Young adults.

Abstract

Background: The accuracy and precision of the BIA method is affected by the electrode system. Failing to adjust for differences in it may result in systematic biases of up to 5.2%.

Methods: Forty females ranging from 18 to 24 years, with a body mass index (BMI) of 18.6 to 27.6 kg/m^2, were measured by BIA in the frequency range 5 to 500 kHz using the manufacturers recommended electrodes and two types of commercial ECG electrodes (3M-2228 and 3M-2330).

Results: The two types of ECG electrodes performed well, but at high frequencies 2330 performed better.

Conclusion: It was concluded that when electrodes recommended by the equipment manufacturer are not available, ECG electrodes with the best performance should be used. In this way, it will be possible to predict and prevent inadequate records of electrical signals

Palabras clave:

Electrodos de electrocardiograma (ECG). Análisis de bioimpedancia eléctrica. Composición corporal. Adultos jóvenes.

Resumen

Introducción: la exactitud y la precisión del método de análisis de bioimpedancia eléctrica (ABE) se ven afectadas por el sistema de electrodos. Cuando no se realizan los ajustes por las diferencias en este sistema se pueden producir errores en los resultados hasta en un 5,2%.

Métodos: cuarenta mujeres de entre 18 y 24 años con un índice de masa corporal (IMC) entre 18,6 y 27,6 kg/m^2 fueron medidas con el ABE en rangos de frecuencia de 5 a 500 kHz, usando los electrodos recomendados por el productor del dispositivo de bioimpedancia (Impedimed®), los cuales fueron tomados como referencia.

Resultados: dos tipos de electrodos comerciales de electrocardiograma (3M-2228 and 3M-2330) fueron comparados con los de referencia. Ambos electrodos comerciales tuvieron un desempeño similar a los de referencia; sin embargo, a frecuencias altas los electrodos 2330 se comportaron mucho mejor.

Conclusión: se concluyó que cuando los electrodos recomendados por el productor del equipo no estén disponibles, se usen los electrodos de ECG que tengan un mejor comportamiento. De esta forma, será posible predecir y prevenir registros inadecuados de las señales eléctricas

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INTRODUCTION

Body composition measurements are useful to estimate adiposity, muscle mass and fluid retention in different clinical conditions (1,2). BIA has been widely used for this purpose after being validated by DEXA, CT and hydrodensitometry (3,4). The accuracy and precision of the technique can be affected by several variables, one of which is the electrode system (5). It has been found that factors such as electrode size, electrode type, electrode positioning, contact impedance, and polarization voltage can influence the stability of the measurement (6). Failing to adjust for differences in electrodes may result in systematic biases in resistance of up to 5.2% (7). The search for new electrode materials and designs attempting to overcome the artifacts produced by these factors is now an area of considerable research (8-10). At the beginning, bioimpedance methods used uncomfortable needle electrodes; then, adhesive gel electrodes were used to optimize electrical contact, and more recently, electrodes evolved to modern plate, textile and simple touch-pad electrodes without the need for invasive techniques (11). However, despite extensive research, ability to determine the electrode system properties is still very limited as noticed by Geddes (6). While some bioimpedance analysis manufacturers claim for specifically suited BIA electrodes to obtain precise and reproducible results in bioimpedance testing, some users recommend standard ECG electrodes for BIA performance (12,13). However, using suitable BIA electrodes could increase the tight budget for health, and sometimes imply difficulties in the importing process (14). For these reasons, many researchers and users have chosen to use ECG electrodes, but certainly, all ECG electrodes do not perform the same, as it was previously shown (14). While the optimal electrode system for BIA body composition continues improving, the validation of ECG electrodes for BIA is an important issue for the technique. Therefore, the aim of this study was to compare suitable previously evaluated BIA electrodes with non-evaluated ECG electrodes.

MATERIALS AND METHODS

SUBJECTS

The methods were approved by the Bioethics Committee of the Universidad de Caldas. A sample of 40 young adult females of the Universidad de Caldas (Colombia) was evaluated. The purpose and procedures of the study were explained to the volunteers and the inclusion/exclusion criteria were verified after completing a questionnaire. Then, the volunteers signed an informed written consent.

Inclusion criteria were being female aged between 18 and 24 years with BMI between 18.6 and 27.6 kg/m^2 and without co-morbidities. Exclusion criteria were smoking, having a metallic or a cardiac pacemaker, being pregnant or using diuretics, and having undergone surgery for weight reduction or silicone implants in the breasts.

DATA ACQUISITION

Measurements were performed in one session early in the morning to minimize environmental and biological variations. Relative humidity and environment temperature were controlled with an electric heater (BFH416, Bionaire®) and a dehumidifier (BMD100, Bionaire®). Relative humidity (RH) and environmental temperature were measured with a thermo-hygrometer (13307, DeltaTrak®, ± 1% RH/± 0.1 °C) and atmospheric pressure was measured with a barometer (K4, Konustar®). Volunteers were asked to comply with the following requirements before the test: not drinking alcohol in the previous 48 hours, 12 hours of no vigorous exercise and 12 hours of fasting but keeping normal water hydration. All were asked to evacuate their bladder and colon 30 minutes before the test and wear a hospital gown during the test. All participants were required to be in the proliferative-follicular phase or in the first seven days of the luteal phase of menstrual cycle (7).

ANTHROPOMETRIC MEASUREMENTS

Height (Heightronic-235®, Seca, ± 0.01 cm) and weight (PP2000, Icob-Detecto®, ± 0.1 kg) were measured twice, and a third measurement was taken if a difference greater than 0.5 cm or 0.1 kg respectively was found (15).

BIA MEASUREMENTS

Volunteers were measured on the dominant side of the body for three times at the end of an exhalation on a nonconductive surface (16) (Hydra 4200, Xitron Technologies). Raw resistance (R), capacitive reactance (Xc) and impedance (Z) data at 5, 10, 50, 100, 200 and 500 kHz were measured according to a standardized protocol described earlier (7). Briefly, legs were separated about 45° and arms were separated from trunk about 30° (7,16) (Fig. 1). Dorsal hand and anterior foot surfaces were cleaned with alcohol and dried with a paper towel (7). Four landmarks were made for the placement of the electrodes: the mid-line between the prominent ends of the radius and ulna of the wrist, the midline of the third metacarpal-phalangeal joint on the dorsal hand surface, the midline between the medial and lateral malleolus of the ankle and the midpoint of the third metatarsal-phalangeal joint on the anterior surface of the foot (5,7,14). Current was applied at the distal electrodes and the voltage was measured at the proximal electrodes (Fig. 1). BIA measurement protocol for each type of electrodes (in random order) was: five minutes standing up, measurements between minutes 6 to 10 minutes after lying down, and then five minutes standing up again before the measurement with another type of electrodes (14).

Results obtained with two types of ECG electrodes commercially available (2230 and 2228, 3M) which had not been evaluated previously were compared to the results obtained with the electrodes recommended by the bioimpedance meter manufacturer (292-STE, Impedimed®) because this type of electrodes is specifically

Table I. Electrode type

Electrode	image	Use	Backing	Gel system	Sensor material	Skin sensor contact area (cm^2)	Cost* (US$)
292-STE		BIA	Printed film	Wet sticky	Proprietary gel ink	5.75	4.0
2228		ECG	Foam	Wet sticky	Ag/AgCL eyelet	3.14	0.50
2330		ECG	Printed film	Wet sticky	Ag/AgCL ink	4.12	0.25

**Cost for testing in one person (four electrodes).*

designed to fit the device. For this reason, in this study, the results obtained with 292-STE electrodes were used as the reference measurements. Table I shows some characteristics of the three different types of electrodes tested in this study.

STATISTICAL METHODS

The Hydra_S_Acquisition Utility (version 1.0 2003) was used to capture the raw data and the Hydra_Data_Model_Vol Utility (version 2.2 1997) was used to obtain the model data and volumes. Mean and standard deviation (SD) were used to evaluate the characteristics of subjects and laboratory conditions. Low and high frequencies were represented from 5 to 500 kHz respectively. Raw data (R, Xc and Z) from 5 to 500 kHz were analyzed to determine the effect of exchanging the order of using the reference electrodes. Raw data, model data (extra-cellular-fluid resistance $R_{ECF,}$ intra-cellular-fluid resistance $R_{ICF),}$ and volume data (extra-cellular-fluid volume ECF and intra-cellular-fluid volume ICF) were analyzed to determine significant differences between electrodes. Bland Altman plots and paired Student's t-test, using $p < 0.01$ as significant, were used for statistical comparisons of the various parameters obtained from the bioimpedance machine (Bland and Altman 1986). The standard error of estimate (SEE) was used to evaluate if body composition data was acceptable. The SEE for ECW and ICW was acceptable if it was between 1.0 l and 1.5 l (17). All analyses were performed using XLSTAT software (version 2013.1.01, Addinsoft).

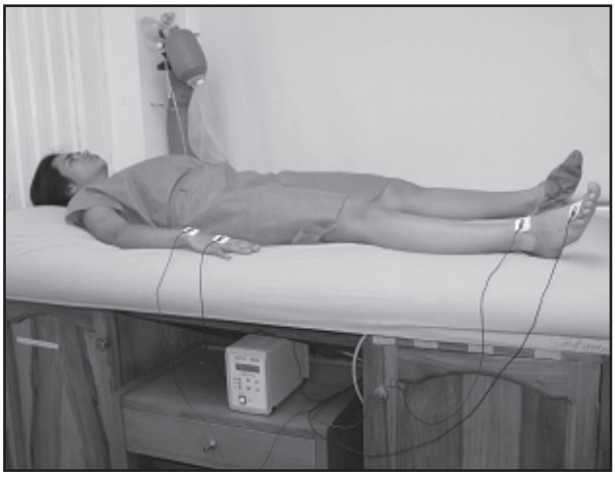


Figure 1.
Position of subject and electrodes position.

RESULTS

Environmental conditions during measurements were stable: temperature was 18.8 ± 0.7 °C, relative humidity was 73.5 ± 1.9% and atmospheric pressure was 787.4 ± 0.6 mmHg. Subjects' characteristics are shown in table II.

Comparison of raw data (R, Xc and Z from 5 to 500 kHz) obtained in 40 subjects using ECG electrodes (2330 and 2228) *versus* the reference electrodes (292-STE) are shown in tables III-V.

Comparison of data volume (ECF, ICF) in 40 subjects using ECG electrodes (2330 and 2228) *versus* reference electrodes (292-STE) showed that the differences for ECF results between the two types of electrodes tested (3M-2330 and 3M-2228) were small and non-significant (-0.01 and -0.05 liters respectively when compared to the 292-STE electrodes). Similar results occurred with ICF estimations; however, in this case the differences were higher than for ECF: -0.06 and 0.20 liters respectively.

Table II. Subject's characteristics (n = 40)

Variables	Mean ± SD	Range
Age (y)	21.2 ± 1.7	(18.1-24.6)
Weight (kg)	54.1 ± 6.0	(43.1-67.7)
Height (cm)	156.8 ± 4.0	(148.7-166.3)
Body mass index (kg/m^2)	22.0 ± 2.3	(18.6-27.6)

Table III. Resistance comparison between ECG and BIA electrodes (n = 40)

Frequency (kHz)	Mean (SD) 292-STE electrodes (Ω)	2330 ECG electrodes			2228 ECG electrodes		
		pt	Bland & Altman		pt	Bland & Altman	
			Bias (Ω)	Limits (Ω) Low, up		Bias (Ω)	Limits (Ω) Low, up
5	740.9 (62.3)	0.60	0.93	-27.9, 29.8	0.30	2.16	-29.8, 34.2
10	724.3 (60.7)	0.61	0.83	-25.2, 26.8	0.30	2.07	-28.5, 32.6
50	646.3 (53.9)	0.38	1.03	-17.8, 19.9	0.28	1.72	-22.9, 26.4
100	610.2 (51.3)	0.29	1.16	-16.5, 18.8	0.34	1.47	-22.1, 25.0
200	580.7 (49.4)	0.29	1.15	-16.4, 18.7	0.56	0.88	-22.4, 24.2
500	551.9 (47.0)	0.23	1.27	-15.5, 18.1	0.62	-0.94	30.4, 28.5

pt: p-value obtained by paired Student's 2-sided t-test. A p < 0.01 was considered as significant.

Table IV. Reactance comparison between ECG and BIA electrodes (n = 40)

Frequency (kHz)	Mean (SD) 292-STE electrodes (Ω)	2330 ECG electrodes			2228 ECG electrodes		
		pt	Bland & Altman		pt	Bland & Altman	
			Bias (Ω)	Limits (Ω) Low, up		Bias (Ω)	Limits (Ω) Low, up
5	34.7 (4.7)	0.78	0.11	-6.1, 6.4	0.02	0.75	-3.9, 5.4
10	50.1 (6.5)	0.84	0.09	-7.4. 7.6	0.08	0.72	-5.6, 7.0
50	75.0 (8.2)	0.71	-0.12	-5.4, 5,2	0.001	1.64	-5.6, 8.9
100	72.3 (7.4)	0.60	-0.13	-4.2, 3.9	0.0001	2.76	-7.3, 12.8
200	67.4 (6.8)	0.75	-0.08	-3.9, 3.8	< 0.0001	5.04	-10.5, 20.6
500	67.4 (8.0)	0.66	0.16	-5.8, 6.1	< 0.0001	11.3	-15.9, 38.4

pt: p-value obtained by paired Student's 2-sided t-test. A p < 0.01 was considered as significant.

Table V. Impedance comparison between ECG and BIA electrodes (n = 40)

Frequency (kHz)	Mean (SD) 292-STE electrodes (Ω)	2330 ECG electrodes			2228 ECG electrodes		
		pt	Bland & Altman		pt	Bland & Altman	
			Bias (Ω)	Limits (Ω) Low, up		Bias (Ω)	Limits (Ω) Low, up
5	741.7 (62.4)	0.60	0.93	-28.11, 29.97	0.29	2.21	-29.9, 34.3
10	726.1 (60.9)	0.61	0.83	-25.52, 27.19	0.29	2.13	-28.7, 33.0
50	650.6 (54.2)	0.40	1.01	-18.14, 20.15	0.24	1.90	-23.0, 26.8
100	614.4 (51.6)	0.31	1.13	-16.67, 18.94	0.24	1.80	-21.7, 25.3
200	584.6 (49.7)	0.30	1.13	-16.55, 18.82	0.30	1.50	-21.1, 24.1
500	556.0 (47.5)	0.23	1.28	-15.65, 18.21	0.72	0.61	-25.6, 26.9

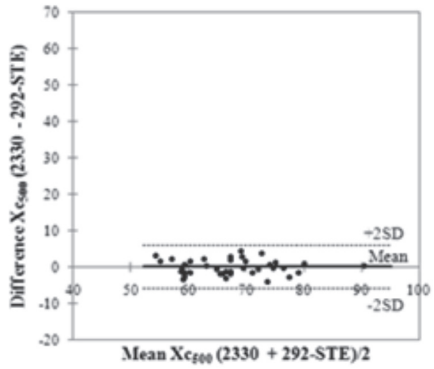
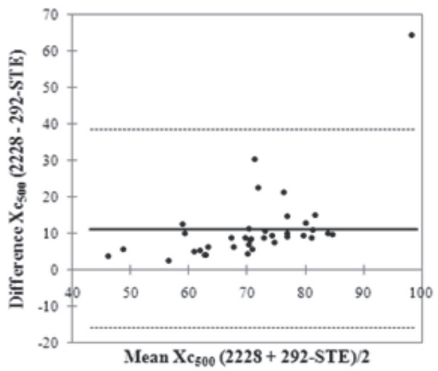
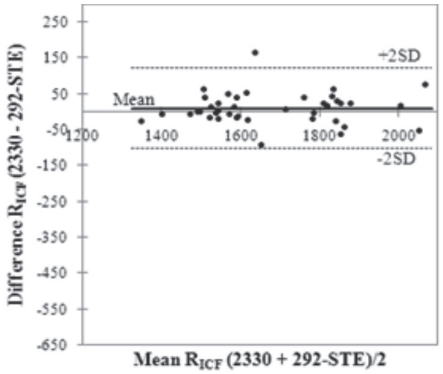
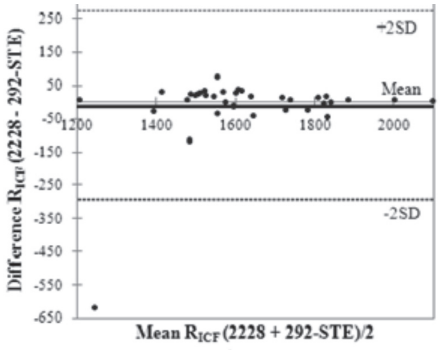
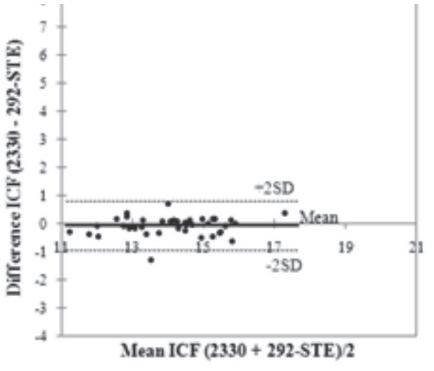
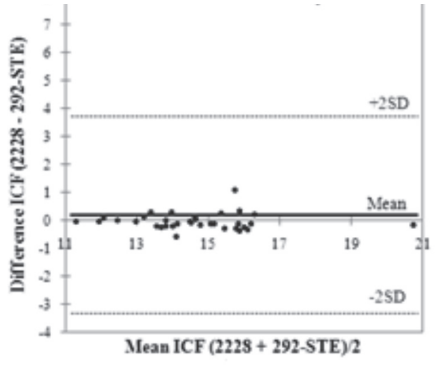
pt: p-value obtained by paired Student's 2-sided t-test. A p < 0.01 was considered as significant.

Bland and Altman plots for some raw, model and volume data from 40 subjects using ECG electrodes (2330 and 2228) *versus* the reference electrodes are presented in table VI to show the biggest discrepancies at high frequency measurements. Simple linear regressions of data volume by 292-STE *versus* ECG electrodes are shown in table VII.

DISCUSSION

There is a constant commitment to improve the quality of BIA measurements and try to minimize the most of all the variables that affect the results and remove the BIA merits. It has been recognized that the type of electrodes for electrical measurements

Table VI. Bland and Altman plots of raw, model and volume data by 292-STE against ECG electrodes

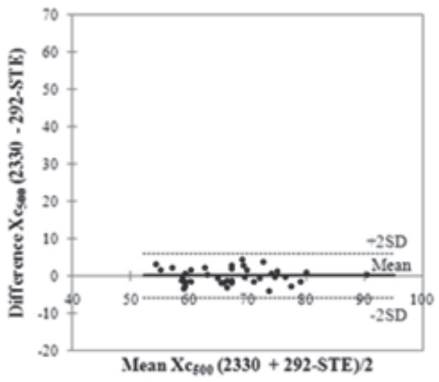
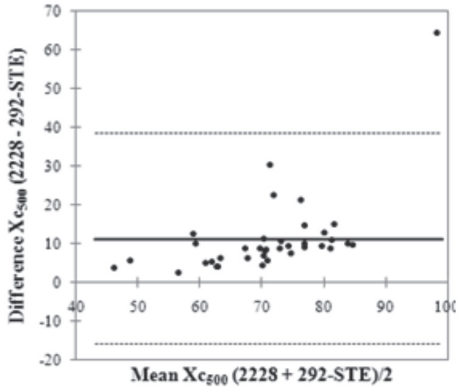
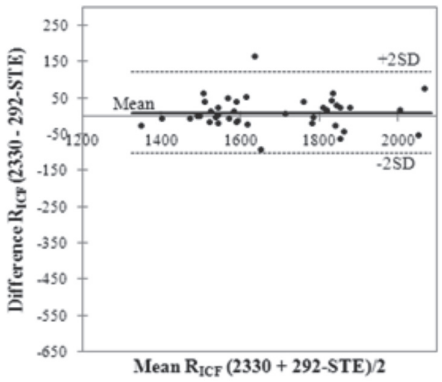
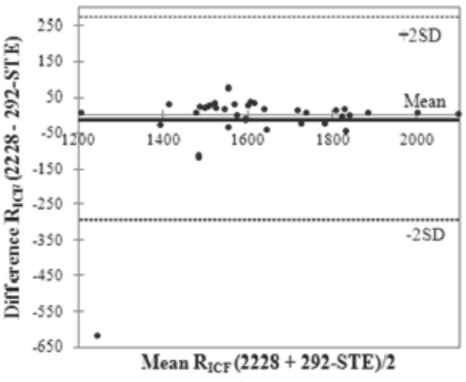
Data	2330	2228
Reactance at 500 kHz (Xc_{500}) (Ω)		
Intra-cellular fluid resistance (R_{ICF}) (Ω)		
Intra-cellular fluid volume (ICF) (l)		

influence the signals that are measured and it is important to find the suitable electrode system for each application, otherwise, the obtained data might produce wrong estimation of BIA parameters and inaccurate diagnosis of body composition (19).

Although the bioimpedance analysis manufacturers have strongly recommended using the electrodes designed for a specific BIA machine, this is not always possible and many researchers use the ECG electrodes. However, some electrodes do not have the minimum recommended area or gel cannot meet the requirements for long-term use in hemodialysis and renal applications (20). Since in many cases studies report using ECG electrodes in bioimpedance measurements, we wanted to compare previously evaluated and not evaluated ECG electrodes from the same brand trying to find those producing the fewest artifacts.

In this study, 40 healthy women normally-hydrated and without clinical skin affections were measured in the frequency range 5 to 500 kHz. Although the device generates data at 1,000 kHz, these measurements were omitted since it is known that at high-

Table VII. Simple linear regressions of model and volume data by 292-STE against ECG electrodes

Data	2330	2228
Reactance at 500 kHz (Xc_{500}) (Ω)		
Intra-cellular fluid resistance (R_{ICF}) (Ω)		

er frequencies, the stray capacitance can produce errors (21). Three types of electrodes were tested: those for reference which are produced for the specific BIA device (Impedimed® 292-STE) used for this study, evaluated ECG electrodes (3M-2228) and non-evaluated ECG electrodes (3M- 2330).

The 3M-2228 and 3M-2330 did not show statistically significant differences with the reference standard electrodes in resistance. However, the 3M-2228 reactance differed significantly from the 50 kHz measurements. When impedance was examined, the differences were not significant for the two types of electrodes (probably because the resistive component is greater than the reactive) but the different reactive component was reflected in the modeling and estimating of the intra-cellular fluid volume. The results showed that albeit the already evaluated ECG electrodes (3M-2228) performed well and within the previously established parameters, the non-evaluated 3M-2330 performed better. Thus, by using the correct ECG electrodes some limitations produced by these electrodes must be previously predicted and prevented to undertake BIA measurements.

Possible explanations for the results may be related to the greater area of the 3M-2330 compared to 3M-2228 electrodes (Table I) since the minimum recommended area is 4 cm^2 (5) and because a smaller area affects the reactive component, increases the impedance (22) and deteriorates the coupling of the gel-electrode and skin interface. Another source of variation could be the backing electrodes (printed *vs* foam) and material sensor (eyelet *vs* ink). In addition, although a formal study for cost-effectiveness was not the intention in this study, we found that 2330 was cheaper than the other two types of electrodes.

Regarding the clinical significance of the findings in ECF and ICF estimations, in adults, perhaps the differences are not of clinical importance but using this ECG of the assessment of children may be more important and further studies might be done (23).

Several controversies remain on using different type of electrodes: dry or wet electrodes (and type of gel for the latter), metal touch or textile electrodes (8,11,24). Although dried gel electrodes would have more advantages over wet gel electrodes, dried gel electrodes are less conductive than wet gel electrodes. The gel is able to get into the skin ensuring better interface gel-electrode-skin. For this reason, wet electrodes are the most commercial ones (25). Previously, it was found that 3M-2228 wet-gel electrodes are more convenient for BIA measurements than the 2290 dried-gel electrodes.

Recently, conductive textile materials have been used for electrodes. However, to date, the results obtained with these materials have low reproducibility and cause errors in the estimation of the

body composition, and more research must be done to provide a textile-based electrode system to allow reliable BIA measurements (8,9). In addition, these types of electrodes are not easily available in developing countries. While both situations changed, we tried to find which ECG electrodes would be more suitable for BIA measurements.

CONCLUSION

The findings in this report suggest the possibility of measuring BIA parameters with ECG electrode system in young adult females when the recommended manufacturers of BIA devices are not available. Since not all ECG electrodes are suitable for these measurements, ECG electrodes should be evaluated for BIA measurements in order to avoid adding errors to the registered signals and making mistakes in assessing body composition in humans.

REFERENCES

1. Pietilainen KH, Kaye S, Karmi A, Suojanen L, Rissanen A, Virtanen KA. A Agreement of bioelectrical impedance with dual energy X-ray absorptiometry and MRI to estimate changes in body fat, skeletal muscle and visceral fat during a 12 month weight loss intervention. Br J Nutr 2013;109(10):1910-6.
2. Dolfing JG, Stassen CM, Van Haard PM, Wolffenbuttel BH, Schweitzer DH. Comparison of MRI assessed body fat content between lean women with polysystic ovary syndrome (PCOS) and matched controls: Less visceral fat with PCOS. Hum Reprod 2011;26(6):1495-500.
3. Li YC, Li CI, Lin WY, Liu CS, Hsu HS, Lee CC, et al. Percentage of body fat assessment using bioelectrical impedance analysis and dual-energy X-ray absorptiometry in a weight loss program for obese or overweight Chinese adults. PloS One 2013;8(4):e58272.
4. Bredella MA, Ghomi RH, Thomas BJ, Torriani M, Brick DJ, Gerweck AV, et al. Comparison of DXA and CT in the assessment of body composition in premenopausal women with obesity and anorexia nervosa. Obesity (Silver Spring, Md) 2010;18(11):2227-33.
5. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gómez J, et al. Bioelectrical impedance analysis - Part II: Utilization in clinical practice. Clin Nutr 2004;23(6):1430-53.
6. Geddes LA. Historical evolution of circuit models for the electrode-electrolyte interface. Ann Biomed Eng 1997;25(1):1.
7. González-Correa CH, Caicedo-Eraso JC. Bioelectrical impedance analysis (BIA): A proposal for standardization of the classical method in adults. J Phys Conf Ser 2012;407(1):012018.
8. Márquez JC, Seoane F, Buendía R, Lindecrantz K. Textrode functional straps for bioimpedance measurements experimental results for body composition analysis. Eur J Clin Nutr 2013;67:S22-7.
9. Beckmann L, Neuhaus C, Medrano G, Jungbecker N, Walter M, Gries T, et al. Characterization of textile electrodes and conductors using standardized measurement setups. Physiol Meas 2010;31(2):233-47.
10. Kirchhof P, Monnig G, Wasmer K, Heinecke A, Breithardt G, Eckardt L, et al. A trial of self-adhesive patch electrodes and hand-held paddle electrodes for external cardio version of atrial fibrillation (MOBIPAPA). Eur Heart J 2005;26(13):1292-7.
11. Tronstad C, Johnsen GK, Grimnes S, Martinsen OG. A study on electrode gels for skin conductance measurements. Physiol Meas 2010;31(10):1395-410.
12. SMT. Medical GmbH & Co Special Skin Electrodes for Bio-Impedance Testing. Germany; 2013. Available from: http://www.smtmedical.com/en/products/akernbioimpedance-measuringdevices/biaelectrodes.html
13. (NHANES) NHaNES. Body Composition Procedure Manual. United States of America; 2000. Available from: http://www.cdc.gov/nchs/data/nhanes/bc.pdf
14. Caicedo-Eraso JC, González-Correa CH, González-Correa CA. Use of electrocardiogram (ECG) electrodes for bioelectrical impedance analysis (BIA). J Phys Conf Ser 2012;407(1):012008.
15. Lohman TG, Roche AF, Martorell R. Anthropometric standardization reference manual. Champaign: Human Kinetics Books; 1988.
16. Technologies X. Hydra ECF/ICF (Model 4200) Bio-impedance Spectrum Analyzer Operating Manual. 1.03 11/2007 MO4200 HE-I. San Diego, CA: Xitron Technologies; 2007. p. 124.
17. Baumgartner RN. Electrical impedance and total body electrical conductivity. In: Roche AF, Heymsfield SB, Lohman TG, eds. Human Body Composition. Champaign: Human Kinetics; 1996. pp. 79-108.
18. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1(8476):307-10.
19. Kafri MW, Myint PK, Doherty D, Wilson AH, Potter JF, Hooper L. The diagnostic accuracy of multi-frequency bioelectrical impedance analysis in diagnosing dehydration after stroke. Med Sci Monit 2013;19:548-70.
20. Kang SH, Cho KH, Park JW, Yoon KW, Do JY. Comparison of bioimpedance analysis and dual-energy X-ray absorptiometry body composition measurements in peritoneal dialysis of patients according to edema. Clin Nephrol 2013;79(4):261-8.
21. Ward LC. Inter-instrument comparison of bioimpedance spectroscopic analyzers. Open Med Dev J 2009;1:3-10.
22. Abdur Rahman AR, Price DT, Bhansali S. Effect of electrode geometry on the impedance evaluation of tissue and cell culture. Sensors and Actuators B 2007;127(1):89-96.
23. Lingwood BE. Bioelectrical impedance analysis for assessment of fluid status and body composition in neonates - The good, the bad and the unknown. Eur J Clin Nutr 2013;67(Suppl 1):S28-33.
24. Meziane N, Webster JG, Attari M, Nimunkar AJ. Dry electrodes for electrocardiography. Physiol Meast 2013;34(9):R47-69.
25. Searle A, Kirkup L. A direct comparison of wet, dry and insulating bioelectric recording electrodes. Physiol Meast 2000;21(2):271-83.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Correlation between skinfold thickness and bioelectrical impedance analysis for the evaluation of body composition in patients on dialysis

Correlación entre la plicometría y el análisis de bioimpedancia eléctrica para la evaluación de la composición corporal en pacientes en diálisis

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Abstract

Introduction: Patients on dialysis have important changes in body composition.

Objectives: To determine the correlation between skinfold thickness (SKF) and bioimpedance analysis (BIA) for estimating fat mass (FM) and lean body mass (LBM) in patients undergoing hemodialysis (HD) and peritoneal dialysis (PD).

Methods: Cross-sectional study. We included 50 patients under dialysis treatment. To measure SKF, we used the Lange® skinfold caliper (Beta Technology, California, USA) and we carried out the impedance analysis with the Bodystat Quadscan 4000® (Quadscan, Isle of Man, UK). The measurements were performed post-hemodialysis. The PD patients were measured with and without peritoneal dialysate and body weight was corrected for peritoneal fluid. We determined the Pearson's correlation coefficient between SKF and BIA for estimating FM and LBM. We also evaluated the influence of age, sex, diuretic use, dialysis vintage, extracellular water (ECW), and intracellular water (ICW) through a multivariate regression analysis.

Results: Of the 50-patient total, 29 were men (58%) and patient mean age was 46.3 ± 16.5 years. The correlation between SKF and BIA was $r = 0.784$ ($p < 0.001$) for FM and $r = 0.925$ ($p < 0.001$) for LBM. Age and sex influenced the variability of FM, whereas sex, age, and ECW influenced the variability of LBM, both evaluated through the SKF and BIA methods.

Conclusion: SKF and BIA are useful methods in clinical practice. The strong and statistically significant correlations between the two methods show they are interchangeable. Age, sex, ECW, and ICW influence the variability of FM and LBM.

Key words:

Fat mass. Lean body mass. Skinfold thickness. Bioelectrical impedance analysis. Dialysis.

Resumen

Introducción: los pacientes en tratamiento con diálisis presentan cambios importantes en la composición corporal.

Objetivos: determinar la correlación entre la plicometría y el análisis de bioimpedancia eléctrica (BIE) para la estimación de la masa grasa (MG) y la masa magra (MM) en pacientes sometidos a hemodiálisis (HD) y diálisis peritoneal (DP).

Métodos: diseño transversal-analítico. Se incluyeron 50 pacientes en tratamiento con diálisis. Se utilizó el plicómetro Lange® (Beta Technology, California, USA) para la medición de pliegues cutáneos y la BIE fue realizada con el Bodystat Quadscan 4000® (Quadscan, Isle of Man, UK). Las mediciones fueron realizadas poshemodiálisis. Los pacientes en DP fueron medidos con y sin líquido peritoneal y el peso corporal fue corregido. Determinamos el coeficiente de correlación de Pearson entre la plicometría y la BIE en la estimación de la MG y la MM. Se evaluaron otras variables como edad, sexo, uso de diuréticos, tiempo en tratamiento de diálisis, agua extracelular (AEC) e intracelular (AIC) a través de un análisis de regresión multivariada.

Resultados: veintinueve pacientes (58%) son del sexo masculino; la edad promedio de 46,3 ± 16,5 años. Se obtuvo una correlación significativa y positiva entre la plicometría y la BIE [$r = 0,784$ ($p < 0,001$) para MG y $r = 0,925$ ($p < 0,001$)] para MM. La edad y el sexo influyeron en la variabilidad de la MG, mientras que el sexo, la edad y el AEC influyeron en la variabilidad de la MM, evaluados con ambos métodos.

Conclusiones: la plicometría y la BIE son métodos útiles en la práctica clínica. La correlación que se obtuvo entre los dos métodos muestra que son intercambiables. Por otro lado, variables como la edad, el sexo, el agua AEC y AIC se identificó que influyen en la variabilidad de la MG y MM.

Palabras clave:

Masa grasa. Masa magra. Pliegues cutaneos. Bioimpedancia eléctrica. Diálisis.

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INTRODUCTION

Nutritional status is one of the most important factors influencing the quality life of patients on hemodialysis (HD) and peritoneal dialysis (PD). Poor nutritional status leads to a high risk of morbidities, hospitalization, catabolic stress, and mortality (1,2).

Patients on dialysis have important changes in body composition because of decreased protein and/or energy intake, chronic inflammation, physical inactivity, concurrent acute or chronic conditions, illness, and catabolism induced by the dialysis process. Previous studies have shown that changes in body composition occur after dialysis treatment, with a significant decrease in lean body mass (LBM) and an increase in body weight and fat mass (FM), whereas other studies state that FM and body weight decrease over time (3-7).

Total body weight can be divided into the compartments of FM and LBM. The FM represents an essential energetic reserve and 50% is situated in the subcutaneous tissue. The LBM includes minerals, proteins, glycogen, extracellular water (ECW) and intracellular water (ICW) (8).

Dual-energy X-ray absorptiometry (DXA) is considered the gold standard in the assessment of body composition in patients on dialysis. However, this method is not always available and is both expensive and impractical. There are various methods for estimating body composition in patients on dialysis, one of which is bioelectrical impedance analysis (BIA). BIA measures impedance and resistance with a small electrical current as it travels through the body's water pool. In addition, BIA divides total body water (TBW) into ECW and ICW. Another available and practical method for estimating FM is skinfold thickness (SKF). It measures specific skinfolds and uses the Durnin and Womersley formulas to estimate density and FM. Both BIA and SKF are methods that have shown significant correlations with the gold standard (1,9-14).

We consider the adequate assessment of body composition with practical and available methods and tools in patients on dialysis to be very important. Therefore the aims of this study were to determine the correlation between SKF and BIA for estimating FM and LBM in HD and PD patients, and to analyze the influence of the variables that can affect body composition.

METHODS

A cross-sectional study was performed in thirty-eight patients undergoing HD and 12 patients undergoing PD at two dialysis units in Colima, Mexico, were included.

The inclusion criteria were: age ≥ 18 years old, on HD or continuous ambulatory PD or automated PD treatment for at least 2 months. Exclusion criteria were patients with pacemakers, patients with metallic implants, amputees, and pregnant women.

The measurements were performed on the HD patients after dialysis, in accordance with previous methodologies. For the PD patients, the measurements were taken during a visit to the outpatient clinic. For practical reasons, measurements were performed with intraperitoneal fluid and body weight was corrected (body weight minus 2 kg corresponding to the peritoneal fluid). Body composition was not affected by intraperitoneal dialysate because the trunk contributes to less than 10% of total body impedance (9,15-20).

ANTHROPOMETRIC MEASUREMENTS

Height, body weight, and mid-upper arm circumference (MUAC) were measured in all patients. MUAC was assessed using Seca 201® (Hamburg, Deutschland) non-stretchable metric tape. The Seca 700® Mechanical Column Scale (Hamburg, Deutschland) was used to measure height and body weight, applying the previously described standard techniques (21).

Four SKF -biceps, triceps, subscapular, and suprailiac- were measured 3 times using a Lange® skinfold caliper (California, USA) and then averaged. The logarithm of the sum of the four SKF was calculated, as well as body density (D) according to age and sex. The Durnin and Womersley equations were used to calculate FM and LBM with the formulas (22): FM = body weight (kg) - [(4.95/D)-4.5)] and LBM = body weight (kg) - FM.

BODY COMPOSITION ANALYSIS

To determine ICW, ECW, FM, and LBM, we used a Bodystat Quadscan 4000® (Isle of Man, UK) multi-frequency body composition analyzer. The measurements were carried out with the patient in the supine position for 5 minutes, with the arms parallel to and separated from the trunk and the legs apart. Two electrodes were placed on the hand and wrist and another two on the foot and ankle. The electrodes were placed on the non-access site of the body of the HD patients and on the right side of the PD patients (19,20,23,24).

STATISTICAL METHODS

The Kolmogorov-Smirnov test was used to test for the distribution normality of the variables. Descriptive analyses were presented as mean ± standard deviation (SD), frequencies, and percentages. We determined the Pearson's correlation coefficient between SKF and BIA for estimating FM and LBM. We also evaluated the influence of age, sex, diuretic use, ECW, and HD and PD vintage on FM and LBM through a multivariate regression analysis. Stepwise regression and backward elimination (automatic procedure) were carried out.

Statistical significance was accepted as $p < 0.05$ and all statistical tests were two-tailed. The statistical analyses were performed using the IBM SPSS version 20 program (IBM, Chicago, IL).

ETHICS STATEMENT

Written informed consent was obtained from each patient before participation. The present study was structured according

to the ethical requirements of the Declaration of Helsinki and approved by the local Ethics and Health Research Committee (2014/SR/CLIN/PED/96).

RESULTS

We evaluated fifty patients and their mean age was 46.3 ± 16.5 years. Demographic, clinical, and body composition characteristics of the patients undergoing dialysis treatment are shown in table I.

The patients with PD presented with greater body weight, FM, LBM, ECW, and ICW. FM measured by the two methods, ECW, and body weight showed statistically significant differences betwzeen the HD and DP patients ($p < 0.05$).

PEARSON'S CORRELATION BETWEEN SKF AND BIA FOR ESTIMATING FAT MASS AND LEAN BODY MASS

Figure 1 show the correlation between SKF and BIA for estimating FM and LBM. They were positive and statistically significant and the SKF and BIA correlation was highest for evaluating LBM.

MULTIVARIATE REGRESSION ANALYSIS

We analyzed the degree of influence of the variables that can influence FM and LBM measured by both methods and the results are shown in table II.

Regarding table II, the variables of sex and age influenced the variability of FM and LBM to different degrees when evaluated by each of the two methods. Sex, age, and ECW influenced the variability of LBM, and the BIA estimate had the greatest influence on the variability of LBM.

Table I. Demographic, clinical, and body composition characteristics in patients undergoing dialysis treatment (n = 50)

	HD (n = 38)	PD (n = 12)	p value
Age (y)	42.1 ± 15.6	59.6 ± 11.9	< 0.001[3]
Sex (male), n (%)	21 (55.3%)	8 (66.7%)	-
HD or PD vintage (months)	22.2 ± 20.69	15.7 ± 12.7	0.202
Access (fistula/ catheter)	27/11	-	-
PD modality (CAPD/APD)	-	4/8	-
Diuretic use n (%)	11 (28.9%)	5 (41.7%)	-
Comorbidities			
Hypertension n (%)	34 (89.5%)	12 (100%)	-
Diabetes n (%)	13 (34.2%)	11 (91.7%)	-
Body composition			
Body weight (kg)	58.2 ± 10.3[1]	68.9 ± 11.3[2]	0.01[3]
FM (kg)	11.65 ± 4.68*	17.1 ± 4.9*	0.001[3]
	13.9 ± 5.59**	19.6 ± 5.7**	0.003[3]
LBM (kg)	46.55 ± 9.69*	51.8 ± 10.8*	0.116
	44.56 ± 10.11**	49.2 ± 11.7**	0.186
ECW (l)	15.4 ± 2.55**	17.8 ± 3.35**	0.014[3]

*HD: hemodialysis; PD: peritoneal dialysis; CAPD: continuous ambulatory PD; APC: automated PD; FM: fat mass; LBM: lean body mass; ECW: extracellular water. [1]Body weight post-dialysis; [2]Body weight corrected in patients with peritoneal fluid; [3]Statistically significant. *Measured with SKF; **Measured with BIA. Data are presented as mean ± standard deviation. $p < 0.05$ statistical significance.*

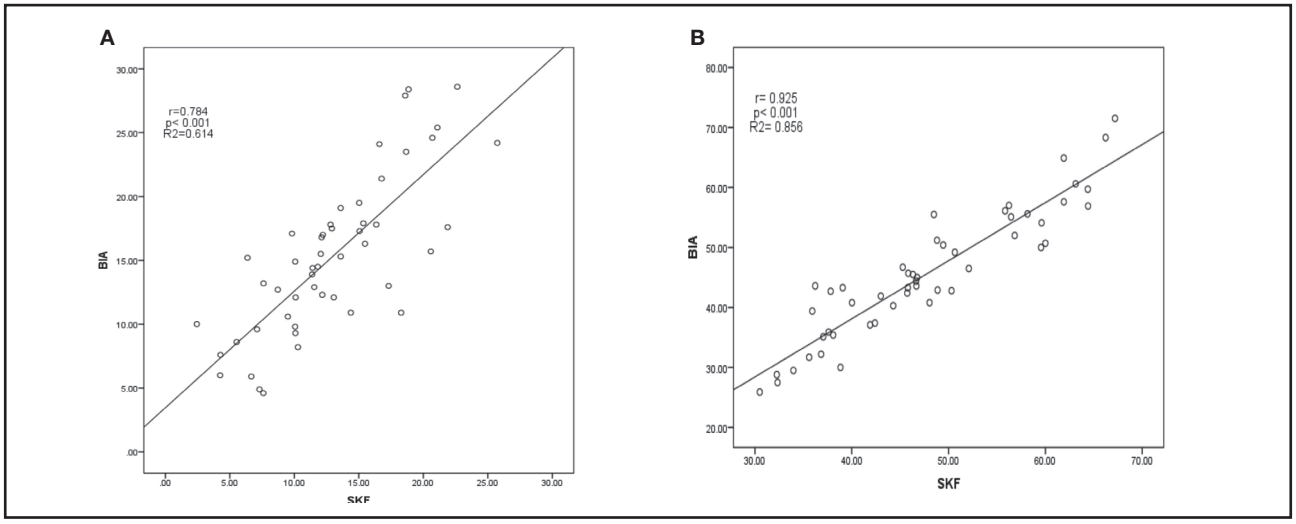

Figure 1.

A. Correlation between SKF and BIA for estimating FM. B. Correlation between SKF and BIA for estimating LBM (SKF: skinfold thickness; BIA: bioelectrical impedance analysis).

Table II. Predictors of FM and LBM according to SKF and BIA (multivariable regression)

Variable	B-Coefficient (95% CI)	p	B-Coefficient (95% CI)	p
FM by SKF R^2 = 57.7%			**FM by BIA R^2 = 47.6%**	
Sex	*-5.46 (-4.2 to -6.6)*	*< 0.001*	-1.37 (0.2 to -2.9)	0.38
Age	*0.17 (0.2 to 0.13)*	*< 0.001*	*0.27 (0.31 to 0.22)*	*< 0.001*
Dialysis vintage (months)	-0.02 (0.002 to -0.05)	0.35	0.029 (0.06 to -0.009)	0.44
Diuretic use	-0.44 (0.6 to -1.5)	0.69	1.25 (2.7 to -0.22)	0.39
ECW	0.41 (0.6 to 0.2)	0.07	-0.52 (-0.23 to -0.81)	0.08
LBM by SKF R^2 = 84.5%			**LBM by BIA R^2 = 90.4%**	
Sex	*10.4 (11.8 to 8.9)*	*< 0.001*	*7.18 (8.3 to 6)*	*< 0.001*
Age	-0.12 (0.02 to -0.05)	0.76	*-0.1 (-0.07 to -0.13)*	*0.002*
Dialysis vintage (months)	0.06 (0.09 to 0.02)	0.06	0.01 (0.03 to -0.01)	0.71
Diuretic use	2.03 (3.3 to 0.7)	0.13	-0.35 (0.74 to -1.4)	0.74
ECW	*2.07 (2.3 to 1.8)*	*< 0.001*	2.83 (3.05 to 2.61)	< 0.001

FM: fat mass; LBM: lean body mass; SKF: skinfold thickness; BIA: bioimpedance analysis; ECW: extracellular water; ICW: intracellular water. CI: confidence interval. p < 0.05 statistical significance.

DISCUSSION

The nutritional status of patients undergoing HD and PD is a survival indicator. Patients, whose FM is lower than the normal range, have been reported to have a higher risk of mortality due to catabolic stress. Patients on dialysis have changes in body composition, such as greater FM, lower LBM, and an altered hydration status. These changes can directly affect nutritional status, making body composition measurement an important issue. Through body composition evaluation, adequate nutritional status can be maintained, resulting in a better quality of life (25-27).

Many methods have been used for assessing body composition in patients undergoing dialysis, but the ideal method should be a noninvasive one with reproducible results, as well as being low cost and easily available. DXA is considered the gold standard, but in relation to clinical practice, it is not always available in dialysis care units or in primary care units, given that it requires a trained staff and a specific area for taking the measurements, in addition to its high cost. Therefore, alternative methods that meet the criteria of an ideal method, such as SKF or BIA, are being used. Both methods have shown a statistically significant correlation with the gold standard, which is why we decided on the two-compartment model and analyzed the correlation between SKF and BIA for estimating FM and LBM in dialysis patients (8,26,28,29).

Our results showed high and statistically significant correlations between SKF and BIA for estimating FM and LBM, with a stronger correlation for the LBM evaluation.

SKF and BIA are methods for estimating FM and LBM that can be available at all dialysis care units, nutrition departments, and primary care units. They are reproducible, low-cost, noninvasive, and can be used by health professionals with a minimum of training. Kamimura et al. analyzed FM in 30 Brazilian HD patients using DXA, BIA, and SKF. They reported excellent and statistically significant correlations with BIA and SKF. Lamarca et al. correlated DXA with BIA and SKF for estimating LBM in 102 Brazilian HD patients. Both correlations were statistically significant, and the correlation between DXA and BIA was superior. Unlike our study, Kamimura et al. and Lamarca et al. analyzed only one body composition compartment and correlated the measuring methods with the gold standard. They did not correlate BIA and SKF with two compartments, as we did. Bravo et al also correlated DXA with BIA and SKF for estimating FM and LBM in 20 Mexican HD patients. They found high and statistically significant correlations, but did not estimate body composition with those methods in PD patients. To the best of our knowledge, ours is the first study conducted on Mexican patients that correlates the two methods in the assessment of FM and LBM in HD and PD patients. In regard to previous studies on method correlations in DP patients, Dong et al reported a statistically significant correlation between SKF and DXA in the analysis of LBM in 60 Korean PD patients. Another relevant study by Chow et al found a statistically significant correlation between SKF and BIA for estimating FM in 60 Chinese PD patients (14,19,23,25,26,30-32).

In the multivariate regression analysis of our study, we showed the influence of the variables of age and sex on the variability of FM assessed through SKF. Only age influenced the variability of fat mass evaluated by BIA. LBM was influenced by sex, age, and ECW, when estimated using BIA and by sex and ECW, when using SKF. In general, age, sex, and ECW influenced different grades of

body composition variability, regardless of the measuring method employed.

Similar to what occurs in the healthy population, body composition suffers changes with age. Once the individual reaches 30 years of age, LBM decreases from 1 to 1.5% per year, and there is a simultaneous increase in FM, mainly in the trunk area. There are also many differences in relation to sex, given that women have more FM and less LBM than men (10,29,33-36).

ECW influenced the variability of LBM, which can be explained by the fact that LBM contains protein mass and minerals and ECW and ICW depend on hydration status, thus affecting LBM by underestimating or overestimating it. It is important to keep in mind that over-hydration can increase SKF, resulting in an overestimation of FM and % of fat. In addition, catabolic stress can increase oncotic pressure and permeability and produce an increase in capillary filtration and interstitial volume, resulting in tissular edema (37,38).

Dialysis vintage was also analyzed in the multivariate regression analysis and did not present statistical significance. However, reports in the literature state that patients have important changes in body composition associated with dialysis vintage and the most significant changes present in the first year of treatment, mainly as increased FM and decreased LBM (1,3,4).

Diuretic use was another variable analyzed in the multivariate regression, but it did not correlate with the body composition compartments.

SKF and BIA are useful methods in clinical practice for estimating FM and LBM in dialysis patients. Our results showed high and statistically significant correlations, signifying that the methods are interchangeable and offer an alternative in the evaluation of dialysis patients when DXA is not available. SKF and BIA can be used in dialysis care units and/or primary and secondary care units to identify early changes in body composition that affect the nutritional status of these patients. Sex and age influenced the variability of FM, whereas age, sex, and ECW influenced the variability of LBM.

REFERENCES

1. Choi SJ, Kim NR, Hong SA, et al. Changes in body fat mass in patients after starting peritoneal dialysis. Perit Dial Int 2011;31(1):67-73.
2. Caetano C, Valente A, Oliveira T, et al. Body Composition and Mortality Predictors in Hemodialysis Patients. J Ren Nutr 2016;26(2):81-6.
3. Broers NJH, Cuijpers ACM, Van Der Sande FM, et al. The first year on haemodialysis: A critical transition. Clin Kidney J 2015;8(3):271-7.
4. Marcelli D, Brand K, Ponce P, et al. Longitudinal Changes in Body Composition in Patients After Initiation of Hemodialysis Therapy: Results From an International Cohort. J Ren Nutr 2016;26(2):72-80.
5. Keane D, Gardiner C, Lindley E, et al. Changes in Body Composition in the Two Years after Initiation of Haemodialysis: A Retrospective Cohort Study. Nutrients 2016;8(11):702.
6. Su CT, Yabes J, Pike F, et al. Changes in anthropometry and mortality in maintenance hemodialysis patients in the HEMO study. Am J Kidney Dis 2013;62(6):1141-50.
7. Gallar-Ruiz P, Di-Gioia MC, Lacalle C, et al. Composición corporal en pacientes en hemodiálisis : relación con la modalidad de hemodiálisis , parámetros inflamatorios y nutricionales. Nefrologia 2012;32(4):467-76.
8. Jiménez EG. Composición corporal : estudio y utilidad clínica. Endocrinol Nutr 2012;60(2):69-75.
9. Broers NJH, Martens RJH, Cornelis T, et al. Body Composition in Dialysis Patients: A Functional Assessment of Bioimpedance Using Different Prediction Models. J Ren Nutr 2015;25(2):121-8.
10. Van Biesen W, Claes K, Covic A, et al. A multicentric , international matched pair analysis of body composition in peritoneal dialysis versus haemodialysis patients. Nephrol Dial Transplant 2013;28 (10):2620-8.
11. Lee SY, Gallagher D. Assessment methods in human body composition. Curr Opin Nutr Clin Metab Care 2008;11(5):566-72.
12. Alvero R, Cabañas M, Herrero A, et al. Protocolo de valoración de la composición corporal para el reconocimiento médico-deportivo. Documento de consenso del Grupo Español de Cineantropometría (GREC) de la Federación Española de medicina del Deporte (FEMEDE). Versión 2010. AMD 2010;27(139):330-43.
13. Espinosa-Cuevas MA, Correa-Rotter R. Alteraciones renales y nutrición. In: Casanueva E, Flores-Quijano ME. Nutriologia Medica. 3rd ed. Médica Panamericana; 2008. pp. 501-38.
14. Kamimura MA, Avesani CM, Cendoroglo M, et al. Comparison of skinfold thicknesses and bioelectrical impedance analysis with dual-energy X-ray absorptiometry for the assessment of body fat in patients on long-term haemodialysis therapy. Nephrol Dial Transplant 2003;18(1):101-5.
15. Rymarz A, Bartoszewicz Z, Szamotulska K, et al. The Associations Between Body Cell Mass and Nutritional and Inflammatory Markers in Patients With Chronic Kidney Disease and in Subjects Without Kidney Disease. J Ren Nutr 2016;26(2):87-92.
16. Noori N, Kovesdy CP, Dukkipati R, et al. Survival predictability of lean and fat mass in men and women undergoing maintenance hemodialysis. Am J Clin Nutr 2010;92(5):1060-70.
17. Pellicano R, Pellicano R, Strauss BJ, et al. Body composition in home haemodialysis versus conventional haemodialysis: a cross-sectional, matched, comparative study. Nephrol Dial Transplant 2010;25(2):568-73.
18. Bataille S, Serveaux M, Carreno E, et al. The diagnosis of sarcopenia is mainly driven by muscle mass in hemodialysis patients. Clin Nutr 2016:1-7.
19. Lamarca F, Carrero JJ, Rodrigues JC, et al. Prevalence of sarcopenia in elderly maintenance hemodialysis patients: the impact of different diagnostic criteria. J Nutr Health Aging 2014;18(7):710-7.
20. van Biesen W, Williams JD, Covic AC, et al. Fluid status in peritoneal dialysis patients: The European body composition monitoring (EuroBCM) study cohort. PLoS One 2011;6(2):e17148.
21. Frisancho A. Anthropometric Standards for the Assessment of Growth and Nutritional Status. Ann Arbor, MI: University of Michigan Press; 1990.
22. Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness : measurements on 481 men and women aged from 16 to 72 years. Br J Nutr 1973;32(1):77.
23. Chow VC, Lee C, Ho EH, et al. Nutritional assessment of continuous ambulatory peritoneal dialysis patients by bioelectrical impedance. Perit Dial Int 2003;23(S2):55-7.
24. Beberashvili I, Azar A, Sinuani I, et al. Geriatric nutritional risk index , muscle function , quality of life and clinical outcome in hemodialysis patients. Clin Nutr 2016 35(6):1522-9.
25. Molfino A, Don BR, Kaysen GA. Comparison of bioimpedance and dual-energy X-ray absorptiometry for measurement of fat mass in hemodialysis patients. Nephron Clin Pract 2012;122(3-4):127-33.
26. Carter M, Zhu F, Kotanko P, et al. Assessment of Body Composition in Dialysis Patients by Arm Bioimpedance Compared to MRI and 40 K Measurements. Blood Purif 2009;27(4):330-7.
27. Oreopoulos A, Noori N, Golden S. Comparing Body Composition Assessment Tests in Long-term Hemodialysis Patients. Am J Kidney Dis 2011;55(5):885-96.
28. Wang Z, Pierson R, Heymsfield S. The five-level model: a new approach to organizing. Am J Clin Nutr 1991;56(1):19-28.
29. Morishita Y, Kubo K, Haga Y, et al. Skeletal Muscle Loss Is Negatively Associated With Single-Pool Kt/V and Dialysis Duration in Hemodialysis Patients. Ther Apher Dial 2014;18(6):612-7.
30. Vogt BP, Ponce D, Costa J, Caramori T. Anthropometric Indicators Predict Metabolic Syndrome Diagnosis in Maintenance Hemodialysis Patients. Nutr Clin Pract 2016;31(3):368-74.
31. Ramírez AMB, Ramos AC, Hurtado GF. Composición corporal en pacientes con insuficiencia renal crónica y hemodiálisis. Nutr Hosp 2010;25(2):245-9.
32. Dong J, Li Y, Xu R, et al. Novel equations for estimating lean body mass in peritoneal dialysis patients. Perit Dial Int 2015;35(22):743-52.
33. Chumlea WC, Guo SS, Kuczmarski RJ, et al. Body composition estimates from NHANES III bioelectrical impedance data. Int J Obes Relat Metab Disord 2002;26(12):1596-609.

34. Leal VO, Mafra D, Fouque D, et al. Use of handgrip strength in the assessment of the muscle function of chronic kidney disease patients on dialysis: a systematic review. Nephrol Dial Transplant 2011;26(4):1354-60.
35. Yamada Y, Watanabe Y, Ikenaga M, et al. Comparison of single- or multifrequency bioelectrical impedance analysis and spectroscopy for assessment of appendicular skeletal muscle in the elderly. J Appl Physiol 2013;115(6):812-8.
36. Stenvinkel P, Carrero JJ, Walden F Von, et al. Muscle wasting in end-stage renal disease promulgates premature death: established , emerging and potential novel treatment strategies. Nephrol Dial Transplant 2016;31(7):1-8.
37. Yamada Y, Schoeller DA, Nakamura E, et al. Extracellular Water May Mask Actual Muscle Atrophy During Aging. J Gerontol A Biol Sci Med Sci 2010;65(5):510-6.
38. Reed RK, Rubin K. Transcapillary exchange : role and importance of the interstitial fluid pressure and the extracellular matrix. Cardiovasc Res 2010;87(2):211-7.

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Nutrición Hospitalaria

Trabajo Original

Epidemiología y dietética

Prevalence of anaemia, risk of haemoconcentration and risk factors during the three trimesters of pregnancy

Prevalencia de anemia y riesgo de hemoconcentración durante los 3 trimestres de embarazo y factores de riesgo

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Abstract

Objective: To evaluate the prevalence of anaemia and the risk of haemoconcentration and its risk factors during all 3 trimesters of pregnancy in women in a Mediterranean area in the south of Europe.

Material and methods: Longitudinal study of 11,259 women whose pregnancies were monitored at primary care centres between 2007 and 2012. The computerised clinical histories of all the pregnancies were used to collect haemoglobin (Hb) data for each trimester. The histories also provided information on the age of the mother, her socioeconomic status, the presence of obesity, tobacco use, type of pregnancy, and number of previous pregnancies and births. Anaemia was defined as Hb < 110 g/L in the 1st and 3rd trimesters of pregnancy and Hb < 105 g/L in the second. The risk of haemoconcentration was defined as Hb > 130 g/L in the 2nd and 3rd trimesters of pregnancy.

Results: The prevalence of anaemia increased from 3.8% in the first trimester to 21.5% in the 3rd trimester. Around 10% of the women had Hb > 130 g/L during the 3rd trimester. Having children previously and/or being younger than 20 increased the chances of anaemia (Adj. OR: 1.4; 95% CI: 1.1-1.9), but being older than 34 increased the chances of Hb > 130 g/L (Adj. OR: 1.3; 95% CI: 1.1-1.5).

Conclusion: The increased prevalence of anaemia is a moderate public health problem. Understanding the factors that influence these problems may help improve the guidelines regarding the use of iron supplements.

Key words:

Risk of haemoconcentration. Anaemia. Risk factors. Prevalence. Pregnancy.

Resumen

Objetivo: valorar la prevalencia de anemia y de riesgo de hemoconcentración y sus factores de riesgo durante los 3 trimestres de embarazo en las mujeres de una zona mediterránea del sur de Europa.

Material y métodos: estudio longitudinal con 11.259 mujeres que realizaron el seguimiento de su embarazo en centros de atención primaria entre el 2007 y 2012. A partir de la historia clínica informatizada se recogieron datos de hemoglobina (Hb) de cada trimestre de gestación, edad de la madre, bajo nivel socioeconómico, presencia de obesidad, hábito tabáquico, tipo de embarazo, número de embarazos y partos previos. Se definió anemia como Hb < 110 g/L para el 1er y 3er trimestre de gestación y como Hb < 105 g/L para el 2º trimestre. Se definió riesgo de hemoconcentración a Hb > 130 g/L en el 2º y 3er trimestre.

Resultados: la prevalencia de anemia aumentó del 3.8% en el primer trimestre al 21.5% en el 3er trimestre. Alrededor de un 10% de las mujeres tuvieron Hb > 130 g/L en el 3er trimestre. Tener hijos previos y/o ser menor de 20 años predispone a tener anemia (adj. OR: 1.4; 95% CI: 1.1-1.9), pero tener más de 34 años predispone a Hb > 130 g/L (adj. OR: 1.3; 95% CI: 1.1-1.5).

Conclusión: la elevada prevalencia de anemia supone un problema moderado de salud pública. El conocimiento de los factores que pueden influir en dichas prevalencias puede ayudar a adaptar mejor la pauta de suplementación con hierro.

Palabras clave:

Riesgo de hemoconcentración. Anemia. Factores de riesgo. Prevalencia. Embarazo.

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INTRODUCTION

The World Health Organisation estimates that around 38.2% of pregnant women around the world have anaemia, although the percentage is lower in industrialised regions such as Europe, where it is between 18.7-25.8% (1,2). In the case of Spain, the few studies to have been conducted indicates a rate of about 15-25% (1,3). The negative effect that these high levels can have on the health of both mother and child mean that this pathology is a public health problem.

At the other extreme are high levels of haemoglobin, thus frequently giving the false impression of healthy iron levels and hiding the fact that the plasma volume is increasing a lower rate than expected. This condition affects between 8.7% and 42% of pregnant women in developed countries (4), it is also related to serious problems for both mother and child such as increased risk of pre-eclampsia, premature birth and low birth weight (5-7). Despite these risks, only one study has been conducted on women in southern Europe; this study found a rate of 13% among women in the third trimester of pregnancy (3).

Both conditions, anaemia and haemoconcentration, vary in their prevalence depending on the trimester of pregnancy and may also be influenced by socio-demographic characteristics such as the mother's age (8,9), the number of children she has had previously (8), the length of time between pregnancies (10), multiple pregnancies (11), the ingestion of iron supplements during pregnancy (10,12), socioeconomic status, illiteracy, obesity and even the mother's origins (8,11,13,14).

In the light of these considerations, we decided to evaluate a broad sample of the population to determine the prevalence of anaemia, the risk of haemoconcentration and the associated risk factors during the 3 trimesters of pregnancy in women from the Mediterranean area of southern Europe.

MATERIALS AND METHODS

Longitudinal study of all the women whose pregnancies were monitored by the Sexual and Reproductive Health Care Service (ASSIR) in Tarragona and Reus (Spain), between 2007 and 2012.

The ASSIR is part of the Catalan Health Institute (ICS) and is a support service provided by specialists whose aim is to promote and coordinate comprehensive sexual and reproductive healthcare for pregnant women. The service belongs to the Catalan public health network and it provides services to almost all women.

The ICS began to computerise the clinical records of its patients in 2006 by assigning each one a Personal Identification Code (PIC). Furthermore, pregnant women are assigned a unique identification code for each pregnancy so that each can be monitored individually.

The ICS recommends that non-anaemic pregnant women take a daily dose of 40 mg of iron from the start of the second trimester. For pregnant women with anaemia, this is increased to 80 mg of iron 1 or 2 times a day depending on the severity of the condition.

Our study includes all the pregnant women monitored by the ASSIR between 2007 and 2012. Fasting blood samples were extracted at the primary care centers between 8 a.m. and 9 a.m. by the primary care nurses and transported on ice to the central laboratory for analyses in as short a time-lapse as possible. The complete hematological profile was performed using Coulter autoanalyser.

In total the study analysed the blood of 11,259 women: 9,488 were analysed in the first trimester, 9,411 in the second, and 9,433 in the third. Seven thousand and six hundred women were analysed in all three trimesters of pregnancy.

DATA COLLECTION

The computerised clinical histories of each pregnancy were used to collect data on the age of the mother, socioeconomic status, the presence of obesity, tobacco use during pregnancy, the type of pregnancy (simple or multiple) and the number of previous pregnancies and births. However, there were no data on the extent to which the women complied with the recommendations regarding the use of iron supplements.

Routine blood analyses provided data on the women's haemoglobin levels during each trimester.

DEFINITION OF ANAEMIA AND RISK OF HAEMOCONCENTRATION

Anaemia was defined as Hb < 110 g/L in the 1st and 3rd trimesters and Hb < 1,05 g/L in the second (15).

The risk of haemoconcentration was defined as Hb > 130 g/L in the 2nd and 3rd trimesters (4).

STATISTICAL ANALYSES

Statistical analyses were carried out using the SPSS Statistics software package version 20.0. The variables were distributed in a standard manner and are presented as the mean and the standard deviation (SD). The qualitative variables are presented as percentages.

Pearson's chi-squared test was used to compare the categorical variables.

Dummy variables were created for different age groups of women so that each age group could be compared with the intermediate age group (20-34 years). Dummy variables were also created for women who had had children previously in order to compare them with first-time mothers.

The magnitude of association between the different risk factors for anaemia (independent variables) and anaemia (dependent variable) was evaluated by means of multiple logistical regression for each trimester, adjusting for: age of the mother (< 20 years, 20-34 years (reference group), > 34 years), parity (first time mother (reference group), 1-2 children, > 3 children); multiple

pregnancy (no, yes); low socioeconomic level (no, yes); obesity (no, yes); tobacco use (no, yes).

The same regression was repeated for haemoconcentration risk.

In all cases the level of significance was set at $p < 0.05$.

RESULTS

Were monitored 13,185 pregnant women by the ASSIR in Tarragona and Reus between 2007 and 2012. Of these, 11,259 underwent blood analyses (Table I). Of the 1,926 women who did not undergo blood analyses, 381 had miscarriages. The remainder (1,545 pregnant women) presented few differences with respect to the women who underwent blood analyses, the main differences being a larger percentage of first-time mothers (47% *vs.* 43%) and a lower number with obesity (10% *vs.* 13%).

Of the 11,259 who underwent blood tests, 67.5% (n = 7,600) did so during all three trimesters. Sixteen point six per cent of the women did not undergo blood tests in each trimester due to miscarriage or premature birth. Apart from the miscarriages and the number of women with more than two previous births (8.8% *vs.* 4.0%), there are no significant differences between those women who had blood tests in each trimester and those who did not.

Table I shows the main characteristics of the pregnant women with Hb measured at least in one trimester and of pregnant women with Hb measured at every trimester. The average age was 29.7 years with a range from 13 to 48 years, of whom 22% were smokers and 12.8% were obese. Around 43% of the women were expecting their first child and 0.8% had more than four children (data not shown in the table).The mean average of haemoglobin levels is above the cut-off point of anaemia in all the trimesters.

Table II shows that the prevalence of anaemia was higher in the second ($p = 0.040$) and third trimesters ($p = 0.001$) among the women aged below 20 compared with the older women. The women who smoked have significantly lower levels of anaemia than the non-smokers ($p = < 0.001$ in the second trimester and $p = 0.009$ in the third); likewise the women with more than three children previously present significantly higher levels of anaemia ($p = < 0.001$). In contrast, the risk of haemoconcentration is significantly higher in the third trimester among those women expecting their first child than it is among those who have had children previously ($p = 0.019$).

Tables III and IV show the risk of anaemia and the risk factors of haemoconcentration during each trimester in relation to the different risk factors. Being over 35 years is a protective factor against anaemia, but it also increases the risk of haemoconcentration. Low socioeconomic status seems to have no effect on anaemia or on the risk of haemoconcentration. However, both obesity and tobacco use are associated with a lower risk of anaemia.

In contrast, having had children previously increases the risk of anaemia, and the risk increases with the number of children.

Table I. General and haematological characteristics of the pregnant women

	Mothers with Hb measured in at least one trimester (n = 11,259)		Mothers with Hb measured at every trimester (n = 7,600)	
	Mean ± SD or n (%)	**% of data missing**	**Mean ± SD or n (%)**	**% of data missing**
Age of mother (years):	29.7 ± 5.7	-	30.0 ± 5.4	-
< 20	465 (4.1%)	-	256 (3.4%)	-
20-34	8,443 (75.0%)	-	5,762 (75.8%)	-
≥ 35	2,351 (20.8%)	-	1,582 (20.8%)	-
Obesity	1,438 (12.8%)	-	930 (12.2%)	-
Low socioeconomic status	200 (1.8%)	-	106 (1.4%)	-
Multiple pregnancy	63 (0.6%)	5.9%	47 (0.4%)	1.1%
Previous births (n)	0.8 ± 1.0	1.5%	0.8 ± 0.9	1.1%
First-time mother:	4,813 (42.7%)	1.5%	3,308 (44.0%)	-
1-2	5,664 (50.3%)	1.5%	3,907 (52%)	-
≥ 3	616 (5.6%)	1.5%	303 (4%)	-
Previous pregnancies (n)	2.2 ± 1.3	1.5%	2.2 ± 1.2	1.1%
Smoker	2,325 (22.0%)	6.1%	1,717 (23.4%)	3.5%
Haemoglobin (g/L):				
1st Trimester	126.3 ± 9.1	18.4%	126.3 ± 9.0	-
2nd Trimester	114.1 ± 8.9	16.4%	114.1 ± 8.7	-
3rd Trimester	117.0 ± 10.0	16.1%	117.4 ± 9.8	-

Table II. Prevalence of anaemia and risk of haemoconcentration in the 3 trimesters of pregnancy in relation to risk factors

	Anaemia						Risk of haemoconcentration			
	1T		2T		3T		2T		3T	
	%	95%CI	%	95%CI	%	95%CI	%	95%CI	%	95%CI
Overall presence	3.8	3.4-4.2	13.1	12.7-14.1	21.5	20.7-22.3	5.8	5.3-6.3	9.9	9.3-10.5
Age of mother (years):										
< 20	4.8 [a]	2.5-7.7	16.7 [a]	12.9-20.5	28.5 [a]	24.1-32.9	2.2 [a]	0.7-3.7	5.3 [a]	3.1-7.5
20-34	3.7 [a]	3.3-4.1	12.9 [b]	12.1-13.7	21.7 [b]	20.7-22.7	3.4 [a]	3.0-3.8	9.9 [b]	9.2-10.6
≥ 35	4.1 [a]	3.2-5.0	13.2 [b]	11.7-14.7	19.7 [c]	17.9-21.5	2.9 [a]	2.2-3.6	10.8 [b]	9.4-12.2
Low socioeconomic status:										
No	3.8 [a]	3.4-4.2	13.0 [a]	12.3-13.7	21.4 [a]	20.6-22.2	3.3 [a]	2.9-3.7	10.0 [a]	9.4-10.6
Yes	6.5 [a]	2.4-10.6	14.6 [a]	9.1-2.1	28.7 [b]	22.0-35.4	1.3 [a]	0.0-3.1	6.9 [a]	3.1-10.7
Obesity:										
No	3.9 [a]	3.5-4.3	13.5 [a]	12.8-14.2	21.5 [a]	20.6-22.4	3.0 [a]	2.6-3.4	10.1 [a]	9.5-10.7
Yes	3.4 [a]	2.4-4.4	9.9 [b]	8.2-11.6	21.5 [a]	19.1-23.9	5.2 [a]	3.9-6.5	8.8 [a]	7.2-10.4
Smoker:										
No	4.1 [a]	3.6-4.6	13.7 [a]	12.9-14.5	22.3 [a]	21.3-23.3	3.1 [a]	2.7-3.5	10.0 [a]	9.3-10.7
Yes	2.5 [b]	1.8-3.2	10.5 [a]	9.2-10.5	19.5 [b]	17.7-21.3	3.8 [b]	3.0-4.6	9.6 [a]	8.3-10.9
Parity (number of children):										
First-time mother	3.0 [a]	2.5-3.5	12.8 [a]	11.8-13.8	17.5 [a]	16.3-18.7	3.9 [a]	3.3-4.5	12.8 [a]	11.8-13.8
1-2	4.1 [b]	3.5-4.7	12.7 [a]	11.8-13.6	24.1 [b]	22.9-25.3	2.9 [b]	2.4-3.4	7.7 [b]	6.9-8.5
≥ 3	7.9 [c]	5.4-10.4	18.4 [b]	15.0-21.8	29.0 [c]	25.0-33.0	2.5 [a,b]	1.1-3.9	6.7 [b]	4.5-8.9
Type of pregnancy:										
Single	3.7 [a]	3.3-4.1	12.7 [a]	12.0-13.4	21.6 [a]	20.8-22.4	3.2 [a]	2.8-3.6	9.8 [a]	9.2-10.4
Multiple	5.5 [a]	0.0-11.5	27.1 [b]	15.8-38.4	18.9 [a]	8.4-29.4	1.7 [a]	0.0-5.0	13.2 [a]	4.1-22.3

Anaemia: Hb < 110 g/L in 1st and 3rd trimester and Hb < 105 g/L in the 2nd trimester; risk of haemoconcentration: Hb > 130 g/L in 2nd and 3rd trimester.
[a,b,c]Mean values within the same column with a different letter in superscript indicates that they are significantly different (p < 0.05).

Women with multiple pregnancies are predisposed to presenting with anaemia, although this finding only appears in the second trimester.

DISCUSSION

The present study shows that in addition to the increased presence of anaemia as pregnancy advances, the risk of haemoconcentration is also a problem for public health and affects around 10% of women in the final stages of pregnancy. This percentage raises the importance of studying the real risks of high haemoglobin levels on the health of both mother and child. Furthermore, it has been seen that under the age of 20 or having had children previously can increase the chances of anaemia and that being over the age of 34 increases the risk of haemoconcentration.

The pregnant women in the study were all of the women attended by the ASSIR service, which is a public health network used, according to the Agència de Salut Pública (Catalan Public Health Agency), by about 70% of pregnant women in Catalonia (16). Both the age of the women and the number of previous births is similar to that recorded in the overall population of Catalonia (16), although the percentage of multiple births is slightly lower than the overall Catalan population (0.6% *vs.* 4.2%) (16) possibly because

Table III. Multiple logistical regression of the principal risk factors for anaemia*

	Women with Hb measured at least in one trimester (n = 10,596)		Women with Hb measured at every trimester (n = 7,517)	
	OR (95% CI)	Adj. OR (95% CI)	OR (95% CI)	Adj. OR (95% CI)
1st Trimester				
Age of mother (years):				
20-34	1	1	1	1
< 20	1.4 (0.7-2.6)	1.5 (0.8-2.9)	1.5 (0.7-3.1)	1.7 (0.8-3.6)
≥ 35	0.7 (0.6-0.9)	0.7 (0.5-0.9)	0.8 (0.7-1.1)	0.7 (0.6-0.9)
Low socioeconomic status (no, yes)	1.9 (0.9-3.7)	1.7 (0.8-3.4)	1.6 (0.7-3.7)	1.4 (0.6-3.4)
Obesity (no, yes)	0.9 (0.7-1.3)	0.7 (0.5-1.0)	0.9 (0.6-1.3)	0.7 (0.5-1.1)
Smoker (no, yes)	1.1 (0.9-1.4)	0.7 (0.5-0.9)	0.7 (0.5-0.9)	0.7 (0.5-0.9)
Parity (number of children):				
First-time mother	1	1	1	1
1-2	1.3 (1.0-1.6)	1.3 (1.0-1.7)	1.4 (1.1-1.8)	1.5 (1.1-1.9)
≥ 3	2.6 (1.7-3.9)	3.1 (1.9-4.9)	3.2 (2.1-5.1)	4.1 (2.5-6.8)
Multiple pregnancy (no, yes)	1.5 (0.4-4.9)	2.7 (0.8-8.7)	1.8 (0.6-5.9)	3.0 (0.9-9.8)
2nd Trimester				
Age of mother (years):				
20-34	1	1	1	1
< 20	1.2 (0.8-1.7)	1.1 (0.8-1.7)	1.4 (0.9-2.2)	1.3 (0.9-2.1)
≥ 35	0.8 (0.7-0.9)	0.7 (0.6-0.8)	0.8 (0.7-0.9)	0.7 (0.6-0.9)
Low socioeconomic status (no, yes)	1.2 (0.8-1.8)	1.0 (0.6-1.7)	1.3 (0.8-2.3)	1.2 (0.7-2.1)
Obesity (no, yes)	0.7 (0.6-0.9)	0.6 (0.5-0.8)	0.7 (0.5-0.9)	0.6 (0.5-0.8)
Smoker (no, yes)	0.7 (0.6-0.9)	0.7 (0.6-0.9)	0.7 (0.6-0.9)	0.7 (0.6-0.8)
Parity (number of children):				
First-time mother	1	1	1	1
1-2	1.0 (0.9-1.1)	1.0 (0.9-1.2)	1.0 (0.9-1.2)	1.1 (0.9-1.3)
≥ 3	1.6 (1.2-2.0)	1.7 (1.3-2.3)	1.4 (1.1-2.0)	1.6 (1.1-2.4)
Multiple pregnancy (no, yes)	2.6 (1.5-4.6)	2.7 (1.4-5.4)	2.4 (1.2-4.7)	2.6 (1.2-5.5)
3rd Trimester				
Age of mother (years):				
20-34	1	1	1	1
< 20	1.3 (0.9-1.7)	1.4 (1.1-1.9)	1.5 (1.1-2.2)	1.7 (1.2-2.5)
≥ 35	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.7 (0.7-0.8)	0.7 (0.6-0.8)
Low socioeconomic status (no, yes)	1.5 (1.1-2.1)	1.3 (0.9-1.8)	1.6 (1.0-2.4)	1.4 (0.9-2.2)
Obesity (no, yes)	1.0 (0.8-1.1)	0.9 (0.8-1.1)	0.9 (0.8-1.1)	0.9 (0.7-1.1)
Smoker (no, yes)	0.8 (0.7-0.9)	0.8 (0.7-0.9)	0.9 (0.8-0.9)	0.9 (0.7-0.9)
Parity (number of children):				
First-time mother	1	1	1	1
1-2	1.5 (1.3-1.7)	1.6 (1.5-1.8)	1.5 (1.3-1.7)	1.7 (1.5-1.9)
≥ 3	1.9 (1.5-2.4)	2.2 (1.7-2.8)	1.9 (1.5-2.6)	2.4 (1.8-3.3)
Multiple pregnancy (no, yes)	0.8 (0.4-1.7)	0.8 (0.3-2.0)	0.5 (0.2-1.2)	0.8 (0.3-1.9)

**Anaemia: Hb < 110 g/L in the 1st and 3rd trimester and Hb < 105 g/L in the 2nd trimester.*
Adj. OR: adjusted Odds ratio. Adjusted for age of the mother (< 20 years, 20-34 years [reference group], > 34 years).

Table IV. Multiple logistical regression of the principal risk factors for haemoconcentration*

	Women with Hb measured at least in one trimester (n = 10,596)		Women with Hb measured at every trimester (n = 7,517)	
	OR (95% CI)	Adj. OR (95% CI)	OR (95% CI)	Adj. OR (95% CI)
2nd Trimester				
Age of mother (years):				
20-34	1	1	1	1
< 20	0.9 (0.4-1.9)	0.8 (0.4-2.0)	0.4 (0.1-1.7)	0.4 (0.1-1.7)
≥ 35	0.8 (0.7-1.1)	0.9 (0.7-.1.1)	0.8 (0.6-1.1)	0.9 (0.7-1.2)
Low socioeconomic status (no, yes)	0.4 (0.1-1.5)	0.4 (0.1-1.6)	No cases	No cases
Obesity (no, yes)	1.8 (1.3-2.4)	1.8 (1.3-2.5)	1.9 (1.4-2.7)	2.1 (1.5-3.0)
Smoker (no, yes)	1.2 (0.9-1.6)	1.1 (0.8-1.4)	1.2 (0.9-1.6)	0.9 (0.7-1.3)
Parity (number of children):				
First-time mother	1	1	1	1
1-2	0.7 (0.6-0.9)	0.7 (0.6-0.9)	0.7 (0.5-0.9)	0.6 (0.5-0.9)
≥ 3	0.6 (0.3-1.1)	0.6 (0.3-1.1)	0.3 (0.1-0.9)	0.3 (0.1-0.9)
Multiple pregnancy (no, yes)	0.5 (0.1-3.7)	0.7 (0.1-5.1)	No cases	No cases
3rd Trimester				
Age of mother (years):				
20-34	1	1	1	1
< 20	0.8 (0.5-1.4)	0.7 (0.4-1.2)	0.5 (0.2-1.1)	0.4 (0.2-0.9)
≥ 35	1.1 (0.9-1.3)	1.3 (1.1-1.5)	1.1 (0.9-1.3)	1.3 (1.1-1.5)
Low socioeconomic status (no, yes)	0.7 (0.4-1.2)	0.7 (0.4-1.4)	0.7 (0.3-1.5)	0.8 (0.6-1.1)
Obesity (no, yes)	0.9 (07.7-1.1)	0.9 (0.7-1.2)	0.8 (0.6-1.0)	0.8 (0.6-1.1)
Smoker (no, yes)	0.9 (0.8-1.1)	0.9 (0.7-1.1)	0.9 (0.8-1.1)	0.9 (0.7-1.0)
Parity (number of children)				
First-time mother:	1	1	1	1
1-2	0.6 (0.5-0.7)	0.5 (0.4-0.6)	0.6 (0.5-0.7)	0.5 (0.5-0.6)
≥ 3	0.5 (0.3-0.7)	0.4 (0.2-0.6)	0.6 (0.4-0.9)	0.5 (0.3-0.8)
Multiple pregnancy (no, yes)	1.4 (0.6-3.1)	1.2 (0.5-3.0)	1.3 (0.5-3.0)	0.9 (0.3-2.7)

**Risk of haemoconcentration: Hb >130 g/L in the 2nd and 3rd trimester.*
Adj. OR: adjusted Odds ratio. Adjusted for age of the mother (< 20 years, 20-34 years [reference group], > 34 years).

higher-risk pregnancies are referred to specialised centres or are monitored by private clinics. This is a possible limitation to the study; however, we have compared the women who were monitored throughout their pregnancies with those who were referred to other centres and clinics and we have found no differences between the groups in terms of risk factors for anaemia or risk of haemoconcentration.

The ASSIR service carries out regular blood tests of all pregnant women during each trimester, regardless of whether they are suspected of having an iron deficiency, which means that the levels of anaemia have been accurately determined. All the blood samples were analysed at the Camp de Tarragona Clinical Laboratory, which is the leading laboratory in the province of Tarragona and which complies with the International Standard ISO 9001:2000. Anaemia was determined by taking in account the different degrees of haemodilution in each trimester of pregnancy (15).

The vast majority of cases of anaemia are caused by iron deficiency (17). For this reason, the ASSIR recommends regular 40 mg iron supplements from the second trimester for all pregnant women without anaemia and iron supplements of 80 mg, 1 or 2 times a day for those who do have anaemia. This ensures that the iron supplements fully meet the needs of each pregnant woman.

The levels of anaemia found in the present study are similar to those found across Europe by the World Health Organisation (1)

and also to those found by other European studies (17,18), which confirms that iron deficiency is high, even in developed countries. However, both Stevens et al. and the WHO state that their data only show the mean values for the entire pregnancy, which made it impossible for those studies to observe how the level of anaemia increased, an aspect that we have improved in the present study.

By the same token, there is little information regarding the prevalence of high levels of haemoglobin during pregnancy in Europe. A recent study conducted in Holland estimates that around 15% of the women analysed had excessive haemoglobin levels (19), which is a similar figure to that found in southern Europe by our own research group (3).

In addition to already well-documented effects of anaemia on the health of mother and child (5,12), more recently, evidence has also been emerging regarding the harmful effects of high haemoglobin levels during pregnancy, including increased oxidative stress and preeclampsia in the mother (6,20) and the increased likelihood of premature birth and low birthweight (5,6), although more studies are needed to confirm these findings. It is important to understand the risk factors in specific populations for both anaemia and haemoconcentration because some risk factors can be more significant depending on the population type (8,19). Our results indicate that being under the age of 20 and previously having had children increases the likelihood of anaemia, whereas being over the age of 34 increases the chances of having haemoconcentration.

With regard to the age of the mother, it is well known that women under the age of 20 are at greater risk of presenting with anaemia during pregnancy because they are still growing themselves (8,19). In contrast, as other authors have found, we observed that the risk of anaemia decreased as the women got older, with the lowest risk being found in pregnant women over the age of 34 (8,9). However, pregnant women over 34 were around 30% more likely to develop haemoconcentration than younger women. As far as we know, only two other studies have looked this relationship and neither one was able to establish a connection (19,21). One of the studies was carried out by our research group and described the risk factors associated with the risk of haemoconcentration in a sample of 217 women (21). However, the sample was not large enough to study this effect in different age groups. It is not known by which mechanism age may be related to the risk of haemoconcentration.

With regard to previous children, the general finding seems to be that the more children a woman has had previously, the greater the risk of presenting with anaemia (8,19,22) and, consequently, the lower the risk of haemoconcentration (19). This may be because the more pregnancies a woman has, the shorter the period between each one, which in turn limits the time she has to recover her iron levels.

Another factor that may increase the chances of anaemia is low socioeconomic status (14,23) because this may lead to poor diet due to lack of financial resources. However, in our sample we found no relation between low socioeconomic status and anaemia, thus coinciding with Gaillard et al., who also found no such relation during the third trimester of pregnancy in a sample of European women. This may be because levels of malnutrition in developed countries are not as high as in developing countries and because the widespread use of iron supplements may correct iron deficiency in women with low socioeconomic status.

The body mass index of pregnant women is also associated with anaemia (24). In the present study, as in other studies, we observed that obese women were less likely to have anaemia, although this was not statistically significant in any trimester (24,25) and that they were more likely to have haemoconcentration (19).

According to our results, tobacco use seemed to reduce anaemia; however, this is an inaccurate finding because although smokers present higher levels of haemoglobin, this is nether functional nor does it transport iron because it is joined with carbon monoxide (26). Consequently, in addition to the already established negative health effects of smoking, tobacco use may also hide an iron deficiency because of the increased levels of non-functional haemoglobin, which in turn may mean that a pregnant woman is not treated with the correct dose of iron supplements.

One of the limitations to our study is that the data are from computerised clinical histories and that we have been unable to evaluate risk factors such as the time between births. Some authors assert that when this is less than two years, women do not have time to recover their iron reserves (10,22).

To conclude, the present study confirms that around 1 in 5 women reach the third trimester of pregnancy with anaemia and around 10% have the risk of haemoconcentration. Risk factors for anaemia and the risk of haemoconcentration are the age of the mother and the number of previous children. Tobacco use may hide a possible iron deficiency.

Understanding these risk factors highlights the need to implement health policies that focus more on risk groups in order to treat both insufficient and excessive iron levels during pregnancy and to adapt iron supplements accordingly.

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REFERENCES

1. World Health Organization. The global prevalence of anaemia in 2011. Geneva: WHO; 2015.
2. McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005. Public Health Nutr 2009;12(4):444-54.
3. Arija V, Ribot B, Aranda N. Prevalence of iron deficiency states and risk of haemoconcentration during pregnancy according to initial iron stores and iron supplementation. Public Health Nutr 2013;16(8):1371-8.
4. Pena-Rosas JP, Viteri FE. Effects and safety of preventive oral iron or iron+-folic supplementation for women during pregnancy. Cochrane Database Syst Rev 2009;CD004736.

5. Scholl TO. Iron status during pregnancy: setting the stage for mother and infant. Am J Clin Nutr 2005;81:1218S-22S.
6. Von Tempelhoff GF, Heilmann L, Rudig L, Pollo K, Hommel G, Koscielny J. Mean maternal second-trimester hemoglobin concentration and outcome of pregnancy: a population-based study. Clin Appl Thromb Hemost 2008;14:19-28.
7. Aranda N, Ribot B, Garcia E, Viteri FE, Arija V. Pre-pregnancy iron reserves, iron supplementation during pregnancy, and birth weight. Early Hum Dev 2011;87:791-7.
8. Barroso F, Allard S, Kahan BC, Connolly C, Smethurst H, Choo L, et al. Prevalence of maternal anaemia and its predictors: a multi-centre study. Eur J Obstet Gynecol Reprod Biol 2011;159(1):99-105.
9. Uche-Nwachi EO, Odekunle A, Jacinto S, Burnett M, Clapperton M, David Y, et al. Anaemia in pregnancy: associations with parity, abortions and child spacing in primary healthcare clinic attendees in Trinidad and Tobago. Afr Health Sci 2010;10(1):66-70.
10. Ahmed F, Al-Sumaie MA. Risk factors associated with anaemia and iron deficiency among Kuwaiti pregnant women. Int J Food Sci Nutr 2011;62:585-92.
11. Adebisi OY, Strayhorn G. Anaemia in pregnancy and race in the United States: blacks at risk. Fam Med 2005;37(9):655-62.
12. Haider BA, Olofin I, Wang M, Spiegelman D, Ezzati M, Fawzi WW. Nutrition Impact Model Study Group (anaemia). Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis. BMJ 2013;346:f3443.
13. Bencaiova G, Burkhardt T, Breymann C. Anaemia -prevalence and risk factors in pregnancy. Eur J Intern Med 2012;23(6):529-33.
14. Noronha JA, Bhaduri A, Vinod Bhat H, Kamath A. Maternal risk factors and anaemia in pregnancy: a prospective retrospective cohort study. J Obstet Gynaecol 2010;30(2):132-6.
15. CDC. Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. MMWR Recomm Rep 1998;47:1-29.
16. Agencia de Salut Pública de Catalunya. Indicadors de salut perinatal a Catalunya. Any 2015. Generalitat de Catalunya. Departament de salut; Barcelona, Spain 2016. [Cited 2017Feb 13]. Available at: http://canalsalut.gencat.cat/web/.content/home_canal_salut/professionals/temes_de_salut/vigilancia_epidemiologica/documents/arxius/informe_complet_2015_perinatal.pdf
17. Stevens GA, Finucane MM, De-Regil LM, Paciorek CJ, Flaxman SR, Branca F, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: A systematic analysis of population-representative data. Lancet Glob Health 2013;1:E16-E25.
18. Milman N. Prepartum anaemia: prevention and treatment. Ann Hematol 2008;87:949-59.
19. Gaillard R, Eilers PH, Yassine S, Hofman A, Steegers EA, Jaddoe VW. Risk factors and consequences of maternal anaemia and elevated haemoglobin levels during pregnancy: a population-based prospective cohort study. Paediatr Perinat Epidemiol 2014;28(3):213-26.
20. Casanueva E, Viteri F, Mares-Galindo M, Meza-Camacho C, Loria A, Schnaas L, et al. Weekly iron as a safe alternative to daily supplementation for non-anemic pregnant women. Arch Med Res 2006;37:674-82.
21. Aranda N, Ribot B, Viteri F, Cavallé P, Arija V. Predictors of haemoconcentration at delivery: association with low birth weight. Eur J Nutr 2013;52(6):1631-9.
22. Obse N, Mossie A, Gobena T. Magnitude of anaemia and associated risk factors among pregnant women attending antenatal care in ShallaWoreda, West Arsi Zone, Oromia Region, Ethiopia. Ethiop J Health Sci 2013;23(2):165-73.
23. Selo-Ojeme DO. Anaemia in pregnancy: case control study of risk factors. Int J Gynaecol Obstet 1997;59(1):53-4.
24. Charles AM, Campbell-Stennett D, Yatich N, Jolly PE. Predictors of anaemia among pregnant women in Westmoreland, Jamaica. Health Care Women In 2010;31(7):585-98.
25. Al-Mehaisen L, Khader Y, Al-Kuran O, Abu Issa F, Amarin Z. Maternal anaemia in rural Jordan: room for improvement. Anaemia 2011;(2011):381812:1-7.
26. Milman N, Pedersen AN. Blood haemoglobin concentrations are higher in smokers and heavy alcohol consumers than in non-smokers and abstainers: should we adjust the reference range? Ann Hematol 2009;88:687-94.

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ARÁN

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Trabajo Original

Epidemiología y dietética

Adherencia a la dieta mediterránea en adultos inactivos, practicantes de ciclo *indoor* y ciclistas aficionados

Adherence to the Mediterranean diet in inactive adults, indoor cycling practitioners and amateur cyclists

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Resumen

Introducción: existe información limitada sobre la relación entre la adherencia a la dieta mediterránea (ADM) y la práctica deportiva.

Objetivo: determinar la posible asociación de la práctica deportiva y el volumen de entrenamiento en bicicleta con la ADM y la influencia de la proximidad de una prueba ciclodeportiva sobre la ADM.

Material y métodos: una primera evaluación de la ADM en 785 (84 mujeres) ciclistas aficionados (volumen ≥ 7 horas/semana), 514 (224 mujeres) practicantes de ciclo indoor (volumen: 2-6 horas/semana) y 718 (411 mujeres) adultos inactivos fue desarrollada en mayo, coincidiendo con la participación de los ciclistas en una prueba ciclodeportiva. Una submuestra de 359 ciclistas y 148 inactivos fueron evaluados nuevamente en noviembre, en fecha alejada de la prueba ciclodeportiva. Se utilizó el cuestionario MEDAS-14 para valorar la ADM y un cuestionario autodiseñado para evaluar el volumen de entrenamiento.

Resultados: un 40% de los sujetos evidenció alta ADM. En ambos sexos, los deportistas mostraron mayor ADM que los inactivos, con los mejores índices para los grupos de ciclistas ($p < 0,001$). La relación entre la ADM y el volumen de entrenamiento fue débil (hombres: $r = 0,137$, mujeres: $r = 0,173$; $p < 0,001$). La ADM de los ciclistas disminuyó de mayo a noviembre ($p < 0,001$) sin cambios en los sujetos inactivos ($p = 0,535$).

Conclusiones: la práctica deportiva en bicicleta se asocia con una mayor ADM con limitada influencia del volumen de entrenamiento y con efectos positivos transitorios de la participación en una prueba ciclodeportiva.

Palabras clave:

Dieta mediterránea. Ciclismo. Ciclo *indoor*. Salud

Abstract

Introduction: There is limited information referred to the relationship between adherence to the Mediterranean Diet (AMD) and sports practice.

Objective: To determinate the association of cycling practice and cycling training volume with the AMD and the influence of the participation in a high-demand cyclist event on the AMD.

Material and methods: A first evaluation of AMD in 785 (84 women) amateur cyclists (volume: ≥ 7 hours/week), 514 (224 women) indoor cycling practitioners (volume: 2-6 hours/week) and 718 (411 women) inactive adults was conducted in May coinciding with the participation of cyclists in a cycling event. A subsample of 359 cyclists and 148 inactive subjects agreed to be retested in November, far from the cycling event date. The MEDAS-14 questionnaire was used to assess the AMD and a self-designed questionnaire was used to assess the volume of training.

Results: 40% of subjects showed high AMD. In both sexes, athletes showed higher AMD than inactive subjects, with the highest indexes for groups of cyclists ($p < 0.001$). The relationship between AMD and training volume was weak (men: $r = 0.137$, women: $r = 0.173$; $p < 0.001$). The AMD of cyclists decreased from May to November ($p < 0.001$) with no significant changes in inactive subjects ($p = 0.535$).

Conclusions: Cycling is associated to higher values of AMD with a limited influence of training volume and transient positive effects of participation in a cycling endurance event.

Key words:

Mediterranean diet. Cycling. Indoor cycling. Health.

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INTRODUCCIÓN

El patrón dietético es uno de los factores más influyentes de la salud (1). La dieta mediterránea (DM) tradicional se considera como una de las más saludables y se caracteriza por un patrón dietético rico en alimentos vegetales (cereales, frutas, verduras, legumbres, frutos secos, semillas y aceitunas), con el aceite de oliva como fuente principal de la grasa añadida, junto con la ingesta alta o moderada de pescado y marisco, consumo moderado de huevos, aves de corral y productos lácteos (queso y yogur), bajo consumo de carne roja y una ingesta moderada de alcohol (principalmente vino durante las comidas) (2). Recientes revisiones resaltan el factor protector de la DM sobre numerosas enfermedades crónicas y degenerativas, como el síndrome metabólico, riesgo cardiovascular, aterosclerosis, cáncer, diabetes, obesidad, enfermedades renales, enfermedades pulmonares, trastornos de la cognición y depresión unipolar (3-5).

La práctica de actividad física, ejercicio o deporte de forma regular es otro de los factores conductuales modificables determinantes de la salud (6-8). "Exercise is Medicine" (7) es un reciente programa internacional de fomento de la actividad física con una sólida evidencia científica. De hecho, numerosos estudios han demostrado las ventajas del ejercicio en el tratamiento y la prevención de múltiples enfermedades crónicas comunes, mostrando una clara evidencia de que los sujetos con un estilo de vida activo tienen vidas más largas, más saludables y de mayor calidad (6). Para obtener estos beneficios y considerar que un sujeto es activo, los adultos deben practicar a la semana al menos 150 min de actividad física aeróbica de intensidad moderada, o 75 min de intensidad vigorosa o una combinación equivalente de ambas intensidades, esperándose mayores beneficios incrementando el tiempo de actividad física (9).

El ejercicio en bicicleta es uno de los más habituales y su práctica se ha asociado con una reducción significativa de todas las causas de mortalidad (10). Muchos ciclistas aficionados están actualmente motivados para participar en eventos ciclodeportivos de carretera y/o de montaña caracterizados por una elevada demanda física y psicológica. Estos ciclistas realizan un volumen de entrenamiento elevado que se ha asociado recientemente con importantes beneficios para la salud (11). La práctica de ciclo *indoor* se caracteriza habitualmente por un menor volumen de entrenamiento y es una de las actividades grupales aeróbicas dirigidas más comunes en los gimnasios y centros deportivos. Esta actividad consiste en pedalear grupalmente en bicicletas estáticas siguiendo el ritmo de la música y los mensajes de motivación del instructor, y ha demostrado ser eficaz en la pérdida de peso y en la prevención de un riesgo elevado de enfermedad cardiovascular (12).

Podría esperarse que la mayor parte de la población presentase una alta adherencia a la DM (ADM) y un alto nivel de práctica de actividades físico-deportivas debido a sus múltiples beneficios. Sin embargo, la ADM ha disminuido a nivel mundial en las últimas décadas, especialmente en los habitantes de la cuenca mediterránea, incluidos los españoles (13), donde únicamente entre un 12-33% de la población, según las características de cada estudio, tiene alta ADM (14,15).

Según Hallal y cols. una mayor proporción de sujetos adultos a nivel mundial son considerados activos (69%) (16), ya que cumplen las recomendaciones de actividad física anteriormente mencionadas. En este estudio, un 50% de los españoles adultos fueron activos (16). Sin embargo, en un estudio europeo más reciente se muestra que la evolución de los españoles es muy positiva y actualmente un 80% de los adultos reportaron ser activos (17).

Conocer qué factores de riesgo conductuales están agrupados puede ayudar al desarrollo de intervenciones preventivas e integrales de salud. Al respecto, existe poco consenso en la literatura, pero algunos estudios sugieren que suele evidenciarse la agrupación de dos tipos de comportamientos: comportamientos adictivos (tabaquismo y alcohol), que requieren moderación o abstinencia; y comportamientos promotores de la salud (actividad física y dieta saludable), que requieren un compromiso activo (18,19).

Pocos estudios han establecido la relación entre actividad física y ADM (14,15,20-22). Los resultados de estos estudios sugieren una relación positiva entre los niveles de actividad física y la ADM (15,20-22), aunque recientemente esto no se ha verificado para sujetos de menos de 49 años o de más de 62 años (14). Todos estos estudios fueron de carácter epidemiológico, basando sus resultados en el análisis de la población general. Ningún estudio ha realizado este análisis focalizando la atención en poblaciones específicas de deportistas. Este análisis es de interés debido a que la práctica deportiva es determinante de los niveles actuales de actividad física (17). Así, actualmente es desconocido si los deportistas que realizan un mayor volumen de entrenamiento se caracterizan por tener una mayor ADM. Este análisis adquiere mayor relevancia entre el elevado porcentaje de deportistas aficionados que actualmente entrenan para participar en pruebas que, como las ciclodeportivas, requieren de una intensa preparación. El éxito en estas pruebas requiere también de un óptimo peso corporal, lo que podría inducir a un patrón dietético más saludable. Actualmente, este aspecto es desconocido, al igual que si el patrón dietético de estos deportistas aficionados se mantiene durante todo el año o difiere en función de la proximidad de la prueba deportiva objeto de la preparación.

En consecuencia, el presente estudio fue desarrollado para: a) determinar si la práctica deportiva en bicicleta está asociada con la ADM; b) establecer la relación entre el volumen de entrenamiento en bicicleta y la ADM; y c) determinar la influencia que sobre la ADM tiene la proximidad de una ciclodeportiva de elevada exigencia.

MATERIAL Y MÉTODOS

PARTICIPANTES

Con el objetivo de reclutar ciclistas aficionados y practicantes de ciclo *indoor*, se envió una invitación por correo electrónico para participar en el estudio a los representantes de los 3.426 clubs de ciclismo aficionado registrados en la Real Federación Española de Ciclismo y a los representan-

tes de los 4.627 gimnasios y centros deportivos registrados oficialmente en España. La invitación incluyó una breve introducción al estudio, una explicación del carácter anónimo y voluntario, el enlace al cuestionario *online*, y una solicitud para que la información fuese distribuida entre los socios y/o clientes. 1.023 ciclistas aficionados y 781 practicantes de ciclo *indoor* fueron reclutados. Todos los sujetos debían tener ≥ 18 años. En el mes previo a la primera valoración, los ciclistas debían de realizar un mínimo de 7 horas/semana de práctica de ciclismo, y los sujetos de ciclo *indoor* entre 2-6 horas/semana. Estos volúmenes de entrenamiento categorizados previamente (11,23) garantizan una práctica regular de ciclismo o de ciclo *indoor* y permiten diferenciar dos grupos con marcadas diferencias en el volumen de pedaleo. Además, los ciclistas debían tener como objetivo prioritario el participar en mayo-junio en un evento ciclodeportivo de carretera (> 100 km) o de bicicleta de montaña (> 45 km). Estos límites en las distancias de los eventos ciclodeportivos han sido seleccionados en base a nuestra experiencia previa (11,23) y permiten, además de englobar a los eventos ciclodeportivos con mayor participación, el establecer un elevado nivel de exigencia que garantice que la mayoría de los participantes hayan realizado un elevado volumen de entrenamiento. Se requirió un mínimo de 6 meses continuados de práctica de ciclismo o ciclo *indoor* para garantizar el efecto residual de su entrenamiento. 238 ciclistas y 267 practicantes de ciclo *indoor* fueron excluidos por no cumplir estos criterios. Finalmente, 785 ciclistas aficionados (701 hombres, 84 mujeres; 403 de carretera y 382 de bicicleta de montaña) y 514 practicantes de ciclo *indoor* (290 hombres, 224 mujeres) fueron incluidos en el estudio. Al objeto de establecer un grupo control de sujetos inactivos, los ciclistas aficionados y los practicantes de ciclo *indoor* fueron instruidos para que invitasen a participar en el estudio a sujetos de similar estatus sociodemográfico y que no practicasen deporte de forma regular. De un total de 1.527 sujetos reclutados, 718 sujetos controlados según edad (307 hombres y 411 mujeres) fueron clasificados como inactivos según la versión corta del Cuestionario Internacional de Actividad Física (24) y, en consecuencia, fueron incluidos en el grupo control (Fig. 1).

Todos los sujetos fueron evaluados la última semana de mayo. Además, los ciclistas aficionados también fueron invitados a una segunda valoración la segunda semana de noviembre con el propósito de establecer posibles diferencias en la ADM entre fechas próximas y alejadas al evento ciclodeportivo desarrollado en mayo-junio. Los sujetos inactivos también fueron invitados a esta segunda valoración a fin de controlar los posibles efectos estacionales sobre la ADM. No incluimos en esta segunda valoración a los practicantes de ciclo *indoor*, debido

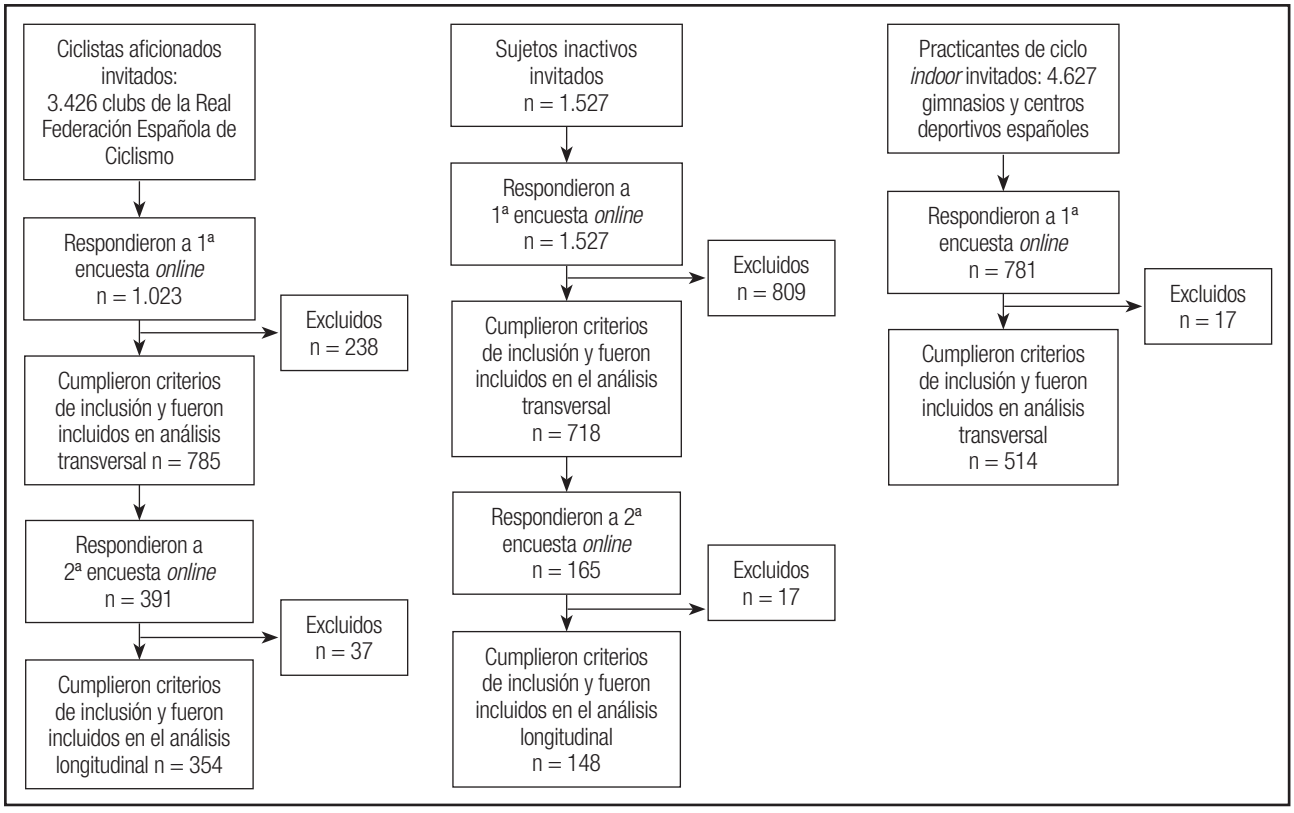

Figura 1.

Diagrama de flujo de los participantes en el diseño transversal y longitudinal.

a que es una actividad dirigida que la mayoría de sujetos deja de realizar durante el periodo estival. 391 ciclistas aficionados (46% del total) y 165 sujetos inactivos (23% del total) accedieron a participar en esta segunda valoración. La proporción de ciclistas aficionados e inactivos que aceptaron responder en la segunda encuesta *online* desarrollada en noviembre fue equiparable en ambos sexos. 37 ciclistas aficionados fueron excluidos al indicar que tenían como objetivo participar en ciclodeportivas durante el otoño, y 17 sujetos inactivos fueron excluidos al ser categorizados como activos en esta segunda valoración. Finalmente, 354 ciclistas aficionados (315 hombres y 39 mujeres) y 148 sujetos inactivos (61 hombres y 87 mujeres) fueron incluidos en el diseño longitudinal (Fig. 1). Los participantes dieron su consentimiento informado para el uso científico de los datos. El presente estudio cumplió con la ley española de protección de datos y la Declaración de Helsinki, y fue aprobado por el Comité Ético de Investigación Clínica de Aragón (PI17/0252).

ADHERENCIA A LA DIETA MEDITERRÁNEA

La ADM fue evaluada mediante la versión española del Cuestionario de adherencia a la dieta mediterránea (MEDAS-14) (21). Este cuestionario consta de 12 preguntas sobre la frecuencia de consumo de alimentos y 2 preguntas sobre hábitos de ingesta de alimentos considerados como característicos de la DM española. Cada pregunta es puntuada con 0 o 1. Un punto es otorgado por usar el aceite de oliva como fuente principal de grasa para cocinar, por preferir la carne blanca sobre la carne roja, o por consumir: a) 4 o más cucharadas de aceite de oliva/día; b) 2 o más raciones de verduras/día; c) 3 o más piezas de fruta/día; d) menos de 1 ración de carne roja o salchicha/día; e) menos de 1 porción de grasa animal/día; f) menos de 1 bebida azucarada/día; g) 7 o más vasos de vino tinto/semana; h) 3 o más raciones de legumbres/semana; i) 3 o más raciones de pescado/semana; j) menos de 2 pasteles o repostería comercial/semana; k) 3 o más porciones de nueces/semana; l) 2 o más veces/semana de un plato con una salsa tradicional de tomates, ajo y cebollas. La puntuación total oscila entre 0 y 14 y permite diferenciar tres niveles de ADM: bajo (0-6), medio (7-8) y alto (≥ 9) (15).

ACTIVIDAD FÍSICA Y ENTRENAMIENTO

El nivel de actividad física fue establecido mediante la versión española (25) y corta del Cuestionario internacional de actividad física (24), que muestra unas aceptables propiedades psicométricas. Este cuestionario fue diseñado para estandarizar los niveles de actividad física a nivel mundial y proporciona información sobre el tiempo empleado en la última semana en caminar, en actividades de intensidad moderada o vigorosa, y en actividades sedentarias. Los valores del cuestionario permiten categorizar a los sujetos con niveles de actividad física baja, media o alta. Los sujetos con niveles de actividad física baja son considerados como inactivos. Se diseñó un cuestionario para evaluar el nivel de entrenamiento de los ciclistas aficionados y de los practicantes de ciclo *indoor*, registrando el volumen (horas/semana en el último mes), frecuencia (días/semana en el último mes) y experiencia de entrenamiento (años de práctica). Una submuestra de participantes fue contactada de nuevo 10 días después del primer cuestionario *online* con las cuestiones sobre el nivel de entrenamiento, demostrando una elevada reproducibilidad descrita en nuestro estudio previo (11).

CONSUMO DE TABACO Y DE ALCOHOL

El consumo y la dependencia del tabaco fueron evaluados mediante la versión española (26) del Test de dependencia de nicotina de Fagerström (27). El consumo de alcohol se evaluó mediante el cálculo de las Unidades estándar de alcohol (28).

ESTATUS SOCIODEMOGRÁFICO E ÍNDICE DE MASA CORPORAL

El índice de masa corporal se calculó sobre la base de los valores autorreportados de peso y altura. Se registró el sexo y la edad y se diseñó un cuestionario para evaluar variables sociodemográficas de interés como estado civil, número de hijos, nivel educativo, ocupación laboral, nivel de ingresos, zona geográfica y tamaño del municipio de residencia. Una submuestra de participantes fue contactada de nuevo 10 días después del primer cuestionario *online* con las cuestiones sobre peso, talla y estatus sociodemográfico, demostrando una elevada reproducibilidad descrita en nuestro estudio previo (11).

ANÁLISIS ESTADÍSTICO

Los análisis estadísticos se realizaron utilizando el Paquete estadístico para ciencias sociales de IBM (IBM SPSS *Statistics*, v. 21.0 WINDOWS). Los datos de cohortes se presentan como media ± desviación estándar o porcentaje. Para medir las diferencias en las variables de interés se realizó un ANOVA de 2 vías con dos factores entre sujetos (grupo: ciclistas aficionados, practicantes de ciclo *indoor* e inactivos; y sexo: mujer y hombre). Este mismo análisis se realizó para el diseño longitudinal con un factor entre sujetos (grupo: ciclistas aficionados e inactivos) y un factor intrasujeto (tiempo: próximo al evento ciclodeportivo y alejado del evento ciclodeportivo). En las comparaciones múltiples se aplicó la corrección de Bonferroni. Estos análisis fueron ajustados para posibles variables de confusión como el estatus sociodemográfico y el consumo de tabaco y alcohol. Se aplicó el test de Chi-cuadrado para establecer las diferencias entre grupos para las variables cualitativas. Utilizamos la correlación de Pearson para establecer relaciones de interés. Los valores se consideraron significativos si $p < 0,05$.

RESULTADOS

DIFERENCIAS ENTRE GRUPOS EN HÁBITOS SALUDABLES

No se observaron diferencias de edad entre grupos ($p = 0,341$) (Tabla I). En ambos sexos, los deportistas mostraron respecto a los sujetos inactivos menores valores de índice de masa corporal, mayores niveles de actividad física y menor consumo de tacaco y alcohol, con los mejores índices en los grupos de ciclistas aficionados (todos $p < 0,05$). Las mujeres tuvieron menor consumo de tabaco y alcohol que los hombres ($p < 0,001$). El volumen y la frecuencia de entrenamiento fueron equiparables entre sexos y superiores en los ciclistas aficionados que en los practicantes de ciclo *indoor* ($p < 0,001$), sin observarse diferencias en los años de práctica deportiva en bicicleta ($p = 0,384$).

DIFERENCIAS ENTRE GRUPOS EN LA ADM

La mayoría de los sujetos mostraron niveles bajos o medios de ADM (Tabla II). Las principales deficiencias, con menos del 50% de cumplidores, están asociadas al consumo de nueces (40%), aceite de oliva (39%), fruta (37%), pescado (35%), legumbres (28%) y vino (7%). Las mujeres mostraron mayor ADM que los hombres en la puntuación total y en todas las preguntas ($p \leq 0,012$), excepto las referentes al uso y consumo de aceite de oliva y al consumo de grasa animal y vino tinto. En ambos sexos, los deportistas mostraron mayor ADM que los inactivos, con los mejores índices para los grupos de ciclistas aficionados ($p < 0,001$). Estas diferencias se mantuvieron después de controlar la influencia del estatus sociodemográfico y del consumo de tabaco y alcohol.

Respecto a los sujetos con baja o media ADM, los sujetos con alta ADM se caracterizaron por realizar un mayor volumen de entrenamiento, ser más mayores, consumir menos tabaco, y un mayor porcentaje residía en Andalucía y tenía hijos ($p \leq 0,001$). El nivel de correlación entre la puntuación total de ADM y la edad fue débil (hombres: $r = 0,180$, $p < 0,001$; mujeres: $r = 0,194$, $p < 0,001$). También se evidenció una débil relación entre la puntuación total de ADM y el volumen de entrenamiento (hombres: $r = 0,137$, $p < 0,001$; mujeres: $r = 0,173$, $p = 0,002$) (Fig. 2). En ambos sexos, esta relación se mantuvo significativa cuando se incluyó en el análisis únicamente al grupo de ciclistas aficionados, pero no cuando solo se incluyó a los practicantes de ciclo *indoor*.

Tabla I. Características básicas de los sujetos

	Hombres			Mujeres			p[1]		
	Ciclistas (n = 701)	Ciclo *indoor* (n = 290)	Inactivos (n = 307)	Ciclistas (n = 84)	Ciclo *indoor* (n = 224)	Inactivos (n = 411)	Grupo	Sexo	Grupo x Sexo
Edad (años)	38,4 ± 8,4	38,1 ± 10,2	38,2 ± 12,0	37,7 ± 7,6	36,3 ± 10,1	37,8 ± 11,2	0,341	0,091	0,438
Índice de masa corporal (kg/m^2)	24,3 ± 2,5	25,3 ± 3,1	26,3 ± 4,5*#	22,0 ± 2,7	22,6 ± 3,3	24,1 ± 4,2*#	< 0,001	< 0,001	0,308
Tabaco TDNF (0-16)	0,22 ± 1,1	0,48 ± 1,6	1,79 ± 3,1*#	0,01 ± 0,1	0,36 ± 1,4	0,93 ± 2,2*#	< 0,001	< 0,001	0,001
Consumo de alcohol (UEA)	5,7 ± 7,6	6,2 ± 8,2	8,3 ± 9,5*#	1,8 ± 3,7	4,4 ± 8,4*	3,2 ± 4,7	< 0,001	< 0,001	0,001
Actividad física (MET-min semana)	7119 ± 4472	3508 ± 1964*	242 ± 193*#	6510 ± 3803	3184 ± 1959*	276 ± 191*#	< 0,001	0,027	0,516
Entrenamiento									
Experiencia deportiva actual (años)	4,7 ± 4,7	4,0 ± 3,6	_	3,0 ± 2,9	3,2 ± 2,9	_	0,384	< 0,001	0,148
Frecuencia último mes (días/semana)	4,1 ± 3,6	2,8 ± 1,1	_	4,2 ± 2,8	2,6 ± 1,1	_	< 0,001	0,591	0,119
Volumen último mes (horas/semana)	12,3 ± 4,4	2,8 ± 1,1	_	11,8 ± 4,4	2,6 ± 1,1	_	< 0,001	0,174	0,526

Los valores son media ± DS. TDNF: test de dependencia de nicotina de Fagerström; UEA: unidades estándar de alcohol.

*[1]Las diferencias fueron examinadas mediante ANOVA de dos vías aplicando la corrección de Bonferroni: *Diferencias significativas respecto a los ciclistas aficionados; #Diferencias significativas respecto a los practicantes de ciclo* indoor*.*

Tabla II. Diferencias entre grupos en la adherencia a la dieta mediterránea

	Hombres			Mujeres			p[1]	
	Ciclistas (n = 701)	Ciclo *indoor* (n = 290)	Inactivos (n = 307)	Ciclistas (n = 84)	Ciclo *indoor* (n = 224)	Inactivas (n = 411)	Grupo	Sexo
Usa aceite de oliva como principal grasa para cocinar	96	97	94	95	96	94	0,134	0,162
≥ 4 cucharadas de aceite de oliva al día	37	42	42	32	38	41	0,091	0,517
≥ 2 raciones de verdura al día	51	54	41*#	74	69	62*	0,014	< 0,001
≥ 3 piezas de fruta al día	47	37*	25*#	50	36*	28*#	< 0,001	0,001
< 1 ración de carne roja o salchicha al día	74	69	59*#	87	76*	76*	0,019	< 0,001
< 1 porción de grasa animal al día	97	91*	91*	96	92	94	< 0,001	0,468
< 1 bebida azucarada al día	84	82	72*#	91	88	84	0,002	0,002
≥ 7 vasos de vino tinto a la semana	7	11*	10*	0	7*	6*	0,086	0,012
≥ 3 raciones de legumbres a la semana	33	28	31	20	23	19	0,002	< 0,001
≥ 3 raciones de pescado a la semana	35	34	26*#	50	43	34*#	0,008	0,005
< 2 pasteles o repostería comercial a la semana	63	64	52*#	79	71	64*#	0,005	0,001
≥ 3 o más porciones de nueces a la semana	49	41*	29*#	49	35*	31*	< 0,001	< 0,001
Consume preferentemente carne blanca sobre carne roja	81	79	62*#	92	87	82*#	< 0,001	< 0,001
≥ 2 veces a la semana plato con una salsa tradicional de tomates, ajo y cebolla	75	66*	71	69	57*	62	< 0,001	< 0,001
Baja adherencia a la dieta mediterránea (< 7 puntos)	21	25	43*#	12	21*	26*	< 0,001	0,022
Media adherencia a la dieta mediterránea (7-8 puntos)	31	39*	35	31	32	38	0,019	0,211
Alta adherencia a la dieta mediterránea (≥ 9 puntos)	48	36*	22*#	57	47*	36*#	< 0,001	0,170
Puntuación total (0-14)	8,3 ± 2,1	7,9 ± 1,9*	7,1 ± 2,0*#	8,9 ± 2,0	8,1 ± 2,0*	7,8 ± 1,9*	< 0,001	0,008

Se presentan las variables como porcentaje de participantes que contestaron positivamente. La puntuación total se muestra como media ± DS.
[1]Las diferencias porcentuales fueron examinadas mediante la prueba de Chi-cuadrado. Las diferencias en la puntuación total fueron analizadas mediante ANOVA de dos vías aplicando la corrección de Bonferroni y controlando por el estatus sociodemográfico y por el consumo de tabaco y alcohol.
**Diferencias significativas respecto a los ciclistas aficionados. #Diferencias significativas respecto a los practicantes de ciclo* indoor*.*

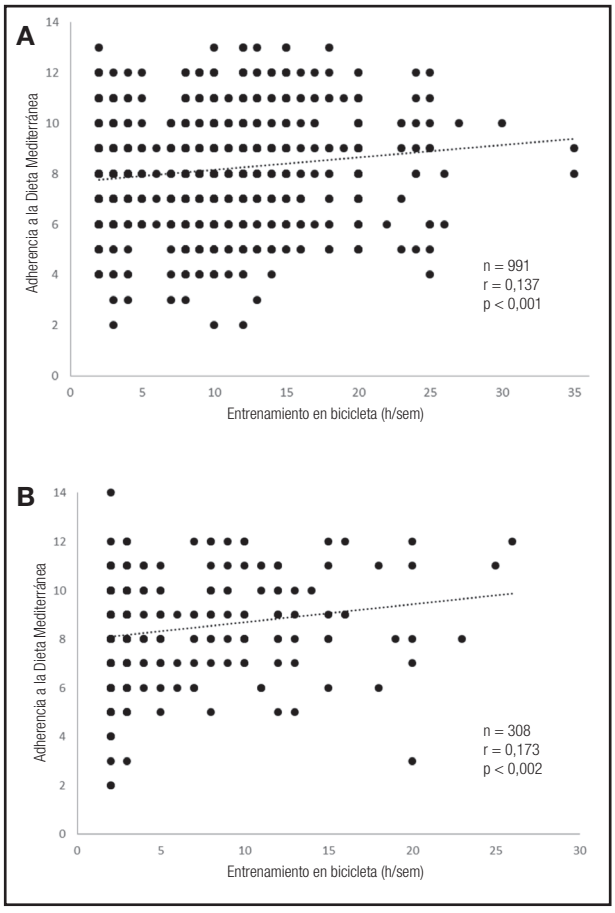

Figura 2.

Relación entre la adherencia a la dieta mediterránea y el volumen de entrenamiento de ciclistas aficionados y practicantes de ciclo *indoor*. A. Hombres; B. Mujeres.

INFLUENCIA DE LA PROXIMIDAD DEL EVENTO CICLODEPORTIVO EN LA ADM

Los ciclistas aficionados que respondieron a la segunda encuesta *online* desarrollada en noviembre respecto a los que no respondieron no se diferenciaron en el volumen de entrenamiento, pero eran más mayores (39,4 ± 8,5 *vs.* 37,4 ± 8,1 años, p = 0,001) y reportaron mayor ADM (8,6 ± 2,1 *vs.* 8,2 ± 2,1, p = 0,01). No hubo diferencias significativas de actividad física, edad y ADM entre los sujetos inactivos que respondieron o no a la segunda encuesta *online* desarrollada en noviembre.

La proximidad de la prueba ciclodeportiva celebrada en mayo-junio influyó significativamente en el volumen de entrenamiento (mayo: 12,1 ± 7,7 horas/semana; noviembre: 7,7 ± 4,2 horas/semana; p < 0,001). No hubo efecto estacional en los niveles de actividad física de los sujetos inactivos (p = 0,555). La proximidad de la prueba ciclodeportiva también influyó significativamente en la ADM de los ciclistas aficionados (mayo: 8,6 ± 2,1; noviembre: 7,0 ± 1,9; p < 0,001). Durante este periodo no se observaron diferencias de ADM en los sujetos inactivos (mayo: 7,5 ± 1,7; noviembre: 7,7 ± 1,9; p = 0,535) (Fig. 3).

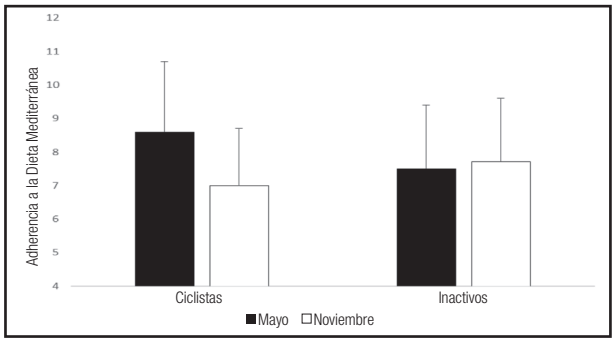

Figura 3.

Diferencias de adherencia a la dieta mediterránea en ciclistas aficionados y sujetos inactivos entre fechas próximas (mayo) y alejadas (noviembre) de la prueba ciclodeportiva.

DISCUSIÓN

Este es el primer estudio centrado en analizar la relación entre la ADM y el volumen de práctica deportiva en bicicleta, y la existencia de cambios en la ADM producidos por la proximidad de un reto ciclodeportivo de elevada exigencia. Los resultados del presente estudio con sujetos inactivos, practicantes de ciclo *indoor* y ciclistas aficionados, proporcionan datos confirmatorios y novedosos sobre los siguientes puntos: a) la mayoría de sujetos evidencia una baja o media ADM; b) la práctica deportiva en bicicleta se asocia con una mayor ADM; c) el volumen de entrenamiento en bicicleta tiene limitada influencia en la ADM; d) la proximidad de una prueba ciclodeportiva de elevada exigencia se asocia con una mayor ADM que no se mantiene con posterioridad al evento.

PUNTUACIÓN DE ADM

Los resultados obtenidos refuerzan ampliamente datos de estudios recientes que sugieren que la mayoría de la población española no tiene una alta ADM, principalmente asociado al escaso consumo de aceite de oliva, verdura, fruta, legumbre, pescado, nueces y vino (14,15). También se confirma que un muy elevado porcentaje de personas cumplen con los objetivos de usar el aceite de oliva como grasa principal para cocinar, así como el bajo consumo de carne roja, grasa animal y bebidas carbonatadas/azucaradas (14,15). De acuerdo con León-Muñoz y cols. (15), el bajo porcentaje de sujetos con alta ADM se debe en parte a los rigurosos criterios del cuestionario de ADM utilizado, cuyo objetivo era reproducir estrictamente la DM tradicional, así como al muy bajo cumplimiento actual de los requisitos establecidos para el consumo moderado de vino, cuyos beneficios para la globalidad de la salud por su contenido de alcohol sigue generando un intenso e interesante debate en la literatura científica (29,30). De hecho, algunos autores sugieren establecer índices de la DM evolucionada y adaptada a los cambios socioeconómicos que se han producido en España en las últimas décadas y que también demuestra efectos beneficiosos para la salud (20). Aun con estos

condicionantes, se evidenció la categoría más baja de ADM en un 26% de la muestra y solo un 40% evidenció alta ADM, lo que es indicativo de que un elevado porcentaje de la población no está adherida a una dieta saludable. Estos resultados refuerzan la necesidad de intervenciones de promoción de una dieta saludable para ambos sexos y todas las edades, pero especialmente dirigida a los jóvenes y a los hombres que, como en otros estudios, evidencian menor ADM (14,22).

ADM Y PRÁCTICA DEPORTIVA EN BICICLETA

En este estudio hemos realizado un análisis específico para determinar en qué medida la práctica deportiva en bicicleta puede ser una vía de especial interés para mejorar los niveles de ADM. Previos resultados han establecido que la actividad física puede ser un factor mediador de la ADM (15,20-22). En ninguno de estos estudios, los investigadores focalizaron la atención en diferenciar la actividad física de la práctica regular de deporte ni en establecer grupos de sujetos activos con diferentes niveles de actividad física. Nuestros resultados sugieren que para ambos sexos la práctica de deporte en bicicleta de forma regular se asocia con niveles de ADM superiores a los reportados por los sujetos inactivos. De hecho, si recalculamos como en otros estudios (15) la puntuación del cuestionario de ADM utilizado, excluyendo el objetivo para el consumo de vino, menos del 10% de los deportistas evidenció la categoría más baja de ADM. Aun con esta exclusión, un 37% de los deportistas no evidenció alta ADM, lo que concuerda con recientes resultados que sugieren que incluso los ciclistas de élite jóvenes llevan dietas desequilibradas (31). Adicionalmente, nuestros resultados confirman que la práctica deportiva en bicicleta se asocia también con otros hábitos saludables, como menor consumo de tabaco y de alcohol (32,33). Este hecho fue especialmente patente entre los ciclistas aficionados, aspecto coherente si consideramos su motivación común de participar en un reto ciclodeportivo de elevada exigencia. Esta interacción entre práctica de deporte en bicicleta, ADM, tabaco y alcohol puede explicar que en relación con lo observado en otros estudios (15,20), el porcentaje de fumadores sea inferior en sujetos con alta ADM. En cambio, no observamos diferencias de ADM entre los consumidores de alcohol, aspecto coherente si consideramos que el consumo de vino está integrado en la ADM.

ADM, VOLUMEN DE ENTRENAMIENTO Y PROXIMIDAD DEL RETO CICLODEPORTIVO

La influencia del volumen de entrenamiento sobre la ADM resulta más controvertida. Nuestros ciclistas aficionados mostraron valores de ADM superiores a los reportados por los practicantes de ciclo *indoor*, lo que podría asociarse a su mayor volumen de entrenamiento. Sin embargo, un análisis más detallado mostró que aun considerando la elevada variabilidad del volumen de entrenamiento (69% en hombres, 93% en mujeres), su relación con la ADM fue muy débil y no hubo asociación significativa entre los practicantes de ciclo *indoor*. Estos datos invitan a pensar que, de forma equiparable a lo observado en los deportistas de élite (34), los ciclistas aficionados mostraron una dieta más saludable como consecuencia de su preparación para una ciclodeportiva de elevada exigencia. Además, la débil asociación entre el volumen de entrenamiento y la ADM en ciclistas aficionados podría ser consecuencia de las diferencias entre sujetos en la motivación para preparar la prueba ciclodeportiva. Así, con el objetivo de afrontar la prueba ciclodeportiva con más probabilidades de éxito, los ciclistas aficionados más motivados han podido realizar una preparación más exhaustiva, incluyendo simultáneamente un mayor volumen de entrenamiento y una dieta más saludable. De hecho, nuestro análisis longitudinal demuestra una elevada relación entre la ADM y la participación en eventos ciclodeportivos de elevada exigencia. También este análisis evidenció que la mayor ADM de los ciclistas aficionados fue transitoria. Futuros estudios deben dilucidar si la disminución en la ADM en fechas alejadas a la prueba ciclodeportiva objeto de la preparación está asociada con un patrón dietético poco saludable.

APLICACIONES PRÁCTICAS

Con base en los resultados de este estudio, los profesionales de la salud y del deporte deben conocer que, en comparación con los sujetos inactivos, aquellos que practican deporte en bicicleta se caracterizan por llevar una dieta más saludable y por tener un menor consumo de tabaco y alcohol. Estos datos invitan a pensar que la práctica de deporte en bicicleta podría ser un adecuado instrumento para generar efectos sinérgicos conductuales deseables para la salud. Para este objetivo, los resultados de este estudio sugieren que no es necesario un excesivo volumen de entrenamiento. El establecimiento de retos ciclodeportivos parece asociarse también con una dieta más saludable. Sobre este aspecto, los resultados del presente estudio indican la importancia de distribuir estos retos durante todo el año, con el objeto de que el patrón dietético saludable no sea transitorio, pero esto debe confirmarse en futuros estudios. Las instituciones deben ser conocedoras de que un elevado porcentaje de la población, incluyendo deportistas, tienen deficiencias de ADM y que, en consecuencia, se requiere de políticas que promuevan la importancia de una dieta saludable.

LIMITACIONES

Hay algunas limitaciones en este estudio. Primero, debido a que la información fue enviada al representante de cada club, gimnasio o centro deportivo, no fue posible controlar si llegó a la totalidad de la muestra objeto de estudio. Aun así, la heterogeneidad de los ciclistas aficionados y practicantes de ciclo *indoor* en la edad, IMC y entrenamiento probablemente es representativa de la globalidad de estos sectores de la población, pero no podemos asegurar la representatividad y la ausencia de sesgo en los participantes respecto a toda la muestra potencial. Segundo, la muestra de ciclistas aficionados estuvo muy sesgada hacia la población masculina, aunque esto representa la diferencia actual en España en la proporción de

hombres y mujeres que participan en ciclodeportivas. Finalmente, nuestro estudio se basó en datos de autoinforme que son vulnerables al sesgo de respuesta y deseabilidad social.

CONCLUSIONES

En conclusión, independientemente de la edad, sexo y estatus socioeconómico, la práctica regular de deporte en bicicleta, tanto ciclo *indoor* como ciclismo de ruta o de montaña a nivel aficionado, se asocia a una mayor ADM que la observada en sujetos inactivos. Desde una perspectiva práctica, nuestros resultados sugieren que para obtener estos beneficios puede ser suficiente un volumen de entrenamiento moderado, esperándose mayores beneficios con el planteamiento de retos ciclodeportivos individualizados y distribuidos durante todo el año. También concluimos que la práctica deportiva en bicicleta es una estrategia insuficiente para que la mayor parte de la población evidencie alta ADM.

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BIBLIOGRAFÍA

1. Katz DL, Meller S. Can we say what diet is best for health? Annu Rev Public Health 2014;35:83-103.
2. Bach-Faig A, Berry EM, Lairon D, Reguant J, Trichopoulou A, Dernini S, et al. Mediterranean Diet Foundation Expert Group. Mediterranean diet pyramid today. Science and cultural updates. Public Health Nutr 2011;14:2274-84.
3. Dernini S, Berry EM, Serra-Majem L, La Vecchia C, Capone R, Medina FX, et al. Med Diet 4.0: the Mediterranean diet with four sustainable benefits. Public Health Nutr 2016;22:1-9.
4. Gotsis E, Anagnostis P, Mariolis A, Vlachou A, Katsiki N, Karagiannis A. Health benefits of the Mediterranean Diet: an update of research over the last 5 years. Angiology 2015;66:304-18.
5. Trichopoulou A, Martínez-González MA, Tong TY, Forouhi NG, Khandelwal S, Prabhakaran D, et al. Definitions and potential health benefits of the Mediterranean diet: views from experts around the world. BMC Med 2014;12:112.
6. Sallis R. Exercise is medicine: a call to action for physicians to assess and prescribe exercise. Phys Sportsmed 2015;43:22-6.
7. Lobelo F, Stoutenberg M, Hutber A. The exercise is medicine global health initiative: a 2014 update. Br J Sports Med 2014;48:1627-33.
8. Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. Physiology (Bethesda) 2013;28:330-58.
9. World Health Organization. Global Recommendations on physical activity for health. Geneva, Switzerland: WHO; 2010.
10. Oja P, Kelly P, Pedisic Z, Titze S, Bauman A, Foster C, et al. Associations of specific types of sports and exercise with all-cause and cardiovascular-disease mortality: a cohort study of 80 306 British adults. Br J Sports Med 2017;51:812-7.
11. Munguia-Izquierdo D, Mayolas-Pi C, Peñarrubia-Lozano C, Paris-Garcia F, Bueno-Antequera J, Oviedo-Caro MA, et al. Effects of Adolescent Sport Practice on Health Outcomes of Adult Amateur Endurance Cyclists: Adulthood Is Not Too Late to Start. J Phys Act Health 2017;14:876-82.
12. Bianco A, Bellafiore M, Battaglia G, Paoli A, Caramazza G, Farina F, et al. The effects of indoor cycling training in sedentary overweight women. J Sports Med Phys Fitness 2010;50:159-65.
13. da Silva R, Bach-Faig A, Raidó Quintana B, Buckland G, Vaz de Almeida MD, Serra-Majem L. Worldwide variation of adherence to the Mediterranean diet, in 1961-1965 and 2000-2003. Public Health Nutr 2009;12:1676-84.
14. Patiño-Alonso MC, Recio-Rodríguez JI, Belio JF, Colominas-Garrido R, Lema-Bartolomé J, Arranz AG, et al. Factors associated with adherence to the Mediterranean diet in the adult population. J Acad Nutr Diet 2014;114:583-9.
15. León-Muñoz LM, Guallar-Castillón P, Graciani A, López-García E, Mesas AE, Aguilera MT, et al. Adherence to the Mediterranean diet pattern has declined in Spanish adults. J Nutr 2012;142:1843-50.
16. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet 2012;380:247-57.
17. Gerovasili V, Agaku IT, Vardavas CI, Filippidis FT. Levels of physical activity among adults 18-64 years old in 28 European countries. Prev Med 2015;81:87-91.
18. Noble N, Paul C, Turon H, Oldmeadow C. Which modifiable health risk behaviours are related? A systematic review of the clustering of Smoking, Nutrition, Alcohol and Physical activity ('SNAP') health risk factors. Prev Med 2015;81:16-41.
19. de Vries HL, van 't Riet J, Spigt M, Metsemakers J, van den Akker M, Vermunt JK, et al. Clusters of lifestyle behaviors: results from the Dutch SMILE study. Prev Med 2008;46:203-8.
20. Guallar-Castillón P, Rodríguez-Artalejo F, Tormo MJ, Sánchez MJ, Rodríguez L, Quirós JR, et al. Major dietary patterns and risk of coronary heart disease in middle-aged persons from a Mediterranean country: the EPIC-Spain cohort study. Nutr Metab Cardiovasc Dis 2012;22:192-9.
21. Schröder H, Fitó M, Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, et al. A short screener is valid for assessing Mediterranean diet adherence among older Spanish men and women. J Nutr 2011;141:1140-5.
22. Sánchez-Villegas A, Delgado-Rodríguez M, Martínez-González MA, De Irala-Estévez J; Seguimiento Universidad de Navarra group. Gender, age, socio-demographic and lifestyle factors associated with major dietary patterns in the Spanish Project SUN (Seguimiento Universidad de Navarra). Eur J Clin Nutr 2003;57:285-92.
23. Mayolas-Pi C, Simón-Grima J, Peñarrubia-Lozano C, Munguía-Izquierdo D, Moliner-Urdiales D, Legaz-Arrese A. Exercise addiction risk and health in male and female amateur endurance cyclists. J Behav Addict 2017;6:74-83.
24. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381-95.
25. Mantilla-Toloza SC, Gómez-Conesa A. International Physical Activity Questionnaire. An adequate instrument in population physical activity monitoring. Revista Iberoamericana de Fisioterapia y Kinesiología 2007;10:48-52.
26. Becoña E, Vázquez FL. The Fagerström Test for Nicotine Dependence in a Spanish sample. Psychol Rep 1998;83:1455-8.
27. Korte KJ, Capron DW, Zvolensky M, Schmidt NB. The Fagerström test for nicotine dependence: do revisions in the item scoring enhance the psychometric properties? Addict Behav 2013;38:1757-63.
28. Guardia J, Jiménez-Arriero MA, Pascual P, Flórez G, Contel M. Alcoholismo. Guías clínicas basadas en la evidencia científica. Barcelona: Socidrogalcohol; 2007.
29. Artero A, Artero A, Tarín JJ, Cano A. The impact of moderate wine consumption on health. Maturitas 2015;80:3-13.
30. Tresserra-Rimbau A, Medina-Remón A, Lamuela-Raventós RM, Bulló M, Salas-Salvadó J, Corella D, et al. Moderate red wine consumption is associated with a lower prevalence of the metabolic syndrome in the PREDIMED population. Br J Nutr 2015;113:S121-30.
31. Sánchez-Benito JL, Sánchez-Soriano E, Ginart Suárez J. Evaluation of the intake of fats and minerals by a group of cyclists of Junior and Sub23 Teams. Clin Invest Arterioscl 2007;19: 269-77.
32. Ruiz-Juan F, Isorna-Folgar M, Ruiz-Risueño J, Vaquero-Cristóbal R. Tobacco consumption among adults in Monterrey: relation to exercise regularly and family. Nutr Hosp 2015;32:808-16.
33. Wang D, Wang Y, Wang Y, Li R, Zhou C. Impact of physical exercise on substance use disorders: a meta-analysis. PLoS One 2014;9:e110728.
34. Broad EM, Cox GR. What is the optimal composition of an athlete's diet? Eur J Sport Sci 2008;8:57-65.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Epidemiología y dietética

Is dietary glycemic load associated with liver fibrosis in hepatitis C?

¿Está asociada la carga glucémica en la dieta con la fibrosis hepática en la hepatitis C?

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Abstract

Introduction: Occidental diet and metabolic profile seems to increase hepatic fibrosis (HF) in patients with chronic hepatitis C virus (HCV) infection, but there is scarce information about the diet components and their role in this setting.

Objectives: This study aims to evaluate the dietary intake, metabolic profile, presence of metabolic syndrome (MetS) and cardiovascular risk in patients with chronic HCV infection according to the presence of fibrosis.

Methods: Cross-sectional study which 58 patients with HCV infection without active antiviral therapy and non-cirrhotic were assessed. All patients were subjected to clinical, laboratorial and dietary evaluation, and classified according to the METAVIR score. Patients were divided as the presence of hepatic fibrosis.

Results: In this sample, fifty-five percent of patients were females, the average age was 51.6 ± 9.7 years, and 79.3% were carriers of HCV genotype 1. Patients with HF presented higher energy, and fat intake as well as higher glycemic load of meals in comparison to those without HF. Patients with HF presented higher systolic and diastolic arterial pressure and higher levels of insulin.

Conclusions: In conclusion, patients with HF had higher total daily energy and total fat intakes, and worse metabolic profile, characterized by a higher insulin resistance and blood pressure.

Key words:

Diet. Glycemic load. Liver fibrosis. Chronic hepatitis C. Nutrition.

Resumen

Introducción: en pacientes infectados crónicamente por el virus de la hepatitis C (VHC), la dieta occidental y el perfil metabólico parecen aumentar la fibrosis hepática (FH), sin embargo existe poca información sobre los componentes de la dieta y su papel en este contexto.

Objetivos: evaluar la ingesta dietética, el perfil metabólico, la presencia de síndrome metabólico (SAT) y el riesgo cardiovascular en pacientes con VHC crónico según la presencia de fibrosis.

Métodos: estudio transversal en el que se evaluaron 58 pacientes con VHC sin terapia antiviral activa ni cirrótica. Todos los pacientes fueron sometidos a evaluación clínica, de laboratorio y dietética, y fueron clasificados según la puntuación METAVIR. Los pacientes se dividieron según la presencia de FH.

Resultados: en esta muestra el 55% de los pacientes eran mujeres, con edad promedio de 51,6 ± 9,7 años, siendo el 79,3% portadores del genotipo 1 del VHC. Los alimentos de los pacientes con FH presentaron una mayor proporción de energía y grasa, así como mayor carga glucémica en comparación con las personas sin FH. Los pacientes con circunferencia de la cintura presentaron mayor presión arterial sistólica y diastólica y mayores niveles de insulina.

Conclusión: en conclusión, los pacientes con FH presentaron un consumo mayor de energía y grasas diario total, y peor perfil metabólico, caracterizado por mayor resistencia a la insulina y presión arterial.

Palabras clave:

Dieta. Carga glicémica. Fibrosis hepática. Hepatitis C crónica. Nutrición.

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INTRODUCTION

The hepatitis C virus infection (HCV) is a serious global public health problem, with a high social and economic impact, since chronic HCV infection is closely related to liver fibrosis, cirrhosis and also to the risk of hepatocellular carcinoma. Furthermore, HCV has notable metabolic consequences, with glycemic and lipid disturbances and may be associated to cardiovascular risk (1,2).

The hepatic fibrosis (HF) is characterized by the accumulation of scar tissue in response to persistent chronic hepatic injury. A number of factors can influence HCV fibrosis progression such as: age over 40 years old, male gender, hepatic steatosis, insulin resistance (IR), immunosuppression, and necroinflammatory activity, among others (3). Moreover, even with the new potent direct antiviral drugs, a weight greater than 75kg and advanced fibrosis continue to be negative factors for a sustained virological response (3).

Metabolic syndrome (MetS), that includes glucose abnormalities, central obesity, dyslipidemia and hypertension, is a common disorder resulting from diabetes and obesity epidemic worldwide. There is a close relationship between HCV infection and MetS, and individual components of MetS are independent predictors of mortality in patients with chronic liver disease, including those infected with HCV (4).

The adoption of a healthier lifestyle, with regular physical activity, diets with normal fat content, and maximum of 10% of saturated fats, seems to improve the metabolic profile, and even prevent hepatic steatosis and non-alcoholic steatohepatitis (5). Beyond that, diet components such as carbohydrates, lipids, polyunsaturated fatty acids, and also alcohol consumption were described as independent factors of liver damage (6).

There is scarce information about the role of the diet profile on HF in chronic HCV infected patients. Therefore, this study aimed to evaluate dietary intake, metabolic profile, presence of MetS and cardiovascular risk in these patients in accordance with the presence of fibrosis.

MATERIALS AND METHODS

This cross-sectional study was conducted in adult patients (more than 18 years-old), chronically infected by HCV, genotypes 1, 2 or 3, all of them attending the Gastroenterology Division's outpatient clinic at Hospital de Clínicas de Porto Alegre (HCPA), Brazil, from October 2013 to July 2014. The study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human patients were approved by the HCPA Research Ethics Committee, number 13-0281. Written informed consent was obtained from all patients.

HCV infection was confirmed by anti-HCV ELISA 3 and by the detection of viral RNA through real-time polymerase chain reaction (HCV RNA PCR). A liver biopsy was performed in every patient up to one year before inclusion in the study. Only specimens with more than 10 portal spaces were considered. The samples were analyzed by the same experienced pathologist, without the knowledge of individual details of each case. The samples were classified accordingly to the METAVIR score: F0 = absence of fibrosis; F1 = portal fibrosis without septum; F2 = portal fibrosis with rare septum; F3 = numerous septum without cirrhosis; and F4 = cirrhosis (7). Patients with alcohol intake (over 10 g of ethanol/day) (8), cirrhosis, hepatocellular carcinoma or other malignant tumors, as well as those coinfected with HIV or hepatitis B virus, transplant recipients, pregnant women and those undergoing any active antiviral were not included. Patients were separated into two groups according to METAVIR score: Group absence of fibrosis (score = F0) and Group HF (scores F1 to F3).

DIETARY ASSESSMENT

The patient's usual diet was assessed by 3-day-diet-record (two non-consecutive weekdays and one-weekend day). Records were analyzed using the Nutribase 2007 software (Clinical Nutritional Manager v.7.14; Cybersoft Phoenix, AZ, USA) (9). Data intake from nutrients were expressed in crude amounts (g/day, mg/day mcg/day or IU/day) or in grams per kilogram of body weight. The data relating to food consumption were obtained throughout the study during different seasons.

The type and content of dietary fibers was estimated according to the data provided in the CRC Handbook of Dietary Fiber in Human Nutrition (10). In the present study, the fibers were classified into two major groups depending on their solubility in water.

The 24-h glycemic index (GI) was estimated by the weighted GI value of each consumed food at 24-h and expressed as percentage. The values of the GI and available carbohydrates of each food were obtained and glucose was used as the reference food (11). Dietary glycemic load was calculated as the product of dietary GI and total carbohydrate intake divided by 100.

ANTHROPOMETRIC MEASUREMENTS

The body weight and height of patients (without shoes or coats) were obtained using an anthropometric scale, with measurements recorded to the nearest 100 g for weight and to the nearest 0.1 cm for height. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) square. The waist circumference was measured at the midpoint between the last rib and the iliac crest) by the World Health Organization (WHO) (12); flexible, non-stretch fiberglass tape measure was used for measurements.

LABORATORY MEASUREMENTS

Blood samples were obtained after a 12-h fast, between seven and fifteen days after inclusion in the study: the following tests were then performed: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), ferritin, triglycerides and total cholesterol, cholesterol

HDL, C-reactive protein (CRP), insulin, serum glucose, cholesterol LDL – calculated by the Friedewald formula: Cholesterol LDL = cholesterol total – (cholesterol-HDL – TG ÷ 5). The estimated insulin resistance (IR) was calculated by the HOMA-IR by the following formula: HOMA = fasting insulin (μU/ml) X fasting glycaemia (mmol/l)/22.5.

CARDIOVASCULAR RISK ASSESSMENT

Cardiovascular risk was assessed by calculating the Framingham score (13), which predicts a 10-year risk of suffering a cardiovascular event on the basis of the following factors: age, total cholesterol, HDL cholesterol, systolic arterial blood pressure and presence/absence of diabetes mellitus and smoking.

METABOLIC SYNDROME

The criteria for the clinical diagnosis of the MetS according to the Consensus (14) definition are the following: presence of 3 or more of these factors: waist circumference ≥ 94 cm for men and ≥ 80 cm for women, arterial blood pressure ≥ 130/85 mmHg or taking medications for blood pressure, triglycerides ≥ 150 mg/dl or taking fibrates, HDL cholesterol < 40 mg/dl for men and < 50 mg/dl for women or taking pharmacological therapy, and fasting glucose ≥ 100 mg/dl or a diagnosis of diabetes.

LEPTIN

Serum leptin levels were determined by a solid phase ELISA based on the sandwich principle (BioSource), accordingly with the manufacturer instructions.

SAMPLE SIZE

Sample size calculation was based on the results from the study conducted by Petit et al. (15), that compared BMI and insulin among HCV infected patients with and without non-alcoholic fatty liver disease (NAFLD). It was calculated a sample size assuming a power of 80%, and an alpha of 5%.

STATISTICAL ANALYSIS

The results were expressed as an average ± SD for the quantitative variables, and as frequencies and percentages for the qualitative variables. The evaluations of the differences between the quantitative variables were analyzed with the Student´s t test or Mann-Whitney U test. For the qualitative variables, the chi square test (χ^2) or where appropriate, the Fisher exact test was used. Results were considered statistically significant with values of $p < 0.05$.

RESULTS

DEMOGRAPHIC DATA

Fifty-eight patients with chronic HCV infection were analyzed. Almost half of participants (46.6%) are classified as lower middle class, 39.7% have studied up to middle school and most of them (70.7%) live in urban area.

CLINICAL ASSESSMENT

Thirty-nine patients (67.2%) presented distinct levels of fibrosis. F1 (37.9%), F2 (27.6%) and F3 (1.7%). There was a predominance of females in the two groups, with the average age being similar between them. Significantly, higher values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were observed in the group of patients with fibrosis. Regarding the investigation of alcohol consumption, 8.6% of patients reported occasional consumption, equivalent to 2 drinks per week, while the remaining patients reported not use any type of alcoholic beverage. The complete description of clinical characteristics of patients is presented in table I.

LABORATORIAL MEASUREMENTS

The HF group showed significantly higher levels of glycaemia, insulin, HOMA-IR, ferritin and, hemoglobin. The other laboratory measurements (hematocrit, total cholesterol, HDL, LDL, triglycerides, AST, ALT and GGT) did not differ statistically between the groups (Table I). When the increase of HOMA_IR is observed, there is also an increase in Ferritin levels between the patients in the sample, 3.18 (0.48-12.40) and 317.10 (28.90-881.91), respectively ($p = 0.05$). Eighteen Patients with HF (46.2%) have MetS, however there was no statistical difference between the groups.

The leptin serum levels did not differ between chronic HCV infected patients with and without fibrosis, though women and men had different levels: 28.5 (15.8-33.1) *versus* 7.2 (5.1-9.3), as well as eutrophic and overweight/obesity patients: 7.2 (4.4-11.7) *versus* 22.8 (8.3-31.4), respectively, with $p < 0.001$ for all.

DIETARY INTAKE x HEPATIC FIBROSIS

The patients with HF presented a significantly higher total daily energy and fat (g/kg/day) intakes. The glycemic load of meals was also higher in this group of patients. The other components of diet (carbohydrate, protein, cholesterol, fiber, calcium, zinc, iron, folic acid, niacin, thiamine, vitamin A, vitamin C, vitamin B6, vitamin B12 and vitamin D) did not show significant differences between the groups (Table II).

Table I. Clinical and laboratory characteristics of chronic HCV infected patients in accordance with the presence of hepatic fibrosis

	Absence HF n = 19	Presence HF n = 39	p-value
Gender (female)	13 (68.4%)	19 (48.7%)	0.157[b]
Ethnicity (Caucasian)	15 (78.9%)	31 (79.5%)	0.795[b]
Age (years)	47.8 ± 12.3	53.4 ± 7.6	0.079[a]
Genotype:			0.078[a]
1	14 (77.8%)	32 (82.1%)	
2	0 (0.0%)	1 (2.6%)	
3	4 (22.2%)	6 (15.4%)	
Physical activity:			0.198[b]
Sedentary/irregularly active	11 (57.9%)	22 (56.5%)	
Economic classification (B2)[d]	7 (36.8%)	9 (23.1%)	0.673[b]
SBP (mmHg)[e]	129.5 ± 17.7	140.1 ± 18.9	0.046[a]
DBP (mmHg)[f]	78.0 ± 8.2	84.8 ± 10.7	0.010[a]
Framingham Score[g]:			0.114[b]
High risk (> 10%)	6 (31.6%)	23 (59.0%)	
High waist circunference:*			0.137[b]
Female	6 (18.8%)	11 (42.3%)	
Metabolic syndrome	4 (21.1%)	18 (46.2%)	0.087[b]
Body mass index (kg/m^2)	26.8 ± 2.1	27.5 ± 4.6	0.440[a]
Glucose (mg/dL)	86 (82-9)	94 (89-102)	0.001[c]
Insulin (µUI/mL)	10.7 (8.2-14.7)	15.3 (10.2-26.0)	0.009[c]
HOMA_IR	2.18 (1.6-3.3)	3.4 (2.4-6.4)	0.002[c]
Ferritin (µg/mL)	143.8 ± 33.0	378.8 ± 200.1	0.009[a]
Albumin (g/dL)	4.2 (4.1-4.4)	4.4 (4.2-4.5)	0.021[c]
Hematocrit (g/dL)	40.6 (38.8-41.5)	42.8 (39.3-45.8)	0.050[c]
Hemoglobin (g/dL)	13.9 (13.2-14.7)	14.8 (13.9-15.8)	0.031[c]
Triglycerides (mg/dL)	87 (63-101)	97 (75-122)	0.097[c]
Cholesterol Total (mg/dL)	166.0 ± 25.3	165.1 ± 26.9	0.901[a]
HDL-cholesterol (mg/dL)	48.5 ± 12.6	43.0 ± 10.2	0.083[a]
LDL-cholesterol (mg/dL)	100.0 ± 23.8	99.8 ± 26.0	0.977[a]
CRP (mg/L)[h]	4 (4-4)	4 (4-4)	0.541[c]
AST (U/L)[i]	39 (29-55)	45 (35-74)	0.125[c]
ALT (U/L)[j]	46 (32-74)	56 (39-104)	0.074[c]
Gama GT (U/L)[k]	59.9 ± 13.7	77.5 ± 12.4	0.158[a]

[a]t test.; [b]χ^2; [c]Mann-Whitney; [d]Brazil Economic Classification Criteria (ABEP, 2008); [e]Systolic blood pressure; [f]Disastolic blood pressure; [g]Cardiovascular disease risk estimate, percentage in 10 years, calculated according to Framingham study, 2008; [h]C-reactive protein; [i]Aspartate aminotransferase; [j]Alanine aminotransferase; [k]Gama glutamyl transpeptidase; [l]Hepatic fibrosis.

Table II. Daily intake of nutrients of chronic HCV patients in accordance with the presence of hepatic fibrosis

	Absence HF[c] n = 19	Presence HF n = 39	p-value
Energy (Kcal/kg/day)	28.8 ± 7.9	34.6 ± 11.2	0.048[a]
Carbohydrates (g/kg)	3.2 (2.6-3.8)	3.7 (2.6-5.0)	0.187[b]
Proteins (g/kg)	1.2 (0.9-1.7)	1.3 (0.9-1.9)	0.588[b]
Lipids (g/kg)	1.1 (0.8-1.3)	1.4 (1.0-1.9)	0.010[b]
Cholesterol (mg)	264.7 (149.9-367.2)	272.3 (173.3-358.6)	0.909[b]
Total Fiber (g/day)	12.6 (9.7-15.8)	15.5 (10.7-21.4)	0.221[b]
Soluble Fiber (g/day)	3.7 (3.3-5.8)	5.2 (3.4-6.5)	0.221[b]
Insoluble Fiber (g/day)	8.9 (6.5-11.4)	10.2 (7.3-14.7)	0.282[b]
Glycemic Load (g)	181.0 (140.5-223.4)	221.9 (168.9-307.8)	0.046[b]
Glycemic Index (%)	61.1 (56.9-62.5)	61.0 (57.2-64.3)	0.740[b]
Calcium (mg)	694.57 ± 288.14	714.63 ± 323.75	0.820[a]
Zinc (mg)	12.74 ± 5.39	14.38 ± 6.47	0.346[a]
Iron (mg)	13.90 ± 5.49	15.00 ± 4.96	0.446[a]
Folic Acid (mcg)	166.11 ± 94.06	156.23 ± 78.07	0.674[a]
Niacin (mg)	21.81 ± 7.93	24.54 ± 9.92	0.300[a]
Thiamine (mg)	1.64 ± 0.84	1.70 ± 0.61	0.746[a]
Vitamin C (mg)	10.91 (41.77-146.98)	94.94 (42.10-173.93)	0.270[b]
Vitamin A (IU)	4370.43 (2146.27-7427.93)	3853.70 (2088.92-8217.622)	0.987[b]
Vitamin B6 (mg)	1.65 ± 0.63	1.80 ± 0.7	0.440[a]
Vitamin B12 (mcg)	4.07 (2.84-5.88)	3.59 (3.05-5.58)	0.866[b]
Vitamin D (IU)	13.33 (0-84)	44.00 (0-74.66)	0.371[b]

[a]t Test, [b]Mann-Whitney; [c]Hepatic fibrosis.

ASSESSMENT OF HEPATIC STEATOSIS

Additionally, hepatic steatosis was evaluated in 54. In only eight cases (13.8% of samples) steatosis was found: minimal (0 to 5%) in five, and mild (5 to 33%) in three. No patient in the study had diagnostic criteria for non-alcoholic steatohepatitis.

DISCUSSION

In the present study, an increased total energy and fat intakes among chronic HCV infected patients was observed, this consumption being especially evident in patients with HF. Fioravante et al. (16) described similar findings in relation to diet; however, the authors did not evaluate differences as to the presence of HF. Another research (5) also assessed patients with chronic HCV infection, however, the patients included in their study presented a significant alcohol consumption, about 40 g of ethanol/day, while, in our study most of patients did not consume any alcohol.

As for the glycemic load of the meals, which translates as the product of the GI and the total carbohydrate consumed, it was observed that in the HF group, it was greater. Meals with a high glycemic load give a reduced level of fullness and are usually associated with an excessive ingestion of food, which may contribute to an increase in body fat and a higher IR (17). In contrast, meals with a low glycemic load can improve IR, since smaller quantities of insulin are required, as well as promoting smaller variations in glycemia (18,19). To the best of our knowledge, this is the first study who analyzed the glycemic load in HCV infected patients. Balanced food intake may modulate the severity of NAFLD development. The association between a high intake of saturated fat, low fiber intake and high intake of fructose leads to a more serious manifestation of NAFLD (20). The role of fructose intake is associated with the development IR, fatty liver, and

hepatic damage in experimental studies, and a clinical study confirmed that a diet rich in fructose-sweetened beverages was also associated with increased insulin resistance (21,22).

Although we show a greater intake of calories and fats by the patients with fibrosis, differences in relation to body weight in the groups of patients were not observed, considering that the measured weight was liquid and ascites free. Moreover, we can infer that components of diet have a more important role than weight in the process of liver disease.

Since patients with fibrosis evaluated in this study presented higher serum glucose and insulin levels Fibrosis itself seems to be important to the relationship with IR and type 2 diabetes mellitus (19). Hui et al. (23) described higher HOMA-IR levels, in patients carrying chronic hepatitis C, without fibrosis (degree of F0) compared to patients with fibrosis (F1-F3) and to healthy individuals, alerting to the fact that even in the early stages of disease, the IR may be present. Moreover, a meta-analysis of more than 2,700 patients indicated that the IR reduces the rates of sustained virological response in patients treated with pegylated interferon and ribavirin regardless of genotype (24).

In this study, increased levels of ferritin in patients with fibrosis were also found, similar to the findings of Petta et al. (25). For the analysis of pathology, we can tell our patients had iron storage related liver disease. Hyperferritinemia thus is probably related to chronic inflammation, secondary to hepatitis C, not to excess iron. Other authors demonstrated increased ferritin levels in hepatitis C (1).

Insulin resistance is a recognized extrahepatic manifestation of hepatitis C, as the virus promotes the secretion of soluble mediators that act on glucose homeostasis (extrahepatic insulin resistance) and also has direct interference with insulin signaling (intravenous insulin resistance-hepatic) (26). In the present study, there was a relationship between insulin resistance and the presence of fibrosis, which suggests that some additional factor may be associated. Whether this factor is caloric intake, systemic inflammation or even both, there is no way to define. The fact is that as there is increased HOMA-IR increases ferritin, an acute phase marker, and suggesting increased inflammation. This ratio, however, was not maintained when inflammation was assessed by C-reactive protein. Perhaps this question deserves to be better explored in studies designed for this purpose, with a control group not infected by virus C.

The overall prevalence of hypertension in the patients studied was almost 40%, being that the patients with hepatic fibrosis presented higher average values of systolic blood pressure and diastolic blood pressure. The systemic arterial blood pressure is a factor in the metabolic syndrome, which in turn correlates to a faster evolution of fibrosis in patients with hepatitis C (27). In general, the pressure levels are associated with body weight, not evident in our study.

MetS was detected in almost half patients with HF, but it was not found significant difference according to the presence of liver fibrosis, as well as, it was not found in a cohort of 10,383 patients with HCV infection (28). Studies have shown that there is a strong association between metabolic disorders and liver disease caused by chronic hepatitis C. This association tends to lead to worse prognosis. Patients with both comorbidities had lower treatment response against HCV and faster progression to cirrhosis and hepatocarcinoma compared to those chronic HCV infected patients without MetS (29).

Behavioral factors are involved in the pathogenesis of NAFLD, therefore, an increased dietary intake, especially an elevated intake of total energy and fat, can be considered as risk factors for disease progression (30); besides the fact that HCV infection *per se* can be responsible for glucose metabolism and lipid profile disorders (31). It has been demonstrated that an increased in the fat intake is also associated to a greater incidence of cirrhosis and liver cancer, by induction of hepatic steatosis and fibrosis (32), once the excess calories in the diet are stored principally as triglycerides, which accumulate in the liver (33). On the other hand, dietary interventions in the management of patients with NAFLD demonstrated that a diet low in carbohydrates (20 g/day) (34), energy restriction and adoption of a Mediterranean style diet (6) were effective in promoting the reduction of hepatic triglycerides, contributing significantly to the reduction of hepatic steatosis and improvement of insulin sensitivity.

Despite an increased fat intake shown in this study, increased rates of steatosis were not found. The low rate of steatosis (13.8%) can be explained in part by the fact that most included patients were infected by genotype 1, and not by genotype 3, that is recognized as being more steatogenic (35). Although finding low steatosis prevalence on the sample, patients with HF were related to dietary and metabolic factors, so it is suggested that steatosis itself should not be the only factor associated with increased development of fibrosis. Inflammation could be an independent factor.

In our study, leptin levels were analyzed, however it was not find any association with the presence of HF. Similar findings were shown by Muzzi et al. (36) that evaluated the leptin levels in 221 patients with hepatitis C, however, there were no differences as to the plasma leptin levels, irrespectively of the presence/absence of steatosis and/or fibrosis. The role of leptin is still controversial, with studies suggesting that this hormone promotes hepatic steatosis and steatohepatitis, and others showing that leptin levels correlate with steatosis, but not with inflammation and fibrosis (37).

Regarding waist circumference, most males showed higher values than recommended. Abdominal fat, irrespective of total fat volume, is an independent predictive factor of fat buildup in hepatocytes, with a crucial role in the pathogenesis of NAFLD. Lipid stocks can reach toxic levels, increasing oxidative stress, with formation of free radicals, mitochondrial damage, inflammation and even fibrosis (38) Furthermore, obesity and, more specifically, intra-abdominal fat, is positively associated with IR and MetS, both related with faster progression to fibrosis in patients with HCV (39). This study found a high prevalence of MetS in the sample. This can be justified because of the hepatitis C virus is associated with IR, an important feature of MetS and present in many of these patients, both (Mets and IR) play a role in the progression of HCV (40).

Although it was found high prevalence of elevated cardiovascular risk in this study, there was no significant difference between patients with and without fibrosis. Indeed, 70% of the patients assessed in this study exhibited moderate or high risk of suffering a cardiovascular event within 10 years, similar to results reported for diabetic patients and patients with metabolic syndrome (41).

STRENGTHS AND LIMITATIONS

Possible limitations of this study are related to unintentional predominance of patients with genotype 1, this fact limits the generalization of our results to patients with other genotypes. Furthermore, regarding data from dietary intake, food records were obtained throughout the study and not in a single season, but as the patients were evenly distributed in the months of the study, we believe that this fact has not affected the results.

Another restriction that could preclude generalization of our data is associated with the number of participants, however it was reached the planned sample size calculation. Patients were carefully selected to avoid confounding factors (especially alcohol intake, cirrhosis and active antiviral treatment); especially this last item was a difficult obstacle along the data collection, since most of the patients attending the Gastroenterology Division's outpatient clinic were using antiviral drugs and could not be included. On the other hand, these factors strengthened data obtained by relating the diet with liver fibrosis. The strong point of this work is the dietary evaluation and it relationship with HF; until now there was not another study that had evaluated the glycemic load meals of these patients. Our data could prove of great value for taking the decision to adopt more specific interventions for HCV patients, especially with emphasis on energy and lipid restrictions, and also on carbohydrates type, considering the glycemic index and glycemic load.

CONCLUSIONS

In conclusion, patients with HF presented elevated total daily energy and total fat intakes, a higher glycemic load of meals, as well as a worse metabolic profile, with higher rates of insulin resistance and increased pressure levels, when compared to patients without fibrosis. These metabolic alterations associated to chronic infection by HCV tend to worsen the prognosis of liver disease, reinforcing the need for early diagnosis and treatment of the disease, including dietary management of patients to minimize morbidity and mortality.

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REFERENCES

1. Oliveira CP, Kappel CR, Siqueira ER, Lima VM, Stefano JT, Michalczuk MT, et al. Effects of hepatitis C virus on cardiovascular risk in infected patients: a comparative study. Int J Cardiol 2013;164:221-6.
2. Michalczuk MT, Kappel CR, Birkhan O, Bragança AN, Álvares-da-Silva MR: HOMA-AD in Assessing Insulin Resistance in Lean Noncirrhotic HCV Outpatients. Int J Hepatol 2012;1012:576584.
3. Brazilian Ministry of Health, Secretary for the Vigilance on Health, Department of STD, AIDS, and Viral Hepatitis: Clinical Protocol and Therapeutic Guidelines for Viral Hepatitis C and coinfections. 1st ed. Brasília: Health of Ministry; 2011.
4. Stepanova M, Rafiq N, Younossi ZM. Components of metabolic syndrome are independent predictors of mortality in patients with chronic liver disease: a population-based study. Gut 2010;59:1410-5.
5. Loguercio C, Federico A, Masarone M, Torella R, Blanco CDV, Persico M. The impact of diet on liver fibrosis and on response to interferon therapy in patients whit HCV-related chronic hepatitis. Am J Gastroenterol 2008;103:3159-66.
6. Ryan MC, Itsiopoulos C, Thodis T, Ward G, Trost N, Hofferberth S, et al. The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease. J Hepatol 2013;59:138-43.
7. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatol 1996;24:289-93.
8. Liagnpunsakul S, Chalasani N. What do we recommend our patients with NAFLD about alcohol consumption? Am J Gastroenterol 2012;107(7):976-8.
9. USDA National Nutrient Database for standard reference, Release 20. Composition of Foods Raw, Processed, Prepared. Washington, 2008. Available at: www.ars.usda.gov/sp2UserFiles/Place/80400525/Data/SR27/sr27_doc.pdf.
10. Schakel S, Sievert YA, Buzzard IM. Dietary fiber values for common foods. In: Spiller GA, editor. CRC Handbook of Dietary Fiber in Human Nutrition. 3rd ed. Boca Raton: CRC Press; 2001.
11. Atkinson F, Foster-Powell K, Brand-Miller J. International tables of glycemic index and glycemic load values: 2008. Diabetes Care 2008;31:2281-3.
12. WHO-World Health Organization. Physical status: the use and interpretation of anthropometry. Geneva: Word Health Organization; 1995.
13. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743-53.
14. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the Metabolic Syndrome: A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-5.
15. Petit JM, Minello A, Jooste V, Bour JB, Galland F, Duvillard L, et al. Decreased Plasma Adiponectin Concentrations Are Closely Related to Steatosis in Hepatitis C Virus-Infected Patients. J Clin Endocrinol Metab 2005;90:2240-3.
16. Fioravante M, Alegre SM, Marin DM, Lorena SL, Pereira TS, Soares EC. Weight loss and resting energy expenditure in patients with chronic hepatitis C before and during standard treatment. Nutrition 2012;28:630-4.
17. Moura CMA, Costa SA, Navarro F. Índice glicêmico e carga glicêmica: aplicabilidade na prática clínica do profissional nutricionista. Rev Bras Obes Nut Emagr 2007;1:1-11.
18. Siqueira FR, Rodrigues FLP, Frutuoso MFP. Índice Glicêmico como ferramenta de auxílio de prescrição de dietas. Rev Bras Nut Clin 2007;22:54-8.
19. Narita R, Abe S, Kihara Y, Akiyama T, Tabaru A, Otsuki M. Insulin resistance and insulin secretion in chronic hepatites C virus infection. J Hepatol 2004;41:132-8.
20. Torres DM, Harrison SA. Diagnosis and therapy of nonalcoholic steatohepatitis. Gastroenterology 2008;134:1682-98.
21. Aeberli I, Hochuli M, Gerber PA, Sze L, Murer SB, Tappy L, et al. Moderate amounts of fructose consumption impair insulin sensitivity in healthy young men: a randomized controlled trial. Diabetes Care 2013;36:150-6.
22. Abdelmalek MF, Suzuki A, Guy C, Unalp-Arida A, Colvin R, Johnson RJ, et al. Nonalcoholic Steatohepatitis Clinical Research Network. Increased fructose consumption is associated with fibrosis severity in patients with nonalcoholic fatty liver disease. Hepatology 2010;51:1961-71.
23. Hui JM, Sud A, Farrel GC, Bandara P, Byth K, Kench JG, et al. Insulin resistance is associated with chronic hepatitis C and virus infection fibrosis progression. Gastroenterology 2003;125:1695-704.

24. Deltenre P, Louvet A, Lemoine M, Mourad A, Fartoux L, Moreno C, et al. Impact of insulin resistance on sustained response in HCV patients treated with pegylated interferon and ribavirin: A meta-analysis. J Hepatol 2011;55:1187-94.
25. Petta S, Cammà C, Scazzone C, Tripodo C, Di Marco V, Bono A, et al. Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. Hepatology 2010;51:1158-67.
26. Domont F, Cacoub P. Chronic hepatitis C virus infection, a new cardiovascular risk factor? Liver Int 2016;36:621-7.
27. Wong GLH. Prediction of fibrosis progression in chronic viral hepatites. Clin Mol Hepatol 2014;20:228-36.
28. Shaheen M, Echeverry D, Oblad MG, Montoya MI, Teklehaimanot S, Akhtar AJ. Hepatitis C, metabolic syndrome, and inflammatory markers: results from the Third National Health and Nutrition Examination Survey [NHANES III]. Diabetes Res Clin Pract 2007;75:320-6.
29. Douglas MW, George J. Molecular mechanisms of insulin resistance in chronic hepatitis C. World J Gastroenterol 2009;15:4356-64.
30. Stefan N, Kantartzis K, Ha HU. Causes and Metabolic Consequences of Fatty Liver. Endoc Rev 2008;29:939-60.
31. Yasutake K, Kohjima M, Nakashima M, Kotoh K, Nakamuta M, Enjoji M. Nutrition Therapy for Liver Diseases Based on the Status of Nutritional Intake. Gastroenterol Res Prac 2012;2012:859697.
32. Yu L, Morishima C, Ioannou GN. Dietary Cholesterol Intake Is Associated With Progression of Liver Disease in Patients With Chronic Hepatitis C: Analysis of the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis Trial. Clin Gastroenterol Hepatol 2013;11:1661-6.
33. Gonzalez C, Ledinghen V, Vergniol J, Foucher J, Le Bail B, Carlier S, et al. Hepatic Steatosis, Carbohydrate Intake, and Food Quotient in Patients with NAFLD. Int J Endocrinol 2013;2013:428542.
34. Browning JD, Baker JA, Rogers T, Davis J, Satapati S, Burgess SC. Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction. Am J Clin Nutr 2011;93:1048-52.
35. Patel JH, Cobbold JFL, Thomas HC, Taylor-Robinson SD. Hepatitis C and hepatic steatosis. QJM-Mon J Assoc Phys 2010;103:293-303.
36. Muzzi A, Leandro G, Rubbia-Brandt L, James R, Keiser O, Mallinverni R, et al. Insulin resistance is associated with liver fibrosis in non-diabetic chronic hepatitis C. J Hepatol 2005;42:41-6.
37. Chitturi S, Farrell GC. Etiopathogenesis of nonalcoholic steatohepatitis. Semin Liver Dis 2001;21:27-41.
38. Christian ML, Zoltan K, Kenichi M, Sthephanie B, Andreas C, Günter D, et al. Serum Ferritin Levels Are Associated With a Distinct Phenotype of Chronic Hepatitis C Poorly Responding to Pegylated Interferon-Alpha and Ribavirin Therapy. Hepatology 2012;55:1038-47.
39. Goossens N, Negr F. The Impact of Obesity and Metabolic Syndrome on Chronic Hepatitis Clin Liver Dis 2014;18:147-56.
40. Wong GLH. Prediction of fibrosis progression in chronic viral hepatites. Clin Mol Hepatol 2014;20:228-36.
41. Rhee SY, Park SY, Hwang JK, Son J Il, Chin SO, Kim YS, et al. Metabolic syndrome as an indicator of high cardiovascular risk in patients with diabetes: Analyses based on Korea National Health and Nutrition Examination Survey (KNHANES) 2008. Rhee et al. Diabetol Metab Syndr 2014;6:98.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Epidemiología y dietética

Síntomas depresivos y niveles séricos de ácidos grasos poliinsaturados omega-3 y omega-6 en universitarios del norte de México

Depressive symptoms and serum levels of polyunsaturated fatty acids omega-3 and omega-6 among college students from Northern Mexico

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Resumen

Introducción: estudios previos sugieren que un bajo consumo de ácidos grasos poliinsaturados (AGPI) omega-3 y razón omega-6/omega-3 alta, así como niveles séricos bajos, se asocian con trastornos depresivos, sin embargo, los resultados no son concluyentes.

Objetivos: evaluar los niveles séricos de AGPI omega-3 (ácido eicosapentaenoico [EPA], docosahexaenoico [DHA], alfalinolenico [ALA]) y la razón omega-6 (ácido araquidónico [AA])/EPA, en relación a los síntomas depresivos en universitarios del norte de México.

Material y métodos: estudio transversal que incluyó 60 participantes (18 a 24 años de edad) de ambos sexos, con determinaciones séricas de EPA, DHA, ALA y AA, quienes respondieron la escala de depresión del Centro de Estudios Epidemiológicos (CES-D) validada para estudiantes mexicanos. La relación de los AGPI omega-3 y omega-6 con los síntomas depresivos se evaluó con modelos de regresión lineal.

Resultados: los niveles séricos de EPA, DHA y razón EPA/DHA no se correlacionaron con síntomas depresivos, un incremento en ALA sérico se correlacionó con menos síntomas depresivos antes y después de ajustar por confusores; sin embargo, los resultados no fueron estadísticamente significativos. En mujeres, la escala CES-D incrementó 5,5 puntos (p = 0,57) por 1% de incremento en EPA y disminuyó 6,7 puntos (p = 0,39) por 1% de incremento en ALA.

Conclusiones: nuestros resultados no confirman la asociación entre los niveles séricos de AGPI omega-3 y razón omega-6/omega-3 con síntomas depresivos. La correlación negativa del nivel sérico de ALA con síntomas depresivos necesita ser confirmada en estudios de seguimiento.

Palabras clave:

Ácidos grasos omega-3 y omega-6. Marcadores biológicos. Sintomatología depresiva. Universitarios.

Abstract

Introduction: Previous studies suggest that low consumption as well as low serum levels of polyunsaturated fatty acids (PUFA) omega-3 and a high omega-6/omega-3 ratio may be implicated in the etiology of depressive disorders, however, epidemiologic evidence is inconclusive.

Objective: To assess the relationship of serum levels of omega-3 fatty acids (docosahexaenoic [DHA], eicosapentaenoic [EPA], alpha-linolenic fatty acid [ALA]) and the omega-6 (arachidonic acid [AA])/EPA ratio with depressive symptoms among Mexican college students.

Material and methods: A cross-sectional study that included 60 male and female participants (ages 18 to 24 years) with serum levels of EPA, DHA, ALA and AA. Depressive symptoms were ascertained with the Center for Epidemiologic Studies Depression (CES-D) scale validated for Mexican students. Linear regression was used to assess the relationship between depressive symptoms and serum PUFA omega-3 and omega-6.

Results: Serum levels of EPA, DHA and EPA/DHA ratio were not related to depressive symptoms, high serum ALA was related with lower depressive symptoms before and after covariate adjustment; however, these results were not statistically significant. Among women, 1% increase in EPA resulted in 5.5. (p = 0.57) increase in the depressive scale scores while 1% increase in ALA resulted in 6.7 decrease (p = 0.39) in the scores.

Conclusions: Our results did not confirm the relationship of serum levels of PUFA omega-3 and omega-6/omega-3 ratio with depressive symptoms; the negative correlation of serum ALA with depressive symptoms remains to be confirmed in prospective studies.

Key words:

Omega-3 and omega-6 fatty acids. Biological markers. Depressive symptoms. College students.

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INTRODUCCIÓN

Los trastornos mentales son un problema de salud pública a escala mundial. En 2010, los trastornos depresivos explicaron el 40,5% de los años de vida ajustados por discapacidad causados por los trastornos mentales y el uso sustancias; se estima que para el 2030 la depresión será uno de los principales padecimientos incapacitantes en la población general (1,2). La presencia de depresión a edades tempranas es un factor de riesgo para la deserción escolar y el embarazo adolescente. Se asocia con el desarrollo de conductas de riesgo como el abuso de tabaco y alcohol en los jóvenes, puede limitar el funcionamiento de la persona afectada en el ámbito laboral y familiar, además de incrementar el riesgo de desarrollar trastornos de ansiedad y de conductas suicidas en la vida adulta (2-4).

La prevalencia nacional de síntomas depresivos estimada para personas de 12 a 65 años de edad en México fue de 5,1% en 2008; dicha prevalencia fue mayor en mujeres (7,5%) que en hombres (2,5%) (5). En estudiantes mexicanos de nivel medio superior y universitarios, la prevalencia de sintomatología depresiva se ha estimado hasta en 14,7% (17,9% en mujeres y 11,1% en hombres) (6). Los factores asociados a un mayor riesgo de depresión incluyen el sexo, la edad, antecedentes familiares de depresión, pobreza, bajo nivel educativo, la exposición a violencia en el núcleo familiar o el ámbito escolar y la disfunción familiar (2,7). Estudios previos sugieren que un bajo consumo así como niveles séricos bajos de ácidos grasos poliinsaturados (AGPI) omega-3 (*i.e.,* ácido eicosapentaenoico [EPA], docosahexaenoico [DHA], alfalinolenico [ALA]) y una razón omega-6 (ácido araquidónico [AA])/EPA alta pueden estar implicados en el desarrollo de trastornos depresivos y alteraciones de la conducta; sin embargo, los resultados no son concluyentes (8-11). El mecanismo detrás de dicha asociación no está claramente establecido. Es posible que alteraciones en los niveles de los omega-3 (*i.e.*, EPA y DHA) incrementen el riesgo de desarrollar problemas mentales debido a su función como reguladores de la neurotransmisión, neurogénesis e inflamación. Existe evidencia que sugiere que la depresión involucra una alteración de neurotransmisores (8,12).

La Organización Mundial de la Salud y la Organización de las Naciones Unidas para la Alimentación y Agricultura (OMS/FAO) recomiendan una ingesta diaria de 250 mg de EPA y DHA para prevenir deficiencias en hombres y mujeres no embarazadas (13). Más de la mitad de la población mexicana tiene un consumo bajo de ácidos grasos omega-3 (mediana EPA + DHA, 30 mg/d) (14). Por tanto, identificar factores de riesgo asociados a la depresión que pueden modificarse es relevante para poblaciones con un consumo global de omega-3 por debajo de las recomendaciones. El objetivo del presente estudio fue evaluar los niveles séricos de AGPI omega-3 (*i.e.,* EPA, DHA, ALA) y omega 6 (AA), en relación a los síntomas depresivos en universitarios del norte de México.

MATERIAL Y MÉTODOS

El presente análisis es parte de un estudio transversal realizado en 2014, los detalles se describen en otra publicación (15). En dicho estudio se encuestaron a 798 estudiantes de 18 a 24 años de edad, que ingresaron en el ciclo escolar 2013-2014 en una universidad pública del estado de Sonora, ubicado al norte de México. Para participar en el estudio, los alumnos debían estar libres de enfermedades que requieren tratamiento continuo como diabetes, enfermedad tiroidea, cardiaca y mental; no estar bajo tratamiento con medicamentos psicotrópicos; y no estar embarazadas, en el caso de las mujeres. Como parte del estudio original, se recolectó información sobre el estilo de vida, la dieta y características sociodemográficas a través de un cuestionario autoaplicado (15). Adicionalmente, se recolectaron muestras de sangre capilar en una submuestra de 60 estudiantes con el propósito de determinar los niveles de AGPI omega-3 y omega-6 (muestra limitada al presupuesto disponible). Para lo cual, fueron invitados todos los participantes (hasta obtener la muestra deseada) que negaron tener enfermedades crónicas, consumir medicamentos, suplementos y sustancias ilegales al momento del estudio. El presente análisis se basa en esta submuestra (n = 60) con mediciones séricas de omega-3 y omega-6. Todos los participantes dieron su consentimiento por escrito, antes de su participación. El protocolo fue aprobado por los Comités de Investigación y Bioética de las Universidades de Sonora y de Guanajuato.

DETERMINACIÓN DE ÁCIDOS GRASOS

Los AGPI omega-3 (DHA, EPA, ALA) y omega-6 (AA) se cuantificaron en el total de fosfolípidos séricos. Muestras de sangre capilar (~375 µL) se recolectaron después de al menos seis horas de ayuno en un tubo Microtainer® con anticoagulante EDTA (ácido etilendiaminotetracético) mediante punción del dedo índice con lanceta de flujo abundante. Dichas muestras se mantuvieron refrigeradas a una temperatura de 4 ºC hasta que se realizó su procesamiento y análisis en el Laboratorio de Medicina Predictiva NDI (Nutrasource Diagnostics Inc.) México, ubicado en la ciudad de Guadalajara.

Los lípidos fueron extraídos usando metanol y cloroformo y la muestra se centrifugó durante 10 minutos para la separación del suero. Una vez purificadosn se transmetilaron extrayéndose con hexano. La determinación de los AGPI omega-3 y omega-6 se realizó por cromatografía de gases (cromatógrafo Agilent 7890A) en una columna capilar DB 23, usando como gas portador H_2. La clasificación de los AGPI fue mediante los estándares 461 y 606 (Nu-Chek-Prep, Inc. EE.UU.), metodología validada por la Universidad de Guelph en Ontario, Canadá. Los valores de los AGPI se reportaron en porcentajes de acuerdo a la composición total de ácidos grasos en fosfolípidos séricos.

SÍNTOMAS DEPRESIVOS

La sintomatología depresiva se evaluó mediante la escala de tamizaje de depresión autoadministrada del Centro de Estudios Epidemiológicos (CES-D) (16), la cual ha sido validada en población estudiantil mexicana (6,17). La escala CES-D consta de 20

reactivos e incluye preguntas relacionadas con afecto depresivo, afecto positivo, disminución psicomotora, manifestaciones somáticas y dificultades interpersonales. Cada reactivo tiene cuatro opciones de respuesta tipo Likert, que va de 0 a 3 (0 = rara vez/nunca a 3 = la mayoría de las veces); la puntuación de la escala va de 0 a 60, valores altos reflejan mayor cantidad de síntomas depresivos. Los valores de la escala de CES-D se modelaron como una variable dependiente en modelos de regresión lineal.

COVARIABLES

La información sobre las características sociodemográficas (*i.e.,* edad, género e ingreso familiar mensual) y el estilo de vida (*i.e.,* ejercicio físico, consumo de tabaco y alcohol) fue reportada en un cuestionario autoadministrado. El ingreso familiar mensual se reportó en salarios mínimos (pesos mexicanos) según la zona geográfica de Sonora, México. Los participantes reportaron si realizaban ejercicio físico al menos 3 veces a la semana por al menos 30 minutos (no, sí); su consumo actual de cigarros (no, sí); y la frecuencia de consumo de 6 o más bebidas por ocasión (no, < 6 bebidas, ≥ 6 bebidas).

ANÁLISIS ESTADÍSTICO

Como parte del análisis descriptivo, se presentan los porcentajes de las variables categóricas y las medianas (rango intercuartil) para las variables discretas y continuas. Para evaluar la relación entre los AGPI (*i.e.,* EPA, DHA, ALA, razón y EPA/DHA y AA/EPA) y los síntomas depresivos (puntuación escala CES-D), se construyeron modelos de regresión lineal para cada uno de los AGPI de manera independiente. Dichos modelos fueron ajustados por la edad (años), género (hombre, mujer), ingreso familiar mensual (ordinal) y ejercicio físico (no, sí). Debido a que la presencia de síntomas depresivos es más frecuente en mujeres y que nuestra muestra incluyó más mujeres que hombres, se presentan los resultados de la regresión lineal restringida a las mujeres únicamente. Todos los análisis se realizaron en el paquete estadístico STATA (versión 10.1; Stata Corp, College Station, TX, EE. UU.).

RESULTADOS

En la tabla I se presentan las características generales de los universitarios de acuerdo al género. La mayoría fueron mujeres (71,7%).

Tabla I. Características de los universitarios del norte de México de acuerdo al género, 2013-2014

	Total (n = 60)	Hombres (n = 17)	Mujeres (n = 43)
	% o mediana (RI)	% o mediana (RI)	% o mediana (RI)
Edad (años)	19,0 (2,0)	19,0 (3,0)	19,0 (2,0)
Ingreso familiar (pesos mx/mes):			
< 5,925	26,7	29,4	25,6
5,925 - 11,850	33,3	17,7	39,5
11,851 - 19,750	25,0	29,4	23,3
> 19,750	15,0	23,5	11,6
Ejercicio físico (30 min 3 veces/semana)	36,7	88,2	53,5
Fumador actual	15,0	23,5	11,6
Consume 6+ bebidas alcohólicas por ocasión			
No consume alcohol	25,0	23,5	25,6
< 6	35,0	23,5	39,5
≥ 6	40,0	53,0	34,9
Ácidos grasos %:*			
EPA	0,37 (0,18)	0,36 (0,15)	0,37 (0,02)
DHA	1,98 (0,70)	1,96 (0,89)	2,02 (0,64)
ALA	0,54 (0,25)	0,61 (0,36)	0,53 (0,20)
AA	9,07 (1,52)	8,77 (1,25)	9,34 (1,39)
EPA/DHA	0,18 (0,09)	0,18 (0,09)	0,18 (0,09)
AA/EPA	25,6 (11,75)	25,17 (10,70)	25,62 (13,18)
Media CES-D**	16,5 (9,0)	12,2 (4,6)	18,2 (9,7)

AA: ácido araquidónico; ALA: ácido alfalinolénico; DHA: ácido docosahexaenoico; EPA: ácido eicosapentaenoico; RI: rango intercuartil.

** Valor-p > 0,05 para la diferencia de medianas comparando hombres y mujeres.*

*** Valor-p = 0,02 para la diferencia de medias comparando hombres y mujeres.*

Tabla II. Coeficientes crudos y ajustados* del puntaje de la escala de síntomas depresivos CES-D y el porcentaje de ácidos grasos en suero de una muestra de universitarios del norte de México, 2013-2014

	Total (n = 60)				Mujeres (n = 43)	
Ácidos grasos (%)	**β crudo**	**(IC 95%)**	**β ajustado***	**(IC 95%)**	**β ajustado***	**(IC 95%)**
EPA	4,2	(-11,1, 19,5)	1,4	(-13,7, 16,5)	5,5	(-13,9, 24,8)
DHA	0,6	(-3,7, 4,8)	1,4	-2,1, 5,4)	2,8	(-3,2, 8,8)
ALA	-4,4	(-15,1, 6,3)	-1,9	(-12,6, 8,7)	-6,7	(-22,4, 9,0)
AA	-0,1	(-2,0, 1,8)	0,4	(-1,4, 2,3)	1,0	(-1,6, 3,5)
Razón EPA/DHA	11,2	(-22,3, 44,8)	1,2	(-33,4, 35,7)	8,7	(-39,8, 57,2)
Razón AA/EPA	-0,2	(-0,4, 0,1)	-0,1	(-0,4, 0,2)	-0,2	(-0,6, 0,1)

AA: ácido araquidónico; ALA: ácido alfalinolénico; DHA: ácido docosahexaenoico; EPA: ácido eicosapentaenoico.

** Ajustados por edad, género, ingreso familiar mensual y ejercicio físico.*

La mediana de edad fue de 19 años; poco más de una tercera parte realizaban ejercicio físico al menos 3 veces a la semana durante al menos 30 minutos; la mayoría de los participantes reportó que no fumaba (85%); y un 40% reportó que consumían 6 o más bebidas alcohólicas por ocasión. Las mujeres reportó menor actividad física (53,5%), menor consumo de cigarros (11,6%) y alcohol (34,9%) que los hombres.

Los porcentajes de ácidos grasos EPA, DHA y ALA reflejan un bajo consumo de omega-3 en esta muestra de universitarios. Los porcentajes de EPA, DHA y AA fueron ligeramente mayores en mujeres que en hombres, aunque estas diferencias no fueron estadísticamente significativas. La razón AA/EPA indica un mayor consumo de ácidos grasos omega-6 que omega-3. La media general de la escala CES-D fue 16,5 (DE = 9,0) puntos; los puntajes fueron mayores en mujeres (18,2, DE = 9,7) que en hombres (12,2, DE = 4,6) (valor-p = 0,02) (Tabla I).

A mayor porcentaje sérico de EPA, DHA y razón EPA/DHA se observó un pequeño incremento en los puntajes en la escala de tamizaje de síntomas depresivos, mientras que a mayor porcentaje de ALA y razón AA/EPA los puntajes disminuyeron. Estos resultados se mantuvieron después de ajustar por potenciales confusores; sin embargo, ninguno fue estadísticamente significativo (Tabla II). En el modelo limitado a mujeres, los resultados fueron similares a los observados para todos, aunque los cambios en la escala de tamizaje CES-D con el incremento en el porcentaje de ácidos grasos en suero fueron moderados. Por ejemplo, por 1% de incremento de ALA en suero se observó una disminución de 6,7 puntos (IC 95%: -22,4, 9,0) en la escala CES-D (Tabla II).

DISCUSIÓN

En el presente estudio que incluyó una muestra de universitarios del norte de México sin enfermedad crónica, no se observaron asociaciones entre los niveles séricos AGPI omega-3 (*i.e.,* EPA y DHA), omega-6 (AA) y las razones EPA/DHA, AA/EPA con mayor sintomatología depresiva. Contrario a lo esperado, mayores porcentajes de EPA, DHA, y razón EPA/DHA mostraron un aumento pequeño en la puntuación de la escala de tamizaje, lo que indica mayor cantidad de síntomas depresivos. Solo los porcentajes mayores de ALA se correlacionaron con puntuaciones menores en dicha escala, indicando una menor cantidad de síntomas depresivos. Dicho hallazgo concuerda con los resultados basados en el consumo de ALA estimado a través de la dieta en esta misma población (15). No obstante, ninguno de los resultados fue estadísticamente significativo, debido al tamaño de la muestra, lo cual limitó el poder estadístico del presente análisis. Los cambios en la escala CES-D en relación al incremento en el porcentaje de ácidos grasos fueron más notorios en las mujeres. Se sabe que las mujeres tienen un mayor riesgo de desarrollar depresión que los hombres, lo cual ha sido reportado en mujeres mexicanas (2,5,6).

Los porcentajes de EPA, DHA y ALA medidos en suero reflejan un consumo bajo de ácidos grasos omega-3 en esta muestra de jóvenes universitarios, lo cual concuerda con el consumo bajo reportado en población mexicana (13,14). Nuestros resultados nulos podrían estar explicados en parte por estos porcentajes bajos de omega-3 observados en los participantes, es posible que si existe un efecto protector se observe al comparar grupos con deficiencia y sin deficiencia de omega-3, lo cual no fue posible en esta población.

Debido a que nuestra muestra incluyó jóvenes sin enfermedad crónica y sin diagnóstico médico de depresión, una comparación directa de nuestros resultados con estudios previos es difícil, ya que los estudios previos incluyen personas con depresión, alteraciones del ánimo y personalidad, o no cuentan con mediciones biológicas de ácidos grasos (9,10). Sin embargo, nuestros resultados nulos son similares a los reportados en dos estudios previos que también incluyeron determinaciones biológicas de ácidos grasos (*i.e.,* en tejido adiposo y membrana de glóbulos rojos) y emplearon la misma escala de tamizaje de síntomas depresivos (CES-D) en adolescentes y mujeres postmenopaúsicas; niveles altos de EPA y DHA no se relacionaron con puntajes bajos de síntomas depresivos (18,19).

Una limitación importante del presente estudio es la falta de tem-

poralidad entre las determinaciones de los ácidos grasos y la presencia de sintomatología depresiva debido a su diseño transversal. Es posible que la presencia de cambios en el estado de ánimo de los participantes haya resultado en una dieta deficiente en omega-3, lo cual podría estar reflejando los porcentajes bajos de EPA, DHA y ALA observados en esta muestra. Los resultados en sentido opuesto a nuestra hipótesis podrían explicarse en parte debido a que dichos cambios no pudieron identificarse con un diseño transversal.

Una fortaleza del presente estudio fueron las determinaciones de los ácidos grasos en suero con técnicas estandarizadas, las cuales minimizan los problemas de sobre o subestimación, en comparación con el reporte de consumo de alimentos. Además, los participantes desconocían los niveles de ácigos grasos al momento de responder la escala de tamizaje de depresión, por lo que es poco probable que hayan reportado de manera diferencial los síntomas depresivos, disminuyendo así la probabilidad de que se haya introducido un sesgo que explique los resultados. Por otra parte, la escala de tamizaje de depresión CES-D es una herramienta de fácil aplicación y de bajo costo que permite identificar personas en riesgo de desarrollar depresión, la cual ha sido validada para población mexicana (6,17).

CONCLUSIÓN

En esta muestra de universitarios sin enfermedad crónica, el porcentaje de EPA, DHA, AA y la razón EPA/DHA en suero no se correlacionó con una menor sintomatología depresiva. Solo el incremento en el porcentaje de ALA se correlacionó con menor sintomatología depresiva, dicho hallazgo necesita ser confirmado en otras poblaciones. Estudios de seguimiento con mediciones biológicas de ácidos grasos omega-3 podrían aportar datos relevantes para identificar factores de riesgo que puedan modificarse a gran escala, para prevenir la depresión y otras alteraciones del ánimo en poblaciones con consumo de ácidos grasos omega-3 por debajo de lo recomendado.

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BIBLIOGRAFÍA

1. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 2013;382(9904):1575-86.
2. World Federation for Mental Health WFMH. DEPRESSION: A Global Crisis, World Mental Health Day. Occoquan, VA; 2012:29.
3. Kessler RC. The costs of depression. Psychiatr Clin North Am 2012;35(1):1-14.
4. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. Lancet 2012;379(9820):1056-67.
5. Fleiz Bautista C, Villatoro Velazquez J, Mora Icaza ME, Moreno Lopez M, Gutierrez Lopez Mde L, Oliva Robles N. Sociodemographic and personal factors related to depressive symptomatology in the Mexican population aged 12 to 65. Rev Bras Psiquiatr 2012;34(4):395-404.
6. González-Forteza C, Solís Torres C, Jiménez Tapia A, Hernández Fernández I, González-González A, Juárez García F, et al. Confiabilidad y validez de la escala de depresión CES-D en un censo de estudiantes de nivel medio superior y superior, en la Ciudad de México. Salud Mental 2011;34(1):7.
7. Saveanu RV, Nemeroff CB. Etiology of depression: genetic and environmental factors. Psychiatr Clin North Am 2012;35(1):51-71.
8. Pusceddu MM, Kelly P, Stanton C, Cryan JF, Dinan TG. N-3 Polyunsaturated Fatty Acids through the Lifespan: Implication for Psychopathology. Int J Neuropsychopharmacol 2016;19(12).
9. Grosso G, Micek A, Marventano S, Castellano S, Mistretta A, Pajak A, et al. Dietary n-3 PUFA, fish consumption and depression: A systematic review and meta-analysis of observational studies. J Affect Disord 2016;205:269-81.
10. Pompili M, Longo L, Dominici G, Serafini G, Lamis DA, Sarris J, et al. Polyunsaturated fatty acids and suicide risk in mood disorders: A systematic review. Prog Neuropsychopharmacol Biol Psychiatry 2017;74:43-56.
11. Hakkarainen R, Partonen T, Haukka J, Virtamo J, Albanes D, Lonnqvist J. Is low dietary intake of omega-3 fatty acids associated with depression? Am J Psychiatry 2004;161(3):567-9.
12. Horrocks LA, Farooqui AA. Docosahexaenoic acid in the diet: its importance in maintenance and restoration of neural membrane function. Prostaglandins Leukot Essent Fatty Acids 2004;70(4):361-72.
13. Vannice G, Rasmussen H. Position of the academy of nutrition and dietetics: dietary fatty acids for healthy adults. J Acad Nutr Diet 2014;114(1):136-53.
14. Ramirez-Silva I, Villalpando S, Moreno-Saracho JE, Bernal-Medina D. Fatty acids intake in the Mexican population. Results of the National Nutrition Survey 2006. Nutr Metab (Lond) 2011;8(1):33.
15. Rubi Vargas M, Gonzalez Lomeli D, Terrazas Medina EA, Peralta Pena SL, Jordan Jinez ML, Ruiz Paloalto ML, et al. [Consumption of Omega- 3 Fatty Acids and Depressive Symptoms in College Students from Sonora, Mexico]. Nutr Hosp 2015;32(4):1744-51.
16. Radloff L. The CES-D Scale: A self report depression scale for research in the general population. Appl Psychol Meas 1977;1(3):17.
17. Gonzalez-Forteza C, Jimenez-Tapia JA, Ramos-Lira L, Wagner FA. [Application of the revised version of the Center of Epidemiological Studies Depression Scale in adolescent students from Mexico City]. Salud Publica Mex 2008;50(4):292-9.
18. Mamalakis G, Kiriakakis M, Tsibinos G, Hatzis C, Flouri S, Mantzoros C, et al. Depression and serum adiponectin and adipose omega-3 and omega-6 fatty acids in adolescents. Pharmacol Biochem Behav 2006;85(2):474-9.
19. Persons JE, Robinson JG, Ammann EM, Coryell WH, Espeland MA, Harris WS, et al. Omega-3 fatty acid biomarkers and subsequent depressive symptoms. Int J Geriatr Psychiatry 2014;29(7):747-57.

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ARÁN

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Trabajo Original

Epidemiología y dietética

Egg consumption and dyslipidemia in a Mediterranean cohort

Consumo de huevo y dislipidemia en una cohorte mediterránea

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Abstract

Introduction and objectives: Our aim was to prospectively evaluate the association between egg consumption and dyslipidemia in a Mediterranean cohort.

Methods: We followed-up 13,104 Spanish university graduates for a mean period of 8 years. Dietary habits at baseline were assessed using a validated semi-quantitative 136-item food-frequency questionnaire. Self-reported blood concentrations of total cholesterol, high-density lipoproteins cholesterol (HDL-c) and triglycerides were evaluated according to categories of egg consumption after 6 and 8 years of follow-up. We also assessed the association between baseline egg consumption and the incidence of hypercholesterolemia, low HDL-c concentrations and hypertriglyceridemia during follow-up.

Results: We observed a significant inverse association for intermediate levels of egg consumption (2 to 4 eggs/week vs. less than 1 egg/week) and hypertriglyceridemia with OR = 0.71 (95% confidence interval [CI]: 0.54 to 0.93, $p < 0.05$) in the multivariable-adjusted model. Using HDL-c values after 8-year follow-up, we found an association between higher egg consumption and lower HDL-c levels (p for trend = 0.02) with an adjusted difference of –4.01 mg/dl (-7.42 to -0.61) for > 4 *vs.* < 1 egg/week. Lower means of triglycerides were found in each of the three upper categories of egg consumption compared to the lowest category (< 1 egg/week) with significant results for some of these categories both after 6 and 8 year follow-up.

Conclusions: Our data do not support that higher egg consumption was associated with abnormal blood levels of total cholesterol or triglycerides; an inverse association with HDL-c as a quantitative variable was found only in one of our analyses.

Key words:

Egg consumption. Cohort. Cholesterol. HDL-c. Triglycerides. Dyslipidemia.

Resumen

Introducción y objetivos: evaluar prospectivamente la asociación entre el consumo de huevo y el riesgo de dislipidemia en una cohorte mediterránea.

Métodos: se siguieron 13.104 graduados universitarios españoles durante un periodo medio de 8 años. La dieta se evaluó al inicio utilizando un cuestionario semicuantitativo de frecuencia de consumo de alimentos repetidamente validado. Las concentraciones sanguíneas de colesterol total, lipoproteínas de alta densidad (HDL-c) y triglicéridos autorreferidas fueron evaluadas según categorías de consumo de huevo tras 6 y 8 años de seguimiento. También se evaluó la asociación entre el consumo basal de huevo y la incidencia de hipercolesterolemia, concentraciones bajas de HDL-c e hipertrigliceridemia durante el seguimiento.

Resultados: se observó una asociación entre los niveles intermedios de consumo de huevo (2-4 unidades/semana frente a < 1 unidad/semana) y menor riesgo de hipertrigliceridemia con OR = 0,71 (intervalo de confianza del 95% [IC]: 0,54 a 0,93, $p < 0,05$) en el modelo más ajustado. Tras 8 años de seguimiento, encontramos una asociación entre un mayor consumo de huevo y menores niveles de HDL-c (p tendencia lineal = 0,02) con una diferencia ajustada de -4,01 mg/dl (-7,42 a -0,61) para > 4 *vs.* < 1 unidad/semana. Se encontraron menores concentraciones de triglicéridos en las tres categorías superiores de consumo de huevo en comparación con la inferior con resultados significativos para algunas de estas categorías después de 6 y 8 años de seguimiento.

Conclusiones: un mayor consumo de huevo no se asoció con niveles anormales de colesterol total o triglicéridos; se encontró una asociación inversa con HDL-c como variable cuantitativa solo en uno de nuestros análisis.

Palabras clave:

Consumo de huevo. Cohorte. Colesterol. HDL-c. Triglicéridos. Dislipidemia.

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INTRODUCTION

Limiting egg consumption to avoid dyslipidemia has been customarily recommended, to reduce the risk of cardiovascular disease (CVD) (1). However, dietary cholesterol is known to have only a limited influence on total serum cholesterol and in low-density lipoprotein cholesterol (LDL-c) levels. Moreover, increasing egg consumption has been associated with beneficial moderate elevations in high-density lipoprotein cholesterol (HDL-c) (2) and even sometimes with beneficial overall serum lipid profiles when the size and number of lipoprotein particles were also taken into account (3-5). Available meta-analyses do not find any association between egg consumption and the risk of CVD (2,6,7). Almost all previous guidelines recommended that cholesterol intake should be limited to no more than 300 mg/day, but the more recent and comprehensive evidence showed no demonstrable harms associated to egg consumption or to a greater dietary cholesterol intake (2,6-8). It is widely assumed that dietary "cholesterol is not considered a nutrient of concern for overconsumption" (9). However, this conclusion has raised some debate (10) given that eggs are one of the major sources of dietary cholesterol, one unit (60 g) provides approximately 230 mg of cholesterol. Hence, the effect of egg consumption on serum lipid levels remains controversial (2,8,11-13), particularly on serum levels of total cholesterol and LDL-c. Some studies relating egg consumption to lipid levels used extreme and unrealistic categories of exposure, or classified subjects at post-hoc in subgroups according to whether or not they were "responders" (8). Most studies did not take into account the effect of ethnicity, dietary confounders and nutritional effect modifiers. Interestingly, some aspects of the overall dietary pattern may differentially affect the serum lipid response to egg consumption (14) and this response has shown marked between-subject variation and between-study heterogeneity (2) which is likely to depend, at least partially, on the overall diet. In this context, studies on different ethnic groups are important. The Mediterranean diet has been proposed by the Dietary Guidelines Advisory Committee as a healthy dietary pattern with strong and robust evidence of protection and its global use is currently on the rise (15). It is therefore interesting to assess the lipid responses to egg consumption in cohorts of free-living subjects who live in Mediterranean areas. We evaluated the association between the frequency of egg consumption and the incidence of hypercholesterolemia, low levels of HDL-c or high values of triglycerides in a large cohort of Spanish university graduates, the SUN (Seguimiento Universidad de Navarra) cohort.

METHODS

The SUN project is a prospective and dynamic cohort. The design, objectives and methods have been previously published (16,17). More than 50% of participants in the SUN cohort are health professionals themselves. The recruitment started in December 1999 and it is permanently open (dynamic design). The answer of the first questionnaire is considered as provision of informed consent. Sociodemographic variables, lifestyles and medically-diagnosed diseases were collected through a baseline questionnaire at the time of recruitment. The protocol for the SUN cohort was approved by the Institutional Review Board at the University of Navarra. We inquired about serum total cholesterol levels and about the criteria for metabolic syndrome (MetS), including HDL-c, TG and fasting blood glucose levels, in the 6-year and 8-year follow-up questionnaires. This self-reported information provided by highly educated participants has previously been validated (18,19). We also inquired about new medical diagnoses of hypercholesterolemia in all follow-up questionnaires (after 2, 4, 6, 8, 10, 12 and 14-year follow-up). We considered the follow-up time as the period between recruitment (reception of the baseline questionnaire) and the date of the last follow-up questionnaire, the date of a new diagnosis of hypercholesterolemia or death, whichever came first. From a total of 22,175 participants in the SUN cohort (Fig. 1), we excluded those participants with less than 6 years and 9 months of follow up (n = 3,072), and those who were lost to follow up or had missing values in the variables of interest (n = 4,208). We also excluded participants taking lipid-lowering drugs at the time of inclusion in the study (n = 417) and those who were outside pre-defined values for total energy intake (< 800 or > 4,000 kcal/day for men and < 500 or > 3,500 kcal/day for women) (n = 1374) (20). The 13,104 remaining participants were available for different analyses. For the assessment of the association between egg consumption and follow-up values of total blood cholesterol, we excluded participants with baseline values of total blood cholesterol above 200 mg/dl (n= 3,017) and those who did not report their total blood cholesterol data at 6 or 8 years of follow up (n= 3,564). Therefore, we included in this analysis 6,523 participants without baseline hypercholesterolemia and with available data for blood total cholesterol at follow-up. To assess the association between egg consumption and HDL-c levels, we excluded participants with prevalent low levels of HDL-c, below 40 mg/dl in men or below 50 mg/dl in women (n = 903) and those who had been in the cohort for less than 6 years (they could not provide lipid values at 6 or 8 years of follow-up) or did not report their levels of HDL-c at 6 or 8 years of follow-up (n = 6,002). The available subsample for the analysis on HDL-c was 6,199 participants. Finally, to study the prospective association between egg consumption and incidence of hypertriglyceridemia we excluded from the initial sample (13,104 participants), participants with triglycerides levels above 150 mg/dl at baseline (n= 739) and those who did not report their data of triglycerides blood levels at 6 or 8 years (n = 5,188). The final subsample for assessing the association between egg consumption and hypertriglyceridemia was 7,177.

DIETARY ASSESSMENT

Baseline egg consumption was assessed with a semi-quantitative 136-item food frequency questionnaire repeatedly validated in Spain (21,22). The amount of egg contained in other products (pastries or sauces) was not considered and the method for the culinary preparation of eggs was not taken into account.

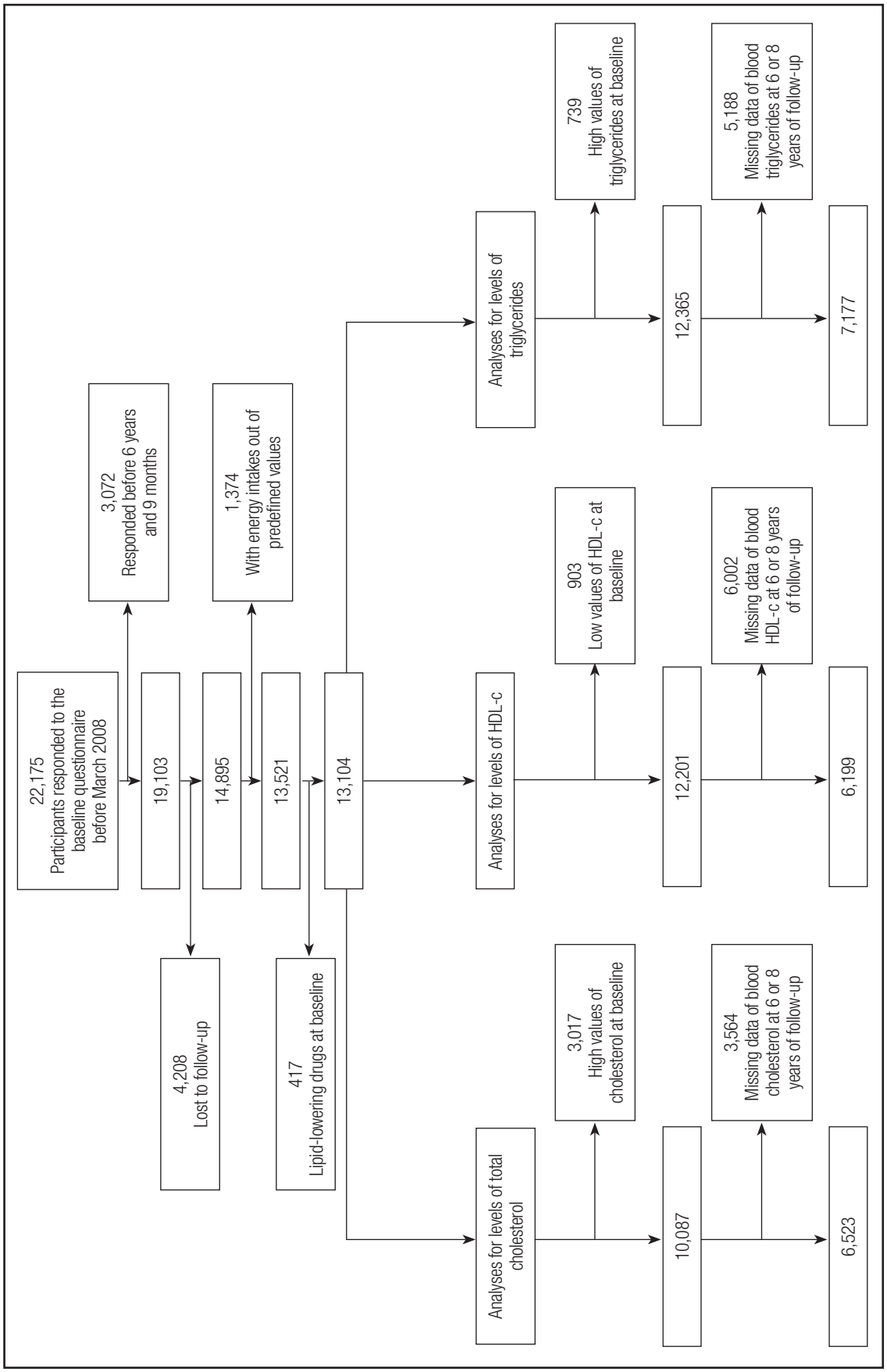

Figure 1.
Flowchart of participants in the SUN Project.

Response options were nine categories: from never or almost never to more than six times a day. We assigned the value 0 egg consumption to participants with missing values in the corresponding item of the food frequency questionnaire (77 for total cholesterol analysis, 71 for HDL-c analysis and 86 for triglycerides analysis). Nutrient intake was calculated and trained dietitians updated the data bank using the latest Spanish food composition tables (23,24).

EXPOSURE ASSESSMENT AND OTHER VARIABLES

The initial questionnaire included questions on medical history and conditions including dyslipidemia, family history of cardiovascular disease, prevalent diagnoses of hypertension or diabetes, lifestyles (smoking habits, physical activity and alcohol consumption) and sociodemographic variables. Participants were classified according to their smoking habits as never smokers, current smokers and former smokers. In addition, physical activity was assessed at baseline with a validated 17-item questionnaire (25). The index of metabolic equivalent task hours per week (METs-h/week) was computed by using the time spent engaging in 17 activities and multiplying the time spent by the resting metabolic rate (MET-score) specific for each activity. The METs-h/week for all activities were combined to obtain a value of total METs-h/week (26). The validity of self-reported weight, BMI, leisure time physical activity and hypertension in the SUN cohort was assessed in specific validation studies (25,27,28). Adherence to the Mediterranean diet was defined according to the 9-item score proposed by Trichopoulou et al. (29).

ASSESSMENT OF INCIDENT HYPERCHOLESTEROLEMIA, HYPERTRIGLYCERIDEMIA OR LOW LEVELS OF HDL-C

The baseline questionnaire included a question on whether the participant had previously received a medical diagnosis of hypercholesterolemia (≥ 240 mg/dl) (30) or hypertriglyceridemia (triglycerides ≥ 150 mg/dl) and the age of these diagnoses. Baseline HDL-c levels also were self-reported in a period of less than 5 years previous to the baseline questionnaire. Information on the concentrations of total serum cholesterol, triglycerides and HDL-c was collected at 6 and 8 years of follow-up. Participants reported their results obtained from their blood test and medical check-ups that they routinely undergo in Spain at no cost using the clinical services of the National Health System or from their Occupational medical services. Information about LDL-c also was collected in the 6- and 8-year follow-up questionnaires, but participants were not asked at baseline about their blood concentrations of LDL-c, therefore we could not exclude those who were prevalent cases at baseline, and due to this reason we did not include in this work any analysis relating egg consumption to serum levels of LDL-c. We assumed that participants had elevated baseline cholesterol (prevalent hypercholesterolemia) if they reported having been diagnosed of hypercholesterolemia by a medical doctor or if they were under usual treatment with lipid-lowering drugs. Incident cases of hypercholesterolemia were defined as those participants without any baseline diagnosis of hypercholesterolemia and without any treatment with lipid-lowering drugs at baseline who subsequently reported a medical diagnosis of high blood cholesterol during follow-up.

STATISTICAL ANALYSIS

We divided participants according to their usual egg consumption in four categories: < 1 egg/week; 1 egg/week; 2-4 eggs/week and > 4 eggs/week. Odds ratios (OR) and 95% confidence intervals (CI) for incident hypercholesterolemia were estimated for the three upper categories of egg consumption using multivariate logistic regression models adjusted for potential confounders. The lowest category of egg consumption was considered as the reference category. We adjusted for the following confounding factors: age (continuous), sex, total energy intake (continuous), quartiles of body mass index (BMI), smoking (never smoker, former smoker and current smoker), physical activity during leisure time (METs-hours/week, continuous), adherence to the Mediterranean dietary pattern (continuous), alcohol intake (continuous), family history of CVD (yes/no), diabetes at baseline (yes/no) and prevalent hypertension (yes/no). Multiple linear regression models were used to evaluate the multivariable-adjusted differences in total cholesterol, HDL-c and triglycerides between each of the 3 upper categories of egg consumption and the lowest category, adjusting for the previously mentioned potential confounding factors. For triglycerides blood concentrations analyses we additionally adjusted for carbohydrate intake as an independent covariate in the regression models. The analyses were run with Stata software version 12 (Stata Corp). Statistical significance was set at the conventional cut-off of $p < 0.05$.

RESULTS

Baseline characteristics of participants according to their baseline categories of egg consumption in the subsample of total cholesterol analysis are presented in table I. The mean age of participants was 38.4 years (range 20-89) and their median egg consumption was 2.79 eggs/week. Table II shows the ORs for the association between baseline categories of egg consumption and the diagnosis of high levels of total blood cholesterol, low concentrations of HDL-c or high concentrations of triglycerides during follow-up (either at 6 or 8 years of follow up). We classified also as cases of incident hypercholesterolemia those participants who reported values of total cholesterol above 240 mg/dl in the 6-year or 8-year follow-up questionnaire. We observed an inverse association between egg consumption and high blood cholesterol in the crude model with a significant linear trend ($p = 0.03$). The comparison between extreme categories also showed, but only in the crude model, a significant inverse association (OR: 0.71; 95% CI: 0.52 to 0.96, $p < 0.05$). However, when we adjusted for age, sex and total energy intake, the inverse association weakened and the statistical significance was lost.

Neither the observed ORs for each of the 3 upper categories, nor the linear trend tests showed any significant association between egg consumption and a medical diagnosis of low HDL-c. For the association between egg consumption and the incidence of hypertriglyceridemia (values of blood levels of triglycerides > 150 ml/dl) we observed a significant *inverse* association only for intermediate levels of egg consumption (2 to 4 eggs/week *vs.* less than 1 egg/week) with OR: 0.71 (95% CI: 0.54 to 0.93, $p < 0.05$) in the multivariable-adjusted model. We additionally adjusted for carbohydrate intake (g/day) and we observed similar results (OR: 0.71; 95% CI: 0.54 to 0.94, $p < 0.05$). However we did not observe any statistically significant linear trend relating higher egg consumption to lower risk of hypertriglyceridemia.

We also treated the lipid levels as continuous variables and applied multiple linear regression models. Tables III and IV show the regression coefficients that represent the adjusted differences in mean levels of lipids between each of the three upper categories of egg consumption *versus* the lowest category (< 1 egg/week) which was always the reference category. Table III presents differences in means after 6-years of follow-up and table IV, after 8-years of follow-up. For average total cholesterol we observed small and non-significant differences between groups of egg consumption. Only in the crude model, higher egg consumption was associated with lower means of HDL-c blood levels (p for trend = 0.004).

Table I. Baseline characteristics of participants of the SUN cohort classified according to categories of egg consumption in the subsample of total cholesterol analyses (n = 6,523)*

	Categories of egg consumption			
	1	2	3	4
	< 1 egg /week	1 egg/week	2-4 eggs/ week	> 4 eggs/week
n	473	1,271	4,071	708
Sex (% female)	67	69.8	66.1	46.6
Age (years)	39.4 (12.01)	37.7 (11.05)	37.7 (11.08)	38.5 (11.3)
BMI at baseline (kg/m2)	23.3 (3.39)	23.1 (3.39)	23.1 (3.22)	23.8 (3.22)
Current smokers	20.1	21.5	20.8	20.2
Former smokers	32.14	29.35	27.29	27.82
Family history of cardiovascular disease	14.4	12.51	12.1	12.3
Prevalent diabetes	1.48	1.89	1.5	1.50
Prevalent hypertension	6.98	5.59	5	6.80
Lipid-lowering drugs at follow-up	5.5	4.2	2.8	1.9
Total energy intake (kcal/day)	2,043 (662)	2,206 (597)	2,414 (573)	2,630 (576)
Carbohydrates intake (g/day)	235 (94.4)	245 (84.1)	262 (80.6)	280 (83.5)
Protein intake (g/day)	86.9 (32.2)	98.4 (26.7)	107.7 (25.6)	116 (25.3)
Fat intake (g/day)	79.4 (31.1)	87.9 (29.2)	98.9 (28.9)	110.3 (29.6)
Saturated fatty acids intake (g/day)	26.2 (12.1)	30 (11.6)	33.71 (11.2)	38.3 (11.9)
Monounsaturated fatty acids intake (g/day)	34.5 (14.6)	37.7 (13.8)	42.6 (13.9)	47 (14.1)
Polyunsaturated fatty acids intake (g/day)	11.4 (5.78)	12.3 (5.24)	14.1 (5.59)	15.9 (5.77)
Trans fatty acids intake (g/day)	0.80 (0.60)	0.91 (0.54)	1 (0.53)	1.14 (0.59)
Omega-3 fatty acids (g/day)	2.40 (1.30)	2.51 (1.20)	2.70 (1.20)	2.80 (1.20)
Omega-6 fatty acids (g/day)	9.12 (5.20)	9.81 (4.89)	11.47 (5.34)	13.17 (5.39)
Cholesterol intake (mg/day)	275 (123)	336 (120.5)	431 (116.9)	574 (152.1)
Alcohol consumption (g/day)	5.6 (7.8)	5.6 (8.2)	6.2 (9.2)	7.6 (12)
Whole-fat dairy products consumption (g/day)	154.4 (171.2)	184.6 (192.6)	211 (196.3)	263 (229)
Low-fat dairy products consumption (g/day)	198.9 (247)	231 (240)	228 (244)	189.5 (227)
Wine consumption (ml/day)	29.42 (60.12)	26.06 (55.12)	29.45 (63.8)	39.85 (89.87)
Fibre intake (g/day)	27.4 (14.3)	28 (13.9)	28.6 (11.9)	27.5 (11.2)
Physical activity (METs-h/week)	20.1 (22.8)	21.7 (23.8)	21.4 (21.8)	23.2 (25.8)

**Baseline characteristics of participants are presented as means ± SDs for quantitative variables and as n (%) for categorical variables.*

Table II. Odds Ratios (ORs) for incidence of high total cholesterol levels (TC), low high-density lipoproteins (HDL-c) levels and high triglycerides (TG) levels according to categories of egg consumption in the SUN cohort at 6 and 8 years of follow-up

	Categories of egg consumption				
	1	2	3	4	
	< 1 egg /week	1 egg/week	2-4 eggs/week	> 4 eggs/week	
High TC	*n = 473*	*n = 1,271*	*n = 4,071*	*n = 708*	p for trend
Incident cases n (%)	94 (19.87%)	228 (17.94%)	694 (17.05%)	106 (14.97%)	
Crude model	1 (ref.)	0.88 (0.67 to 1.15)	0.83 (0.65 to 1.05)	0.71 (0.52 to 0.96)*	0.03*
Multivariable 1	1 (ref.)	0.94 (0.72 to 1.24)	0.91 (0.71 to 1.16)	0.77 (0.56 to 1.06)	0.11
Multivariable 2	1 (ref.)	0.92 (0.70 to 1.21)	0.88 (0.69 to 1.13)	0.75 (0.55 to 1.04)	0.08
Low HDL-c	*n = 501*	*n = 1,255*	*n = 3,805*	*n = 638*	
Incident cases n (%)	85 (16.97%)	194 (15.46%)	535 (14.06%)	98 (15.36%)	
Crude model	1 (ref.)	0.89 (0.68 to 1.18)	0.80 (0.62 to 1.03)	0.89 (0.65 to 1.22)	0.31
Multivariable 1	1 (ref.)	0.91 (0.69 to 1.21)	0.84 (0.65 to 1.08)	0.96 (0.69 to 1.33)	0.67
Multivariable 2	1 (ref.)	0.94 (0.71 to 1.26)	0.87 (067 to 1.13)	0.93 (0.67 to 1.30)	0.52
High TG	*n = 569*	*n = 1,417*	*n = 4,444*	*n = 747*	
Incident cases n (%)	78 (13.7%)	159 (11.22%)	449 (10.10%)	95 (12.71%)	
Crude model	1 (ref.)	0.80 (0.60 to 1.06)	0.71 (0.55 to 0.92)*	0.92 (0.13 to 0.20)	0.62
Multivariable 1	1 (ref.)	0.83 (0.62 to 1.12)	0.72 (0.55 to 0.74)*	0.79 (0.56 to 1.10)	0.13
Multivariable 2	1 (ref.)	0.83 (0.61 to 1.11)	0.71 (0.54 to 0.93)*	0.79 (0.56 to 1.11)	0.13
Multivariable 3	1 (ref.)	0.83 (0.61 to 1.12)	0.71 (0.54 to 0.94)*	0.80 (0.56 to 1.12)	0.16

**p < 0.05; **p < 0. 01.*

Multivariable 1: adjusted for age (continuous), sex and total energy intake (continuous).

Multivariable 2: additionally adjusted for quartiles of body mass index (continuous), smoking status, hypertension at baseline, family history of cardiovascular disease, diabetes at baseline, physical activity during leisure time (continuous), adherence to the Mediterranean food pattern (continuous) and alcohol intake (continuous).

Multivariable 3: additionally adjusted for carbohydrate intake.

Table III. Multivariable-adjusted differences of blood concentrations of total cholesterol (TC), high-density lipoproteins (HDL-c) and triglycerides (TG) according to categories of egg consumption in the SUN cohort at 6 years of follow-up

	Categories of egg consumption				
	1	2	3	4	
	< 1 egg /week	1 egg/week	2-4 eggs/week	> 4 eggs/week	
TC (mg/dl)	*n = 363*	*n = 1,027*	*n = 3,256*	*n = 549*	p for trend
Crude model	0 (ref.)	+0.47 (-3.47 to +4.42)	+0.57 (-3.00 to +4.14)	-1.33 (-5.70 to +3.04)	0.48
Multivariable 1	0 (ref.)	+1.69 (-2.18 to +5.56)	+2.12 (-1.43 to +5.67)	+0.60 (-3.79 to +4.99)	0.96
Multivariable 2	0 (ref.)	+1.23 (-2.68 to +5.13)	+1.55 (-2.03 to +5.13)	–0.25 (-4.69 to +4.19)	0.78
HDL-c (mg/dl)	*n = 378*	*n = 968*	*n = 2,855*	*n = 477*	
Crude model	0 (ref.)	+0.85 (-1.77 to +3.47)	-0.00 (-2.37 to +2.36)	-3.43 (-6.40 to -0.45)*	0.004**
Multivariable 1	0 (ref.)	-0.05 (-2.56 to +2.46)	-0.49 (-2.78 to +1.80)	-2.03 (-4.93 to +0.88)	0.11
Multivariable 2	0 (ref.)	+0.43 (-2.11 to +2.98)	-0.16 (-2.49 to +2.17)	-2.02 (-4.98 to +0.95)	0.08
TG (mg/dl)	*n = 437*	*n = 1,124*	*n = 3,450*	*n = 747*	
Crude model	0 (ref.)	-7.60 (-12.66 to -2.53)**	-7.81 (-12.37 to -3.25)**	-6.77 (-12.49 to -1.05)*	0.17
Multivariable 1	0 (ref.)	-5.67 (-10.54 to -0.80)*	-5.69 (-10.13 to -1.25)*	-7.69 (-13.31 to -2.07)**	0.05
Multivariable 2	0 (ref.)	-6.31 (-11.14 to -1.48)*	-6.80 (-11.21 to -2.40)**	-7.91 (-13.51 to -2.30)**	0.04*
Multivariable 3	0 (ref.)	-5.99 (-10.83 to -1.16)*	-6.24 (-10.67 to -1.80)**	-7.24 (-12.87 to -1.60)*	0.08

**p < 0.05; **p < 0.01.*

Multivariable 1: adjusted for age (continuous), sex and total energy intake (continuous).

Multivariable 2: additionally adjusted for quartiles of body mass index (continuous), smoking status, hypertension at baseline, family history of cardiovascular disease, physical activity during leisure time (continuous), adherence to the Mediterranean food pattern (continuous) and alcohol intake (continuous).

Multivariable 3: additionally adjusted for carbohydrate intake.

Table IV. Multivariable-adjusted differences of blood concentrations of total cholesterol (TC), high-density lipoproteins-(HDL) and triglycerides (TG) according to categories of egg consumption in the SUN cohort at 8 years of follow-up

	Categories of egg consumption				
	1	2	3	4	
	< 1 egg/week	1 to 2 eggs/week	2-4 eggs/week	> 4 eggs/week	
TC (mg/dl)	*n = 315*	*n = 803*	*n = 2,710*	*n = 481*	p for trend
Crude model	0 (ref.)	-2.32 (-6.71 to -2.06)	-1.64 (-5.56 to 2.29)	-0.05 (-4.83 to +4.73)	0.53
Multivariable 1	0 (ref.)	-1.39 (-5.70 to +2.91)	-0.30 (-4.20 to +3.60)	+1.17 (-3.63 to +5.97)	0.28
Multivariable 2	0 (ref.)	-1.85 (-6.21 to +2.51)	-0.71 (-4.67 to +3.24)	+1.00 (-3.87 to +5.87)	0.27
HDL-c (mg/dl)	*n = 333*	*n = 791*	*n = 2,468*	*n = 419*	
Crude model	0 (ref.)	-0.16 (-3.17 to +2.86)	-0.42 (-3.11 to +2.28)	-4.56 (-7.95 to -1.17)*	0.01*
Multivariable 1	0 (ref.)	-0.86 (-3.79 to +2.07)	-0.78 (-3.44 to +1.87)	-3.28 (-6.64 to +0.09)	0.09
Multivariable 2	0 (ref.)	-0.52 (-3.48 to +2.43)	-0.98 (-3.66 to +1.71)	-4.01 (-7.42 to -0.61)*	0.02*
TG (mg/dl)	*n = 378*	*n = 906*	*n = 2,919*	*n = 498*	
Crude model	0 (ref.)	-6.06 (-11.47 to -0.64)*	-6.90 (-11.73 to -2.06)**	-5.20 (-8.63 to +3.43)	0.78
Multivariable 1	0 (ref.)	-5.30 (-10.53 to -0.07)*	-6.15 (-10.88 to -1.42)*	-5.20 (-11.14 to +0.75)	0.22
Multivariable 2	0 (ref.)	-4.95 (-10.15 to +0.25)	-5.81 (-10.51 to -1.10)*	-4.01 (-9.94 to +1.92)	0.38
Multivariable 3	0 (ref.)	-4.92 (-10.12 to +0.29)	-5.74 (-10.48 to -1.01)*	-3.94 (-9.90 to +2.03)	0.41

**p < 0.05; **p < 0.01.*

Multivariable 1: adjusted for age (continuous), sex and total energy intake (continuous).

Multivariable 2: additionally adjusted for quartiles of body mass index (continuous), smoking status, hypertension at baseline, family history of cardiovascular disease, physical activity during leisure time (continuous), adherence to the Mediterranean food pattern (continuous) and alcohol intake (continuous).

Multivariable 3: additionally adjusted for carbohydrate intake.

When we repeated this assessment using HDL-c values after 8-years of follow-up we did find an association between egg consumption and lower HDL-c levels (p for trend = 0.02) with a fully adjusted difference of -4.01 (-7.42 to -0.61) mg/dl in HDL-c between extreme categories of egg consumption (> 4 *vs.* < 1 egg/week). Results for blood levels of triglycerides showed *lower* means of triglycerides in each of the three upper categories of egg consumption than in the lowest category (< 1 egg/week). Results were statistically significant for all comparisons after 6-year follow-up and for many of them after 8-year follow-up. However, the linear trend test was never significant in the follow-up after 8-years (Table IV), it lost its statistical significance in the fully-adjusted model after 6 years (Table III) and the point estimates suggested a plateau effect instead of a monotonically decreasing trend. As sensitivity analyses we fitted logistic regression and multiple linear regression models after adjusting for BMI as a continuous variable instead of quartiles of BMI and we observed similar results (data not shown). We did not observe any significant interaction between egg consumption and adherence to the Mediterranean dietary pattern (cut-off ≥ 6 *vs.* < 6 in the 9-item Trichopoulou score) (31).

DISCUSSION

This longitudinal study did not identify any clear harmful association between egg consumption and the incidence of hypercholesterolemia or hypertriglyceridemia in a prospective cohort of highly educated Mediterranean subjects. We did observe an inverse association between egg consumption and mean serum HDL-c levels with a decreasing linear trend that was statistically significant only after 8 years of follow-up. Lower average concentrations of HDL-c were observed in subjects who consumed more than 4 eggs/week after adjusting for a wide array of potential confounders. However, the size of the difference was small and probably it was not clinically relevant, because we did not observe any increased risk of a new diagnosis of low HDL levels (considered as a clinically relevant dichotomous outcome). On the other hand, we found a reduction in the incidence of medically-diagnosed hypertriglyceridemia and lower average levels of triglycerides in subjects who had higher egg consumption. Due to the fact that egg is the major source of dietary cholesterol, metabolic studies have focused on the effect of dietary cholesterol contained in eggs on serum lipids but their influences on plasma concentrations of serum cholesterol the effect is quite small (32,33). Thus, it seems more appropriate to recommend healthy dietary habits and active lifestyle instead of recommendations focused on the restriction of dietary cholesterol from eggs. In this same cohort we found no association between egg consumption and the incidence of CVD among 14,185 university graduates (34). Furthermore, in a prospective cohort study of 21,327 participants from the Physicians' Health Study, the consumption of ≥ 6 eggs/week had no major

effect on the risk of CVD and mortality and the consumption of ≥ 7 eggs/week was associated with a modestly greater risk of total mortality (35-37). Other studies with experimental designs (4) reported that daily whole egg consumption during moderate carbohydrate restriction diets were associated with greater increases in plasma HDL-c and improvements in HDL-c profiles in patients with the MetS (38-40). Therefore, our unexpected result of an inverse association with HDL-c in some analyses (only present after 8 years), should be viewed with caution, because it is not consistent with previously reported results and with our analyses after 6 years. Approximately one third of individuals tend to have a high plasma response to dietary cholesterol (hyper-responders). The increases in LDL-c and HDL-c due to increased egg consumption in hyper-responders are not likely to be related to an increased number of LDL or HDL-c particles but, to an increase in the less atherogenic lipoprotein subfractions. These data suggested that additional dietary cholesterol did not increase the risk of developing an atherogenic lipoprotein profile in healthy men, regardless of their response classification.

The most apparent potential limitation of our study is the self-report nature of lipid levels, but these self-reported values were previously validated in specific studies conducted in sub-samples of the SUN cohort (18,19). A second potential concern may be related to the generalizability of our findings which are based on a young cohort of university graduates that is a non-representative sample of the general population. On the other hand, their high educational level ensures a more accurate response. In addition, egg consumption might be underestimated because FFQs inquired about units of egg consumed and the amount of eggs contained in other products (pastries or sauces), were not considered. In addition, we only assessed egg consumption at baseline. However, several important strengths are the prospective design and large sample size of our study, our long-term follow-up, a high retention rate (81.5%), the ability to control for a wide array of potential confounders, the robustness of our results in sensitivity analyses and the existence of published validation studies for self-reported measurements, including dietary assessment (18,21,22,25,27,28).

Our data do not support that higher egg consumption is associated with abnormal blood levels of total cholesterol or triglycerides; however, an inverse association with HDL-c as a quantitative variable was found in only one of our assessments and future studies are warranted to confirm this result. Results from the SUN cohort do not provide any evidence to recommend a reduction in egg consumption in healthy subjects as a means to reduce lipid levels.

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REFERENCES

1. Spence JD, Jenkins DJA, Davignon J. Dietary cholesterol and egg yolks: not for patients at risk of vascular disease. Can J Cardiol 2010;26:336-9.
2. Berger S, Raman G, Vishwanathan R, Jacques PF, Johnson EJ. Dietary cholesterol and cardiovascular disease: a systematic review and meta-analysis. Am J Clin Nutr 2015;102:276-94.
3. Waters D, Clark RM, Greene CM, Contois JH, Fernandez ML. Change in plasma lutein after egg consumption is positively associated with plasma cholesterol and lipoprotein size but negatively correlated with body size in postmenopausal women. J Nutr 2007;137:959-63.
4. Andersen CJ, Blesso CN, Lee J, Barona J, Shah D, Thomas MJ, et al. Egg consumption modulates HDL lipid composition and increases the cholesterol-accepting capacity of serum in metabolic syndrome. Lipids 2013;48:557-67.
5. Greene CM, Waters D, Clark RM, Contois JH, Fernandez ML. Plasma LDL and HDL characteristics and carotenoid content are positively influenced by egg consumption in an elderly population. Nutr Metab 2006;3:6.
6. Shin JY, Xun P, Nakamura Y, He K. Egg consumption in relation to risk of cardiovascular disease and diabetes: a systematic review and meta-analysis. Am J Clin Nutr 2013;98:146-59.
7. Rong Y, Chen L, Zhu T, Song Y, Yu M, Shan Z, et al. Egg consumption and risk of coronary heart disease and stroke: dose-response meta-analysis of prospective cohort studies. BMJ 2013;346:e8539.
8. Fuertes Garcia A. Consumo de huevos y enfermedad cardiovascular. Nutr Hosp 2016;33:41-3.
9. Scientific Report of the 2015 Dietary Guidelines Advisory Committee (DGAC) (2015) Evidence Basis and Key Recommendations. Available at: http://health.gov/dietaryguidelines/2015-scientific-report/06-chapter-1/d1-2.asp (accessed March 2016).
10. Levin S, Wells C, Barnard N. Dietary Cholesterol and Blood Cholesterol Concentrations. Jama 2015;314:2083-4.
11. Schersten T, Rosch PJ, Arfors KE, Sundberg R. The cholesterol hypothesis: time for the obituary? Scand Cardiovasc J 2011;45:322-3.
12. KA SW, Krause AJ, Shearer S, Devries S. The 2015 Dietary Guidelines Advisory Committee Report Concerning Dietary Cholesterol. Am J Cardiol 2015;116:1479-80.
13. Komaroff AL. By the way, doctor. Ever since the 1960s, I haven't eaten more than one egg a week because egg yolks have a lot of cholesterol. Now my wife says she heard on the news that it's okay to eat eggs every day. What do you think? Harv Health Lett 2005;30:8.
14. Schonfeld G, Patsch W, Rudel LL, Nelson C, Epstein M, Olson RE. Effects of dietary cholesterol and fatty acids on plasma lipoproteins. J Clin Invest 1982;69:1072-80.
15. Anand SS, Hawkes C, de Souza RJ, Mente A, Dehghan M, Nugent R, et al. Food Consumption and its Impact on Cardiovascular Disease: Importance of Solutions Focused on the Globalized Food System: A Report From the Workshop Convened by the World Heart Federation. J Am Coll Cardiol 2015;66:1590-614.
16. Martinez-Gonzalez MA, Sanchez-Villegas A, Irala J De, Marti A, Martinez JA. Mediterranean diet and stroke: objectives and design of the SUN project. Seguimiento Universidad de Navarra. Nutr Neurosci 2002;5:65-73.
17. Martinez-Gonzalez MA. The SUN cohort study (Seguimiento University of Navarra). Public Health Nutr 2006;9:127-31.
18. Barrio-Lopez MT, Bes-Rastrollo M, Beunza JJ, Fernandez-Montero A, Garcia-Lopez M, Martinez-Gonzalez MA. Validation of metabolic syndrome using medical records in the SUN cohort. BMC Public Health 2011;11:867.
19. Fernandez-Montero A, Beunza JJ, Bes-Rastrollo M, Barrio MT, de la Fuente-Arrillaga C, Moreno-Galarraga L, et al. Validity of self-reported metabolic syndrome components in a cohort study. Gac Sanit 2011;25:303-7.
20. Willett WC. Issues in Analysis and Presentation of Dietary Data. In: 2nd edition. New York: Oxford University Press; 1998. pp. 322.
21. Martin-Moreno JM, Boyle P, Gorgojo L, Maisonneuve P, Fernandez-Rodriguez JC, Salvini S, et al. Development and validation of a food frequency questionnaire in Spain. Int J Epidemiol 1993;22:512-9.

22. de la Fuente-Arrillaga C, Ruiz ZV, Bes-Rastrollo M, Sampson L, Martinez-González MA. Reproducibility of an FFQ validated in Spain. Public Health Nutr 2010;13:1364-72.
23. Moreiras O, Carbajal A, Cabrera L, Cuadrado C. Tabla de composición de alimentos. 16th ed. Madrid: Piramide; 2013.
24. Mataix J. Tabla de composición de alimentos. 5th ed. Granada: Universidad de Granada; 2009.
25. Martinez-Gonzalez MA, Lopez-Fontana C, Varo JJ, Sanchez-Villegas A, Martinez JA. Validation of the Spanish version of the physical activity questionnaire used in the Nurses' Health Study and the Health Professionals' Follow-up Study. Public Health Nutr 2005;8:920-7.
26. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32:498-504.
27. Bes-Rastrollo M, Pérez JR, Sánchez-Villegas A, Alonso A, Martínez-González MA. Validation of self reported weight and body mass index in a cohort of university graduates in Spain. Rev Esp Obes 2005;3:352-8.
28. Alonso A, Beunza JJ, Delgado-Rodriguez M, Martinez-Gonzalez MA. Validation of self reported diagnosis of hypertension in a cohort of university graduates in Spain. BMC Public Health 2005;5:94.
29. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med 2003;348:2599-608.
30. National Cholesterol Education Program. High Blood Cholesterol ATP III Guidelines At-A-Glance Quick-Desk-Reference. U.S. Department of Health and Human Services Public Health Service National Institutes of Health National Heart, Lung, and Blood Institute. Available at: https://www.nhlbi.nih.gov/files/docs/guidelines/atglance.pdf
31. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean Diet and Survival in a Greek Population. N Engl J Med 2003;348:2599-608.
32. Kanter MM, Kris-Etherton PM, Fernandez ML, Vickers KC, Katz DL. Exploring the factors that affect blood cholesterol and heart disease risk: is dietary cholesterol as bad for you as history leads us to believe? Adv Nutr 2012;3:711-7.
33. Howell WH, McNamara DJ, Tosca MA, Smith BT, Gaines JA. Plasma lipid and lipoprotein responses to dietary fat and cholesterol: a meta-analysis. Am J Clin Nutr 1997;65:1747-64.
34. Zazpe I, Beunza JJ, Bes-Rastrollo M, Warnberg J, de la Fuente-Arrillaga C, Benito S, et al. Egg consumption and risk of cardiovascular disease in the SUN Project. Eur J Clin Nutr 2011;65:676-82.
35. Djousse L, Gaziano JM. Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study. Am J Clin Nutr 2008;87:964-9.
36. Alexander DD, Miller PE, Vargas AJ, Weed DL, Cohen SS. Meta-analysis of Egg Consumption and Risk of Coronary Heart Disease and Stroke. J Am Coll Nutr 2016;35(8):704-16.
37. Díez-Espino J, Basterra-Gortari FJ, Salas-Salvadó J, Buil-Cosiales P, Corella D, Schröder H, et al. Egg consumption and cardiovascular disease according to diabetic status: The PREDIMED study. Clin Nutr Clin Nutr 2017;36(4):1015-21. DOI: 10.1016/j.clnu.2016.06.009
38. Blesso CN, Andersen CJ, Bolling BW, Fernandez ML. Egg intake improves carotenoid status by increasing plasma HDL cholesterol in adults with metabolic syndrome. Food Funct 2013;4:213-21.
39. Klangjareonchai T, Putadechakum S, Sritara P, Roongpisuthipong C. The Effect of Egg Consumption in Hyperlipidemic Subjects during Treatment with Lipid-Lowering Drugs. J Lipids 2012;2012:672720.
40. Woo HW, Choi BY, Kim MK. Cross-Sectional and Longitudinal Associations between Egg Consumption and Metabolic Syndrome in Adults >/= 40 Years Old: The Yangpyeong Cohort of the Korean Genome and Epidemiology Study (KoGES_Yangpyeong). PLoS One 2016;11:e0147729.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Otros

Effect of fish and olive oil on mitochondrial ATPase activity and membrane fluidity in patients with relapsing-remitting multiple sclerosis treated with interferon beta 1-b

Efecto del aceite de pescado en la actividad hidrolítica de la ATPasa y en la fluidez de la membrana mitocondrial en pacientes con esclerosis múltiple remitente-recurrente tratados con interferón beta 1-b

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Abstract

Background: Multiple sclerosis (MS) is an inflammatory disease of the central nervous system associated with increased oxidative stress (OS) and mitochondrial alterations. Fish oil consumption has neuroprotective, antioxidant and anti-inflammatory effects in patients with relapsing-recurrent MS (RR-MS).

Objective: To evaluate changes in the hydrolytic activity of ATP synthase and mitochondrial membrane fluidity in patients with RR-MS who receive fish oil or olive oil as a dietary supplement.

Methods: Clinical, controlled, randomized, double-blind trial. Patients consumed fish oil or olive oil for one year. The hydrolytic activity of ATPase and the fluidity of the mitochondrial membrane of platelets were quantified.

Results: In patients with RR-MS, a decrease in the fluidity of mitochondrial membranes and an increase in the hydrolytic activity of ATP synthase was observed in comparison with healthy controls. After 6 or 9 months of treatment with fish oil or olive oil, respectively, these values were normalized.

Conclusion: The consumption of fish oil and olive oil increases the fluidity of the mitochondrial membranes and decreases the catabolic activity of ATP synthase in platelets from patients with RR-MS.

Key words:

Multiple sclerosis. Mitochondrial ATPase. Membranal fluidity. Olive oil. Fish oil.

Resumen

Introducción: la esclerosis múltiple (EM) es una enfermedad inflamatoria del sistema nervioso central asociada con estrés oxidativo (EO) y alteraciones mitocondriales. El aceite de pescado tiene efectos neuroprotectores, antioxidantes y antiinflamatorios en pacientes con EM remitente-recurrente (EM-RR).

Objetivo: evaluar los cambios en la actividad hidrolítica de la ATPasa y de la fluidez de membrana mitocondrial en pacientes con EM-RR que reciben aceite de pescado o aceite de oliva como suplemento alimenticio.

Métodos: ensayo clínico, controlado, aleatorizado, doble ciego. Los pacientes consumieron aceite de pescado o aceite de oliva durante un año. Se cuantificó la actividad hidrolítica de la ATPasa y la fluidez de la membrana mitocondrial de plaquetas.

Resultados: en pacientes con EM-RR hay una disminución de la fluidez de las membranas mitocondriales y un incremento de la actividad hidrolítica de la ATPasa en comparación con controles sanos. Después de 6 y 9 meses de tratamiento con aceite de oliva y de aceite de pescado, respectivamente, los valores se normalizaron y se mantuvieron así hasta el fin del estudio.

Conclusión: el consumo de aceite de pescado y aceite de oliva incrementan la fluidez de membrana y disminuye la actividad catabólica de la ATP sintasa en pacientes con EM-RR.

Palabras clave:

Esclerosis múltiple. ATPasa mitocondrial. Fluidez membranal. Aceite de oliva. Aceite de pescado.

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INTRODUCTION

Multiple sclerosis (MS) is a neurodegenerative, chronic, progressive and inflammatory disease that affects the central nervous system (CNS) (1). Its etiology is partially known and includes immunological, genetic and environmental factors (i.e., nutrition) (2). MS is the most frequent cause of neurological disability in young adults and is characterized by the perivenous infiltration of lymphocytes and macrophages in the cerebral parenchyma resulting in demyelination and axonal damage. Approximately 85% of patients start with a relapsing-remitting (RR) clinical course in which there are exacerbations of neurological deficit associated with an inflammatory demyelinating event lasting at least 24 hours in the absence of fever or infection. This is followed by a recovery period in which there is no progression of the disease and may last for months or years (3).

A higher incidence of MS is found in the northernmost latitudes of the northern and the southern hemispheres compared to southernmost latitudes. Recent evidence shows that feeding patterns strongly influence the geographical distribution of MS. For example, MS is uncommon in Japan. Furthermore, Japanese who move to Hawaii change their eating habits and increase the risk of MS. In the Faroe Islands, the incidence of MS was very low compared to other countries of similar latitude and this increased to double as a consequence of the western influence in the diet. The common dietary factor that might explain the previous exceptions is increased fish consumption combined with reduced consumption of meat products (4). The risk of MS increases in non-Hispanic inhabitants of the United States of America, who consume less fish and more foods high in saturated fats (5). It is also known that a diet with a low proportion of polyunsaturated fats in relation to saturated fats is associated with a higher mortality in MS (6).

Increased levels of interleukin-1 (IL-1) and other proinflammatory cytokines play a role in initiating an inflammatory response (7). Dysregulation of proinflammatory cytokines as well as a decrease in antioxidants such as glutathione (8) causes an increase in oxidative stress (OS) by the excessive production of reactive oxygen (ROS) and nitrogen (RNS) species (9,10). ROS and RNS are produced mainly by mitochondrion, which under normal physiological conditions are controlled through several antioxidant mechanisms (11).

Mitochondria are spherical or filamentous organelles that are localized in all eukaryotic cells and are the main site where adenosine triphosphate (ATP) is synthesized by ATP synthase (12). ATP synthase is the enzyme that uses adenosine diphosphate (ADP), inorganic phosphate (Pi) and electrochemical gradient of protons through the internal mitochondrial membrane as substrates (12). The enzyme can function as ATP synthase (ATP synthesis) or ATPase (ATP hydrolysis) (12) and is formed by a soluble portion F_1 and a F_0 portion embedded in the lipid membrane (13). The F_1 moiety is rich in phenylalanine and methionine amino acids that are highly susceptible to being oxidized by free radicals (13,14). This oxidation results in a conformational change of the F_1 portion and as a consequence alters both the synthesis and the hydrolysis of ATP (13). Under physiological conditions the F_1 portion maintains the conformational change suitable for the production of ATP and under pathological conditions is modified by increasing the hydrolysis of ATP (15).

Recent evidence shows a relationship between OS and mitochondrial dysfunction with inflammation in MS. The inflammatory phenomenon conditions severe mitochondrial dysfunction and axonal damage (16). Derived from the inflammatory process, in acute lesions, the intra-axonal mitochondria are damaged by the excessive production of nitric oxide (NO) and RNS (16). ROS and RNS oxidize the membrane phospholipids, which causes a decrease in the flexibility of their chains, altering membrane fluidity (17). This phenomenon of excessive ROS production could be assessed indirectly by changes in ATPase activity and in the physical properties of the membrane, particularly membrane fluidity.

Current treatments for MS (particularly in Mexico) involve anti-inflammatory and immunomodulatory drugs (18). In the present study, patients receive interferon β (INF-β), a pleiotropic molecule that increases the secretion of interleukins with anti-inflammatory properties (i.e. interleukin 4 [IL-4] and interleukin 10 [IL-10]). In addition, INF-β stabilizes tumor necrosis factor α (TNF-α) levels as well as decreases the production of proinflammatory cytokines (interleukins 1, 6 and 12) (18).

On the other hand, previous studies have shown that the administration of omega-3 fatty acids decreases the production of proinflammatory cytokines and OS (9). In particular, dietary supplementation with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 polyunsaturated fatty acids (PUFAs) are able to reduce the production of proinflammatory cytokines such as IL-1, IL-6, kin 8 (IL-8) and TNFα (10). In addition omega-3-PUFAs favors the production of prostaglandins E1 and E2 (19), diminish the proliferation of T (19) lymphocytes and proinflammatory cytokines (IL-1β, TNF-α and IL-6) (20). In addition, the intake of omega-3-PUFAs increases the synthesis of pro-resolution molecules such as lipoxins, resolvins and protectins (21). Finally the EPA (an omega-3-PUFAs), is a substrate of cyclooxygenase 1 and 2 (COX-1 and COX-2), and lipoxygenase 5 (19). EPA competes for the site of action of these oxygenases with arachidonic acid (AA), the latter being responsible for favoring the synthesis of inflammatory cytokines and leukotrienes in conditions where OS prevails (19).

Olive oil mainly contains oleic acid, a monounsaturated fatty acid and a number of bioactive compounds such as polyphenols. According to Puertollano 2015, oleic acid replaces palmitic acid in phospholipids and dissociates lipid rafts (22). This phenomenon is associated with decreases in the incidence of inflammatory diseases, OS markers and in the production of proinflammatory cytokines (23). There is evidence that a diet rich in monounsaturated fatty acids (i.e. oleic) significantly decreases the amount of the IL-1 adhesion molecule in peripheral blood monocyte cells (24). Similarly, the Mediterranean diet (rich in olive oil) decreases the serum levels of interleukins 18, 7 and 6 (23). Finally, it is reported that serum levels of omega-3 and 6-fatty acids are decreased in patients with MS (8).

The objective of this work was to evaluate the mitochondrial membrane fluidity and the hydrolytic activity of ATPase of platelets of patients with RR-MS who received dietary supplementation

of fish or olive oil as a support for their treatment of interferon beta-1b over a year.

MATERIALS AND METHODS

STUDY DESIGN

A randomized, double blinded clinical trial was performed in the multiple sclerosis clinic of the Neurology Department, Unidad Médica de Alta Especialidad (UMAE), Hospital de Especialidades (HE), Centro Médico Nacional de Occidente (CMNO), IMSS, Guadalajara, JAL, Mexico. Age of participants was 18-55 years. Patients had clinically definite and magnetic resonance image supported MS, at least one relapse in the year before entry into the study, and a baseline EDSS score of < 5 and were treated with subcutaneous 250 µg interferon beta-1b (Betaseron, Bayer) every other day at least one year before the trial. Interferon beta-1b was routinely administered in the afternoon.

Identification numbers were assigned to assure patient confidentiality. This study was performed according with the updated Declaration of Helsinki and all procedures were approved by the Ethics and Health Research Committee of the Mexican Social Security Institute (clave R-2010-1301-8).

Patients were randomly assigned in a 1:1 ratio to receive oral fish oil (4 g/day: 0.8 g EPA and 1.6 g DHA) or olive oil (1 g oleic acid), with a computer-generated randomization sequence. To ensure masking between the fish oil and olive oil, capsules were identical in appearance, packaging, and labeling. Participants reported daily consumption of the supplement in a consumption posting sheet. The rate of adherence to the treatment was > 80% and was determined by using the following formula:

Adherence to treatment (%) = number of capsules actually taken from the last count/number of tablets should be taken at the same stage x 100%. An independent physician evaluated the EDSS score and collected the samples at each clinical visit. Fasting blood samples were taken at 0, 3, 6, 9, and 12 months.

Patients were excluded if they were taking another supplement; had progressive forms of MS; had chronic-degenerative diseases (*i.e.* diabetes mellitus, hypertension arterial) had history of acute liver or renal dysfunction; had history of tobacco, drug, or alcohol abuse; had intolerance, contraindication, or allergy to fish oil; and had customary antioxidant intake.

Baseline clinical markers (glucose, cholesterol, triglycerides, total bilirubin and amino transferases are reported in the results section (Table I). The groups of olive oil (O), fish oil (P) and control group (C) were matched by age and sex. To form the control group, 25 clinically healthy individuals were included in order to compare the baseline values of the parameters analyzed in this study.

OUTCOMES MEASUREMENTS

Peripheral venous blood (ten milliliters) was collected in tubes containing etilendiaminotetracetic acid (EDTA) and centrifuged at 310 g for 10 minutes at 4 °C, in order to obtain the plasma and globular concentrate. The plasma was separated and deposited in Eppendorf tubes and centrifuged for 15 minutes at 1,160 g at 4 °C, and the platelet pellet was obtained. The platelet pellet was re-suspended in 200 µl of cold buffer (138 mM NaCl, 2.7 mM KCl, 1 mM $MgCl_2$, 3 mM NaH_2PO_4, 5 mM glucose, 10 mM Hepes (pH 7.4) y 0.01% bovine serum albumin. Platelet mitochondrial membranes were obtained as reported elsewhere (25) and were frozen at -80 °C until processing. The protein concentration of the samples was quantified by the Lowry method using bovine serum albumin as standard (26).

The hydrolytic activity of the mitochondrial ATPase was evaluated using a colorimetric method through the liberation of inorganic phosphate using ATPase buffer (125 mM KCl, 40 mM of Mops (pH 8), 3 mM $MgCl_2$). Inorganic phosphate was quantified according to Sumner (27).

Membrane fluidity was estimated from the excimer to monomer fluorescence intensity ratio (Ie/Im) of the fluorescent probe 1,3 dipyrenylpropane (DyPP) incorporated in mitochondrial membranes of platelets as reported previously (28). Fluorescence corrections obtained from readings of membranes without DyPP were applied to all fluorescence values.

STATISTICAL ANALYSIS

Data were analyzed as mean values ± standard deviation. Differences in the parameters studied between groups were evaluated using analysis of variance (ANOVA and MANOVA). A value of $p < 0.05$ was considered statistically significant. Homogeneity test of variance was performed by Levene test with a 92% result and the Shapiro Wilk test to verify the normal distribution yields a value of 95%. The analyses were done in SPSS version 21.

RESULTS

As shown in figure 1, of the 300 MS patients treated at the neurology clinic, 50 of them met the inclusion criteria. However, 4 of them dropped out of the study, so 23 patients were assigned per treatment group. The mean age of the patients who participated in this study was 35.1 ± 7.6 years and the baseline EDSS score was 2.1 ± 0.98, after 12 months of the intervention was 2.84 ± 0.94, with a $p = 0.79$ being non-significant statistically. The evolution of the disease in years is 7.1. Prior to the intervention and at the end of the study, a biochemical safety profile was determined which consisted of blood biometrics, lipid profile, and liver and renal function tests. There was a significant difference between the study groups in the baseline measurements of leukocytes and total cholesterol, being lower in the control group; after 12 months a significant difference was observed in low-density lipoprotein (LDL) (Table I).

Table I. Biosafety profile before and after the intervention

Variable	Mean value Fish oil (CI 95%)	Mean value Olive oil (CI 95%)	Fish oil-Olive oil difference (CI 95%)	p value
Leukocytes, miles/mL:				
Baseline	5.8	5.1	0.7	*0.03*
12 months	5.8	5.2	0.6	*0.05*
Hemoglobin, g/dL:				
Baseline	13.7	13.8	-0.1	0.86
12 months	13.8	13.4	0.4	0.44
Glucose, mg/dl:				
Baseline	82.4	79.0	3.4	0.40
12 months	81.3	80.1	1.2	0.56
Urea, mg/dL:				
Baseline	26.1	25.5	0.6	0.94
12 months	29.1	26.4	2.7	0.73
Creatinine, mg/dL:				
Baseline	0.7	0.7	0.0	0.59
12 months	0.7	0.7	0.0	0.61
Total bilirubin, mg/dL				
Baseline	0.5	0.5	0.0	0.87
12 months	0.4	0.5	-0.1	0.42
ALT, U/L:				
Baseline	38.5	32.5	6.0	0.14
12 months	37.0	36.0	1.1	0.66
Alkaline phosphatase, U/L:				
Baseline	79.9	88.2	-8.3	0.12
12 months	70.5	79.4	-8.9	0.14
Total cholesterol, mg/dL:				
Baseline	184.9	168.0	16.9	*0.03*
12 months	190.5	178.1	12.4	0.26
Triglycerides, mg/dL:				
Baseline	125.7	99.9	25.8	0.17
12 months	112.1	118.8	-6.7	0.30
HDL, mg/dL:				
Baseline	48.8	49.1	-0.3	0.73
12 months	46.2	49.6	-3.4	0.69
LDL, mg/dL:				
Baseline	106.9	97.9	9.0	0.15
12 months	122.8	105.5	17.3	*0.04*

Data expressed as mean and standard deviation. Test U Mann Whitney. HDL: high density lipoprotein; LDL: low density lipoprotein; CI: confidence interval; ALT: alanine transaminase.

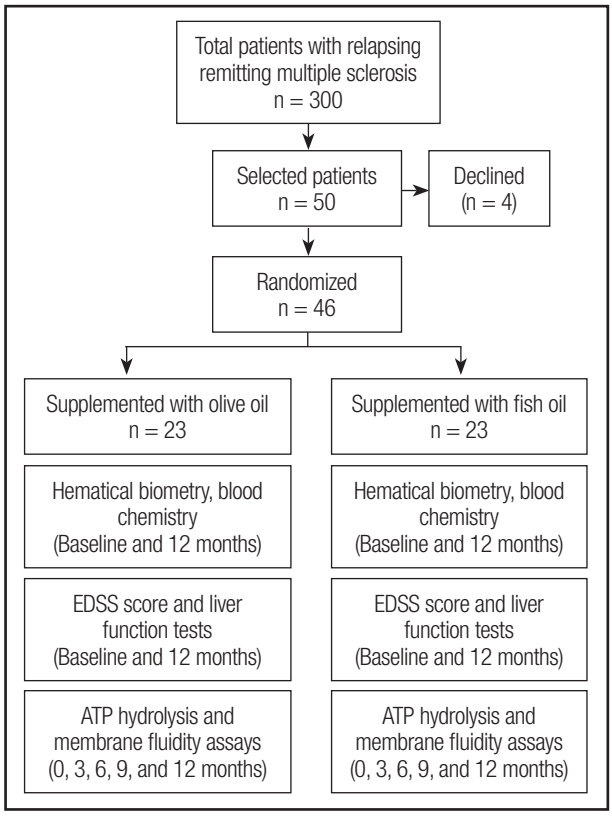

Figure 1.

Flow diagram for patients follow-up.

BIOCHEMICAL PARAMETERS

Figure 2 shows a significant decrease in the fluidity of the platelet mitochondrial membranes of patients with RR-MS (baseline) compared to the group of clinically healthy individuals (control). At three months of the diet supplemented with fish or olive oil, no significant difference was observed in contrast to that observed at baseline. However, after 6 months of treatment (fish or olive oil, respectively), membrane fluidity in mitochondrial membrane of platelets from patients with RR-MS reached values similar to those of control individuals and remained so until the end of the study.

The hydrolytic activity of the mitochondrial ATPase is significantly higher in the patients compared to the individuals in the control group. In addition, the enzymatic activity decreases significantly after 6 months in the olive oil group, in contrast to the basal state. Whereas for the fish oil group the significant decrease of the enzymatic activity is reached after 9 months of treatment. With both treatments, the activity is maintained at levels similar to the control group until the end of the study (Fig. 3).

DISCUSSION

Epidemiological and experimental studies suggest a high prevalence of MS in populations with a high intake of saturated fats,

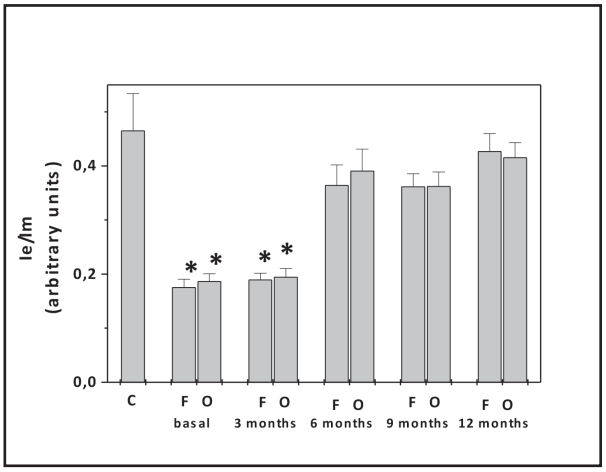

Figure 2.

Mitochondrial membrane fluidity index (Ie/Im) in patients receiving fish oil (F) or olive oil (O) as a dietary supplement, at each experimental time and of individuals in the control group (C). *p ≤ 0.05.

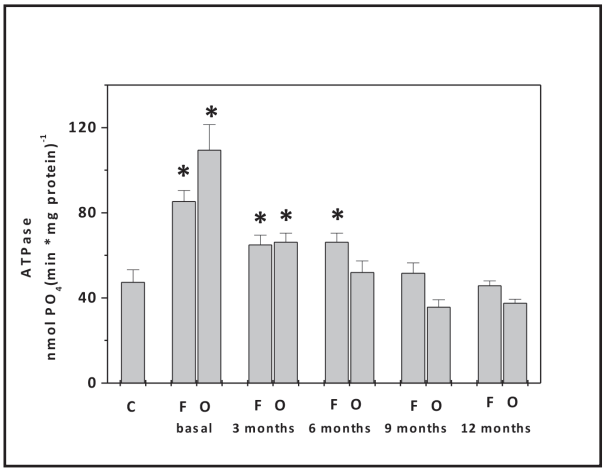

Figure 3.

Mitochondrial ATPase activity in patients receiving fish oil (F) or olive oil (O) as a dietary supplement, at each experimental time and of individuals in the control group (C). *p ≤ 0.05.

especially of animal origin (29). It has been proposed that consumption of saturated fat causes a change in membrane integrity and functionality (29), which is consistent with the decrease in membrane fluidity in patient's platelets detected in this study. We also observed that the hydrolytic activity of ATPase decreased with the treatments of fish or olive oil in relation to the basal group. These changes are inversely associated with changes in membrane fluidity, i.e. at higher membrane fluidity there is less hydrolytic activity of ATPase.

The fluidity of cell membranes depends on the temperature, the ratio of saturated fatty acids/polyunsaturated fatty acids, the presence of lipid rafts, the proportion of cholesterol present in

the membrane, among other factors (30). Our results showed that an appropriate value of membrane fluidity is restored with the consumption of unsaturated fatty acids, whether fish oil or olive oil are given. In the case of the PUFAs present in fish oil, the change in fluidity can be attributed to the incorporation of EPA into the cell membranes. This fact is consistent with the results found in our work group where there was an increase in omega-3-PUFAs levels in patients after treatment with fish oil, in addition to a decrease in levels of AA (8). The recovery of membrane fluidity is accompanied by a decrease in ATPase activity. This would ensure that ATP synthesis activity remains elevated in the mitochondria.

These results provide an encouraging picture of the use of both types of oil; the reduction decrease in the synthesis of inflammatory cytokines (TNFα, IL-1β and IL-6) and NO catabolites in patients receiving oil fish (20). At this regard, it is known that the synthesis of proinflammatory cytokines are derived from the AA cascade, so an increase in EPA and DHA from supplementation is associated with a decrease in proinflammatory cytokines (21). On the other hand, the required ratio of AA/EPA to diminished cellular inflammation is 1.5/3, this ratio increases to 3/6 for moderate cellular inflammation. Consistent with this proposal, we have previously found that the AA/EPA and omega6/omega 3 ratios decreases significantly with fish oil treatment. Although there are significant differences in the lipid profile of the membranes analyzed in the above work (8), the values of our study of membrane fluidity and ATP hydrolysis of the group supplemented with fish or olive oil group are almost similarly. The result described is attributed to the fact that olive oil contains a high proportion of oleic acid (31) and bioactive polyphenols that have anti-inflammatory and antioxidant properties *in vitro* and *in vivo* studies (31). This allows us to explain why both groups (fish or olive oil) have similar behavior. The data obtained in this study are consistent with the decrease in markers of inflammation and OS that occur with fish oil consumption in patients with RR-MS. This has repercussions in reestablishing the membrane fluidity to its physiological ranges and the reduction of pathological activity of the ATPase.

In a previous study it's recommended that optimal nutrition should include the consumption of 35% of polyunsaturated fatty acids (with dietary equilibrium omega 3/omega 6) (29). This for an optimal functioning of the blood-brain barrier (29), which avoids the activation of autoreactive $CD4^+$ T cells within the CNS. Therefore, the vicious cycle of the production of proinflammatory cytokines and OS (5) is limited.

At the recommended doses of interferon beta, lymphopenia can occur. However, leukocytes remained within clinically normal range in both treatment groups. Although there are some differences in absolute amounts of leukocytes between treatments, these changes were not significant at the end of the clinical trial in each intervention group. Therefore, the presence of secondary lymphopenia could be not noteworthy. One limitation of this work is that the study time was short to observe changes in the clinical score EDSS.

CONCLUSIONS

In this clinical trial, an increase in fluidity in the mitochondrial membrane was observed over a year of supplementation in the diet of those patients with RR-MS who received fish or olive oil. These results are directly related to a decrease in ATP hydrolysis and are consistent with the antioxidant and anti-inflammatory properties of both, fish oil and olive oil. The results for fluidity mitochondrial membrane and ATP hydrolysis were very similar to the control group.

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REFERENCES

1. Hernández CJ, Castañeda LG, Rodríguez RA. Esclerosis Múltiple en México: la clínica de su historia. Rev Fac Med 2006;49(2):73-8.
2. Mejía BL, Agudelo RC, Gómez HJ, et al. Genética de la Esclerosis Múltiple: Una perspectiva epidemiológica y molecular. iMedPub Journals, Archivos de Medicina 2009;5(1:5):123-32.
3. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: Results of an international survey. Neurology 1996;46:907-11.
4. Franklin GM, Nelson L. Environmental risk factors in multiple sclerosis: causes, triggers, and patient autonomy. Neurology 2003;61(8):1032-4.
5. Zhang SM, Willett WC, Hernan MA, et al. Dietary fat in relation to risk of multiple sclerosis among two large cohorts of women. Am J Epidemiol 2000;152(11):1056-64.
6. Liuzzi GM, Latronico T, Rossano R, et al. Inhibitory effect of polyunsaturated fatty acids on MMP-9 release from microglial cells—implications for complementary multiple sclerosis treatment. Neurochem Res 2007;32(12):2184-93.
7. Riccio P. The molecular basis of nutritional intervention in multiple sclerosis: a narrative review. Complement Ther Med 2011;19(4):228-37.
8. Sorto-Gomez TE, Ortiz GG, Pacheco-Moises FP, et al. Effect of fish oil on glutathione redox system in multiple sclerosis. Am J Neurodegener Dis 2016;5(2):145-51.
9. Anderson GM, Fritsche KL. (n-3) Fatty acids and infectious disease resistance. J Nutr 2002;132:3566-76.
10. Valenzuela BR, Tapia OG, González EM, et al. Omega-3 Fatty Acids (EPA and DHA) and its Application in Diverse Clinical Situations. Rev Chil Nutr 2011;38(3):356-67.
11. Martínez-Lazcano JC, Boll-Woehrlen MC, Hernández-Melesio A, et al. Radicales libres y estrés oxidativo en las enfermedades neurodegenerativas. Rev Fac Med 2010;34(2):43-59.
12. Westermann B. Merging Mitochondria Matters, cellular role and molecular machinery of mitochondrial fusion. EMBO Rep 2002;3(6):527-31.
13. Vázquez-Memije ME, Cárdenas-Méndez MJ, Tolosa A, et al. Respiratory chain complexes and membrane fatty acids composition in rat testis mitocondria throughout development and ageing. Experimental Gerontology 2005;40(6):482-90.
14. Laemmli UK. Cleavage of structural proteins during the assembly of the head of bacteriophage T4. Nature 1970;227:680-5.
15. Green DW, Grover GJ. The IF1 inhibitor protein of the mitochondrial F1Fo- ATPase. Biochemica et Biophysical Acta (BBA) Bioenergetics 2000;1458(2-3):343-55.
16. Witte ME, Mahad DJ, Lassmann H, et al. Mitochondrial dysfunction contributes to neurodegeneration in multiple sclerosis. Trends in Molecular Medicine 2014;20(3):179-87.
17. Bagasra O, Michaels FH, Zheng YM, et al. Activation of the inducible form of nitric oxide synthase in the brains of patients with multiple sclerosis. Proc Nat Acad Sci USA 1995;92(26):12041-5.
18. Prieto JM, Lema M. Interferon β in multiple sclerosis. Rev Neurol 2003;36(10):980-90.
19. Caballero R, Gómez R, Núñez L, et al. Farmacología de los ácidos grasos omega-3. Rev Esp Cardiol Supl 2006;6:3-19.

20. Ramírez-Ramírez V, Macias-Islas MA, Ortiz GG, et al. Efficacy of fish oil on serum of TNFα, IL-1β and IL-6 Oxidative Stress Markers in Multiple Sclerosis Treated with Interferon Beta-1b. Oxidative Medicine and Cellular Longevity 2013:1-8.
21. Calder PC. n-3 Polyunsaturated fatty acids, inflammation, and inflammatory diseases. Am J Clin Nutr 2006;83(Suppl):1505-19.
22. Puertollano MA, Puertollano E, Alvarez CG, et al. Aceite de oliva, sistema inmune e infección. Nutr Hosp 2015;32(6):2594-9.
23. Esposito K, Marfella R, Ciotola M, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. J Am Med Assoc 2004;292:1440-6.
24. Yaqoob P, Knapper JA, Webb DH, et al. Effect of olive oil on immune function in middle-aged men. Am J Clin Nutr 1998;67:129-35.
25. Baracca A, Barogi S, Carelli V, et al. Catalityc activities of mitochondrial ATP synthase in patients with mitochondrial DNA T8993G mutation in the ATPase 6 gene enconding subunit a. J Biol Chem 2000;275:4177-82.
26. Lowry OH, Rosebrough NJ, Farr AL, et al. Protein measurement with the folin phenol reagent. J Biol Chem 1951;193:265-75.
27. Sumner JB. A method for the colorimetric determination of phosphorus. Science 1994;100:413-4.
28. Ortiz GG, Pacheco-Moisés F, Hafidi ME, et al. Detection of membrane fluidity in submitochondrial particles of platelets and erythrocyte membranes from Mexican patients with Alzheimer disease by intramolecular excimer formation of 1,3 dipyrenylpropane. Dis Markers 2008;24(3):151-6.
29. Mehta LR, Dworkin RH, Schwid SR. Polyunsaturated Fatty Acids and Their Potential Therapeutic Role in Multiple Sclerosis. Nat Clin Pract Neurol 2009;5(2):82-92.
30. Solans R, Motta C, Solá R, et al. Abnormalities of erythrocyte membrane fluidity, lipid composition and lipid peroxidation in systemic sclerosis: Evidence of free radical-mediated injury. Arthritis Rheum 2000;43(4):894-900.
31. Bulotta S, Celano M, Massimo LS, et al. Beneficial effects of the olive oil phenolic components oleuropein and hydroxytyrosol:focus on protection against cardiovascular and metabolic diseases. J Transl Med 2014;12:219-23.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Otros

High fat diet and high polyphenols beverages effects in enzymatic and non-enzymatic antioxidant activity

Efectos de dieta con alto contenido de grasa y bebidas ricas en polifenoles en la actividad antioxidante enzimática y no enzimática

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Abstract

Background: High fat diets have been implicated in the generation of reactive oxygen species (ROS). Polyphenols from grapes may reduce ROS and restore oxidative balance. The aim of this study is to investigate the antioxidant properties of high polyphenols beverages associated with a high fat diet in enzymatic and non-enzymatic antioxidant activity.

Material and methods: Fifty female rats were divided into five groups: a) control group (CG) - control diet (4% fat); b) high fat diet group (HFD) - high fat diet (20% fat); c) grape juice group (GJ) - grape juice (15 ml/day) + high fat diet; d) red wine group (RW) - red wine (10 ml/day) + high fat diet; and e) resveratrol solution group (RS) – resveratrol solution (15 ml/day) + high fat diet. Eight weeks later, the superoxide dismutase, catalase and glutathione peroxidase activities were measured. Superoxide dismutase activity was assayed by measuring the inhibition of adrenaline auto-oxidation, catalase by the decrease rate in hydrogen peroxide and glutathione peroxidase by monitoring the oxidation of nicotinamide adenine dinucleotide phosphate. Non-enzymatic antioxidant activity was assessed by oxygen radical absorbance capacity and DDPH (free radical sequestration 2,2-diphenyl-1-picryhydracil) method in the animal's plasma.

Results: GC and GJ presented the lowest glutathione peroxidase activity, pointing to a possible protective effect of grape juice against high levels of ROS ($p < 0.05$). RW increased catalase activity when compared to the RS ($p < 0.05$). Superoxide dismutase activity and non-enzymatic antioxidant plasma activity were similar in all groups.

Conclusion: Grape juice showed to be the most effective in minimizing the deleterious effects of a high fat diet. Resveratrol did not present any benefit and red wine possibly shows a harmful effect due to ethanol content.

Key words:

Grape polyphenols. Redox homeostasis. Superoxide dismutase. Catalase. glutathione peroxidase.

Resumen

Introducción: las dietas ricas en grasas se han implicado en la generación de especies reactivas del oxígeno (ROS). Los polifenoles de las uvas pueden reducir el ROS y restaurar el equilibrio oxidativo. El objetivo de este estudio es investigar las propiedades antioxidantes de las bebidas ricas en polifenoles asociadas con una dieta rica en grasa en la actividad antioxidante enzimática y no enzimática.

Material y métodos: cincuenta ratas fueron divididas en cinco grupos: a) grupo control (CG) - dieta de control (4% de grasa); b) grupo rica en grasa (HFD) - dieta con 20% de grasa; c) jugo de uva (GJ) - jugo (15 ml/día) + dieta rica en grasas; d) vino tinto (RW) - vino tinto (10 ml/día) + dieta rica en grasas; y e) grupo solución de resveratrol (RS) - solución de resveratrol (15 ml/día) + dieta rica en grasas. Se midieron superóxido dismutasa, catalasa y glutatión peroxidasa. La actividad de superóxido dismutasa para la inhibición de la auto-oxidación de adrenalina, la catalasa por la tasa de disminución de peróxido de hidrógeno y glutatión peroxidasa monitorizando la oxidación de nicotinamida adenina dinucleótido fosfato. La actividad antioxidante no enzimática se midió por el método de capacidad de absorción de radicales de oxígeno y DDPH (moléculas estables de radicales libres 2,2-difenil-1-picrihidrazilo).

Resultados: GC y GJ presentaron la menor actividad de glutatión peroxidasa, señalando un posible efecto protector del jugo de uva frente a altos niveles de ROS ($p < 0,05$). RW aumentó la actividad de catalasa en comparación con RS ($p < 0,05$). Superóxido dismutasa y la actividad antioxidante no enzimática fueron similares.

Conclusiones: el jugo demostró ser el más eficaz para minimizar los efectos deletéreos de una dieta rica en grasas. Resveratrol no presentó ningún beneficio y el vino tinto posiblemente muestra un efecto perjudicial debido al contenido de etanol.

Palabras clave:

Polifenoles de las uvas. Homeostasis Redox. Superóxido dismutasa. Catalasa. Glutatión peroxidasa.

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INTRODUCTION

Diet plays an important role in maintaining human health and the progression of disease states (1,2). A permanent exposure to high saturated fat diets leads to metabolic abnormalities such as obesity development and progression, type II diabetes, cardiovascular diseases and some forms of cancer. It is proposed that the link between a high fat diet and the development of diseases is provided by oxidative imbalance, which is mediated by an increase in reactive oxygen species (ROS) production such as hydrogen peroxide and hydroxyl radical (2).

The generation of free radicals is a continuous and physiological process, playing important biological functions such as cell signaling and defense against micro-organisms. However, the imbalance between the prooxidant and antioxidant systems, with predominance of oxidative reaction, results in oxidative stress (3,4). To limit the intracellular levels of ROS and control the damage occurrence, cells have an important enzymatic defense system composed by endogenous antioxidant enzymes such as glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT) (5,6).

CAT catalyzes the conversion of hydrogen peroxide to water, whereas SOD catalyzes the dismutation of superoxide to hydrogen peroxide. GPx reduces lipid hydroperoxides to their corresponding alcohols and free hydrogen peroxide to water (7).

Unbalanced diets can affect cellular oxidative responses. During a high saturated and/or transaturated fat diet, the production of free radicals is increased and, due to a compensatory response to maintain the redox homeostasis, an antioxidant enzyme also increases (8,9).

Epidemiological and prospective studies have demonstrated the role of poliphenolic rich foods such as fruits, nuts and vegetables as non-enzymatic antioxidants. These components, obtained through diet and/or supplementation, can act in synergy with enzymatic antioxidants, controlling oxidative stress (3,10-12).

Red grape derivatives, due to their high pholyfenols levels, present a major role in scavenging free radicals. It has been reported that regular intake of red grape juice and its derivatives, such as wine, are associated to anti-inflammatory activity, lower expression and activity of antioxidants enzymes as CAT and GPx and reduced lipid peroxidation, oxidative damage and apoptotic cell death (3,10-12). Therefore, this study was undertaken to determine the effects of a daily intake of phenolic-rich beverages obtained from red grape on antioxidants enzymes concentrations of rats fed a high-fat diet (HFD).

MATERIALS AND METHODS

ANIMALS

The study was conducted in the Experimental Nutrition Laboratory of the Department of Nutrition and Dietetics, School of Nutrition Emilia Jesus Ferreiro at the Federal Fluminense University (LabNE-UFF). It was approved by the Brazilian Society of Science in Laboratory Animals (SBCAL) of the Federal Fluminense University, according to the guidelines of the Brazilian College on Animal Experimentation (protocol n° 473).

Fifty female *Rattus novergicus Wistar albino*, all adults (90 days), weighing 200 ± 20 g obtained at the LabNE-UFF were housed in plastic cages in a controlled environment (24 °C ± 2 °C, with a 12 h daylight cycle), with free access to food and water. The experiment lasted for 8 weeks.

The animals were randomly divided into five groups (n = 10/group):

1. *Control group (CG):* fed a control diet (4% of total calorie intake from fat) based on the American Institute of Nutrition Recommendations for adult-rodents (AIN 93M) (13).
2. *High fat diet group (HFD):* fed high fat diet (20% of total calorie intake from fat).
3. *Grape Juice group (GJ):* fed a high fat diet (20% of total calorie intake from fat) and received red grape juice (15 mL/day).
4. *Red wine group (RW):* fed a high fat diet (20% of total calorie intake from fat) and received red wine (10 mL/day).
5. *Resveratrol solution group (RS):* fed a high fat diet (20% of total calorie intake from fat) and resveratrol solution (15 mL/day).

Table I show the formulation of ingredients for the chow and the chemical composition of the high fat and control diet.

SAMPLES COLLECTION AND PREPARATION

At the end of the experiment, all animals were subjected to vaginal smear procedure to identify the stage of the estrous cycle.

Table I. Ingredients used for formulation of control and high fat diets (g/100 g chow)

Ingredients	Control	High fat
Casein*	14.0	14.0
Starch	62	46.07
Soybeanoil	4.0	-
Lard	-	20
Celulose	5.0	5.0
Vitaminmix[1]	1.0	1.0
Mineralsmix[2]	3.5	3.5
B-colin	0.25	0.25
L-cystine	0.18	0.18
Sugar	10.0	10.0
Total	100	100

**% protein in casein = 92.5% protein/100 g casein; [1]Vitaminmix (mg/kg dieta): retynilpalmitate 2.4, cholecalciferol 0.025, benadionasodiumbisulfite 0.8, biotin 0.22, cyanocobalamin 0.01, riboflavin 6.6, thiaminehydrochloride 6.6 and tocopherolacetate 100; [2]Mineralsmix (g/kg dieta): coppersulphsate 0.1, ammoniummolybdate 0.026, sodiumiodate 0.0003, potassiumchromate 0.028, zinco sulfate 0.091, calciumhydrogenphosphate 0.145, iron sulfate 2.338, magesium sulfate 3.37, manganese sulfate 1.125, sodiumchloride 4, calciumcarbonate 9.89 and potassiumdiidrogenophosphate 14.75.*

The rats were fasted for 6h prior to sacrifice and anesthetized with ketamine chloride (90 mg/kg) and xylazine hydrochloride (10 mg/kg). Their blood was collected by cardiac puncture into tubes with EDTA. The plasma was separated by centrifugation at 3000 rpm (20 minutes; 4 °C) and its samples were stored at - 70 °C for biochemical analysis.

ANTIOXIDANTS ENZYMATIC ACTIVITY

Glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT) activities

To determine the SOD, CAT and GPx activities, plasma was used. The SOD activity was assayed by measuring the inhibition of adrenaline auto-oxidation as absorbance at 480 nm (Beckman Spectrophotometer mod DU 640; Fullerton, CA, USA) (14). The CAT activity was measured by the rate of decrease in hydrogen peroxide absorbance at 240 nm (15). The GPx activity was measured by monitoring the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) at 340 nm in the presence of H_2O_2 (16). The total protein content in the plasma was determined by the Bradford method.

The specific activity of SOD and CAT are expressed as U/mg protein. GPx is expressed as K/gHb/s (17).

PLASMA ORAC METHOD

The oxygen radical absorbance capacity (ORAC) assay was conducted to measure the peroxyl radical-scavenging activity in plasma using a method previously reported by Prior et al. (18).

Briefly, 100 µL plasma were mixed with 200 µL ethanol and 100 µLMilli-Q water. The organic phase containing the lipophilic antioxidants was extracted twice with hexane, followed by evaporation with nitrogen. The residue was diluted with 0.7% bcyclodextrin and acetone. The hydrophilic residue was mixed with 400 lL 0.5 M perchloride acid and centrifuged at 2500 g for 5 min at 20 °C. The upper phase was diluted in 75 mM phosphate buffer (pH 7.4). The Trolox standard solutions were prepared at concentrations ranging from 6.25 to 100 lM. The Multi-Detection microplate reader (Synergy HT, Bio-Tek Instruments Inc., Winooski, VT) was programmed to record the fluorescence of the diluted samples (25 lL) every minute after the incubation of the samples with 150 lL 40 mM fluorescein in 75 mM phosphate buffer, pH 7.4, and addition of 25 lL AAPH (153 mM in 75 mM phosphate buffer, pH 7.4) for 60 min. The area under the curve of the fluorescence decay was calculated using Gen5 software. The antioxidant activity was measured four times for each plasma sample, and results are expressed as mmolTrolox equivalents/g.

PLASMA DPPH METHOD

The percentage of antioxidant activity (aa%) of each substance was assessed by DPPH free radical assay. The measurement of the DPPH radical scavenging activity was performed according to the methodology described (19). The plasma was reacted with the stable DPPH radical in an ethanol solution. The reaction mixture consisted on adding 0.5 mL of plasma, 3 mL of absolute ethanol and 0.3 mL of DPPH radical solution 0.5 mM in ethanol. The changes in color were read [absorbance (abs)] at 517 nm after 100 min of reaction using a uV-ViS spectrophotometer (du 800; Beckman coulter, Fullerton, CA, USA). The mixture of ethanol (3.3 mL) and plasma (0.5 mL) served as blank. The control solution was prepared by mixing ethanol (3.5 mL) and dPPH radical solution (0.3 mL). The scavenging activity percentage (aa%) was determined according to Mensor et al. (20).

STATISTICAL ANALYSIS

The data were expressed as mean ± standard deviation. The student´s *t* test was applied to establish differences within the group (before *versus* after).

For means of comparison among the groups, analysis of variance (ANOVA one-way) and Duncan post-test was used. For data correlation, Pearson's correlation was used. The assumption of normality (Gaussian distribution) was verified by Kolmogorov-Smirnov tests to support the use of the statistical methods described above. The analyses were performed using Graphpad Prism for Windows.

RESULTS

Three specific enzymes involved in the antioxidant endogenous defense mechanisms have been analyzed. Additionally, the antioxidant activity in beverages and plasma were also evaluated.

The SOD activity is shown in figure 1. All groups showed similar SOD activity (CG 9.01 ± 2.96; HFD 11.00 ± 2.59; GJ 10.23 ± 1.63; VT 10.34 ± 2.89; SR 9.19 ± 1.07 U/mg protein).

The CAT activity in HFD (5.40 ± 1.85 U/mg protein), GJ (4.11 ± 1.39 U/mg protein), RW (6.82 ± 1.5 U/mg protein), RS (2.86 ± 1.49 U/mg protein) were similar to CG (2.98 ± 1.28 U/mg protein), as can be observed in figure 2.

Although there was no significant difference in the CAT activity between animals that received a high fat or a control diet, it is evident that this diet, associated with high polyphenol beverages, increased the enzimatic activity in 125% in GJ, 82% in RS, 196% in HFD and 273% in RW when compared to CG.

Additionally, the CAT activity increased 138% after exposure to red wine when compared to the resveratrol solution ($p < 0.05$).

The glutathione peroxidase is shown in figure 3. The GJ presents (63.20 ± 12.8 K/gHb/s) similar enzymatic activity to CG (14.6 ± 8.21 K/gHb/s), showing that grape juice was effective in controlling oxidative stress mediated by high fat diet. Compared to GJ, enzymatic activities were 85% higher in HFD (117.34 ± 15.21 K/gHb/s), 257% in SR (225.57 ± 24.42 K/gHb/s) and 162% in RW (165.00 ± 20.04 K/gHb/s).

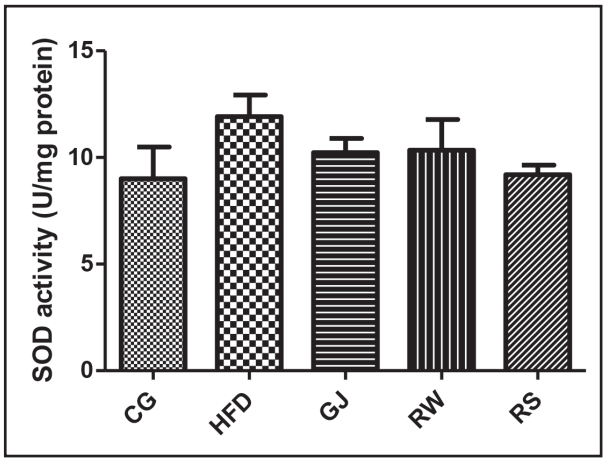

Figure 1.

Superoxide dismutase activity (measurements of plasma superoxide dismutase activity from all experimental groups: a) control group (CG) - control diet (4% fat); b) high fat diet group (HFD) - high fat diet (20% fat); c) grape juice group (GJ) - received 15 ml/day grape juice + high fat diet; d) red wine group (RW) - received 10 ml/day red wine + high fat diet; and e) resveratrol solution group (RS) - received 15 ml/day resveratrol solution + high fat diet.

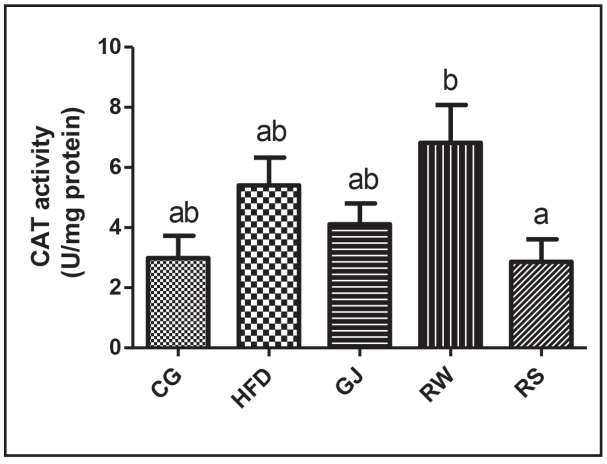

Figure 2.

Catalase activity (measurements of catalase (CAT) activity from all experimental groups. Different letters represent statistically differences between groups ($p < 0.020$); a) control group (CG) - control diet (4% fat); b) high fat diet group (HFD) - high fat diet (20% fat); c) grape juice group (GJ) - received 15 ml/day grape juice + high fat diet; d) red wine group (RW) - received 10 ml/day red wine + high fat diet; and e) resveratrol solution group (RS) - received 15 ml/day resveratrol solution + high fat diet).

In the other groups, there was an increase in the GPx activity, possibly demonstrating a greater need of GPx in the neutralization of EROS from the high fat diet (117.34 ± 15.21 K/gHb/s), red wine (165.00 ± 20.04 K/gHb/s) and/or resveratrol solution (225.57 ± 24.42 K/gHb/s) ($p < 0.0001$). Comparing all groups to CG, an enzimatic activity increase of 431% in GJ, 803% in HFD, 1.160% in RW and 1.573% in RS can be observed.

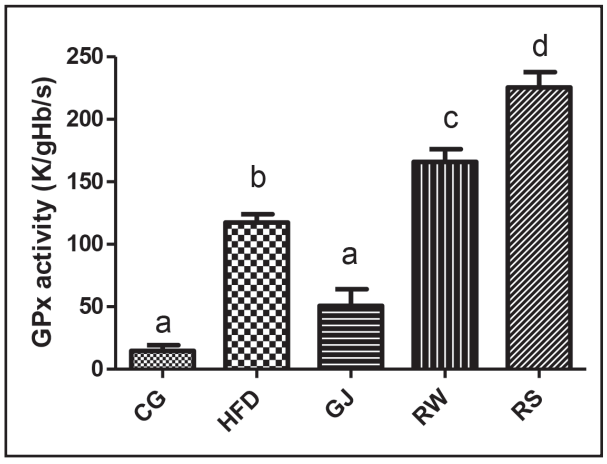

Figure 3.

Gluthatione peroxidase activity (measurements of gluthatione peroxidase (GPx) activity from all experimental groups. Different letters represent statistically differences between groups ($p < 0.0001$); a) control group (CG) - control diet (4% fat); b) high fat diet group (HFD) - high fat diet (20% fat); c) grape juice group (GJ) - received 15 ml/day grape juice + high fat diet; d) red wine group (RW) - received 10 ml/day red wine + high fat diet; and e) resveratrol solution group (RS) - received 15 ml/day resveratrol solution + high fat diet).

Using DPPH (CG 59.20 ± 4.47; HFD 60.43 ± 4.84; GJ 52.78 ± 11.71; RW 59.33 ± 13.06; RS 67.19 ± 2.77 K/gHb/s) or ORAC method (GC 45.70 X 10^6 ± 4.56 X 10^6; HFD 44.43 X 10^6 ± 2.03 X 10^6; GJ 46.89 X 10^6 ± 4.90 X 10^6 RW 55.52 X 10^6 ± 1.09 X 10^6 RS 55.28 X 10^6 ± 1.22 X 10^6 µmolET/g), there was no statistical difference in plasma antioxidant activity of animals treated with high fat diet or high fat diet associated with polyphenol-rich beverages when compared to control group, as seen in figures 4 and 5.

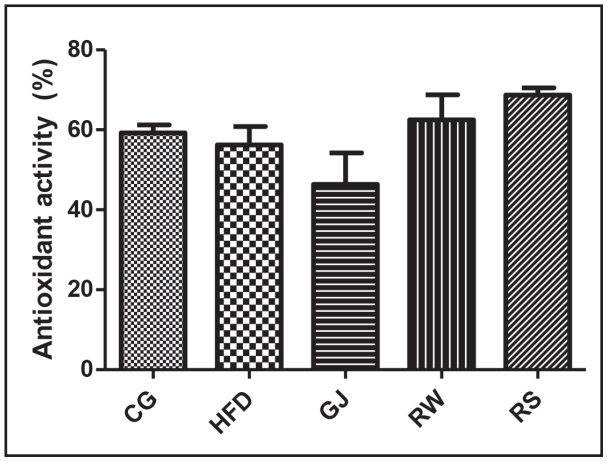

Figure 4.

DPPH plasma antioxidant activity (plasma antioxidant activity from all experimental groups using DPPH. Control group (CG) - control diet (4% fat); high fat diet group (HFD) - high fat diet (20% fat); grape juice group (GJ) - received 15 ml/day grape juice + high fat diet; red wine group (RW) - received 10 mL/day red wine + high fat diet; resveratrol solution group (RS) - received 15 ml/day resveratrol solution + high fat diet).

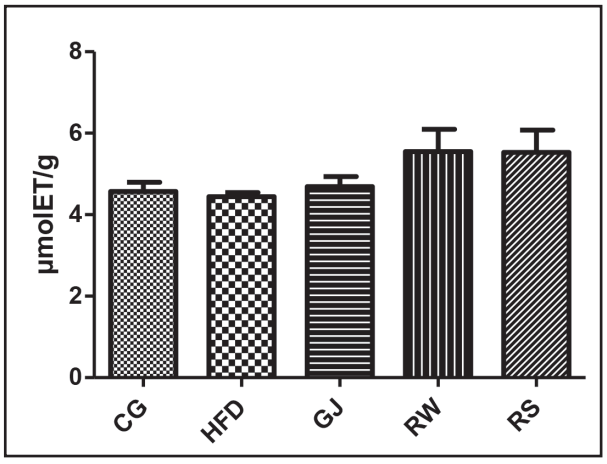

Figure 5.

ORAC plasma antioxidant activity (plasma antioxidant activity from all experimental groups using ORAC. Control group (CG) - control diet (4% fat); high fat diet group (HFD) - high fat diet (20% fat); grape juice group (GJ) - received 15 ml/day grape juice + high fat diet; red wine group (RW) - received 10 ml/day red wine + high fat diet; resveratrol solution group (RS) - received 15 ml/day resveratrol solution + high fat diet).

Correlations were observed between activities of CAT and GPx enzymes ($r = 0.47$, $p = 0.029$) and ORAC/GPx in HFD group ($r = 0.9823$, $p = 0.0177$). No other associations were observed.

DISCUSSION

High fat diets are associated with increased oxidative stress, lipid peroxidation and inflammation (2,12). To counterbalance the production of EROS (superoxide anion and hydroxyl radical), SOD, CAT and GPx are produced naturally and daily, conferring protection against damage to macromolecules such as DNA, lipids and proteins (21). Non-enzymatic antioxidants act synergistically to those enzymes. High levels of oxidative stress are directly related to several pathologies and metabolic disorders, reducing the life expectancy of individuals (2,22).

According to AIN-93M (13) recommendations, the daily consumption of lipid for adult rats should be 4%. The dietary model adopted in this study was a high fat diet containing 20% saturated fat, being this concentration five times higher than the recommended.

Some reports in literature have shown an over activity of antioxidant enzymes when there is an increase in saturated fats from diet, maintaining cellular steady-state (2,4). High fat diets increase fatty acid oxidation for energy production. Additionally, the mitochondria produces more H_2O_2 when oxidizing fatty acids than pyruvate derived from glycolysis (4).

However, in this study, the SOD and CAT activities had similar results when comparing control and treated groups. Only GPx activity was affected by high lipid intake, presenting greater activity in groups that received high fat diet. It must be noted that, in this study, 20% of saturated fat in the diet were used, but others studies found in the literature have used higher amounts of saturated fats (40-70%). Possibly, such dietary models provide a more prooxidative and EROS-rich environment, justifying an expressive increase in the SOD and CAT activity (23,24).

Although there was no statistical difference between treated and control groups in relation to the CAT activity, an important percentage difference was noted. The RW group presented three times more CAT activity than the CG, followed by the HFD, RS and GJ group.

Corroborating with other studies assessing high fat diets and GPx (25,26), groups that received a high fat diet presented a higher GPx enzymatic activity than CG. As previous studies show, high fat diet upregulates genes related to glutathione metabolism and the largest increase in GPx activity makes the cell more adapted to tolerates high concentrations of O_2 - and H_2O_2 (25).

Observing the correlation between ORAC/GPx in HFD groups, possibly the enzymatic and non-enzymatic systems are recruited to neutralize and/or minimize the damages mediated by the high fat diet, since GPx is strongly associated with lipid peroxidation as previous reported (4,26,27).

Evaluating the CAT and GPx activities, a correlation between these enzymes was expected to be found, as demonstrated in the literature. The coordination of these enzymes is crucial for the correct redox balance in cellular environment. Probably, both enzymes act in synergy, presenting the same function: convert H_2O_2 to H_2O and O_2. However, GPx is the one with the higher specificity when it comes to lipid peroxidation as demonstrated by Rindler et al. (4).

Dietetic polyphenols derived from grapes, such as resveratrol, catechin and epicatechin, are known by their antioxidant and scavenging properties against a wide range of free radicals (7,28-30). Some experimental studies suggest that treatment with resveratrol or polyphenol-rich foods/beverages, as grape juice and red wine, maintain the properly enzymatic activity of SOD, CAT and GPx (25,31).

Nevertheless, in the present study, no changes were observed in enzymatic activity of SOD and CAT in groups that received polyphenol-rich beverages.

In GPx activity, GJ presented enzymatic activity equal to CG. Similar to other studies that reported a better control of oxidative stress after grape juice ingestion (32) GC and GJ groups presented the lowest GPx activity, pointing to a possible protective effect of grape juice against high levels production of EROS induced by a high fat diet consumption. The positive result may be explained by a complex matrix of polyphenols found in grape juice, which include proanthocyanidins, ellagic acid, kampferol, myricetin, quercetin, malvidin, peonidine, cyanidin and catechin and resveratrol which act in synergy, amplifying the response in the maintenance of redox homeostasis (33).

On the other hand, red wine, despite being a source of polyphenols, including resveratrol, presents ethanol. Due to its deleterious prooxidative effect, ethanol and its main metabolite, acetaldehyde, can counteract or nullify the protective effects of polyphenols (5). Experimental studies using alcoholic beverages (wines, spirit or gin) with high fat diets show a significant increase in the produc-

tion of mitochondrial H_2O_2 and free radical reactions, producing alkoxyl and hydroxyl free radicals, being positively associated with increased lipid peroxidation, with consequent alteration of the enzymatic activity (23,34,35).

No differences in the SOD activity was noticed in RW group when compared to all groups. A study in humans using high fat diet associated with wine consumption did not find any variation in the SOD activity (36). Another study with 80 animals submitted to treatment with ethanol, water, wine and non-alcoholic wine also did not show alterations under this enzyme (37).

Comparing the difference between CAT in RW and RS group, wine consumption increased the enzymatic activity. The presence of ethanol in RW provides a more oxidative environment, leading to a higher activity when compared to the group that received resveratrol supplementation. Additionally, the consumption of ethanol led to an important percentage increase of the CAT activity (273%) when compared to all groups. Similar to our findings, the above mentioned experimental study using 80 animals also found an increase in CAT activity in groups that had chronic alcohol consumption (37).

Corroborating with the above mentioned results, GPx activity in RW group was higher than in CG, GJ and HFD groups. As was previously mentioned, ethanol and high saturated fat from diet act as prooxidants, possibly leading to a high hepatic production of EROS. Previous studies mentioned that cytochrome P450, NADPH reductase and NADPH oxidase are involved in this process, due to the inducibility of these enzymes after chronic consumption of alcoholic beverages, altering the redox status and recruiting larger amounts of GPx to maintain the oxidative balance (31,34,35).

Resveratrol supplementation, although appearing to be a promise in controlling oxidative stress, in this experimental model does not bring any benefit.

Observing the CAT and SOD activities, there were no differences between CG and RS groups. However, in the GPx activity, RS showed the highest activity when compared to the remaining groups. Animals that received higher doses of resveratrol solution and/or supplementation are prone to form higher concentrations of EROS through two distinct routes: higher expression of genes related to glutathione metabolism in response to an increased lipid peroxidation, and prooxidant activity of resveratrol when used alone at very high doses, as demonstrated in previous studies (38,39).

It is worth to observe that different sources of nutrients, as the natural antioxidants present in high polyphenols beverages used in this study, should not necessarily affect all enzymatic activicty from redox system. Antioxidant enzymes respond independently to different radicals and it can not be expected that these enzymes respond similarly (40).

In short, analyzing the antioxidant activity related to the enzymatic system, in the experimental model adopted by this study, resveratrol did not demonstrate any effect or benefit, wine may act as a prooxidant due to the ethanol content and grape juice seems to minimize the effects of a high fat diet.

Non-enzymatic system is constituted by a great variety of antioxidant substances, which can have endogenous or dietetic origin. From food sources, those that stand out most are vitamins, minerals and phenolic compounds such as vitamin A and C, selenium and zinc, lutein, resveratrol, catechins, among others (5).

The use of polyphenol-rich beverages and the mega dose of resveratrol do not seem to influence non-enzymatic antioxidant activity measured by DPPH and ORAC method, although they present an influence on CAT and GPx activity. It must be noted thatpolyphenols, in this experimental model, acted in enzymatic system but without changes in the non-enzymatic system.

CONCLUSION

In this experimental model, grape juice showed to be the most effective in minimizing the deleterious effects of a high fat diet, possibly due to a set of bioactive compounds that acted synergistically. Resveratrol did not presented any benefits and red wine demonstrates a possible harmful effect due to ethanol presence.

Thus, the use of natural matrices or food products, instead of wine and supplements, may represent a more reliable and effective alternative in nutritional and therapeutic approaches.

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REFERENCES

1. Pereira AR, Duffey KJ, Schieri R, Popkin B. Sources of excessive saturated fat, trans fat and sugar consumption in Brazil: an analysis of the first Brazilian nationwide individual dietary survey. Public Health Nutr 2014;17(1):113-21.
2. Selvi MNK, Sridhar MG, Swaminathan P, Sripradha R. Curcumin attenuates oxidative stress and activation of redox-sensitive kinases in high fructose and high-fat-fed male wistar rats. Sci Pharm 2015;83(1):159-75.
3. Oliveira TB, Rogero MM, Genovese MI. Poliphenolic-rich extracts from cocoa (Theobroma cacao L.) and cupuaçu (Theobroma grandiflorum Wild. Ex Spreng. K. Shum) liquors: A comparison of metabolic effects in high-fat fed rats. Pharma Nutr 2015;3(2):20-8.
4. Rindler PM, Plafker, SM, Szweda, LI, Kinter, M. High dietary fat selectively increases catalase expression within cardiac mitochondria. J Biol Chem 2013;288(3): 1979-90.
5. Barbosa K, Costa N, Alfenas R, Paula S, Minim V, Bressan J. Estresse oxidativo: conceito, implicações e fatores modulatórios. Rev Nutr Campinas 2010;23(4):629-43.
6. Rover Junior LR, Hoehr NF, Vellasco AP, Kubota LT. Sistema antioxidante envolvendo o ciclometabólico da glutationa associado a métodos eletro analíticos na avaliação do estresse oxidativo. Quim Nova 2001;24(1):112-9.
7. Noguer MA, Cerezo AB, Navarro ED, Garcia-Parilla MC. Intake of alcohol-free red wine modulates antioxidante enzyme activities in a human intervention study. Pharmacol Res 2012;65(6):609-14.
8. Yuzefovych LV, Musyienko SI, Wilson G, Rachek L. Mitochondrial DNA damage and dysfunction, and oxidative stress are associated with endoplasmic reticulum stress, protein degradation and apoptosis in high fat diet-induced insulin resistance mice. PLOS One 2013;8(1):1-8.

9. Charradi K, Elkahoui S, Limann F, Aouani E. High-fat diet induced an oxidative stress in white adipose tissue and disturbed plasma transition metals in rat: prevention by grape seed and skin extract. J Physiol Sci 2013;63(6):445-55.
10. Rahal A, Kumar A, Singh V, Yadav B, Tiwari R, Chakraborty S, et al. Oxidative stress, prooxidants and antioxidants: the interplay. BioMed Res Int 2014:1-19.
11. Ghanim H, Sia CL, Korzeniewski K, Lohano T, Abuaysheh S, Marumganti A, et al. Resveratrol and polyphenol preparation suppresses oxidative and inflammatory stress response. J Clin Endocrinol Metab 2011;96(5):1409-14.
12. Patil BS, Jayaprakasha GK, Chidambara Murthy KN, Vikram A. Bioactive compounds: historical perspectives, opportunities and challenges. J Agric Food Chem 2009;57(18):8142-60.
13. Reeves PG, Nielsen FH, Fahey Jr GC. AIN-93 purified diets for laboratory rodents: final report of the American Institute of Nutrition ad hoc writing committee on the reformulation of the AIN-76A rodent diet. J Nutr 1993;123(11):1939-51.
14. Bannister JV, Calabrese L. Assays for superoxide dismutase. Methods Biochem Anal 1987;32:279-312.
15. Aebi H. Catalase in vitro. Methods Enzymol 1984;105:121-6.
16. Flohe L, Gunzler WA. Assays of glutathione peroxidase. Methods Enzymol 1984;105:114-21.
17. Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem 1976;72:248-54.
18. Prior RL, Hoang H, Gu L, Wu X, Bacchiocca M, Howard L, et al. Assays for hydrophilic and lipophilic antioxidant capacity (oxygen radical absorbance capacity (ORACFL) of plasma and other biological and food samples. J Agric Food Chem 2003;51(11):3273-9.
19. Brand-Wiliams W, Cuvelier ME, Berset C. Use of a free radical method to evaluate antioxidant activity. Food Sci Technol 1995;28(1):25-30.
20. Mensor LL, Menezes FS, Leitao GG, Reis AS, Santos TC, et al. Screening of brazilian plant extracts for antioxidant activity by the use of dPPH free radical method. Phytother Res 2001;15(2):127-30.
21. Vargas-Robles H, Rios A, Arrellano-Mendoza M, Escalante B, Schnoor M. Antioxidative diet supplementation reverses high-fat diet-induced increases of cardiovascular risk factors in mice. Oxid Med Cell Longev 2015;1-9.
22. Catagol B, Batirel S, Taga Y, Ozer N. Resveratrol: French paradox revisited. Front Pharmacol 2012;3(141):1-18.
23. Macedo LFL, Rogero MM, Guimarães JP, Granato D, Lobato LP, Castro IA. Effect of red wines with different in vitro antioxidant activity on oxidative stress of high-fat diet rats. Food Chem 2013;137(1-4):122-9.
24. Cui R, Gao M, Qu S, Liu D. Over expression of superoxide dismutase 3 gene blocks high fat diet-induced obesity, fatty liver and insulin resistance. Gene Ther 2014;21(9):840-8.
25. Sekine Y, Osei-Hwedieh D, Matsuda K, Raghavachari N, Liu D, Furuya Y, et al. High fat diet reduces the expression of glutathione peroxidase 3 in mouse prostate. Prostate 2011;71(14):1499-509.
26. Buchner I, Medeiros N, Lacerda SL, Normann CA, Gemelli T, Rigon P, et al. Hepatoprotective and antioxidant potential of organic and conventional grape juices in rats fed a high-fat diet. Antioxidants (Basel) 2014;3(2):323-38.
27. Weydert C, Cullen J. Measurement of superoxide dismutase, catalase and glutatione peroxidase in cultured cells and tissue. Nat Protoc 2010;5(1):51-66.
28. Inglés M, Gambini J, Miguel MG, Bonet-Costa V, Abdelaziz K, El Alami M, et al. Mediates the antioxidant effect of resveratrol at nutritionally relevant concentrations. Biomed Res Int 2014:1-6.
29. Meng C, Liu J, Du A. Cardioprotective effect of resveratrol on atherogenic diet-fed rats. Int J Clin Exp Pathol 2014;7(11):7899-906.
30. Madrigal-Perez LA, Ramos-Gomes M. Resveratrol inhibition of cellular respiration: new paradigm for an old mechanism. Int J Mol Sci. 2016;17(3):368.
31. Pires KMP, Valença SS, Resende AC, Porto LC, Queiroz EF. Grape skin extract reduced pulmonary oxidative response in mice exposed to cigarette smoke. Med Sci Monit 2011;17(8):BR187-95.
32. Toaldo M, Cruz FA, Silva EL, Bordignon-Luiz MT. Acute consumption of organic and conventional tropical grape juices (V.L.) increases antioxidants in plasma and erythrocytes, but not glucose and uric acid levels in healthy individuals. Nutr Res 2016;36(8):1-34.
33. Melo PS, Massarioli AP, Denny C, Santos FL, Franchin M, Pereira GE, et al. Winery by-products: extraction optimization, phenolic composition and cytotoxic evaluation to act as a new source of scavenging of reactive oxygen species. Food Chem 2015;181:160-9.
34. Demori I, Voci A, Fugassa E, Burlando B. Combined effects of high-fat diet and ethanol induce oxidative stress in rat liver. Alcohol 2006;40(3):185-91.
35. Das SB, Vasudevan DM. Alcohol-induced oxidative stress. Life Sci 2009;81(3):177-87.
36. Renzo L, Carraro A, Valente R, Iacopino L, Colica C, De Lorenzo A. Intake of red wine in different meals modulates oxidized LDL level, oxidative and inflammatory gene expression in healthy people: a randomized crossover trial. Oxid Med Cell Longev 2014:1-9.
37. Rodrigo R, Rivera G, Orellana M, Araya J, Bosco C. Rat kidney antioxidant response to long-term exposure to flavonol rich red wine. Life Sci 2002;71(24):2881-95.
38. Brown L, Kroon P, Das DK, Das S, Tosaki A, Chan V et al. The biological responses to resveratrol and other polyphenols from alcoholic beverages. Alcohol Clin Exp Res 2009;33(9):1513-23.
39. Mukherjee S, Dudley J, Das D. Dose-dependency of resveratrol in providing health benefits. Dose Response 2010;8(4):478-500.
40. Marineli RS, Lenquiste SA, Moraes EA, Marostica Junior MR. Antioxidant potential of dietary chia seed and oil (Salvia hispanica L.) in diet-induced obese rats – part III. Food Res Int 2015;76:666-76.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Otros

Metabolic, inflammatory and oxidative stress markers in the nitric oxide variation of hemodialysis subjects

Marcadores de estrés metabólico, inflamatorio y oxidativo en la variación del óxido nítrico de los individuos de hemodiálisis

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Abstract

Introduction: Oxidative stress markers such as nitric oxide (NO) have been investigated in hemodialysis (HD).

Objective: Evaluate the association of NO variation with adiposity indicators, metabolic, inflammatory and oxidative stress markers in individuals to HD.

Methods: Cross-sectional study with 85 subjects on HD treatment (≥ 18 years). The clinical-nutritional status was evaluated through subjective global assessment modified (SGAm), anthropometric measurements and body composition. Dietary intake was evaluated using a food frequency questionnaire. Metabolic markers were obtained from medical records. Inflammatory markers (IL-6 and IL-10) and oxidative stress, (TACs), (SOD), (GST), (MDA) and NO were determined using standardized protocols.

Results: Those individuals with a high concentration of NO (> 4.32 µmol/L) had lower values for SGAm score ($p = 0.012$) and higher iron values ($p = 0.050$), Fe saturation ($p = 0.037$) and triacylglycerol ($p = 0.003$). The same subjects still had lower consumption of copper ($p = 0.026$), manganese ($p = 0.035$), vitamin E ($p = 0.050$), ω3 ($p = 0.021$) and ω6 ($p = 0.020$). In a multiple regression model, concentrations of ferritin, triacylglycerol, IL6 and SOD contributed to a 54.8% increase in NO concentrations, whereas triacylglycerol and SOD concentrations were independent factors for NO variation ($p < 0.001$).

Conclusions: The clinical and nutritional status as well as intake of nutrients with antioxidant properties (Cu, Zn, Mn, vitamin C and ω3) appears to modulate the variation of NO in this population.

Key words:

Reactive nitrogen species. Inflammation. Superoxide dismutase. Food intake. End-stage renal disease.

Resumen

Introducción: se han investigado marcadores de estrés oxidativo como el óxido nítrico (NO) en hemodiálisis (HD).

Objetivo: evaluar la asociación de la variación del NO con los indicadores de adiposidad, los marcadores metabólicos, inflamatorios y de estrés oxidativo en individuos a HD.

Métodos: estudio transversal con 85 sujetos en tratamiento HD (≥ 18 años). El estado clínico-nutricional se evaluó a través de la evaluación global subjetiva modificada (SGAm), medidas antropométricas y composición corporal. La ingesta dietética se evaluó mediante un cuestionario de frecuencia alimentaria. Marcadores metabólicos se obtuvieron de los registros médicos. Se determinaron marcadores inflamatorios (IL-6 e IL-10) y estrés oxidativo (TAC), (SOD), (GST), (MDA) y NO mediante protocolos estandarizados.

Resultados: los individuos con una alta concentración de NO (> 4,32 µmol/L) tuvieron valores más bajos de puntuación de SGAm ($p = 0,012$) y mayores valores de hierro ($p = 0,050$), saturación de Fe ($p = 0,037$) y triacilglicerol ($p = 0,003$). Los mismos sujetos tuvieron un menor consumo de cobre ($p = 0.026$), manganeso ($p = 0,035$), vitamina E ($p = 0,050$), ω3 ($p = 0,021$) y ω6 ($p = 0,020$). En un modelo de regresión múltiple, las concentraciones de ferritina, triacilglicerol, IL6 y SOD contribuyeron a un aumento de 54,8% en las concentraciones de NO, mientras que las concentraciones de triacilglicerol y SOD fueron factores independientes para la variación del NO ($p < 0,001$).

Conclusiones: el estado clínico y nutricional así como la ingesta de nutrientes con propiedades antioxidantes (Cu, Zn, Mn, vitamina C y ω3) parecen modular la variación del NO en esta población.

Palabras clave:

Especies nitrogenadas reactivas. Inflamación. Superóxido dismutasa. Ingesta de alimentos. Enfermedad renal terminal.

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INTRODUCTION

Chronic kidney disease (CKD) is a worldwide health problem due to its high incidence (1). High morbidity and mortality in CKD is associated with its own progression to end-stage renal disease (ESRD) and the development of other metabolic disorders that increase the risk for cardiovascular diseases (2).

In turn, hemodialysis (HD), an essential treatment in ESRD, contributes to the increase of oxidative stress due to a diminished antioxidant system, and subsequently to the manifestation of inflammation and endothelial dysfunction, all risk factors for atherosclerosis in this population (3). Thus, oxidative stress markers have gained interest as non-traditional cardiometabolic risk factors in ESRD (4).

Among the markers of oxidative stress, nitric oxide (NO), a recognized vasodilator and cardioprotector, is prominent (5). Many cells are able to synthesize NO by the activity of the enzyme nitric oxide synthase (NOS), which converts the amino acid L-arginine to NO and L-citrulline (6). NO has important functions in renal physiology such as maintenance of homeostasis in blood flow, renal excretion and renin secretion; and tubule glomerular return (7). However, NO may be toxic under conditions of oxidative stress, from the generation of reactive oxygen species (ROS) and deficiency of the antioxidant system (8).

In this context, NO concentrations could be associated with other markers of oxidative stress and inflammation in the ESRD, although there were little studies regarding this topic (9).

Overall, the present cross-sectional study aimed to evaluate the potential association of NO variation with adiposity indicators, as well as metabolic, inflammatory and oxidative stress markers in individuals submitted to HD.

MATERIAL AND METHODS

STUDIED POPULATION

This is a cross-sectional study with 85 subjects on HD treatment (≥ 18 years old), the majority of participants were men (65.9%; n = 56) and the average age was 62 ± 13.7 years old attended in a single dialysis center. Patients underwent three weekly sessions of HD with an average duration of 4 hours, blood flow greater than 250 mL/min and dialysate flow of 500 mL/min. Individuals who did not show interest in participating in the study, with a treatment time of less than one month in HD and those with hearing impairment, newly implanted catheters, hemodynamic instability, evaluated by the doctor of the sector, and those unable to stand for anthropometric evaluation were not included in the study.

CLINICAL-NUTRITIONAL STATUS ASSESSMENT

The clinical-nutritional status was assessed using nutritional risk score subjective global assessment modified (SGAm), and anthropometric and body composition measurements. The SGAm used was based on the model proposed by Kalantar- Zadeh et al. (10) for renal patients on dialysis.

Anthropometry and tetrapolar electrical bioimpedance (BIA) were performed approximately 30 minutes after the end of HD. The anthropometric measures included dried weight (kg), height (cm), and waist circumference (WC), which were performed according to previously standardized procedures (11-13).

Body mass index (BMI) was calculated and individuals were classified according to the cut-off points of the World Health Organization (14) for adults and Lipschitz (15) for the elderly. The individuals were classified according to the cardiometabolic risk, according to the CP values, using the WHO cut-off points, 1995 (14).

DIETARY INTAKE ASSESSMENT

A semi-quantitative food frequency questionnaire was constructed, based on an Australian questionnaire validated for renal patients (16,17). Thus, the food portions of each group were analyzed according to the Food Guide for the Brazilian Population (2006) (18): cereals, tubers and roots, fruits, vegetables and legumes, and other vegetable foods rich in proteins, milk and dairy products, meat and eggs, fats, sugars and salt, water. The oilseeds group was also inserted, according to the Food Guide for Brazilian Population (2014) (19). The reference portion was based on the Family Budget Survey (POF) 2008 table (19). The fruit and vegetable group was divided into high, medium and low potassium.

Nutrient intake was calculated as frequency x nutrient composition of each portion size for each consumed food item, in spreadsheet in Microsoft Excel 2010, according to the nutritional composition of foods of Brazilian tables (20). Therefore, we evaluated the daily caloric intake (kcal), carbohydrates, protein, lipids and fatty acid profile (in percentage of caloric intake), fiber (g), calcium (g), phosphorus (mg), potassium (mg) and sodium (mg), magnesium (mg), manganese (mg), iron (mg) , selenium (µg), thiamine (mg), niacin (mg), cyanocobalamin (µg), vitamin E (IU), vitamin C (mg) and folate (mg).

METABOLIC MARKERS

The metabolic markers analyzed in the present study were those obtained from medical records: albumin, urea, urea removal rate (URR), creatinine, potassium, phosphorus, calcium, calcium-phosphorus (Ca-P) product, parathyroid hormone (PTH), hemoglobin (Hb), hematocrit (Ht), ferritin, iron (Fe), transferrin saturation (SatFe), C-reactive protein (CRP), triacylglycerol and total cholesterol. The Kt/V was calculated using the equation proposed by Daugirdas II (21). Values of urea Kt/V > 1.2 were considered indicative of efficiency in HD.

INFLAMMATORY AND OXIDATIVE STRESS MARKERS

Blood samples were collected before the beginning of HD. Blood was collected in (Vacutainer®) tubes containing EDTA as anticoag-

ulant. Serum was separated in a refrigerated centrifuge (15 min, 3000 rpm, 4 °C) and both stored at -80 °C for posterior analysis. Serum IL-2, IL-4, IL-6, IL-10 concentrations were measured by flow cytometry technique with the BD FACverse Cytometer, using the Human Th1/Th2/Th17 CBA Kit (BD Biosciences, USA) at the Laboratory of General Biology, Department of General Biology, Universidade Federal de Viçosa. The results were obtained using the software Facsuite (BD®). Serum total antioxidant capacity (TAC), enzymes activity superoxide dismutase (SOD), and glutathione S-transferase (GST), the lipid peroxidation product malondialdehyde (MDA) and NO were considered as biomarkers of oxidative stress. TAC was measured by colorimetric assay using the Antioxidant Assay Kit (CS0790, Sigma Aldrich), according to the protocol provided by the manufacturer, and other markers were assessed standardized protocols of the Laboratory of Echophysiology of Chiroptera - Department of Animal Biology, Universidade Federal de Viçosa, as follows.

Activity of antioxidant enzymes

SOD activity was measured in serum in a microplate reader (λ = 570 nm) (22), based on the ability of this enzyme to catalyze the reaction of superoxide radical (O_2^-) thus decrease the auto-oxidation ratio of pyrogallol. The results were expressed as U SOD/ mg protein.

GST was measured through the formation of GSH conjugate, 2.4- dinitrobenzene (CDNB), and estimated by the change in absorbance at 340 nm for 60s. The molar extinction coefficient of CDNB at 340 nm is 9.6 $mM^{-1}cm^{-1}$, which was used for the calculations (23). GST activity was expressed as µmol/min^-/g.

Malondialdehyde

The concentration of MDA was estimated as described by Wallin et al. (24). 200 µl aliquots of each serum sample were separated and added to a 400 µl of heated, vortex homogenized solution TBARS whit trichloroacetic acid (15%) / thiobarbituric acid (0.375%) / hydrochloric acid (0.25 M) for 40 minutes in boiling water (90 °C) and then cooled in an ice bath for 5 minutes. 600 µL of butyl alcohol were added and again homogenized in vortex for ~ 2 minutes. The solutions were centrifuged at 3,000 rpm at room temperature (10 minutes at 900g). 200 uL of the supernatant were separated for quantifying the MDA concentration in microplate reader (λ = 535 mm). The concentration of MDA was determined by standard curve from known concentrations of 1,1,3,3-tetramethoxypropane (TMPO). The results were expressed as µM/mg protein.

Nitric oxide

The serum for the NO tests was prepared as described above. The production of nitric oxide was indirectly quantified through nitrite content in the serum sample by the Griess reaction(25), composed of 1% sulfanilamide and 0.1% naphthyl-ethylene-diamine in 2.5% in 2,5% H_3PO_4. Thus, 50 µL of the supernatant from the samples were added to microplates with equal volume of the Griess Reactant and incubated at room temperature for 15 minutes, then determined on a microplate reader (λ = 570 nm). The nitrite concentration of the samples was determined using standard curve with known concentrations of sodium nitrite ($NaNO_2$) and expressed in **M**m/mg protein.

The protein concentration used in the calculations of the activity of antioxidant enzymes, MDA, and NO was measured by the method of Lowry et al. (1951), using bovine serum albumin as previously standardized (26).

STATISTICAL METHOD

Normal distribution of the data was determined using the Kolmogorov-Smirnov test. Data were expressed as mean ± standard deviation, median (interquartile range). The study population was divided by the median NO concentrations (4.32 µmol/L) in low and high NO concentration. The median cutoff criteria have been previously applied based (27) on a valid and reliable method to assign two groups of risk in epidemiological studies (28).

Comparisons between groups were performed using Student's t-test for parametric variables, or Mann-Whitney, for non-parametric variables. The correlation analysis between variables of interest was performed using Pearson or Spearman correlation coefficient, as appropriate. Multiple regression analysis was used to determine indicators of the variation of NO concentration of the sample studied. For the construction of multiple linear models, the value of $p \leq 0.20$ obtained in the bivariate analysis was used as criterion for inclusion of the variables. In the final model, the backward method was used, for which the variables with less significance (greater p value) were removed one by one from the model.

Statistical analysis was performed using the SPSS 20.0 program (SPSS, Inc., Chicago, IL, USA) and a significance level of less than 5% was applied.

RESULTS

STUDY SAMPLE

The majority of the participants were men (65.9%; n = 56) and elderly (61.2%, n = 52). The main causes of CKD in the study population were hypertensive nephrosclerosis (41.2%; n = 35) and diabetes mellitus (32.9%; n = 28). The HD time ranged from 1 to 245 months, with a median of 41.5 months, presenting a statistical tendency when associated with NO (p = 0.062). In addition, the sample presented mean of Kt/V (1.52 ± 0.39) and serum albumin (4.08 ± 0.24 g/dL) as excepted to HD efficiency and nutritional adequacy. Regarding dietary intake, these individuals have an energy balance for macronutrients, with a high consumption of food sources of potassium 2,548.50 mg/d (935.4-8, 276, 0).

NO AND CLINICAL-NUTRITIONAL STATUS

In relation to weight status evaluated by BMI, 9.1% (n = 3) of adults were classified as underweight, 72.7% (n = 24) as normal weight, 15.2% (n = 5) pre-obese and 3% (n = 1) obesity class I. Among the elderly, 34.6% (n = 18) were classified as underweight, 44.2% (n = 23) normal weight and 21.2% (n = 11) were overweight. There was no statistical difference in relation to NO concentration (p = 0,395), according to weight status.

According to mSGA, nutritional status was adequate in 10.6% (n = 9) of the individuals, while 89.4% (n = 76) were at nutritional risk / mild malnutrition. Interestingly, the mSGA score was statistically lower in subjects with high NO (p = 0.012). By the WC, central adiposity indicator according to WHO (1997) (18), 22.4% of the patients had a high risk and a very high risk of obesity-related metabolic complications, with a very high risk being greater among women. By total body fat, 20.0% had fat shortage and 23.5%, excess fat. There was no statistical difference with these adiposity indicators in relation to NO concentration (Table I).

NO AND DIETARY INTAKE

Daily intake of total calories, alpha-linolenic fatty acid (ω3) and linoleic acid (ω6) were different according to median of NO concentration (Table II). In relation to micronutrients, a higher consumption of manganese, copper, zinc, selenium, vitamin B12 and Vitamin C was observed as well as a statistical tendency for lower consumption of vitamin E and niacin in those individuals with high NO.

Table I. Clinical and metabolic characteristics of the studied sample (n = 85), according to the median of nitric oxide concentrations (4.32 µmol/L)

Variables	Low NO (n = 43)	High NO (n = 42)	p-value
Age (years)	61.3 ± 14.0	62.7 ± 13.4	0.637
Dried body weight (kg)	60.4 ± 10.2	62.4 ± 11.8	0.425
HD time (months)	52.0 (0.0-245.0)	33.5 (1.0-147.0)	0.062
BMI (kg/m^2)	23.1 ± 3.9	23.8 ± 3.5	0.395
WC (cm)	88.1 ± 9.6	91.0 ± 10.35	0.198
Lean mass (kg)	44.5 ± 9.0	44.8 ± 8.7	0.877
Visceral fat mass (kg)	8.6 ± 3.8	9.9 ± 3.9	0.145
Total body fat (%)	21.9 ± 10.9	23.6 ± 7.6	0.145
SGAm	13.0 (9.0-21.0)	11.0 (8.0-19.0)	*0.012*
Albumin (g/dL)	4.0 (3.8-5.0)	4.0 (4.0-5.0)	0.449
RRU	67.5 ± 7.4	69.0 ± 8.3	0.389
Ferritin (ng/mL)	455.5 ± 333.1	606.1 ± 449.1	0.084
Iron (µg/dL)	58.2 ± 21.8	67.1 ± 21.1	*0.050*
SatFe (%)	26.7 ± 12.0	32.1 ± 11.4	*0.037*
Hb (mg/dL)	11.0 (5.0-14.0)	11.0 (7.0-14.0)	0.664
Creatinine (mg/dL)	8.89 ± 2.4	8.69 ± 3.7	0.743
Pre-dialysis urea (mg/dL)	123.9 ± 32.2	121.9 ± 34.3	0.778
Post-dialysis urea (mg/dL)	37.0 (14.5-83.0)	42.0 (10.0-110.0)	0.283
Kt/V	1.49 ± 0.31	1.54 ± 0.47	0.601
PTH (pg/mL)	308.0 (75.0-1771.0)	250.5 (34.9-883.6)	*0.044*
Calcium (mg/dL)	9.0 (4.5-10.0)	9.0 (7.0-10.0)	0.956
Phosphorus (mg/dL)	4.0 (2.0-8.0)	4.9 (2.0-10.0)	0.618
Ca-P product	39.23 ± 14.9	39.3 ± 16.5	0.971
Triacylglycerol (mg/dL)	147.0 (42.0-330.0)	181.0 (65.0-934.0)	*0.003*
Cholesterol (mg/dL)	183.3 ± 41.8	195.5 ± 42.4	0.185

BMI: body mass index; WC: waist circumference; SGAm: subjective global assessment modified; RRU: rate of reduction of urea; SatFe: transferrin saturation; Hb: Hemoglobin; PTH: parathyroid hormone. Values expressed as mean ± SD or median and confidence interval according to distribution; p-values by Student t-test or Mann-Whitney test, as appropriated.

Table II. Dietary intake of the studied sample (n = 85), according to the median of nitric oxide concentrations (4.32 µmol/L)

Daily intake	Low NO (n = 43)	High NO (n = 42)	p-value
Caloric intake (Kcal)	2726.5 (821.0-6666.9)	2205.3 (912.4-6241.6)	*0.045*
Protein (%VCT)	11.6 (7.07-19.37)	12.9 (8.52-24.20)	*0.035*
Lipid (%VCT)	31.5 (18.51-62.83)	30.1 (17.02-46.50)	0.705
Carbohydrate (%VCT)	56.52 ± 9.28	56.21 ± 6.35	0.857
Fiber (g)	27 (12.2-86.1)	25.5 (9.2-68.1)	0.271
Cholesterol (mg)	242.0 (35.4-759.5)	232.3 (63.6-729.8)	0.806
Saturated fat (%VCT)	7.95 (4.66-23.51)	8.37 (5.49-15.33)	0.429
Monounsaturated fat (%VCT)	9.63 (4.98-26.87)	9.07 (4.46-16.40)	0.660
Polyunsaturated fat (%VCT)	10.93 ± 3.92	9.72 ± 3.38	0.131
Linoleic fatty acid (ω6) (g)	39.9 (5.2-103.1)	21.6 (3.7-61.9)	*0.020*
α-linoleic fatty acid (ω3) (g)	4.3 ± 2.9	3.2 ± 1.9	*0.021*
Calcium (g)	684.1 (199.4-2952.7)	645.6 (229.1-2036.8)	0.847
Magnesium (mg)	271.1 (115.3-907.2)	247.9 (102.0-779.9)	0.345
Manganese (mg)	5.0 (1.5-16.7)	3.8 (1.1-21.4)	*0.035*
Potassium (mg)	2564 (1005-8276)	2439 (935-8268)	0.285
Sodium (mg)	1526.0 (448.6-8346.5)	1517.3 (279.3-5189.1)	0.368
Phosphorus (mg)	417.3 (120.6-1213.0)	350.0 (121,61574,6)	0.277
Iron (mg)	14.4 (4.4-180.2)	12.3 (4.8-337.7)	0.482
Copper (µg)	1.6 (0.5-219.7)	1.2 (0.4-221.0)	*0.026*
Zinc (mg)	116.3 (3.1-385.8)	133.4 (3.9-559.8)	0.900
Selenium (µg)	100.3 (27.8-302.4)	87.2 (28.1-290.0)	0.552
Thiamine (mg)	1.6 (0.6-5.5)	1.3 (0.5-5.2)	0.084
Niacin (mg)	14.0 (4.2-42.5)	13.0 (4.0-59.5)	0.058
Vitamin B6 (mg)	1.8 (0.4-5.5)	1.6 (0.4-6.8)	0.117
Vitamin B9 (mg)	417.3 (120.6-1213.0)	350 (121.6-1574.4)	0.277
Vitamin B12 (µg)	2.7 (0.4-20.2)	3.5 (1.0-39.9)	0.549
Vitamin E (UI)	8.1 (2.8-19.5)	7.2 (1.5-19.0)	*0.050*
Vitamin C (mg)	177.1 (19.3-2575.6)	151.7 (11.6-1505.8)	0.241

Values expressed as mean ± SD or median and confidence interval according to distribution; p-values by Student t-test or Mann-Whitney test, as appropriated.

NO AND METABOLIC MARKERS

Regarding metabolic markers, mean values of iron and satFe are in the normal range and are statistically higher in subjects with a high NO concentration (Table I). PTH presented lower values for median in subjects with high NO concentrations ($p = 0.044$), whereas an inverse behavior was observed with serum triglyceride levels ($p = 0.003$) at high NO concentrations. On the other hand, ferritin presented a significant trend ($p = 0.084$) with a mean higher than that recommended for high NO concentrations.

NO, INFLAMMATORY MARKERS AND OXIDATIVE STRESS

Interestingly, there was a positive correlation of NO with the SOD enzyme ($r = 0.616$ $p < 0.001$), and negative correlation with total protein ($r = -0.214$ $p = 0.049$), as shown in figure 1. No significant correlations were found among others markers such as MDA and GST, or TAC when related to NO. Furthermore, NO concentrations were negatively correlated with IL-6 and IL-10 concentrations, pro- and anti-inflammatory markers, respectively (Fig. 2).

In addition, the possible contribution of clinical and anthropometric variables, as well as metabolic, inflammatory and oxidative stress markers, and dietary intake to the NO variation in HD individuals were evaluated through bivariate regression analysis. Thus, IL-6, SOD, triacylglycerols, iron, transferrin saturation, ferritin and ingestion of ω6 were significantly association with NO concentration (Table III). In relation to inflammatory and oxidative stress markers, MDA, SOD, GST and IL-10 were positively associated, whereas IL-2, IL-4 and IL-6 formed negative predictors of NO (Table IV).

Finally, in the multiple regression model, the concentrations of ferritin, triacylglycerols, IL-6 and SOD contributed with a 54.8% of variation in NO concentrations, whereas triacylglycerols and SOD concentrations were independent predictors (Table V).

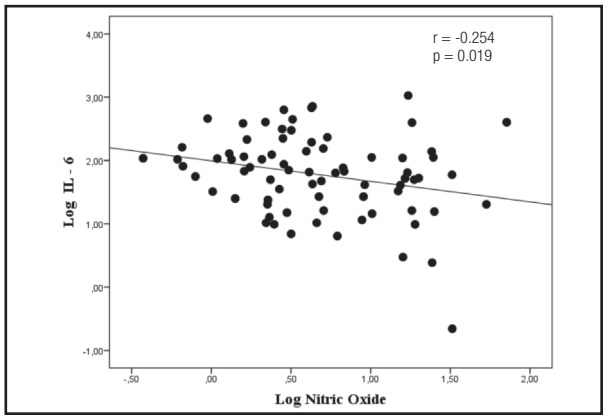

Figure 1.

Spearman correlation between nitric oxide and Interleukin 6 in subjects in HD (n = 85).

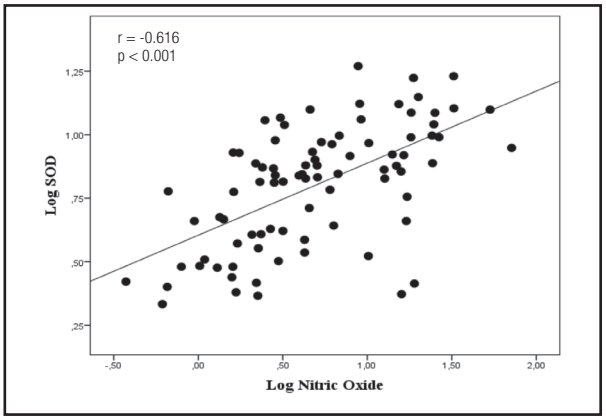

Figure 2.

Spearman correlation between nitric oxide and SOD (superoxide dismutase) in subjects in HD (n = 85).

Table III. Bivariate linear regression to explain the variation of NO concentrations (dependent variable) in subjects in HD (n = 85) in relation to clinical-metabolic variables

Independent variables	Coefficient (β)	CI 95%	p-value	R^2
Gender	-0.360	-0.262-0.191	0.756	0.00
Age (years)	-0.165	-0.382-0.053	0.135	0.02
HD time (months)	-0.001	-0.003-0.001	0.219	0.01
Kt/V	0.128	-0.142-0.398	0.348	0.01
BMI (kg/m²)	0.018	-0.010-0.047	0.206	0.01
WC (cm)	0.008	-0.003-0.018	0.154	0.01
RCQ	1.171	-0.212-2.555	0.096	0.03
Lean mass (kg)	0.000	-0.013-0.012	0.967	0.00
Visceral fat (kg)	0.019	-0.008-0.046	0.159	0.02
Total corporal fat (%)	0.004	-0.008-0.015	0.536	0.00
Liquid rate	-0.008	-0.021-0.005	0.217	0.01
SGAm	0.032	-0.073-0.010	0.135	0.02
Albumin (g/dL)	-0.046	-0.493-0.400	0.837	0.00
PTH (pg/mL)	0.000	0.000-0.000	0.258	0.01
Calcium (mg/dL)	0.009	-0.113-0.132	0.879	0.00
Triacylglycerol (mg/dL)	0.002	0.001-0.002	*< 0.001*	0,26
Ferritin (ng/mL)	0.000	0.000-0.001	*0.026*	0.05
Iron (µg/dL)	0.004	- 0.001-0.009	0.111	0.03
SatFe (%)	0.009	0.00-0.018	*0.049*	0.04
Calorie intake (Kcal)	0.005	0.000-0.000	0.096	0.03
Protein consumption (g)	-0.002	-0.005-0.001	0.232	0.01
Lipid consumption (g)	-0.002	-0.004-0.000	*0.070*	0.03
Carbohydrate consumption (g)	0.000	-0.001-0.000	0.108	0.03
Polyunsaturated fat (g)	-0.005	-0.011-0.000	*0.050*	0.04
ω3 (g)	-0.044	-0.091-0.003	*0.064*	0.04
ω6 (g)	-0.006	-0.012-0.000	*0.049*	0.21
Manganese (mg)	-0.022	-0.056-0.011	0.187	0.02
Copper (mg)	-0.002	-0.005-0.001	0.208	0.01
Zinc (mg)	0.000	-0.001-0.001	0.819	0.00
Selenium (µg)	0.001	-0.002-0.001	0.569	0.00
Vitamin E (mg)	-0.019	-0.047-0.009	0.176	0.02
Vitamin C (mg)	0.000	-0.001-0.000	0.237	0.01
Niacin (mg)	-0.009	-0.021-0.003	0.153	0.02

BMI: body mass index; WC: waist circumference; SGAm: subjective global assessment modified; RRU: rate of reduction of urea; SatFe: saturation transferrin; PTH: parathyroid hormone.

Table IV. Bivariate linear regression to explain the variation of NO concentrations (dependent variable) in subjects in HD (n = 85) in relation to inflammatory markers and oxidative stress

Independente variables	Coefficient (β)	CI 95%	p-value	R^2
Superoxide dismutase	0.532	0.352-0.713	*< 0.001*	0.293
Malondialdehyde	0.279	0.073-0.485	*0.009*	0.080
Glutathione-S- tranferase	0.140	- 0.073-0.353	0.194	0.020
Total antioxidant capacity	-0.134	- 0.347-0.079	0.216	0.018
IL-2	-0.024	- 0.053-0.005	0.101	0.032
IL-4	- 0.113	- 0.214-0.013	*0.028*	0.057
IL-6	- 0.253	- 0.461- 0.045	*0.018*	0.066
IL-10	0.171	- 0.180- 0.024	*0.011*	0.075
IL-17	- 0.010	- 0.093-0.072	0.807	0.001
C-reactive protein	0.002	- 0.994-0.998	0.997	0.000

Table V. Multiple linear regression to explain the variation of NO concentrations (dependent variable) in subjects in HD (n = 85)

Independent variables	Coefficient (β)	CI 95%	(β) Standardized	p-value
Ferritin (ng/mL)	0.084	-0.100-0.267	0.073	0.366
Triacylglycerols (mg/dL)	0.931	0.598-1.265	0.455	*< 0.001*
IL-6 (pg/ml)	- 0.55	-0.183-0.072	-0.070	0.388
SOD (U/mg protein)	0.973	0.644-1.302	0.479	*< 0.001*

Adjusted R2: 0.548. F-test p < 0.0001. IL-6: interleukin 6; SOD: superoxide dismutase.

DISCUSSION

The present study evaluated the potential association of NO variation with metabolic, inflammatory and oxidative stress markers in individuals submitted to HD. Our most relevant result was the concentration of SOD, also recognized marker of oxidative stress, as an independent predictor of NO variation.

In this context, NO produced by eNOS under favorable conditions may induce the production of SOD in the muscular layer of the vessel and extracellularly reducing available superoxide radicals (O_2^-) and, consequently, peroxynitrite production (ONOO-) and oxygen reactive species (ROS) expression. In fact, increased production of ROS, such as superoxide, hydrogen peroxide and lipoperoxides, in addition to decreased NO synthesis and concentrations of antioxidants such as vitamin E and SOD, has been observed in hypertension patients when compared to normal individuals. These individuals with hypertension still have decreased concentrations of antioxidants such as vitamin E and SOD (29). It is worth mentioning that vitamin E could also have a pro-oxidant action under special conditions that can be found in HD patients (30). In fact, oral administration of α-tocopherol (500 mg/day) for 1 year for HD patients caused a reduction in SOD activity and total antioxidant status (31). This may be due to the low level of other antioxidants needed to restore the reduced form of vitamin E (e.g., vitamin C) (31). Although vitamin E therapy has been extensively studied in patients with CKD, there is no consensus on the benefit obtained from its administration (32). The same was found in study by Hambali et al. (33) also found reduced plasma NO in all subjects after HD when compared to controls and consequently reduced SOD, demonstrating a direct relationship between SOD and NO.

Moreover, the cytosolic SOD enzyme is copper and zinc dependent. The decrease of these ions in patients receiving HD may contribute to a decrease in SOD activity and a consequent increase in inflammatory expression (34). In this context, some studies have described interactions between zinc/ copper deficiency and nitrosamine stress with iNOS induction and inflammation, which may contribute to the pathogenesis of diarrheal and cardiovascular diseases (35). Zinc, in turn, has anti-inflammatory properties *in vivo* because of its ability to suppress the induction of cytokines by iNOS, since it is an antioxidant enzyme. Zn supplementation can improve taste and smell and gastrointestinal function, increase food intake, and reduce protein-energy waste (36). Thus, patients with Zn deficiency receiving Zn supplementation have improvements in their antioxidant-antioxidant balance and nutritional status (37), which probably contributes to the increase in plasma SE status. In this sense, consumption above recommendations was observed both in individuals with high and low NO concentrations of minerals (Mn, Cu and Zn), vitamin C and α-linolenic fatty acids (ω3), all nutrients with antioxidant properties. Thus, we hypothesized that our sample

presents a favorable antioxidant system, since these nutrients act as enzymatic cofactors. Studies highlight them by inhibiting lipoprotein oxidation as an anti-peroxidation agent, and indirectly promote iNOS activation antagonistic action, improving NO vasodilator vascular action, decreasing the available (O_2^-) (38). Evidence also shows that polyunsaturated fatty acids, especially ω3, promote an increase in the regulation of the NO system by iNOS (39). Thus, the results of dietary intake in relation to NO concentrations reinforce our hypothesis that there is a suitable system for NO activity. However, these benefits were not confirmed by Kooshki et al. (40) who did not observe improvements in F2-isoprostane levels nor in carbonylic proteins after supplementation with 2.08 g/day EPA 1 DHA and 800 mg/day DHA 1 vitamin E, respectively. These findings corroborate the results of the study by Mattos et al. 2017 (41) in which supplementation at physiological doses of n-3 PUFA was not able to alter oxidative stress profiles. However, linear regression analysis showed that n-3 PUFA is associated with improved rates of isoprostane and advanced oxidation protein products (AOPP) in HD patients.

The second relevant result of this study was a negative association between inflammatory markers and NO concentrations. In fact, the increase of NO, through the regulation of iNOS by inflammatory cytokines, such as IL-1, IL-6, and TNF in patients submitted to HD has been demonstrated in the literature (42). In addition, Amore et al. (43) demonstrated that abnormal stimulation of iNOS by cytokines was closely associated with the development of vasculopathy in long-term dialysis patients, consistent with the inverse assumption in our study.

Another interesting result of our study was the higher concentrations of triacylglycerols in those individuals with high NO concentration. The same was observed in the study by Volpe et al. (44). Free fatty acids are stored in the body in the form of triacylglycerols and are released into the tissues by lipolysis. This triacylglycerol increases NO production in the skeletal muscle, through the iNOS, contributing to the initiation of the inflammatory cascade, by activation of transcription factor NF-κB (45). Taken together, our and previous outcomes suggest that high triacylglycerol may contribute to increase NO production in situations of inadequate antioxidant defense.

In addition, our results showed a positive association between serum iron values and transferrin saturation and a significant trend for ferritin and NO concentration in the individuals studied. Iron supplementation is a common recommendation for patients with renal disease; however, excess iron can act as a pro-oxidant factor, thus contributing to the oxidation of molecules, such as NO. This, produced by eNOS, induces the synthesis of ferritin, which binds to free iron ions and prevents the generation of O_2^-. However, under conditions of vascular endothelium impairment, activated macrophages produce O_2^-, express iNOS and produce NO. In this way, $ONOO^-$ and hydroxyl radical (OH^-) are produced, compromising tissue integrity, which favors the activation of coagulation and contributes to vascular lumen obstruction, increasing the response of vasoconstrictors such as Angiotensin II (AII) (46). Thus, it appears that iron being free can aggravate oxidative stress in individuals in HD and, consequently, contribute to atherosclerosis and oxidative stress.

Another important finding is that anemia is a common complication observed in renal patients and the administration of recombinant human erythropoietin (RHE) and intravenous iron are recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines (47). Previous studies have indicated that anemia acts as a contributing factor associated with CKD and oxidative stress, while adjuvant therapies, mainly intravenous (i.v.) iron, seem to further increase this process (48). However, in our study, mean values of ferritin higher than 500 ng/mL were observed in those individuals with high NO concentrations and adequate Fe and SatFe values in the majority of participants, remembering that Fe supplementation in this population is common. Since ferritin with higher values in the group of individuals with high NO concentration and eNOS stimulating the synthesis of ferritin to sequester the free Fe (49) we could suggest that there is an adequate production of NO with vasodilator function in this population.

Finally, in the present study, mGSA presented significantly higher scores, corresponding to malnutrition status, being statistically significant at low NO concentrations ($p = 0.012$). In this sense, the pro-inflammatory state, oxidative stress, endothelial dysfunction and malnutrition resulting from these pathological processes are common to CKD. mGSA is a reliable tool for assessing early malnutrition (50). The presence of malnutrition may contribute to the reduction of NO synthesis, release and activity by eNOS, activating several components of the atherogenic process, such as vasoconstriction (51). The study by Silva et al. corroborates with these findings, since they observed a blockade in the transport of L-arginine and synthesis of nitric oxide, being this one associated with the increase of the platelet aggregation in individuals with malnourished DRT (52). In our study, there was no association between the markers of body composition and NO. One explanation for this result is that the majority of study participants presented normal albumin values. In this sense, Danielski et al. (53) demonstrated that inflammatory and oxidative stress markers were increased in patients with hypoalbuminemia when compared to normoalbuminemic patients. In addition, our samples presented in majority normal weight and adequate body fat mass. Thus, the lack of association between oxidative stress and body fat composition markers may be influenced by the low prevalence of malnutrition or by the antioxidant effect of albumin.

In conclusion, the present cross-sectional study showed a significant association of NO with markers of lipid and iron metabolism, as well as with inflammatory markers (IL6 and IL10) and oxidative stress (SOD) in HD patients, indicating its important risk mediator of this population. In addition, the clinical-nutritional status and nutrient consumption with antioxidant properties (Cu, Zn, Mn, vitamin C and ω3) seem to modulate this relationship.

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REFERENCES

1. Balasubramanian S. Progression of chronic kidney disease: mechanisms and intervention in retardation. J Ap Med 2010;10:19-28.
2. Shah S, Baliga R, Rajapurkar M, et al. Oxidants in chronic kidney disease. J Am Soc Nephrol 2007;18:16-28.
3. Cachofeiro V, Goicochea M, Vinuesa S. Oxidative stress and inflammation a link between chronic kidney disease and cardiovascular disease. Kidney Int 2008;74:4-9.
4. Kuo K, Tarng D. Oxidative stress in chronic kidney disease. Adaptive Medicine; 2010;2:87-94.
5. Snyder SH, Bredt DS. Biological role of nitric oxide. Science Am 1992;266:68-77.
6. Förstermann U, Sessa W. Nitric oxide synthases: regulation and function. European Heart Journal, Oxford 2011;31:829-37.
7. Baylis C. Nitric oxide deficiency in chronic kidney disease. American Journal of Physiology - Renal Physiology, Bethesda 2008;294:F1-F9.
8. Modlinger PS, Wilcox CS, Aslam S. Nitric oxide, oxidative stress, and progression of chronic renal failure. Seminars in Nephrology 2004;24:354-65.
9. Harrison DG. The mosaic theory revisited: common molecular mechanisms coordinating diverse organ and cellular events in hypertension. Journal of the American Society of Hypertension 2013;7:68-74.
10. Kalantar-Zadeh K, Kleiner, M, Dunne E, et al. A modified quantitative subjective global assessment of nutrition for dialysis patients. Nephrol Dial Transplant 1999;14:1732-8.
11. Jeliffe DB. Evaluation del estado de nutrición de la comunidad com especial referencia a lãs encuestas em lãs regions in desarrollo. Genebra: Organización Mundial de la Salud; 1968.
12. World Health Organization – WHO Physical status: the use and interpretation of anthropometry. Geneva: Technical Report Series, 854; 1995.
13. Coelho MASC, Amorim RB. Avaliação nutricional em geriatria. In: Duarte ACG. Avaliação nutricional: Aspectos clínicos e laboratoriais. São Paulo: Atheneu; 2007. pp. 155-76.
14. World Health Organization Obesity: preventing and managing the global epidemic. Genebra; 1997.
15. Lipschitz DA. Screening for nutritional status in the elderly. Prim Care 1994;21:55-67.
16. Kalantar-Zadeh K, Kopple JD, Deepak S et al. Features food consumption G. Block hemodialysis patients as obtained by food frequency questionnaire. J Nutr Ren 2002;12:17-31.
17. Molina MDB, Bensenor I, Cardoso LO, et al. Reprodutibilidade e validade relativa do Questionário de Frequência Alimentar do ELSA-Brasil. Cad. Saúde Pública 2013;29:79-389.
18. Brasil, Ministério da Saúde: Guia Alimentar para População Brasileira promovendo a alimentação saudável. Normas e manuais técnicos: Brasília; 2006.
19. Brasil, Ministério da Saúde (2014): Guia Alimentar para População Brasileira promovendo a alimentação saudável. 2ªed. Normas e manuais técnicos: Brasília. IBGE – Instituto Brasileiro de Geografia e Estatística. Pesquisa de Orçamentos Familiares 2002-2003 – POF. Rio de Janeiro, 2004. Pesquisa de Orçamentos Familiares 2008-2009 – POF. Rio de Janeiro; 2010.
20. NEPA – Núcleo de estudos e Pesquisas em Alimentação. Tabela Brasileira de Composição de Alimentos (TACO). 1ª ed. Campinas: NEPA – UNICAMP 2004;42.
21. Hemodialysis Adequacy 2006 Work Group. Clinical practice guidelines for hemodialysis adequacy, update 2006. Am J Kidney Dis 2006;48(1): S2-S90.
22. Dieterich S, Bieligk U, Beulich K. Gene expression of antioxidative enzymes in the human heart: increased expression of catalase in the end-stage failing heart. Circulation 2000;101:33-9.
23. Habig W, Jakoby WB. Assays for determination of glutathione S-transferase. Methods Enzymol 1981;77:398-405.
24. Wallin B, Rosengren B, HG Shertzer, et al. Lipoprotein oxidation and measurements of thiobarbituric acid reacting substances formation in single micrititer plate: its use of evaluation of antioxidants. Analytical Biochemistry 1993;208:10-5.
25. Green LC, Wagner DA, Glogowski J. Analysis of nitrate, nitrite and ['5N] nitrate inbiological fluids. Anal Biochem 1982;126:131-8.
26. Lowry OH, Rosebrough NJ, Farr AL, et al. Protein measurement with the folin phenol reagent. J Biol Chem 1951;193:265-75.
27. Hermsdorff HHM, Puchau B, Bressan J, et al. Association of body Fat distribution with proinflammatory gene expression in peripheral blood mononuclear cells from young adult subjects. OMICS: J Integr Biol 2010;14:297-307.
28. Willett WC. Nutritional epidemiology. 2nd ed. New York: Oxford University Press; 1998.
29. Kumar KV, Das UN. Are free radicals involved in the pathobiology of human essential hypertension? Free Rad Res Comms 1993;19:59-66.
30. Antoniadi G, Eleftheriadis T, Liakopoulos V, et al. Effect of one-year oral α-tocopherol administration on the antioxidant defense system in hemodialysis patients. Ther Apher Dial 2008;12:237-42.
31. Sesso HD, Buring JE, Christen WG, et al. Vitamins E and C in the prevention of cardiovascular disease in men: The Physicians' Health Study II randomized controlled trial. JAMA 2008;300:2123-33.
32. Chen S-C, Lee M-Y, Huang J-C, et al. Association of diabetes mellitus with decline in ankle-brachial index among patients on hemodialysis: A 6-year follow-up study. Cheng X, editor. PLoS ONE 2017;12(4).
33. Hambali Z. Oxidative Stress and Its Association with Cardiovascular Disease in Chronic Renal Failure Patients. Indian Journal of Nephrology 2011;21(1):21-5.
34. Gheddouchi S, Mokhtari-Soulimane N, Merzouk H, et al. Low SOD activity is associated with overproduction of peroxynitrite and nitric oxide in patients with acute coronary syndrome. Nitric Oxide 2015;49:40-6.
35. Torregrossa A, Berkson, Moncrief J. Nitric Oxide 2011;24:S21-S22.
36. Guo CH, Wang CL, Chen PC. Micronutrient Metabolism in Hemodialysis Patients. In: Maria GP, editor. Hemodialysis - Different Aspects. Croatia: InTech: Rijeka; 2011. pp. 173-204.
37. Mazani M, Argani H, Rashtchizadeh N, et al. Effects of zinc supplementation on antioxidant status and lipid peroxidation in hemodialysis patients. J Ren Nutr J Ren Nutr 2013;23(3):180-4.
38. Thomas SR, Stocker R. Molecular action of vitamin E in lipoprotein oxidation: implications for atherosclerosis. Free Radic Biol Med 2000;28:1795.
39. Kooshki A, Taleban FA, Tabibi H, et al. Effects of omega-3 fatty acids on serum lipids, lipoprotein (a), and hematologic factors in hemodialysis patients. Ren Fail 2011;33:892-8.
40. Kooshki A, Taleban FA, Tabibi H, et al. Effects of Marine Omega-3 Fatty Acids on Serum Systemic and Vascular Inflammation Markers and Oxidative Stress in Hemodialysis Patients. Ann Nutr Metab 2011;58(3):197-202.
41. de Mattos AM, da Costa JAC, Jordão Júnior AA, et al. Omega-3 fatty acid supplementation is associated with oxidative stress and dyslipidemia, but does not contribute to better lipid and oxidative status on hemodialysis patients. J Ren Nutr 2017;17:S1051-2276.
42. Madore F, Prud'homme L, Austin JS, et al. Impact of nitric oxide on blood pressure in hemodialysis patients. Am J Kidney Dis 1997;30:665-671.
43. Amore A, Bonaudo R, Ghigo D, et al. Enhanced production of nitric oxide by blood-dialysis membrane interaction. J Am Soc Nephrol 1995;6:1278-83.
44. Volpe, CMO et al. The Production of Nitric Oxide, IL-6, and TNF-Alpha in Palmitate-Stimulated PBMNCs Is Enhanced through Hyperglycemia in Diabetes. Oxidative Medicine and Cellular Longevity 2014. 479587. PMC. Web. 30 Sept. 2016.
45. Suganami T, Tanimoto-Koyama K, Nishida J, et al. Role of the Toll-like receptor 4/NFkappaBthwayIn saturated fatty acidinduced inflammatory changes in the interaction between adipocytes and macrophages. Arterioscler Thromb Vasc Biol 2007;27:84-91.
46. Dusse LMS, Vieira LM, Carvalho MG. Revisão sobre óxido nítrico. Jornal Brasileiro de Patologia e Medicina Laboratorial, Rio de Janeiro 2003;39:343-50.
47. National Kidney Foundation (KDOQI). Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis 2006;47:S11-145.
48. Capusa C, Mircescu G. Oxidative stress, renal anemia, and its therapies: Is there a link? J Ren Nutr 2010;20:S71-S76.
49. Davis DW, Lewis ML, Hart DA. Age dependent expression and distribution of nitric oxide (NO) synthase isoforms in the ovine kidney. Open Journal of Molecular and Integrative Physiology 2013;3:61-70.
50. Jones CH, Newstead CG, Will EJ, et al. Assessment of nutritional status in CAPD patients: serum albumin is not a useful measure. Nephrol Dial Transplant 1997;12:1406-13.
51. Noris M, Benigni A, Boccardo P, et al. Enhanced nitric oxide synthesis in uremia: Implications for platelet dysfunction and dialysis hypotension Kidney Int 1993;44:445-50.
52. Silva CDD , Brunini MCT, Reis MB, et al. Effects of nutritional status on the L-arginine-nitric oxide pathway in platelets from hemodialysis patients. Kidney International 2005;68:2173-9.
53. Danielski M, Ikizler TA, McMonagle E, et al. Linkage of hypoalbuminemia, inflammation, and oxidative stress in patients receiving maintenance hemodialysis therapy. Am J Kidney Dis 2003;42:286-94.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Otros

Tissular growth factors profile after teduglutide administration on an animal model of intestinal anastomosis

Perfil tisular de factores de crecimiento postadministración de teduglutida en un modelo animal de anastomosis intestinal

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Abstract

Background: Teduglutide is an enterotrophic analogue of glucagon-like peptide-2, with an indirect and poorly understood mechanism of action, approved for the rehabilitation of short-bowel syndrome. This study aims to analyze the response of tissue growth factors to surgical injury and teduglutide administration on an animal model of intestinal anastomosis.

Methods: Wistar rats (n = 59) were distributed into four groups: "ileal resection" or "laparotomy", each one subdivided into "postoperative teduglutide administration" or "no treatment"; and sacrificed at the third or the seventh day, with ileal sample harvesting. Gene expression of *insulin-like growth factor 1 (Igf1), vascular endothelial growth factor a (Vegfa), transforming growth factor β1 (Tgfβ1), connective tissue growth factor (Ctgf), fibroblast growth factor 2 (Fgf2), fibroblast growth factor 7 (Fgf7), epidermal growth factor (Egf), heparin-binding epidermal-like growth factor (Hbegf), platelet-derived growth factor b (Pdgfb) and glucagon-like peptide 2 receptor (Glp2r)* was studied by real-time polymerase chain reaction.

Results: Upregulation of *Fgf7, Fgf2, Egf, Vegfa* and *Glp2r* at the third day and of *Pdgf* at the seventh day was verified in the perianastomotic segment. Teduglutide administration was associated with higher fold-change of relative gene expression of *Vegfa* (3.6 ± 1.3 *vs.* 1.9 ± 2.0, p = 0.0001), *Hbegf* (2.2 ± 2.3 *vs.* 1.1 ± 0.9, p = 0.001), *Igf1* (1.6 ± 7.6 *vs.* 0.9 ± 0.7, p = 0.002) and *Ctgf* (1.1 ± 2.1 *vs.* 0.6 ± 2.0, p = 0.013); and lower fold-change of *Tgfβ1, Fgf7* and *Glp2r*.

Conclusions: Those results underscore the recognized role of *Igf1* and *Hbegf* as molecular mediators of the effects of teduglutide and suggest that other humoral factors, like *Vegf* and *Ctgf*, may also be relevant in the perioperative context. Induction of *Vegfa, Igf1* and *Ctgf* gene expressions might indicate a favorable influence of teduglutide on the intestinal anastomotic healing.

Key words:

Teduglutide. Growth factors. Intestinal anastomosis. Vascular endothelial growth factor. Connective tissue growth factor.

Resumen

Introducción: teduglutida es un análogo intestinotrófico do péptido-2 similar al glucagón, con un mecanismo de acción indirecto y poco conocido, aprobado para la rehabilitación del síndrome de intestino corto. Este estudio propone analizar la respuesta de los factores de crecimiento tisulares a la agresión quirúrgica y a la administración de teduglutida en un modelo animal de anastomosis intestinal.

Métodos: ratones Wistar (n = 59) fueron distribuidos en cuatro grupos: "resección ileal" o "laparotomía", cada uno subdividido en "administración post-operatoria de teduglutida" o "sin tratamiento"; y sacrificados en el tercero o el séptimo día, con recogida de muestras ileales. La expresión génica de *Igf1, Vegfa, Tgfβ1, Ctgf, Fgf2, Fgf7, Egf, Hbegf, Pdgfb* y *Glp2r* fue analizada por qRT-PCR.

Resultados: en el segmento perianastomótico se verificó una sobrerregulación de *Fgf7, Fgf2, Egf, Vegfa* y *Glp2r* al tercer día y de Pdg al séptimo día. La administración de teduglutida se asoció con mayor cambio de la expresión génica relativa de *Vegfa* (3.6 ± 1.3 *vs.* 1.9 ± 2.0, p = 0.0001), *Hbegf* (2.2 ± 2.3 *vs.* 1.1 ± 0.9, p = 0.001), *Igf1* (1.6 ± 7.6 *vs.* 0.9 ± 0.7, p = 0.002) y *Ctgf* (1.1 ± 2.1 *vs.* 0.6 ± 2.0, p = 0.013); y menor cambio de *Tgfβ1, Fgf7* y *Glp2r*.

Conclusiones: estos resultados refuerzan el reconocido papel de *Igf1* y *Hbegf* como mediadores moleculares de los efectos de la teduglutida y sugieren que otros factores humorales, como *Vegf* y *Ctgf*, también pueden ser relevantes en el contexto perioperatorio. La inducción de las expresiones de los genes *Vegfa*, *Igf1* y *Ctgf* podría indicar una influencia favorable de teduglutida en la cicatrización anastomótica intestinal.

Palabras clave:

Teduglutida. Factores de crecimiento. Anastomosis intestinal. Factor de crecimiento vascular endotelial. Factor de crecimiento del tejido conectivo.

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INTRODUCTION

Failure of intestinal anastomotic repair still remains a major source of morbidity and mortality in digestive surgery and one of the most feared postoperative complications (1).

Intestinal anastomotic healing is a complex multi-cellular multi-molecular dynamic process involving a coordinated interplay between multiple signaling networks and a rigorous spacial and temporal control (1-3). Traditionally, wound healing model considers three overlapping phases: inflammatory, proliferative and reparative (2,3). After injury, clotting cascades origin thrombin, an inducer of platelet degranulation, and release of bioactive mediators that stimulate the recruitment of inflammatory cells. Those cells participate in the wound debridement, antigen presentation and phagocytosis and release of reactive oxygen species, inflammatory cytokines, chemokines and growth factors that amplify the repair process (3). Usually, inflammatory phase lasts one to four days (2). Proliferative phase is characterized by re-epithelialization ("restitution" and crypt stem cells proliferation and differentiation), fibroplasia and angiogenesis and, generally, occurs between the fourth and the fourteenth postoperative days (2,3). In the reparative phase, which may elapse up to six months (2), extracellular matrix undergoes continuous synthesis and remodeling by proteolytic enzymes leading to wound maturation and contraction (3).

Numerous experimental studies have been published on the effect of adjuvants of intestinal anastomotic repair. Perioperative strategies to improve anastomotic healing described in those studies included tissue adhesives (4), growth factors, stem cells-based therapies (5), artificial matrixes and patches (4,6,7), topical or systemic pharmacological interventions (8,9), perfusion reinforcement techniques (10), among others. Nevertheless, despite extensive research, no substantial evidence was documented to justify the implementation of any of those strategies for daily clinical use (2,4).

Several experimental studies, analyzing the effects of growth factors on the gastrointestinal anastomotic healing, suggest participation in all phases of tissue healing and potential benefit from insulin-like growth factor 1, vascular endothelial growth factor, epidermal growth factor, heparin-binding epidermal growth factor, transforming growth factor-β, fibroblast growth factor 2 and keratinocyte growth factor (2,9).

Glucagon-like peptide 2 (Glp2) is a potent gastrointestinal growth factor, produced in enteroendocrine L cells, with intestinotrophic, antisecretory, transit-modulating and anti-inflammatory effects (11). Glp2 demonstrates a complex, indirect and poorly understood mechanism of action with intricate signaling pathways and multiple mediators' participation (including insulin-like growth factor 1, ErbB superfamily of ligands, fibroblast growth factor 7, vasoactive intestinal polypeptide and endothelial nitric oxide synthase) (11). Teduglutide is a long-acting dipeptidylpeptidase IV-resistant analogue of GLP2 recently approved for the pharmacological rehabilitation of adult patients with short-bowel syndrome (12). Response of tissue growth factors, key mediators of the anastomotic repair, to teduglutide administration in the perioperative context of intestinal anastomosis is yet to be defined.

This study aims to analyze the response of tissue growth factors to surgical injury and teduglutide short-term administration on an animal model of intestinal anastomosis.

METHODS

STUDY PROTOCOL AND SURGICAL PROCEDURES

Study was approved by the Ethics Committee of the Faculty of Coimbra, Coimbra, Portugal (Official Letter nº32-06-2009) and performed according to institutional and national animals' protection guidelines.

Adult male Wistar *albinus* rats were randomly allocated into four groups: "*ileal resection and anastomosis*" ("*Res*") or "*laparotomy*" ("*Lap*"), each one subdivided into "*postoperative teduglutide administration*" ("*Ted +*") or "*no treatment*" ("*Ted -*"). Evaluation was performed at the operation and sacrifice moments, at the third or the seventh postoperative day (eight subgroups), with ileal segment harvesting and blood collection (Fig. 1). Blinded assessment was guaranteed in the laboratorial analysis.

Animals weighting 250 to 300 g were harboured in ventilated cages with a controlled environment of temperature (22 ± 1 °C), relative humidity (50 ± 10%) and light-dark cycles of 12 hours; and with free access to water and standard rodent diet.

All the surgical interventions were performed by the same surgeon after a period of two hours solid fasting, with clean surgical technique and under anaesthesia with intraperitoneal ketamine hydrochloride (75 mg/kg; Pfizer Inc., NY, USA) and chlorpromazine (3 mg/kg; Laboratórios Vitória, Amadora, Portugal). In "*Res*" groups, a 10 cm length ileal resection was undertaken, 5 cm upstream of ileocecal valve, after a 3 cm abdominal wall midline incision. A standard end-to-end anastomosis was constructed with eight equidistant full-thickness polydioxanone USP 6/0 stitches (PDS II, Ethicon, Johnson-Johnson Intl). Abdominal wall was closed with muscle-aponeurotic and cutaneous running sutures of braided coated polyglactin 910 USP 4/0 (Surgilactin, Sutures Limited, United Kingdom) and natural silk USP 4/0 (Surgisilk, Sutures Limited, United Kingdom), respectively. In "*Lap*" groups, animals were subjected to a 3 cm midline laparotomy (without resection) with gentle manipulation of the small bowel.

In "*Ted +*" groups, teduglutide (American Peptide Company) was administered in the postoperative period (from the operation day), 200 µg/kg/day, subcutaneously, dissolved in 0.25 ml phosphate buffered saline pH 7.4 (PBS, pH 7.4, Gibco, Life Technologies), after preparation according to the manufacturer's recommendations.

In the first postoperative day, ingestion of water with 5% glucose at a 1:1 ratio was allowed and then unrestricted oral hydration and chow were reassumed. Daily surveillance was performed and operative mortality and morbidity were registered. At the third or seventh postoperative day, animals were sacrificed by cervical displacement and a re-laparotomy with ileal resection was performed (10 cm length, preserving distal 3 cm).

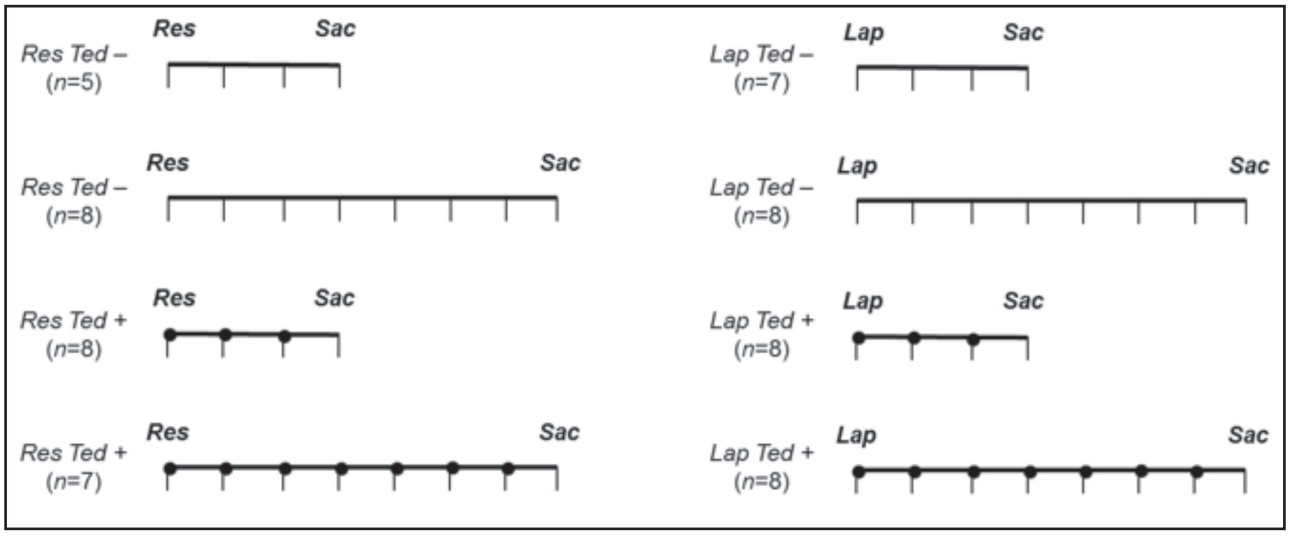

Figure 1.

Study design. Adult male Wistar *albinus* rats were randomly distributed into four groups: *"ileal resection" ("Res") versus "laparotomy" ("Lap")*, each one subdivided into *"postoperative teduglutide administration" ("Ted +") versus "no treatment" ("Ted -").* Evaluation was performed at the moments of the operation and sacrifice (Sac), at the third or the seventh postoperative day (eight subgroups), with ileal segment harvesting and blood collection. Baseline values of *"ileal resection"* groups were considered for comparison with postoperative results of the "*laparotomy*" groups; tissue samples recovered at the sacrifice in those animals corresponded to the perianastomotic segments. • Teduglutide administration.

TISSUE AND BLOOD HARVESTING

Three similar longitudinal strips of the most distal 4 cm length of each ileal operative specimen, each one corresponding to one third of the circumference, were carefully recovered, after gentle washing with normal saline solution, for homogenization and additional procedures, respectively. Tissue baseline values of "*ileal resection*" groups were considered for comparison with postoperative results of the "*laparotomy*" groups; tissue samples recovered at the sacrifice in those animals corresponded to the perianastomotic segments.

Blood samples of 1 ml were drawn in the morning, before the operations, from the tail vein, into polyethylene therephthalate K3 ethylenediaminetetraacetic acid (K3EDTA) vacutainers. Samples were stabilized immediately with 0.1 mg/ml of aprotinin from bovine lung (Sigma-Aldrich) and 0.037 mg/ml of dipeptidylpeptidase IV competitive inhibitor nicotinonitrile dihydrochloride hydrate (Sigma-Aldrich) and centrifuged for 20 min at 1500x *g* and 4 °C. Plasma aliquots were stored at -80 °C.

INTESTINAL TISSUE HOMOGENIZATION

Briefly, fragments from one ileal longitudinal strip recovered according to previous description, with approximately 1 ml, were rapidly introduced in a mixture of protease inhibitors in a proportion of 1 ml/100 mg and submitted to mechanical homogenization. Proteases cocktail was previously prepared by adding aprotinin from bovine lung (Sigma-Aldrich), leucopeptin hemisulfate salt (Sigma-Aldrich) and pepstatin A (Sigma-Aldrich) (1 µl of each, all diluted in a 10 mg/ml stock concentration) to 10 ml of phosphate buffered saline (PBS, pH 7.4, Gibco, Life Technologies) and stored on ice. Preparation was sonicated twice with one short pulse of ten seconds, cooled during ten seconds and distributed into two tubes of 1.5 ml. Sonication (one pulse of ten seconds) was repeated and centrifugation was undertaken, 14000x *g*, for 10 min, at 4 °C. Supernatant was removed to a new tube and pellet was preserved on ice for posterior ribonucleic acid (RNA) extraction.

ANALYSIS OF GROWTH FACTORS AND Glp2 RECEPTOR GENE EXPRESSIONS

Gene expression of growth factors in the rats ileum was determined by quantitative estimation of messenger ribonucleic acid (mRNA) using quantitative real-time reverse-transcription polymerase chain reaction (qRT-PCR). Studied growth factors and receptor included: *insulin-like growth factor 1, transcript variant (Igf1), vascular endothelial growth factor A, transcript variant 2 (Vegfa), transforming growth factor, beta 1 (Tgfß1), connective tissue growth factor (Ctgf), fibroblast growth factor 2 (Fgf2), fibroblast growth factor 7 (Fgf7), epidermal growth factor (Egf), heparin-binding Egf-like growth factor (Hbegf); platelet-derived growth factor beta polypeptide (Pdgfb)* and *glucagon-like peptide 2 receptor (Glp2r)*.

Total RNA was extracted from homogenates of rats longitudinal strips of ileum using the Isolate II RNA Mini Kit (Bioline). One microgram of isolated total RNA was used for reverse-transcription, which was performed with the Tetro cDNA Synthesis Kit (Bioline) and using random hexamer. Real-time PCR primers were designed with Bea-

con Designer software (Premier Biosoft, PA, USA) and were obtained from Sigma-Aldrich (Sintra, Portugal). All the genes included in this study were described in the National Center for Biotechnology Information (NCBI) Gene database (http://www.ncbi.nlm.nih.gov/) as indicated in table I. *Hypoxanthine phosphoribosyltransferase* (*Hprt*) was used as housekeeping gene. qRT-PCR was performed on a Bio-Rad iQ5 real-time PCR instrument (BioRad, Hercules, CA, USA) using the SensiFAST™ SYBR & Fluorescein Kit (Bioline). For each sample, PCR was performed in duplicate.

Data were analyzed by relative quantification (13). All values were normalized to the values of the reference gene of those samples.

DETERMINATION OF PLASMA Glp2 CONCENTRATION

Plasma Glp2 levels were determined by competitive enzyme immunoassay (EIA) using the glucagon-like peptide 2 (Glp2) EIA Kit 96-Well Plate (Phoenix Europe GmbH, Karlsuhe, Germany), in accordance to the manufacturer's recommended protocol. All determinations were done in duplicate. Glp2 plasma concentrations were calculated using the corresponding standard curve and the microplate reader with Gen5 software (Synergy HT, Biotek, Winooski, VT, USA), and expressed in ng/ml.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 18 software (SPSS, Chicago, IL, USA). Type of distribution of variables was determined using Shapiro-Wilk and Kolmogorov-Smirnov-Lillifors tests. Data were indicated as median and interquartile range (median±IQR). Non-parametric continuous variables were compared by Mann-Whitney *U* test and analysis of variance by ranks (Kruskall-Wallis test) with pairwise comparisons; correlations were determined by the Spearman's rank correlation coefficient (σ). Differences were considered statistically significant at a level of 95% ($p < 0.05$).

Table I. Primers used in the analysis of gene expression levels of growth factors and Glp2 receptor by qRT-PCR

Gene[a]	GenBank Accession nº	Orientation	Sequence	Size (bp)
Rat Igf1	NM_001082477	Forward	GCCATTAGCCCTGCCCTTTCTT	78
Rat Igf1	NM_001082477	Reverse	GCCACCCAGTTGCTATTGCTTTCG	
Rat Vegfa	NM_001110333	Forward	CAGCGACAAGGCAGACTATTC	193
Rat Vegfa	NM_001110333	Reverse	CCGAAGTAATTTGAGGGAGTGAAG	
Rat Tgfb1	NM_021578	Forward	GTGGACCGCAACAACGCAATCT	100
Rat Tgfb1	NM_021578	Reverse	GTTCTGGCACTGCTTCCCGAATG	
Rat Ctgf	NM_022266	Forward	TGCCGGTAACAAGCCAGATT	394
Rat Ctgf	NM_022266	Reverse	GCAGCAAACACTTCCTCGTG	
Rat Fgf2	NM_019305	Forward	TGCTCTAGGGGACTGGAGATT	86
Rat Fgf2	NM_019305	Reverse	GACCAGCCTTCCACCCAAAG	
Rat Fgf7	NM_022182	Forward	TGGCAATCAAAGGGGTGGAA	249
Rat Fgf7	NM_022182	Reverse	TAGGAAGAAAGTGGGCCGTT	
Rat Egf	NM_012842	Forward	TGACCTTAGAACCACCGAGACCAT	92
Rat Egf	NM_012842	Reverse	TCTGCTGTGCTGTGACACTGAG	
Rat Hbegf	NM_012945	Forward	AGAGAGGACGGATGAGTGGT	99
Rat Hbegf	NM_012945	Reverse	GGAGGGTCCAAACAGCAGAT	
Rat Pdgfb	NM_031524	Forward	GCACAGAGACTCCGTAGAC	77
Rat Pdgfb	NM_031524	Reverse	CCGACTCGACTCCAGAATG	
Rat Glp2r	NM_021848	Forward	ACCTGTTCGCTTCGTTCA	106
Rat Glp2r	NM_021848	Reverse	GACATCCATCCACTCTCATCAT	
Rat Hprt1	NM_012583.2	Forward	CTCCTCAGACCGCTTTTC	86
Rat Hprt1	NM_012583.2	Reverse	CTGGTTCATCATCACTAATCAC	

[a]*Igf1: insulin-like growth factor 1, transcript variant 1, mRNA; Vegfa: vascular endothelial growth factor A, transcript variant 2, mRNA; Tgfb1: transforming growth factor, beta 1, mRNA; Ctgf: connective tissue growth factor, mRNA; Fgf2: fibroblast growth factor 2, mRNA; Fgf7: fibroblast growth factor 7, mRNA; Egf: epidermal growth factor, mRNA; hbegf: Heparin-binding EGF-like growth factor, mRNA; Pdgfb: platelet-derived growth factor beta polypeptide, mRNA; Glp2r: glucagon-like peptide 2 receptor, mRNA; Hprt1: hypoxanthine phosphoribosyltransferase 1, mRNA (housekeeping gene) (Rattus norvegicus).*

RESULTS

Fifty-nine animals were studied and included into the different groups (Fig. 1).

RESPONSE OF TISSUE GROWTH FACTORS GENE EXPRESSION TO ILEAL RESECTION AND ANASTOMOSIS

In the perianastomotic segment, upregulation of gene expression of *Fgf7* (fold-change: 12.6 ± 2.8), *Fgf2* (fold-change: 6.1 ± 2.2), *Egf* (fold-change: 2.7 ± 2.2), *Vegfa* (fold-change: 2.7 ± 1.0) and *Glp2r* (fold-change: 2.3 ± 2.1) at the third postoperative day (Fig. 2A); as well as of *Pdgfb* (fold-change: 2.0 ± 1.5), *Igf1*, *Egf*, *Hbegf*, *Vegfa* and *Glp2r* at the seventh day was verified (Fig. 2B). Moreover, downregulation of *Igf1* (fold-change: 0.2 ± 0.3), *Hbegf* (fold-change: 0.4 ± 0.5), *Tgfβ1* (fold-change: 0.4 ± 0.3) and *Ctgf* at the third day (Fig. 2A); as well as of *Tgfβ1* (fold-change: 0.5 ± 0.3), *Fgf7* (fold-change: 0.5±0.4), *Ctgf* (fold-change: 0.5 ± 0.3) and *Fgf2* at the seventh day was also observed (Fig. 2B).

G*lp2r* expression was upregulated after ileal resection and anastomosis, particularly at the third postoperative day, while it was downregulated after isolated laparotomy.

In the perianastomotic segment, lower fold-change of relative gene expression of *Vegfa* and *Ctgf* at the third day and of *Fgf7* at the seventh day was observed in comparison with the ileal sample recovered after isolated laparotomy (Figs. 2A and B).

RESPONSE OF TISSUE GROWTH FACTORS GENE EXPRESSION TO ISOLATED LAPAROTOMY

In the ileal samples recovered after isolated laparotomy, upregulation of gene expression of *Vegfα* (fold-change: 4.1 ± 1.1), *Ctgf* (fold-change: 3.4 ± 1.6) and *Egf* at the third postoperative day and of *Egf* (fold-change: 3.4 ± 1.3), *Fgf7* (fold-change: 3.1 ± 1.0), *Vegfa* and *Hbegf* at the seventh day was documented (Figs. 2A and B). Furthermore, downregulation of *Tgfβ1* (fold-change: 0.1 ± 0.1), *Pdgfb* (fold-change: 0.3 ± 0.1), *Fgf2* (fold-change: 0.5 ± 0.3), *Igf1*, *Fgf7*, *Hbegf* and *Glp2r* at the third day after the operation; as well as of *Ctgf* (fold-change: 0.2 ± 0.1), *Glp2r* (fold-change: 0.5 ± 0.4), *Tgfβ1* (fold-change: 0.5 ± 0.1), *Fgf2* and *Pdgfb* at the seventh day was also evident.

RESPONSE OF TISSUE GROWTH FACTORS GENE EXPRESSION TO TEDUGLUTIDE POSTOPERATIVE ADMINISTRATION

At the third postoperative day (in the anastomotic segment and in the ileal sample recovered after isolated laparotomy), teduglutide was significantly associated with a higher fold-change of relative gene expression of *Igf1* (5.6 ± 8.0 *vs.* 0.7 ± 0.7, p = 0.0001) and *Hbegf* (1.5 ± 2.8 *vs.* 0.6 ± 0.4, p = 0.001) and lower fold-change of *Fgf2* (0.5 ± 0.2 *vs.* 0.8 ± 5.5, p = 0.002) and *Fgf7* (0.2 ± 0.7 *vs.* 1.3 ± 11.4, p = 0.0001) (Fig. 3). At the seventh postoperative day, teduglutide was significantly associated with higher fold-change of relative gene expression of *Vegfa* (3.6 ± 2.0 *vs.* 1.5 ± 0.6, p = 0.0001), *Ctgf* (1.1 ± 2.4 *vs.* 0.3 ± 0.4, p = 0.0001) and *Hbegf* (3.0 ± 1.6 *vs.* 1.3 ± 0.7, p = 0.004) and lower fold-change of *Tgfβ1* (0.02 ± 0.04 *vs.* 0.5 ± 0.5, p = 0.0001), *Fgf7* (0.4 ± 0.4 *vs.* 0.9 ± 2.6, p = 0.007) and *Glp2r* (0.4 ± 0.2 *vs.* 1.0 ± 0.7, p = 0.0001) (Fig. 3).

In all the animals (n = 59), at the sacrifice, teduglutide was significantly associated with higher fold-change of relative gene expression of *Vegfa* (3.6 ± 1.3 *vs.* 1.9 ± 2.0, p = 0.0001), *Hbegf* (2.2 ± 2.3 *vs.* 1.1 ± 0.9, p = 0.001), *Igf1* (1.6 ± 7.6 *vs.* 0.9 ± 0.7, p = 0.002) and *Ctgf* (1.1 ± 2.1 *vs.* 0.6 ± 2, p = 0.013) and lower fold-change of *Tgfβ1* (0.1 ± 0.4 *vs.* 0.4 ± 0.4, p = 0.002), *Fgf7* (0.4 ± 0.6 *vs.* 1.2 ± 3.0, p = 0.0001) and *Glp2r* (0.5 ± 6.1 *vs.* 1.0 ± 0.9, p = 0.042) (Fig. 4).

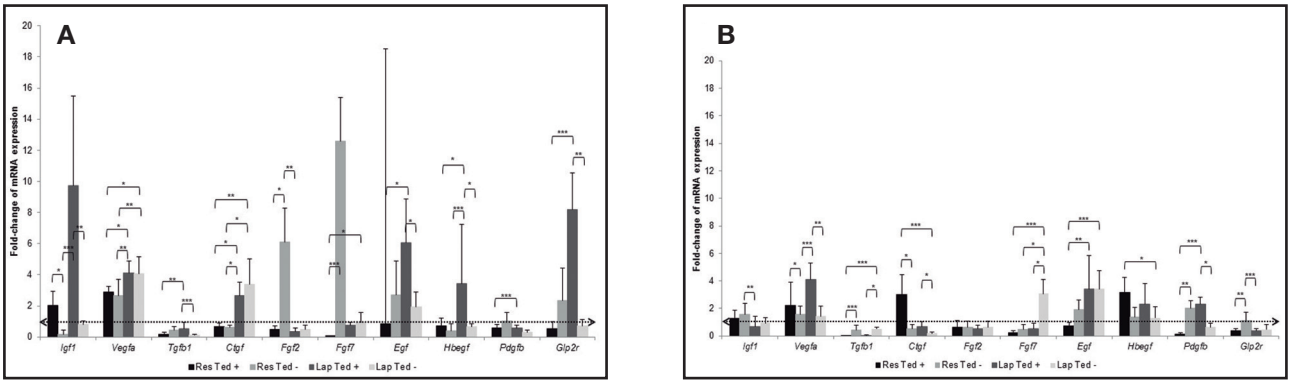

Figure 2.

Fold-changes of relative gene expression of growth factors and Glp2 receptor in the rats' ileum, at the third (A) and the seventh (B) days after operation determined by qRT-PCR. Animals *(n = 59)* were submitted to ileal resection and anastomosis *("Res")* or laparotomy *("Lap")* and sacrificed at the third or at the seventh postoperative days; in groups *"Res Ted +"* and *"Lap Ted +"*, teduglutide was administered after the operation. Samples recovered at the sacrifice from rats that underwent ileal resection corresponded to the anastomotic segment. Values were normalized to *Hprt* gene and fold-changes were generated by comparing with baseline values of rats submitted to ileal resection (n = 28). Results were expressed as median±interquartile range. Kruskal-Wallis test with pairwise comparisons was used. *p < 0.05; **p < 0.01; ***p < 0.001.

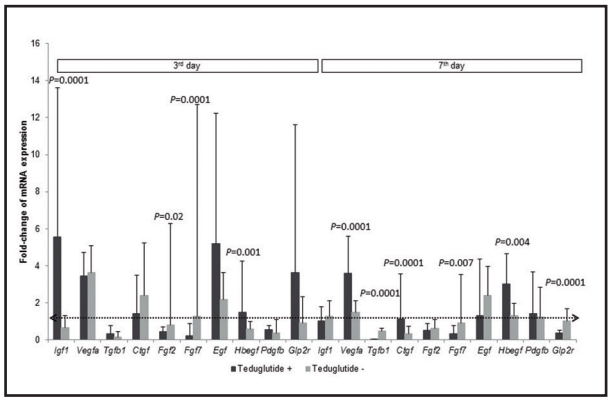

Figure 3.

Fold-change of relative gene expression of growth factors and *Glp2 receptor*, in the ileum of rats from all groups *(n = 59)*, according to teduglutide administration. Relative gene expression was determined at the moment of sacrifice (third or seventh day after ileal resection and anastomosis or after laparotomy) by qRT-PCR. Samples recovered at the sacrifice from rats submitted to ileal resection corresponded to the anastomotic segment. Values were normalized to *Hprt* gene and fold-changes were generated by comparing with baseline values of rats submitted to ileal resection *(n = 28)*. Results were expressed as median ± interquartile range. Mann-Whitney U test was used.
Teduglutide + Postoperative teduglutide administration; *Teduglutide* - Without teduglutide administration.

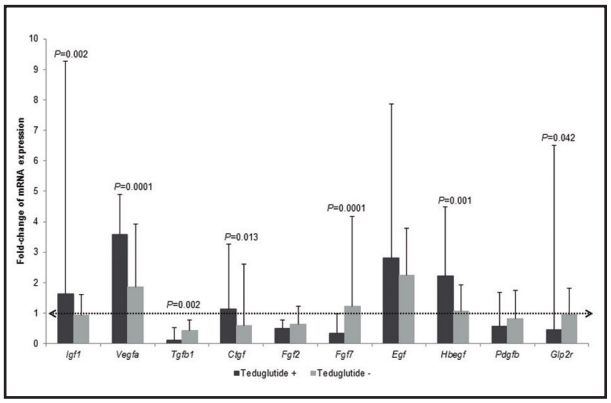

Figure 4.

Fold-change of relative gene expression of growth factors and *Glp2 receptor*, in the ileum of rats from all groups *(n = 59)* at the moment of sacrifice, according to teduglutide administration. Relative gene expression was determined at the moment of sacrifice (third or seventh day after ileal resection and anastomosis and after laparotomy) by qRT-PCR. Samples recovered at the sacrifice from rats submitted to ileal resection corresponded to the anastomotic segment. Values were normalized to *Hprt* gene and fold-changes were generated by comparing with baseline values of rats submitted to ileal resection *(n = 28)*. Results were expressed as median ± interquartile range. Mann-Whitney U test was used.
Teduglutide + Postoperative teduglutide administration; *Teduglutide* - Without teduglutide administration.

CORRELATIONS BETWEEN TISSUE GROWTH FACTORS GENE EXPRESSION AT THE SACRIFICE

At the sacrifice, *Glp2r* relative gene expression correlated directly with *Egf*, *Hbegf*, *Ctgf, Fgf7* and *Igf1* gene expressions and inversely with Glp2 plasma levels (Table II).

DISCUSSION

Results of present study, namely the upregulation of *Fgf7, Fgf2*, *Egf* and *Vegfa* gene expression levels at the third postoperative day and of *Pdgfb*, *Vegfa*, *Egf* and *Igf1* at the seventh day in the perianastomotic segment, re-enforce the recognized participation of those growth factors in the wound healing process (2,3). Upregulation of *Pdgfb* and *Igf1* gene expression occurred in the proliferative phase; whereas that of *Vegfa* was verified in both inflammatory and proliferative stages, as expected (2,3). However, downregulation of *Tgf*β1 and *Ctgf* gene expressions observed in the anastomotic segment at the third and at the seventh postoperative days was unexpected, giving the relevant participation of those growth factors in the anastomotic repair (2,14). In fact, Seigert GJ et al. (14) demonstrated recently a consistent upregulation of tissue *Tgf*β, *Ctgf* and *Igf1* gene expressions after ileo-ileal anastomosis.

In this experiment, teduglutide administration was significantly associated with higher fold-change of relative gene expression of *Igf1*, *Hbegf*, *Vegfa* and *Ctgf*, as well as with lower fold-change of *Tgf*β1 and *Fgf7* in the postoperative period.

Induction of *Igf1* messenger RNA expression in teduglutide-treated animals documented in this study was according to the literature (11) and was observed at the third day, both in the anastomotic segment and in the ileal sample recovered after isolated laparotomy. Igf1 is considered a critical mediator of the enterotrophic effects of Glp2 (15), although not systematically required (11). Igf1 promotes proliferation of small intestinal epithelium and participates in the fibroplasia, modulating the proliferation of fibroblasts and myofibroblasts and the collagen synthesis (15,16). Several studies demonstrated that this growth factor administration improves healing parameters, on animal models of colonic anastomosis, in high risk contexts (2,9).

An increase of *Hbegf* messenger RNA expression levels in teduglutide-treated animals was verified in present study, at both postoperative time points (although statistically significant only at the seventh day after isolated laparotomy). Involvement of the ErbB ligant-ErbB signaling pathway in the proliferative actions of Glp2 was suggested in previous experiments (11). Studies about the refeeding-induced mucosal proliferation revealed also the importance of ErbB signaling for the actions of endogenous Glp2 (11).

Hbegf has mitogenic and chemotactic effects on epithelial cells, smooth muscle cells and fibroblasts; promotes extracellular matrix synthesis and angiogenesis; modulates vasodilatation and preserves microcirculatory blood flow; improves intestinal motility and demonstrates anti-inflammatory effects (2,17,18). Moreover, this growth factor preserves the intestinal mucosa and restores gut barrier function after intestinal injury (17). Indeed, a potent intestinal cytoprotective effect of Hbegf on intestinal epithelial cells (including stem cells), endothelial cells, pericytes, immunocytes and neuronal cells has been demonstrated in animal models of

Table II. Correlations between relative gene expression of growth factors and Glp2 receptor in rats' small intestine and plasma levels of Glp2 at the moment of sacrifice (n = 59)[a]

σ / p	Igf1	Vegfa	Tgfβ1	Ctgf	Fgf2	Fgf7	Egf	Hbegf	Pdgfb	Glp2r	Plasma [Glp2]
Igf1			34.2% p = 0.009		-27.7% p = 0.036	-31.4% p = 0.016				30.4% p = 0.02	
Vegfa			-28.6% p = 0.029			-41.3% p = 0.001					
Tgfβ1	34.2% p = 0.009	-28.6% p = 0.029		-28.2% p = 0.032		34% p = 0.009	36.7% p = 0.005		29,6% p = 0,024	48.2% p = 0.0001	
Ctgf			-28.2% p = 0.032				27.3% p = 0.038		-52,6% p = 0,0001	37% p = 0.004	-40.7% p = 0.002
Fgf2	-27.7% p = 0.036					30.3% p = 0.021	53.2% p = 0.0001	31.8% p = 0.015			
Fgf7	-31.4% p = 0.016	-41.3% p = 0.001	34% p = 0.009		30.3% p = 0.021		44.4% p = 0.0001			37.6% p = 0.004	-40.5% p = 0.002
Egf			36.7% p = 0.005	27.3% p = 0.038	53.2% p = 0.0001	44.4% p = 0.0001		44.3% p = 0.001		52.7% p = 0.0001	-31.9% p = 0.016
Hbegf					31.8% p = 0.015		44.3 % p = 0.001			39.9% p = 0.002	
Pdgfb			29.6% p = 0.024	-52.6% p = 0.0001							
Glp2r	30.4% p = 0.02		48.2% p = 0.0001	37% p = 0.004		37.6% p = 0.004	52.7% p = 0.0001	39.9% p = 0.002			-30.6% p = 0.022
Plasma [Glp2]				-40.7% p = 0.002		-40.5% p = 0.002	-31.9% p = 0.016			-30.6% p = 0.022	

[a]*Relative gene expression of growth factors and Glp2 receptor and postoperative plasma levels of Glp2 ([Glp2]) were determined by qRT-PCR and competitive enzyme immunoassay, respectively. Spearman's rank correlation coefficient (σ) and level of significance (p) were presented.*
Igf1: insulin-like growth factor 1, transcript variant 1, mRNA; Vegfa: vascular endothelial growth factor A, transcript variant 2, mRNA; Tgfb1: transforming growth factor, beta 1, mRNA; Ctgf: connective tissue growth factor, mRNA; Fgf2: fibroblast growth factor 2, mRNA; Fgf7: fibroblast growth factor 7, mRNA; Egf: epidermal growth factor, mRNA; Hbegf: heparin-binding EGF-like growth factor, mRNA; Pdgfb: platelet-derived growth factor beta polypeptide, mRNA; Glp2r: glucagon-like peptide 2 receptor, mRNA.

necrotizing enterocolitis, ischemia/reperfusion injury, and hemorrhagic shock and resuscitation (17). Furthermore, in 2011, Radulescu A et al. (18) demonstrated, on an animal model, that exogenous Hbegf promoted intestinal anastomotic repair and that *Hbegf* (-/-) knockout mice had worse healing scores and higher morbidity and mortality rates after intestinal anastomosis.

Induction of *Vegfa* and *Ctgf* gene expression levels observed in this study in teduglutide-treated animals at the seventh day suggest that these growth factors may be also relevant as downstream mediators of Glp2 effects in the perioperative context.

Vegfa has an important participation in wound healing as it promotes the early events of angiogenesis (namely endothelial cell migration, proliferation and differentiation) and lymphangiogenesis (2,19). In 2012, Enestvedt CK et al. (20) demonstrate a favorable impact of recombinant *Vegf* gene therapy on the healing of an ischemic esophagogastrostomy on an animal model, including enhanced neovascularization, blood flow and bursting pressure. After intraoperative local Vegfa administration in a rabbit model of colonic anastomoses, Ishii M et al. (21) found improved bursting pressure, increased hydroxyproline levels and, also, significantly enhanced submucosal capillary vascular counts.

Ctgf is considered a key determinant in the formation and maintenance of connective tissues and in the wound repair process (19,22,23). In fact, this growth factor promotes proliferation, differentiation and chemotaxis of fibroblasts, epithelial-mesenchymal transition, extracellular matrix formation and remodeling, re-epithelialization (by stimulation of cell migration) and angiogenesis (19,22,23). Discrepant responses of *Ctgf* and *Tgf*β1 gene expressions to teduglutide administration, observed in our study, were surprising because Ctgf is controlled by Tgfβ1 in a Smad-dependent way and acts as a downstream mediator of Tgfβ action on connective tissue cells (19,22).

Our data indicated that teduglutide administration was associated with downregulation of *Tgfβ1* gene expression in the anastomotic segment at both moments of evaluation. This fact raises concern about a potential negative impact on the anastomotic healing, since Tgfβ participates in all phases of wound healing (2,19).

Tgfβ is a pleiotropic polypeptide hormone that modulates the mucosal immune response and tissue remodeling in the gut. In fact, Tgfβ downregulates the production of proinflammatory cytokines, promotes the differentiation of regulatory T-cells and induces the production of Immunoglobulin A (22,24). This growth factor also regulates extracellular matrix turnover and exerts an important role in tissue physiologic remodeling and wound repair in the intestine. Indeed, Tgfβ promotes the recruitment, proliferation, differentiation and activation of extracellular matrix-production cells (16,19,22,24) and the epithelial- and endothelial-mesenchymal transition (22); it also stimulates extracellular matrix production and deposition (including types I and III collagens, fibronectin and proteoglycans) and inhibits its degradation (including inhibition of matrix metalloproteinases 1, 3 and 9) (16,19,22). Tgfβ promotes epithelial restitution inducing the migration of epithelial cells across the wound margin (22,24), stimulates the recruitment of inflammatory cells and macrophage-mediated tissue debridement (19), promotes angiogenesis (thought upregulation of Vegf) (19,22) and participates in wound contraction (19). Adenoviral-mediated transfer of *Tgfβ*1 on an animal model of colonic anastomoses, through intraluminal local administration, was associated with a significant increase of the anastomotic bursting pressure (25).

Downregulation of *Fgf7* gene in animals submitted to teduglutide treatment documented in our study (statistically significant only in the anastomotic segment at the third day and in the ileal sample recovered after isolated laparotomy at the seventh day) was also unexpected because this growth factor has been proposed as one of the mediators of Glp2 action, particularly on the colonic mucosa (11). Fgf7 (also known as keratinocyte growth factor 1, Kgf1) is a mitogenic growth factor with an important role in the intestinal epithelial growth, maintenance and repair and in preservation of the barrier function (2,19,26). A favorable effect of this growth factor on intestinal mucosal protection has been demonstrated, on experimental studies, in chemically induced inflammatory bowel disease, chemotherapy and radiation mucositis, ischemia/reperfusion syndrome, short bowel syndrome and total parenteral nutrition contexts (26). Intraperitoneal administration of truncated Kgf on an animal model of colonic anastomosis was associated with enhanced anastomotic bursting pressure, lower inflammatory activity on histological examination and higher crypt cell proliferation rates (27).

As outlined above, most of the Glp2 effects are indirect and secondary to endocrine, paracrine, autocrine and neural signaling activated by the Glp2r (11). In present study, higher correlation coefficients were expected between relative mRNA expressions of *Glp2r* and *Igf1*, *Hbegf* and *Fgf7* gene expression levels, because those growth factors have been recognized as molecular downstream mediators of the Glp2r signaling in gastrointestinal tract (11).

Gene expressions of *Fgf2* and *Vegfa*, two of the most important mediators of neoangiogenesis (3), did not correlated significantly. In relation to the Glp2/Glp2r axis, our study suggests that tissue G*lp2r* expression may be negatively affected by increased Glp2 plasma concentrations.

In conclusion, results of present study underscore the recognized role of *Igf1* and *Hbegf* as molecular mediators of the effects of teduglutide and suggest that other humoral factors, like *Vegfa* and *Ctgf* may be also relevant in the perioperative context of intestinal anastomosis. A negative influence of teduglutide on postoperative *Tgfβ*1 relative gene expression was also indicated.

Albeit the negative impact on postoperative tissue *Tgfβ*1, induction of *Vegfa*, *Igf1* and *Ctgf* gene expressions might indicate a favorable influence of teduglutide on the intestinal anastomotic healing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Study was approved by the Ethics Committee of Faculty of Medicine, University of Coimbra, Coimbra, Portugal (License nº32-06-2009) and undertaken according to institutional and national animals' protection guidelines.

AUTHORS' CONTRIBUTIONS

- Study conception and design: Costa B.
- Acquisition of data: Costa B, Gonçalves AC, Alves R, Abrantes AM, Matafome P.
- Analysis and interpretation of data: Costa B.
- Drafting of manuscript: Costa B.
- Critical review: Seiça R, Sarmento-Ribeiro AB, Botelho MF, Castro Sousa F.

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REFERENCES

1. Thompson SK, Chang EY, Jobe BA: Clinical review: Healing in gastrointestinal anastomoses, Part I. Microsurgery 2006;26:131-6.
2. Rijcken E, Sachs L, Fuchs T, Spiegel HU, Neumann PA. Growth factors and gastrointestinal anastomotic healing. J Surg Res 2014;187:202-10.
3. Greaves NS, Ashcroft KJ, Baguneid M, Bayat A. Current understanding of molecular and cellular mechanisms in fibroplasia and angiogenesis during acute wound healing. J Dermatol Sci 2013;72:206-17.
4. Vakalopoulos KA, Daams F, Wu Z, Timmermans L, Jeekel JJ, Kleinrensink GJ, et al. Tissue adhesives in gastrointestinal anastomosis: a systematic review. J Surg Res 2013;180:290-300.

5. Adas G, Kemik O, Eryasar B, Okcu A, Adas M, Arikan S, et al. Treatment of ischemic colonic anastomoses with systemic transplanted bone marrow derived mesenchymal stem cells. Eur Rev Med Pharmacol Sci 2013;17:2275-85.
6. Yamaguchi R, Terashima H, Yoneyama S, Tadano S, Ohkohchi N. Effects of platelet-rich plasma on intestinal anastomotic healing in rats: PRP concentration is a key factor. J Surg Res 2012;173:258-66.
7. Hoeppner J, Wassmuth B, Marjanovic G, Timme S, Hopt UT, Keck T. Anastomotic sealing by extracellular matrices (ECM) improves healing of colonic anastomoses in the critical early phase. J Gastrointest Surg 2010;14:977-986.
8. Ayten R, Çetinkaya Z, Girgin M, Ozercan I, Ustundag B, Aygen E. The effects of intraperitoneal sildenafil administration on healing of left colonic anastomoses and intra-abdominal adhesion formation in the presence of intra-abdominal infection. Dis Colon Rectum 2008;51:1837-41.
9. Oines MN, Krarup P, Jorgensen LN, Agren MS. Pharmacological interventions for improved colonic anastomotic healing: A meta-analysis. World J Gastroenterol 2014;20:12637-48.
10. Holzner PA, Kulemann B, Kuesters S, Timme S, Hoeppner J, Hopt UT, et al. Impact of remote ischemic preconditioning on wound healing in small bowel anastomoses. World J Gastroenterol 2011;17:1308-16.
11. Drucker DJ, Yusta B. Physiology and pharmacology of the enteroendocrine hormone glucagon-like peptide-2. Annu Rev Physiol 2014;76:561-83.
12. Burness CB, McCormack PL. Teduglutide: a review of its use in the treatment of patients with short bowel syndrome. Drugs 2013;73:935-47.
13. Pfaffl MW. Quantification strategies in real-time PCR. In: Bustin SA, editor. A-Z of quantitative PCR; International University Line (IUL); La Jolla, CA, USA; 2014. pp. 87-112.
14. Seifert GS, Seifert M, Kulemann B, Holzner PA, Glatz T, Timme S, et al. Searching for the molecular benchmark of physiological intestinal anastomotic healing in rats: an experimental study. Eur Surg Res 2014;53:73-85.
15. Bortvedt SF, Lund PK. Insulin-like growth factor 1: common mediator of multiple enterotrophic hormones and growth factors. Curr Opin Gastroenterol 2012;28:89-98.
16. Latella G, Sferra R, Speca S, Vetuschi A, Gaudio E. Can we prevent, reduce or reverse intestinal fibrosis in IBD? Eur Rev Med Pharmacol Sci 2013;17:1283-304.
17. Yang J, Su Y, Zhou Y, Besner GE. Heparin-binding EGF-like growth factor (HB-EGF) therapy for intestinal injury: Application and future prospects. Pathophysiology 2014;21:95-104.
18. Radulescu A, Zhang HY, Chen CL, Chen Y, Zhou Y, Yu X, et al. Heparin-binding EGF-like growth factor promotes intestinal anastomotic healing. J Surg Res 2011;171:540-50.
19. Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. Wound Rep Reg 2008;16:585-601.
20. Enestvedt CK, Hosack L, Hoppo T, Perry KA, O'Rourke RW, Winn SR, et al. Recombinant vascular endothelial growth factor 165 gene therapy improves anastomotic healing in an animal model of ischemic esophagogastrostomy. Dis Esophagus 2012;25:456-64.
21. Ishii M, Tanaka E, Imaizumi T, Sugio Y, Sekka T, Tanaka M, et al. Local VEGF administration enhances healing of colonic anastomoses in a rabbit model. Eur Surg Res 2009;42:249-57.
22. Speca S, Giusti I, Rieder F, Latella G. Cellular and molecular mechanisms of intestinal fibrosis. World J Gastroenterol 2012;18:3635-61.
23. Jacobson A, Cunningham JL. Connective tissue growth factor in tumor pathogenesis. Fibrogenesis Tissue Repair 2012;5:S8.
24. Biancheri P, Giuffrida P, Docena GH, MacDonald TT, Corazza GR, Sabatino AD. The role of transforming growth factor (TGF)-β in modulation the immune response and fibrogenesis in the gut. Cytokine & Growth Factor Reviews 2014;25:45-55.
25. Migaly J, Lieberman J, Long W, Fisher C, Rolandelli RH. Effect of adenoviral-mediated transfer of transforming growth factor-beta1 on colonic anastomotic healing. Dis Colon Rectum 2004;47:1699-705.
26. Cai Y, Wang W, Liang H, Sun L, Teitelbaum DH, Yang H. Keratinocyte Growth Factor Improves Epithelial Structure and Function in a Mouse Model of Intestinal Ischemia/Reperfusion. PLoS ONE 2012;7:e44772.
27. Egger B, Inglin R, Zeeh J, Dirsch O, Huang Y, Büchler MW. Insulin-like growth factor I and truncated keratinocyte growth factor accelerate healing of left-sided colonic anastomoses. Br J Surg 2001;88:90-8.

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Trabajo Original

Otros

Biochemical and histological changes produced by sweeteners and cytarabine in the brain of young rats

Cambios bioquímicos e histológicos producidos por edulcorantes y citarabina en el cerebro de ratas jóvenes

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Abstract

Objective: The aim of this study was to evaluate the effect of splenda and stevia on dopamine and 5-HIAA levels, and some biomarkers of oxidative stress in the presence of cytarabine.

Methods: Forty-eight young male Wistar rats each with a weight of 80 g (four weeks of age), distributed in six groups of eight animals each, were treated as follows: group 1, control (NaCl 0.9% vehicle); group 2, cytarabine (0.6 g/kg); group 3, stevia (0.6 g/kg); group 4, cytarabine + stevia; group 5, splenda; and group 6, cytarabine + splenda. Cytarabine was given intravenously (IV) while stevia and splenda were administered orally for five days, using orogastric tube. At the end of treatment, the animals were sacrificed and glucose levels in blood were measured. The brains were dissected for histological analysis and homogenated to measure levels of dopamine, lipid peroxidation (TBARS), serotonin metabolite (5-HIAA), Na^+, K^+ ATPase activity, and glutathione (GSH), using validated methods.

Results: Sweeteners increased the glucose in animals that received cytarabine. Dopamine increased in cortex and decreased in striatum of animals that received stevia alone and combined with cytarabine. 5-HIAA decreased in striatum and cerebellum/medulla oblongata of animals that received sweeteners and cytarabine alone or combined. GSH increased in animals that received sweeteners and decreased with cytarabine. Lipoperoxidation decreased in groups that received sweeteners and cytarabine. Histopathological changes revealed marked degeneration of neuronal cells in animals treated with cytarabine.

Conclusion: These results show that sweeteners as stevia or splenda may lead to the onset of unfavorable changes in dopamine and 5-HIAA. Antioxidant effects may be involved. Besides, histological changes revealed marked lesions of neuronal cells in experimental animals treated with cytarabine.

Key words:

Cytarabine. Dopamine. Oxidative stress. Sweeteners.

Resumen

Objetivo: el objetivo fue evaluar el efecto de edulcorantes (splenda y stevia) sobre los niveles de dopamina, acido 5-hidroxiindolacetico (HIAA) y algunos biomarcadores de estrés oxidativo en presencia de citarabina.

Métodos: cuarenta y ocho ratas Wistar machos con un peso aproximado de 80 g (cuatro semanas de edad), distribuidas en seis grupos de ocho animales cada uno, fueron tratados como sigue: grupo 1, control (NaCl 0,9% vehículo); grupo 2, citarabina (0,6 g/kg); grupo 3, stevia (0,6 g/kg); grupo 4, citarabina + stevia; grupo 5, splenda; y el grupo 6, citarabina + splenda. La citarabina fue administrada por vía intravenosa y la stevia y la splenda, por vía oral durante cinco días, utilizando una sonda orogástrica. Al final del tratamiento, los animales fueron sacrificados y se midieron los niveles de glucosa en sangre. Los cerebros fueron disecados para su análisis histológico y homogenizados para medir los niveles de dopamina, peroxidación lipídica (TBARS), metabolito de la serotonina (5-HIAA), actividad de la Na^+, K^+ ATPasa y glutatión (GSH), usando métodos validados.

Resultados: los edulcorantes aumentaron la glucosa en los animales que recibieron citarabina. La dopamina aumentó en la corteza y disminuyó en el estriado de los animales que recibieron stevia sola y combinada con citarabina. La 5-HIAA disminuyó en el estriado y el cerebelo/médula oblongata de animales que recibieron edulcorantes y citarabina sola o combinada. El GSH se incrementó en los animales que recibieron edulcorantes. La lipoperoxidación disminuyó en los grupos que recibieron edulcorantes y citarabina. Estudios histopatológicos revelaron una degeneración neuronal importante en animales tratados con citarabina.

Conclusión: los resultados muestran que los edulcorantes como stevia o splenda pueden conducir a la aparición de cambios desfavorables en los niveles de dopamina y 5-HIAA. Los cambios histológicos revelaron, además, lesiones marcadas de células neuronales en animales tratados con citarabina.

Palabras clave:

Citarabina. Dopamina. Estrés oxidante. Edulcorantes.

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INTRODUCTION

The industrialization of food processing in the twentieth century paralleled with loss of quality have given rise to increased palatability, digestibility, overconsumption and the current obesity epidemic (1). Containment of the obesity epidemic is compounded by the addictive properties of sugar which involve the dopamine receptors (2). Adolescents are the highest consumers of sugar sweetened drinks (3), and factors linked to glucose metabolism are involved in the etiology of several cancers. High glycemic index (GI) or high glycemic load (GL) diets, which chronically raise postprandial blood glucose, may increase cancer risk (4). In spite of this, cancer is actually the principal cause of death in children under 15 years old (5). Metabolic syndrome (MS), an important problem of the childhood in Mexico, is another kind of pathology that befalls on young patients with cancer (6). Today in Mexico, oncological diseases are the second leading cause of death in the general population. Official statistics reported 80% of prevalence diagnoses patients on treatment survive to malignant tumors (7). Chemotherapy is a useful tool to attack cancer and mellow down the sufferings which it entails, and cytarabine is the most common chemotherapeutic agent used in children (8), although its use is accompanied by elevation of monoamine concentrations in the brain regions (9). Guidelines on sugar consumption by the World Health Organization (WHO) recommend non-sugar sweeteners such as stevia and splenda as healthy sugar replacement alternatives (10). Recently, the cultivation of *Stevia rebaudiana Bertoni* has gained interest for its potential use as a non-caloric sweetener with antioxidant properties (11).

Some studies suggest that chemotherapeutic agents such as cytarabine induce the interaction of proteins and activating factor (GcMAF) that inhibit cancer cell proliferation and metastatic potential, and may lead to nitric oxide (NO) release (12).

Since free radicals are known to damage cell components (13), mainly plasma membrane lipids (14), nitric oxide is a neuromodulator; however, an extra amount may lead to cell damage by oxidative stress or by forming nitroso-glutathione (NOGSH) within the cell (15). The central nervous system (CNS) intervenes in the control of food consumption and free radicals (FR) and actively participates in the metabolic functions of the same (16). It has been demonstrated that many biological processes are influenced by mechanical changes in membrane lipid components (17), and regulates energy and glucose homeostasis by acting on hypothalamic neurocircuits and higher brain circuits such as the dopaminergic system (18). Plasma membrane phospholipids in brain are in close contact with structural proteins that are embedded in the lipid bilayer (19), and through which the ionic interchange is maintained by the action of Na^+, K^+ ATPase that stimulates Na^+ and K^+ flows (20). The inhibition of the Na^+, K^+ ATPase activity induces excitatory amino acids release within the central nervous system (21).

Based on the above backgrounds, the purpose of the present study is to compare the protective effect of stevia and splenda on the levels of dopamine and 5-HIAA monoamines, and selected oxidative stress markers in brain regions of young rats treated with cytarabine.

METHODS

Forty-eight young male Wistar rats each with a weight of 80 g (four weeks old), distributed in six groups of eight animals each, were treated as follows: group 1, control (NaCl 0.9% vehicle); group 2, cytarabine (0.6 g/kg); group 3, stevia (0.6 g/kg); group 4, cytarabine + stevia; group 5, splenda; and group 6, cytarabine + splenda. Cytarabine was given intravenously (IV) while stevia and splenda were administered orally for five days, using orogastric tube. At the end of treatment, the animals were sacrificed and glucose levels in blood were measured. The animals were sacrificed by decapitation at the end of the treatment, and their brains were immediately dissected in cortex, striatum, and medulla/oblongata and immersed in a solution of NaCl at 0.9% and maintained at 4 °C. In the last day of treatment, blood samples were obtained and used to measure the levels of glucose. Each brain region was homogenized in 3 ml of tris-HCl 0.05 M pH 7.2 and used to determine lipid peroxidation (TBARS), Na^+, K^+ ATPase activity, levels of glutathione (GSH), serotonin metabolite (5-HIAA) and dopamine, using previously validated methods. The samples were kept at -20 °C until their assessment and others were stained with eosin-nigrosin to evaluate the histological abnormalities. Rats were procured from the Bioterium of the Instituto Nacional de Pediatría of Mexico City, and housed eight per cage in clean plastic cages and allowed to acclimatize in the room environment for one day. Animals were maintained in a mass air displacement room with a 12-h light/12-h dark cycle at 22 ± 2 °C with a relative humidity of 50 ± 10%. Balanced food (Rodent diet 5001) and drinking water were given to the animals *ad libitum* before and during study. The study protocol was previously approved by the Committee of Laboratory Animals Care of the National Institute of Pediatrics. Besides, all experimental procedures were performed following the national and international guidelines for Animal Care.

TECHNIQUE TO MEASURE BLOOD GLUCOSE

The measurement of blood glucose was carried out at the end of the treatment. Two blood samples (20 µl each) were drawn from the tail-end without anticoagulant and placed on Accu-Chek® (Roche Mannheim, Germany) equipment reactive paper. The blood glucose concentrations were measured and reported in mg/dl.

MEASUREMENT OF DOPAMINE

The levels of dopamine were measured in the supernatant of tissue homogenized in $HClO_4$ after centrifugation at 9,000 rpm for ten minutes in a microcentrifuge (HettichZentrifugen, model Mikro 12-42, Germany), with a version of the technique reported by Calderón et al. (22). An aliquot of the $HClO_4$ supernatant, and 1.9 ml of buffer (0.003 M octyl-sulphate, 0.035 M KH_2PO_4, 0.03 M citric acid, 0.001 M ascorbic acid), were placed in a test tube. The mixture was incubated for five minutes at room temperature in total darkness, and subsequently the samples were read in a

spectrofluorometer (PerkinElmer® LS 55, England) with 282 nm excitation and 315 nm emission lengths. The FL WinLab version 4.00.02 software was used. Values were inferred in a previous standardized curve and reported as nMoles/g of wet tissue.

MEASUREMENT OF 5-HYDROXYINDOL ACETIC ACID (5-HIAA)

5-HIAA levels were measured in the supernatant of tissue homogenized in $HClO_4$ after centrifugation at 9,000 rpm for ten minutes in a microcentrifuge (HettichZentrifugen, model Mikro 12-42, Germany), with a modified version of the technique reported by Beck et al. (23). An aliquot of the $HClO_4$ supernatant, and 1.9 ml of acetate buffer 0.01M pH 5.5 were placed in a test tube. The mixture was incubated for five minutes at room temperature in total darkness, and subsequently, the samples were read in a spectrofluorometer (PerkinElmer® LS 55, England) with 296 nm excitation and 333 nm emission lengths. The FL WinLab version 4.00.02 software was used. Values were inferred in a previously standardized curve and reported as nM/g of wet tissue.

MEASUREMENT OF GLUTATHIONE (GSH)

GSH levels were measured from the supernatant of the homogenised tissue, which was obtained after centrifuging at 9,000 rpm during five minutes (Mikro 12-42 centrifuge, Germany) based on a modified method of Hissin and Hilf (24); 1.8 ml phosphate buffer pH 8.0 with EDTA 0.2%, 20 µl taken from the supernatant and 100 ml of ortho-phthaldehyde at 1 mg/ml in methanol were mixed in a test tube and incubated for 15 min at room temperature in absolute darkness. Following the incubation, the mixture was spectrophotometrically read in PerkinElmer® LS 55, with excitation and emission wavelengths of 350 and 420, respectively. FL WinLab version 4.00.02 software was used. Values were inferred from a previous standardized curve and expressed as nM/g.

MEASUREMENT OF TOTAL ATPase

The activity of ATPase was assayed according to the method proposed by Calderón et al (25); 1 mg (10%) w/v of homogenised brain tissue in tris-HCl 0.05 M pH 7.4 was incubated for 15 minutes in a solution containing 3 mM $MgCl_2$, 7 mM KCl, and 100 mM NaCl. To this, 0.5, 1, 2, 3, and 4 mMtris-ATP were added and incubated for another 30 min at 37 °C in a shaking water bath (Dubnoff Labconco); 100 µl 10% trichloroacetic acid w/v was used to stop the reaction, and samples were centrifuged at 100 g for five minutes at 4 °C. Inorganic phosphate (Pi) was measured in duplicates using one supernatant aliquot as reported by Fiske and Subarrow (26). The absorbance of a supernatant sample was read at 660 nm in a Helios-α, UNICAM spectrophotometer and expressed as mM Pi/g wet tissue per minute.

MEASUREMENT OF LIPID PEROXIDATION (TBARS)

Determination of TBARS was carried out using the modified method of Gutteridge and Halliwell (15), as described below: from the homogenized brain in tris-HCl 0.05 M pH 7.4, 1 ml was taken, and 2 ml of thiobarbaturic acid (TBA) which contains 1.25 g of TBA, 40 g of trichloroacetic acid, and 6.25 ml of concentrated chlorhydric acid (diluted in 250 ml of deionized H_2O) were added. Samples were heated to boiling point for 30 minutes (Thermomix® 1420), after which they were immersed in ice bath for five minutes and, finally, centrifuged at 700 g for 15 minutes (Sorvall® RC-5B Dupont). The absorbance of the supernatants tissues was read in triplicate at 532 nm in a spectrophotometer (Helios-α, UNICAM). The concentration of reactive substances to thiobarbaturic acid (TBA-RS) was expressed as µM of malondialdehyde/g of wet tissue.

HISTOLOGICAL ANALYSIS IN BRAIN REGIONS

Histological examination of the tissue was conducted after immediately following brain extraction. The tissues were gently rinsed with a physiological saline solution (0.9% NaCl) to remove blood and adhering debris. Brains were taken and fixed in a 10% neutral-buffered formalin solution for 24 h. The fixed specimens were then trimmed, washed and dehydrated in ascending grades of alcohol. These specimens were cleared in xylene, embedded in paraffin, sectioned at 4-6 mm thickness and stained with hematoxylin and eosin (H&E) and then examined microscopically (27).

STATISTICAL ANALYSIS

Analysis of variances (ANOVA) and Kruskal-Wallis test were used with their corresponding contrasts and previous variance homogeneity comparison. Values of $p < 0.05$ were considered as statistically significant (28). The JMP version 8.0.0 for academic was used.

RESULTS

The levels of blood glucose discretely increased in each of the treatments administered in the study groups without statistically significant difference (Fig. 1).

Dopamine concentration in cortex decreased significantly in the group treated with stevia + cytarabine when compared with those that received stevia alone (Fig. 2). Compared with the rest of the groups, this bioamine did not register significant differences. In striatum, an important reduction in the concentrations of dopamine was observed in all the groups when compared with the control group. The comparison among the groups treated with splenda or splenda + cytarabine did not show any differences; however, in the groups treated with stevia or stevia + cytara-

bine, a significant reduction in the later could be appreciated. In cerebellum/medulla oblongata, a high significant reduction in dopamine concentration was found in the groups that received cytarabine, splenda, splenda + cytarabine and stevia + cytarabine with respect to the control. With the exception of the group treated with stevia, the same behavior was seen in those which were administered cytarabine. When the stevia group was compared with the stevia + cytarabine group, there was a significant decrease of this bioamine in the later.

In cortex, differences in the concentration of 5-HAA among the study groups were not observed (Fig. 3). In striatum, all the groups showed a significant reduction in the concentration of the bioamine when compared with the control. In cerebellum/medulla oblongata, a significant decrease was seen in the groups treated with splenda, splenda + cytarabine and stevia + cytarabine with respect to the control, while the same behavior was appreciated in the group that received splenda or splenda + cytarabine when compared with the group that was administered cytarabine alone.

The activity of GSH witnessed a significant decrease in the groups treated with splenda and splenda + cytarabine in the cortex, while in striatum the GSH activity reduced significantly in the group treated with splenda + cytarabine when compared with those that exclusively received splenda (Fig. 4). When comparing the activity of this bioamine among the group that received splenda + cytarabine with the control or cytarabine or splenda alone, a significant decrease was seen, while the comparison stevia *vs* stevia + cytarabine did not show any differences in cerebellum/medulla oblongata.

Lipid peroxidation in cortex reduced significantly in all the groups with respect to the control, and this was more evident in the group that received stevia (Fig. 5). In striatum, the same pattern was observed except in the group that received splenda + cytarabine. In cerebellum/medulla oblongata, a decrease in lipid peroxidation was seen in the groups with cytarabine, stevia and stevia + cytarabine in comparison with the control. The comparison of splenda *vs* splenda + cytarabine and stevia *vs*

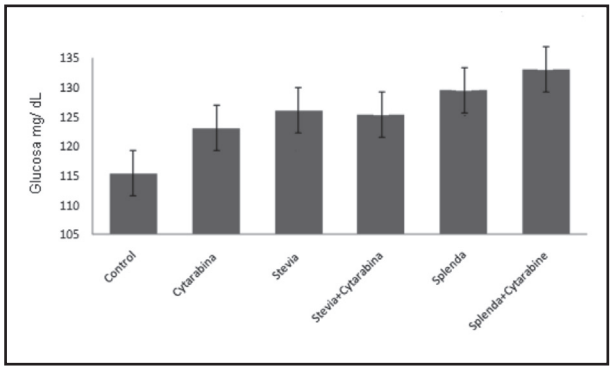

Figure 1.

Levels of glucose in blood of young rats treated with cytarabine and sweeteners. Mean values ± SD.

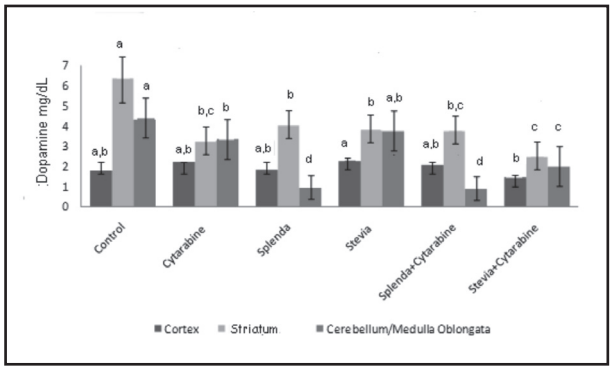

Figure 2.

Levels of dopamine in brain regions of young rats treated with cytarabine and sweeteners. Levels not connected by same letter are significantly different. Cortex: Kruskal-Wallis $\chi^2 = 11.78$, $p = 0.037$; striatum: Kruskal-Wallis $\chi^2 = 52.04$, $p < 0.0001$; cerebellum/medulla oblongata: Kruskal-Wallis $\chi^2 = 110.47$, $p < 0.0001$.

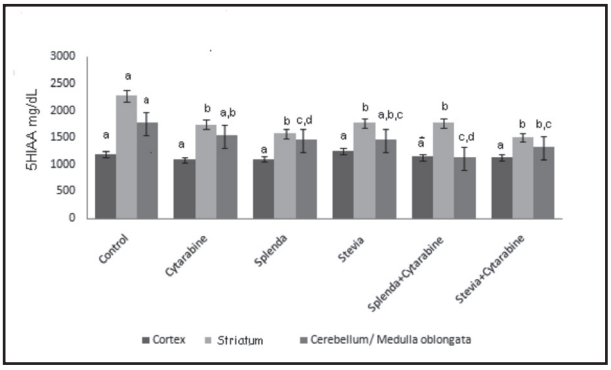

Figure 3.

Levels of 5-HAA in brain regions of young rats treated with cytarabine and sweeteners. Levels not connected by same letter are significantly different. Cortex: Anova $F = 1.23$, $p = 029$; striatum: Kruskal-Wallis $\chi^2 = 30.99$, $p < 0.0001$; cerebellum/medulla oblongata: Kruskal-Wallis $\chi^2 = 60.98$, $p < 0.0001$.

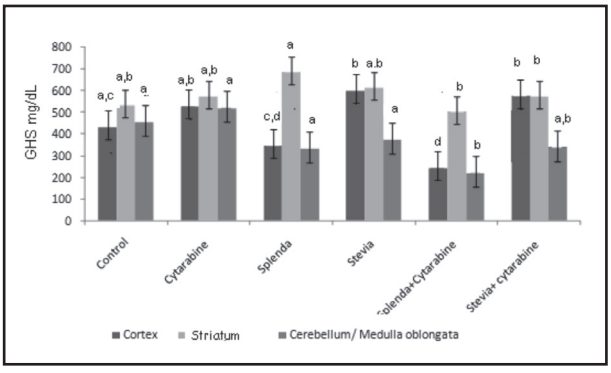

Figure 4.

Levels of GSH in brain regions of young rats treated with cytarabine and sweeteners. Levels not connected by same letter are significantly different. Cortex: Anova $F = 21.50$, $p = < 0.0001$; striatum: Anova = 2.29, $p < 0.048$; cerebellum/medulla oblongata: Kruskal-Wallis $\chi^2 = 29.30$, $p < 0.0001$.

stevia + cytarabine did not show any differences in the levels of the bioamine.

ATPase activity in cortex and in all the groups witnessed a light increase with respect to the control. This increase was statistically significant in the groups treated with splenda, splenda + cytarabine and stevia + cytarabine (Fig. 6). Comparison among the groups treated with the antineoplasic or the sweeteners did not show significant differences. The bioamine showed significant increased activity in the group that received cytarabine + splenda when compared with animals treated with cytarabine only.

In striatum, there was no difference in the activity of the enzyme. However, in cerebellum/medulla oblongata, a significant reduction in the ATPase activity was observed in the group treated with stevia when compared with the control. When comparing the activity of the enzyme in the group that received only cytarabine with those treated with cytarabine + sweetener, a statistically significant difference was observed only in those that received stevia and stevia + sweetener.

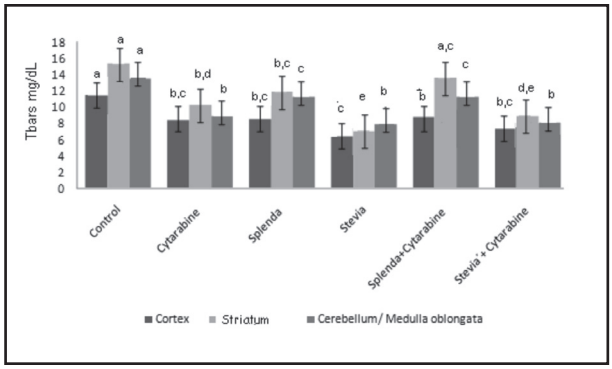

Figure 5.

Levels of Tbars (lipid peroxidation) in brain regions of young rats treated with cytarabine and sweeteners. Levels not connected by same letter are significantly different. Cortex: Anova F = 21.50, p = < 0.0001; striatum: Anova = 2.29, p < 0.048; cerebellum/medulla oblongata: Kruskal-Wallis $\chi^2 = 29.30$, p < 0.0001.

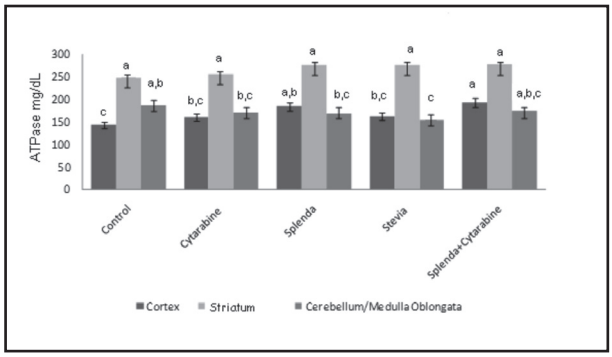

Figure 6.

Levels of ATPase activity in brain regions of young rats treated with cytarabine and sweeteners. Levels not connected by same letter are significantly different. Cortex: Anova F = 9.62.

HISTOLOGICAL ANALYSIS

The control animals' brains presented a normal cytoarchitecture, the well-defined form of the cellular and nuclear membrane being evident, with thin chromatin and homogenous neuropile in the three analyzed structures, cortex, striatum and cerebellum/medulla oblongata (Fig. 7A-C).

The treatment with cytarabine caused evident damage in the same structures analyzed. In the cortex (Fig. 7D), a reduction in cell size, loss of shape and evident pyknosis were observed in a significantly high number of cells (arrow head). In the striatum (Fig. 7E) the damage was slightly lower and cells were preserved, although the damage is evident, presenting cellular retraction and vacuolization in addition to pyknosis and loss of definite form (arrow head). In the cerebellum/medulla oblongata of rats treated with cytarabine (Fig. 7F) the same type of cell damage was found (arrow head).

In the panels (Fig. 8G-I) corresponding to cortex, striatum and cerebellum/medulla oblongata of rats treated with the splenda sweetener, there is slight cellular damage and the cytoarchitecture is very similar to that of the controls. In the cerebellum/medulla oblongata (Fig. 8I) we find more damaged cells than in cortex and striatum, without becoming significant (arrow head).

In the cortex, striatum and cerebellum/medulla oblongata sections of animals co-administered with splenda and cytarabine (Fig. 8J-L), damage is apparently similar to that of animals treated only with cytarabine (Fig. 7D-F), so we think that the sweetener splenda had no effect on those animals.

The analyzed structures of animals treated with the stevia sweetener (Fig. 9M-O for cortex, striatum and cerebellum/medulla oblongata respectively) do not present evident damage. In cortex, striatum and cerebellum/medulla oblongata of animals co-administered with stevia plus cytarabine (Fig. 9P-R) there are pyknotic cells with angled borders, cellular retraction and neuropile a little evident. However, minor damage is observed in cortex when it is compared with the cortex of animals treated only with cytarabine (Figs. 9P *vs* 7D), which suggests a slight protective effect of stevia against damage induced by cytarabine in the cortex. Striatum and cerebellum/medulla oblongata of animals with co-administration of stevia with cytarabine (Figs. 9Q and R) have a similar damage produced only with cytarabine.

DISCUSSION

Consumption of sugar-sweetened beverages may be one of the dietary causes of metabolic disorders (29). In the present study, the sweeteners slightly increased the glucose levels in blood of animals that received cytarabine, suggesting hypoinsulinemia effects.

Precursors of neuroactive substances can be obtained from dietary sources, which can affect the resulting production of such substances in the brain (30). The brain levels of dopamine in males can be controlled by an intake of tyrosine in food, and chronic food restriction induces dopamine conservation (31). However, in the

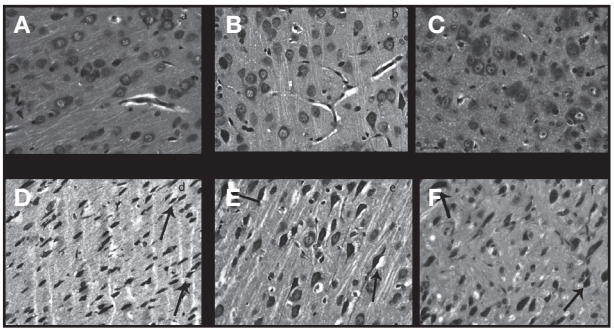

Figure 7.

Micrographs of cortex (A), striatum (B) and cerebellum/medulla oblongata (C) of control rats, where normal cells are seen, with well-defined, rounded cysts, nucleus with evident thin chromatin. In cortex (D), striatum (E) and cerebellum/medulla oblongata (F) of animals treated with cytarabine, morphological alterations such as pyknotic cells characterized by gradual acidophilia, evidenced by darkening of the nucleus and cytoplasm, contraction of the pericarp and loss of the boundaries of cytoplasmic membranes, spindle cells and angled edges (arrow heads), can be observed.

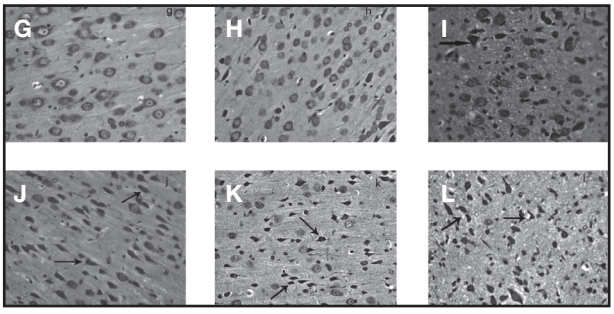

Figure 8.

Micrograph of cortex (G), striatum (H) and cerebellum/medulla oblongata (I) of animals treated with splenda sweetener. Cells with normal morphology were found in cortex and striatum (G and H), as well as in the cerebellum/medulla oblongata a slight damage was found with cells in the degeneration process (I, indicated by the arrow). In J, K and L cells, corresponding to cortex, striatum and brain stem of animals co-administered with splenda and cytarabine respectively, damaged cells are seen, although slightly smaller than in the cells of animals treated with cytarabine alone.

present study dopamine increased in cortex and decreased in striatum of animals that received stevia alone or combined with cytarabine, suggesting changes in the hypothalamus for the control of energy homeostasis and within the brain regions related with rewards (32). These results were contrary to those of Abhilash et al. (33), who found that other artificial sweeteners as aspartame decreased dopamine in corpus striatum and cerebral cortex, and serotonin in corpus striatum.

With respect to 5-HIAA levels, precursor of serotonin, it decreased in striatum and cerebellum/medulla oblongata of animals that received sweeteners and cytarabine alone or combined. These findings coincide with those of El-Merahbi et al. (34), who pinpointed that peripheral serotonin has an impact on the regulation of the function of the organs involved in glucose and lipid homeostasis. Indeed, peripheral 5HT plays an important role in

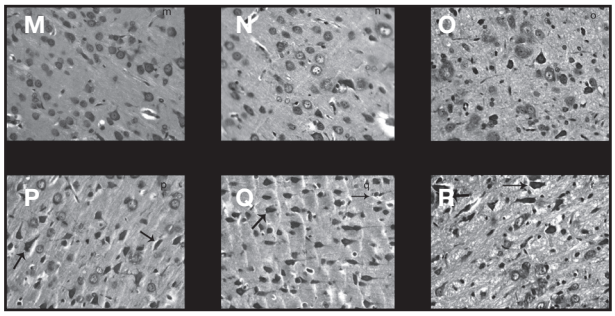

Figure 9.

Micrograph of cortex (M), striatum (N) and cerebellum/medulla oblongata (O) of animals administered with stevia sweetener. Normal cytoarchitecture with homogeneous distribution and well defined forms in cortex and striatum are observed. In figure O, which corresponds to cerebellum/medulla oblongata, some cells in the process of degeneration are appreciated, but nucleus and nucleolus are still visible. Cortex (P) striatum (Q) and cerebellum/medulla oblongata (R) of rats with co-administration of stevia and cytarabine also showed cells damaged in the process of degeneration, but in a smaller number than those treated only with cytarabine.

the regulation of glucose homeostasis through the differential expression and activation of 5-HT membrane receptors on the surface of hepatocytes, adipocytes and pancreatic β-cells (35).

GSH concentration increased in striatum of animals that received sweeteners (splenda and stevia) and decreased with the cytarabine administration. These results suggest neuroprotection and antioxidant effects, and coincide with previous reports of stevia, a diterpenic carboxylic alcohol with three glucose molecules, mainly used as a substitute for non-alcoholic sweetener (10).

Lipoperoxidation levels decreased in cortex, striatum and cerebellum/medulla oblongata regions in groups that received sweeteners and cytarabine. This effect of neuroprotection could be due to polar compounds obtained during the extraction of compounds like chlorophylls, carotenoids, phenolic and flavonoids involved in stevia and splenda. These substances are not physiologically inert compounds and their consumption may have potential biological mechanisms which may impact on energy balance and metabolic function (36).

Ca^{2+}, Mg^{2+} ATPase activity increased in cortex and striatum regions, and decreased in cerebellum/medulla oblongata of animals that received sweeteners and cytarabine. These results suggest that glucose concentration, which mimics fasting, decreased intracellular NADPH and increased Na(+) concentration in single arcuate nucleus neurons, of the body's energy state, which subsequently exhibited $Ca^{(2+)}$ responses to lower glucose (37).

CONCLUSIONS

These results show sweeteners as stevia or splenda may lead to the onset of unfavorable changes in biogenic amines, dopamine and 5-HIAA, independent of significant effects of cytarabine administration. Antioxidant effects may be involved. Besides, histological changes revealed marked lesions of neu-

ronal cells in experimental animals treated with cytarabine compared to those in the normal controls. Further studies are needed to confirm the opposing effects of high dietary glucose levels on risks of cancer.

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REFERENCES

1. Bilton R. Averting comfortable lifestyle crises. Sci Prog 2013;96:319-68.
2. Pandit R, Omrani A, Luijendijk MC, De Vrind VA, Van Rozen AJ, Ophuis RJ. Melanocortin 3 receptor signaling in midbrain dopamine neurons increases the motivation for food reward. Neuropsychopharmacology 2016;41(9):2241-51. DOI: 10.1038/npp.2016.19.
3. Reichelt AC, Abbott KN, Westbrook RF, Morris MJ. Differential motivational profiles following adolescent sucrose access in male and female rats. Physiol Behav 2016;157:13-9.
4. Sieri S, Agnoli C, Pala V, Grioni S, Brighenti F, Pellegrini N, et al. Dietary glycemic index, glycemic load, and cancer risk: Results from the EPIC-Italy study. Sci Rep 2017;7:9757.
5. Ross JA, Severson RK, Pollock BH, Robison LL. Childhood cancer in the Unites States. A geographical analysis of cases from the Pediatric Cooperative Clinical Trials groups. Cancer 1996;77:201-7.
6. Herrera-Silva JC, Treviño-Moore A, López-Beltrán AL. Metabolic syndrome in cancer patients during chemotherapy treatment. Bol Med Hosp Infant Mex 2008;65:110-20.
7. Increases the incidence of cancer in children. Available from: www.generoysaludreproductiva.gob.mx/article.2006.
8. Gabor KM, Schermann G, Lautner-Csorba O, Rarosi F, Erdelyi DJ. Impact of single nucleotide polymorphisms of cytarabine metabolic genes on drug toxicity in childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2015;62:622-8.
9. Matsutani T, Tamaru M, Hayakawa Y, Nagayoshi M, Nakahara T, Tsukada Y. A neurochemical study of developmental impairment of the brain caused by the administration of cytosine arabinoside during the fetal or neonatal period of rats. Neurochem Res 1983;8:1295-306.
10. Stuckler D, Reeves A, Loopstra R, McKee M. Textual analysis of sugar industry influence on the World Health Organization's 2015 sugars intake guideline. Bull World Health Organ 2016; 94:566-73.
11. Ruiz Ruiz JC, Moguel Ordóñez YB, Matus Basto Á, Segura Campos MR. Antioxidant capacity of leaf extracts from two Stevia rebaudiana Bertoni varieties adapted to cultivation in Mexico. Nutr Hosp 2014;31:1163-70.
12. Ruggiero M, Ward E, Smith R, Branca JJ, Noakes D, Morucci G, et al. Oleic acid, deglycosylated vitamin D-binding protein, nitric oxide: A molecular triad made lethal to cancer. Anticancer Res 2014;34:3569-78.
13. Hogg N, Singh RJ, Kalyanaraman B. The role of glutathione in the transport and catabolism of nitric oxide. FEBS Let 1996;382:223-8.
14. Beckman JS, Beckman TW, Chen J, Marshall PA, Freeman BA. Apparent hydroxyl radical production by peroxynitrite: Implications for endothelial injury from nitric oxide and superoxides. Proc Natl Acad Sci USA 1990;87:1624-9.
15. Gutteridge JM, Halliwell B. The measurement and mechanism of lipid peroxidation in biological systems. Trends Biochem Sci 1990;15:129-35.
16. Driver AS, Kodavanti PR, Mundy WR. Age-related changes in reactive oxygen species production in rat brain homogenates. Neurotoxicol Teratol 2000;22:175-81.
17. Shamitko-Klingensmith N, Molchanoff KM, Burke KA, Magnone GJ, Legleiter J. Mapping the mechanical properties of cholesterol-containing supported lipid bilayers with nanoscale spatial resolution. Langmuir 2012;28:13411-22.
18. Vogt MC, Brüning JC. CNS insulin signaling in the control of energy homeostasis and glucose metabolism - From embryo to old age. Trends Endocrinol Metab 2012;24:76-84.
19. Swapna I, Sathya KV, Murthy CR, Senthilkumaran B. Membrane alterations and fluidity changes in cerebral cortex during ammonia intoxication. Neuro-Toxicol 2005;335:700-4.
20. Stefanello FM, Chiarani F, Kurek AG. Methionine alters Na+, K+ ATPase activity, lipid peroxidation and nonenzymatic antioxidant defences in rat hippocampus. Int J Dev Neurosc 2005;23:651-6.
21. Calderón GD, Juárez OH, Hernández GE, Labra RN, Barragán MG, Trujillo JF, et al. Effect of an antiviral and vitamins A,C,D on dopamine and some oxidative stress markers in rat brain exposed to ozone. Arch Biol Sci Belgrade 2013;65:1371-9.
22. Calderón GD, Osnaya BN, García AR, Hernández GE, Guillé PA. Levels of glutathione and some biogenic amines in the human brain putamen after traumatic death. Proc West Pharmacol Soc 2008;51:25-32.
23. Beck O, Palmskog G, Hultman E. Quantitative determination of 5-hydroxyindole-3-acetic acid in body fluids by HPLC. Clin Chim Acta 1977;79:149-54.
24. Hissin PJ, Hilf R. A flurometric method for determination of oxidized and reduced glutathione in tissue. Anal Biochem 1974;4:214-26.
25. Calderón-Guzmán D, Espitia-Vázquez I, López-Domínguez A, Hernández-García E, Juárez-Olguín H. Effect of toluene and nutritional status on serotonin, lipid peroxidation levels and Na+/K+ATPase in adult rat brain. Neurochem Res 2005;30:619-24.
26. Fiske CH, Subbarow Y. The colorimetric determination of phosphorus. J Biol Chem 1972;66:375-400.
27. Luna LT. Manual of Histologic Staining Methods of the Armedforce Institute of Pathology. New York: McGraw Hill Book Co.; 1968. pp. 1-39.
28. Castilla-Serna L. Practical Statistical Manual for Health Sciences. 1ª ed. Mexico DF: Ed. Trillas; 2011.
29. Anton SD, Martin CK, Han H, Coulon S, Cefalu WT, Geiselman P, et al. Effects of stevia, aspartame, and sucrose on food intake, satiety, and postprandial glucose and insulin levels. Appetite 2010;55:37-43.
30. Sasaki K. Nutrition and dopamine: An intake of tyrosine in royal jelly can affect the brain levels of dopamine in male honeybees (Apismellifera L). J Insect Physiol 2016;87:45-52.
31. Carr KD. Nucleus accumbens AMPA receptor trafficking upregulated by foodrestriction: An unintended target for drugs of abuse and forbidden foods. Curr Opin Behav Sci 2016;9:32-9.
32. Yoon YR, Baik JH. Melanocortin 4 receptor and dopamine D2 receptor expression in brain areas involved in food intake. Endocrinol Metab (Seoul) 2015;30:576-83.
33. Abhilash M, Alex M, Mathews VV, Nair RH. Chronic effect of aspartame on ionic homeostasis and monoamine neurotransmitters in the rat brain. Int J Toxicol 2014;33:332-41.
34. El-Merahbi R, Löffler M, Mayer A, Sumara G. The roles of peripheral serotonin in metabolic homeostasis. FEBS Lett 2015;589:1728-34.
35. Cataldo LR, Cortés VA, Galgani JE, Olmos PR, Santos JL. Role of peripheral serotonin in the insulin secretion and glucose homeostasis. Nutr Hosp 2014;30:498-508.
36. Burke MV, Small DM. Physiological mechanisms by which non-nutritive sweeteners may impact body weight and metabolism. Physiol Behav 2015;152:381-8.
37. Kurita H, Xu KY, Maejima Y, Nakata M, Dezaki K. Arcuate Na+, K+-ATPase senses systemic energy states and regulates feeding behavior through glucose-inhibited neurons. Am J Physiol Endocrinol Metab 2015;309:E320-33.

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Revisión

Appetite hormones in children and adolescents with cancer: a systematic review of observational studies

Las hormonas del apetito en niños y adolescentes con cáncer: una revisión sistemática de los estudios observacionales

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Abstract

Introduction: Malnutrition in children with cancer is a significant risk factor for negative outcomes, but in the clinical practice setting, it is difficult to pinpoint which factors operate to cause substantial weight loss and malnutrition in a given patient. Appetite-related hormones like ghrelin and leptin are among possible mediators. However, only few studies have examined the role of these hormones in pediatric patients with cancer to date. Thus, the purpose of this study was to systematically review possible changes in the levels of appetite hormones, specially leptin and ghrelin, in pediatric patients with cancer.

Material and methods: We systematically reviewed the literature using PubMed, Lilacs and Scielo, as well as manual bibliographical reference search of the studies. According to the Medical Subject Headings of the National Library of Medicine (MeSH), "childhood cancer", "ghrelin" and "leptin" were used as descriptors.

Results: Fifteen studies were included in this systematic review published in English, from 2000 to 2015. A total of 863 patients were evaluated, ages ranging from 0 to 21 years, and most of the studies reported on children and adolescents with acute lymphoblastic leukemia (ALL) survivors. Most studies analyzed leptin levels; only two studies evaluated levels of ghrelin.

Conclusion: This review confirms that changes in the responses of the ghrelin and leptin hormones in children and adolescents with cancer are quite diverse, probably due to the different types of cancer observed, different treatments performed and biological characteristics of this age group.

Key words:

Ghrelin. Leptin. Childhood cancer. Nutritional status. Appetite.

Resumen

Introducción: la desnutrición en niños con cáncer es un factor de riesgo significativo para resultados negativos, pero en la práctica clínica, es difícil determinar qué factores operan para causar pérdida de peso sustancial y desnutrición en un paciente dado. Entre los posibles mediadores están las hormonas relacionadas con el apetito como la grelina y la leptina. Sin embargo, hasta la fecha, solo unos pocos estudios han examinado el papel de estas hormonas en pacientes pediátricos con cáncer. El propósito de este estudio fue revisar sistemáticamente los posibles cambios en los niveles de hormonas del apetito, especialmente la leptina y la grelina, en pacientes pediátricos con cáncer.

Material y métodos: se llevó a cabo una revisión sistemática de la bibliografía empleando PubMed, Lilacs y Scielo, así como la búsqueda bibliográfica manual de referencia de los estudios. Según los encabezamientos médicos de la Biblioteca Nacional de Medicina (MeSH), "cáncer infantil", "grelina" y "leptina" se utilizaron como descriptores.

Resultados: en esta revisión sistemática, se incluyeron 15 estudios publicados en inglés de 2000 a 2015. Fueron evaluados un total de 863 pacientes, con edades comprendidas entre 0 y 21 años, y la mayoría de los estudios informaron sobre niños y adolescentes supervivientes de leucemia linfoblástica aguda. La mayoría de los estudios analizaron los niveles de leptina y solo dos estudios evaluaron los niveles de grelina.

Conclusión: esta revisión confirma que los cambios en las respuestas hormonales de la grelina y la leptina en niños y adolescentes con cáncer son muy diversos, probablemente debido a los diferentes tipos de cáncer observado, los diferentes tratamientos realizados y las características biológicas de este grupo de edad.

Palabras clave:

Grelina. Leptina. Cáncer infantil. Valor nutricional. Apetito.

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INTRODUCTION

Good nutritional status is highly relevant for children with cancer. It enables them to cope better with the intensive cancer treatment regimens (1). The prognosis for childhood cancer has improved in recent decades, with five year survival rates reaching approximately 80% (2). Nonetheless, this improvement in the survival rate in childhood cancer has given rise to a number of treatment-related complications (3). Malnutrition in children with cancer is a significant risk factor for negative outcomes, such as decreased treatment tolerance, increased susceptibility to infections and reduced survival (4). This may occur because the energy intake is diminished, because the energy requirement is increased, or both. Inflammation and alterations in neurotransmitters and neuropeptides (4-6) are relevant factors for malnutrition. However, in the clinical practice setting, it is difficult to pinpoint which factors operate to cause substantial weight loss and malnutrition in a given patient.

Cancer anorexia-cachexia syndrome is multifactorial in origin. Its etiology is gradually being defined. This syndrome is related to malnutrition. Appetite-related hormones (7), like ghrelin and leptin, are among the possible mediators. Ghrelin is a peptide hormone with a potent orexigenic effect, directly related to food intake, and is mainly produced in the stomach (8). Leptin, an adipocyte-derived protein, was identified as a product of the obesity gene (whose autosomal recessive mutation results in profound hyperphagia and obesity) (9). Both hormones are related to the regulation of food intake and, consequently, body weight control, and can play an important role in the occurrence of obesity and metabolic syndrome in healthy children and adults (3,7). Increased ghrelin levels and decreased leptin levels were reported in patients with a variety of cancers (10,11), and were reported in adult cachectic patients compared with non-cachectic cancer patients (12). However, only very few studies have examined the role of these hormones, or other adipocytokines, in pediatric patients with cancer to date.

Chemotherapeutic agents, in the long term, can also result in changes in leptin secretion, leading to increased plasma levels (13). However, the plasma levels of leptin vary substantially in the available studies on childhood cancer. In the study of Park et al. (14), children with pediatric cancer showed higher plasma concentrations of leptin when compared to healthy children, but lower plasma levels of ghrelin. Moschovi et al. (15) followed nine pediatric ALL patients from the diagnosis to the maintenance phase, and no significant decreases in leptin levels were observed in these patients. In another study, the same authors observed an expressive increase in the levels of ghrelin after the eighth cycle of chemotherapy (16). However, very few studies evaluated alterations of ghrelin and leptin during chemotherapy in different types of cancer, and these discrepant results may be due to the different treatments adopted. Thus, the purpose of this study was to systematically review possible changes in the levels of appetite hormones, specially leptin and ghrelin, in pediatric patients with cancer.

METHODS

SEARCH STRATEGY

We systematically reviewed the literature using a protocol suggested by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to search research databases, screened published studies, applied inclusion and exclusion criteria and selected relevant literature for review (14). An extensive electronic search was carried out in December 2016 to identify the relevant articles. The following databases were used: PubMed, Lilacs and Scielo, as well as manual bibliographical reference search of the studies. According to the *Medical Subject Headings of the National Library of Medicine* (MeSH), "childhood cancer", "ghrelin" and "leptin" were used as descriptors.

INCLUSION/EXCLUSION CRITERIA

Studies (prospective and cross-sectional) with ghrelin and leptin as outcome during follow-up treatment of children and adolescents (age below 20 years) with any type of cancer were included. To be included in this review, articles also had to be peer-reviewed full report, and published either in English or in Portuguese. Book chapters, reviews, letters, abstracts or dissertations, or any clinical trial with an experimental treatment for childhood cancer were excluded.

STUDY SELECTION AND DATA EXTRACTION

We used a spreadsheet to manage screening and selection of studies. Two reviewers (APTF and ADLB) completed an initial, independent screening of all titles and abstracts retrieved from the database searches, and independently reviewed the full texts of the studies. A third reviewer (RF) resolved any conflicts at both stages. In an effort to prevent the false exclusion of a relevant study, among any conflicted decisions in which the third reviewer moved to exclude the study, all three reviewers discussed the article and came to a consensus. Methodological quality was not an inclusion criterion.

Furthermore, reported limitations or limitations found during reading were abstracted.

RESULTS

Initially, 76 articles were identified. After removing duplicate articles (03) and reading their title names and abstracts, a total of 23 articles were selected to be read in full. After careful reading, ten articles were excluded of final analyses and two articles were included. A flowchart showing the details of the selection process is shown in figure 1. In the end, 15 studies were included in this systematic review. Table I shows the result of the systematic review.

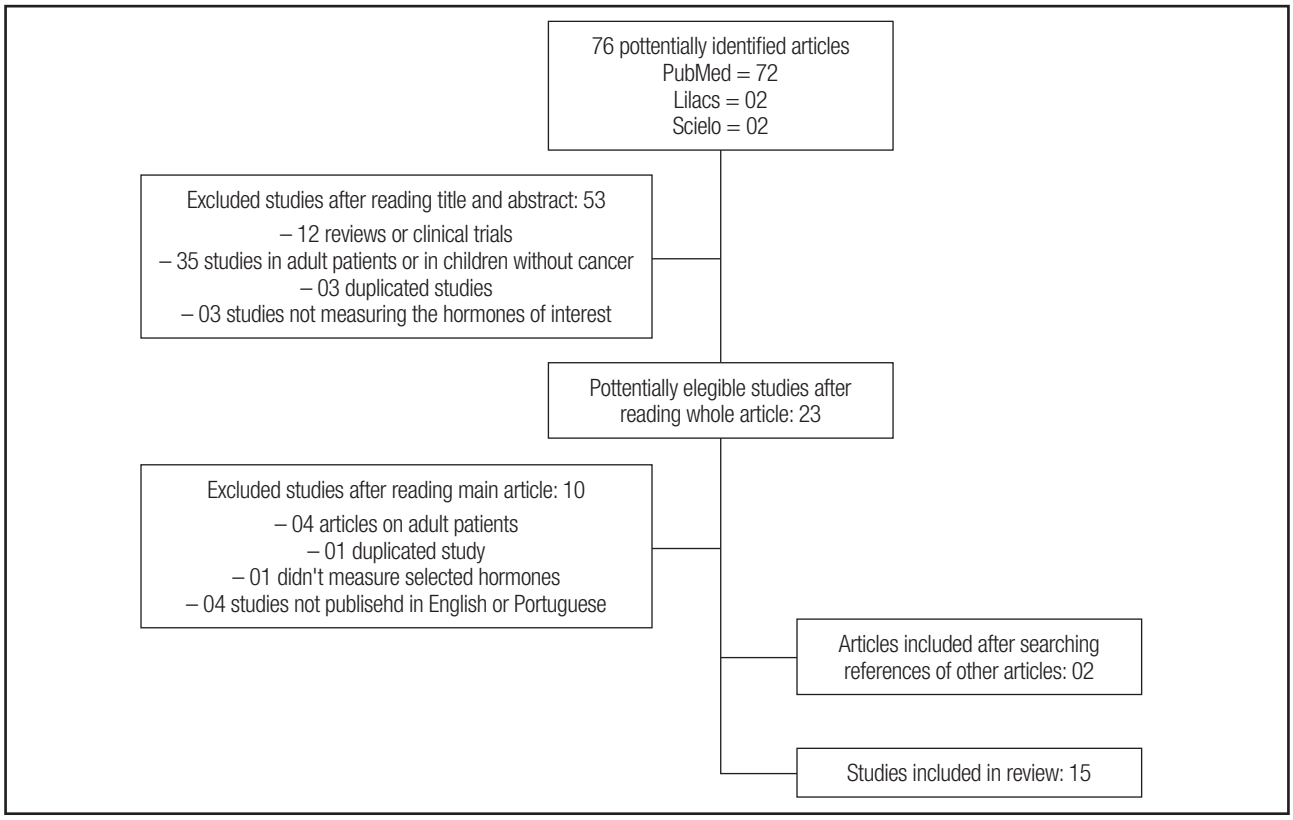

Figure 1.

Detailed flowchart showing the process for studies selection.

CHARACTERISTICS OF THE POPULATION INCLUDED IN THE STUDIES

A total of 863 patients were evaluated, ages ranging from 0 to 21 years. Most of the studies reported on children and adolescents with ALL (3,16,18,20-23,26-29), with non-Hodgkin's lymphoma (20,25,27) being the second most prevalent. The studies included a population of both genders, and many of them had completed their treatment and were considered as cancer survivors. Four studies (16,19,21,28) followed the patients up, including measures before and after treatment.

HORMONE CONCENTRATIONS IN CASE-CONTROL STUDIES

Most studies analyzed leptin levels; only two studies (16,19) evaluated levels of ghrelin. In one of these studies (16), children with cancer had lower ghrelin concentrations when compared to their controls, but this concentration increased significantly after the maintenance phase of chemotherapy. The studies showed discrepant results in relation to leptin levels when compared to controls. While one study showed that leptin levels were higher in the cancer group (26), others showed that the levels were significantly lower in patients with pediatric cancer (20,27), while still others found no difference between the groups (21,24,25).

HORMONE CONCENTRATIONS DURING TREATMENT OR BETWEEN DIFFERENT CONDITIONS OF CANCER

The studies showed a wide variation in the health conditions of patients, and some studies compared the hormonal levels in different cancer treatment regimens. Srivastava et al. found that leptin levels were slightly higher in obese children with cancer (18), and Kojima et al. found that patients with metabolic syndrome had higher concentrations of leptin (3). As to the impact of treatment on hormonal concentrations, Trivin et al. found that patients with craniopharyngioma and hypothalamic involvement had lower concentrations of ghrelin and higher concentrations of leptin (19). In this same study, after one year of the surgical procedure, ghrelin levels were significantly reduced only in patients with moderate hypothalamic involvement, while leptin levels increased independently of hypothalamic involvement. Treatment with high doses of methylprednisolone during seven days significantly increased leptin levels in patients with leukemia (21), but another study demonstrated a reduction in leptin levels at day 33 of chemotherapy (28).

Table I. Summary of studies and their results

Reference	Design of study	Characteristics of patients	Type of cancer	Control group	Hormone	Mean values of hormones: result at diagnostic	Mean values of hormones: result during treatment
Srivastava et al., 2015 (18)	Cross-sectional	159 (123 boys) acute leukemia survivors aged ≤ 18 years who had completed the treatment at least 1 year before enrollment in this study Mean age: 10.7 ± 4.2 years Patients were stratified according to their nutritional status in obese (26.4%) and non-obese (73.6%)	Acute lymphoblastic leukemia	None	Leptin (pg/ml)	Obese: 3.70 ± 2.27 Non-obese: 2.85 ± 1.91 (p = 0.06 between)	-
Trivin et al., 2009 (19)	Longitudinal	27 patients (15 boys) with craniopharyngioma stratified according to hypothalamic involvement Mean age: 8.3 ± 3.5 (2.8-15.7)	Craniopharyngioma	None	Grhelin (ng/l)	- Without hypothalamic involvement: 2,256 ± 331 - With light hypothalamic involvement: 1,091 ± 251 - With moderate hypothalamic involvement: 1,083 ± 222 p < 0.05 for hypothalamic involvement between other groups	One year after surgery: - With light hypothalamic involvement: 994 ± 263 - With moderate hypothalamic involvement: 722 ± 126
					Leptin (µg/l)	- Without hypothalamic involvement: 5.6 ± 2.6 - With light hypothalamic involvement: 7.7 ± 4.5 - With moderate hypothalamic involvement: 14 ± 9.8	One year after surgery: - Without hypothalamic involvement: 14.2 ± 14 - With light hypothalamic involvement: 32 ± 14 - With moderate hypothalamic involvement: 61 ± 26 p < 0.05 between light and moderate hypothalamic involvement
					Free leptin index	- Without hypothalamic involvement: 12.7 ± 13 - With light hypothalamic involvement: 12.4 ± 9.0 - With moderate hypothalamic involvement: 34 ± 33 p < 0.05 for moderate hypothalamic involvement	One year after surgery: - With light hypothalamic involvement: 113 ± 63 - With moderate hypothalamic involvement: 279 ± 102 p < 0.05 between light and moderate hypothalamic involvement

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[Nutr Hosp 2018;35(1):201-210]

Table I (Cont.). Summary of studies and their results

Reference	Design of study	Characteristics of patients	Type of cancer	Control group	Hormone	Mean values of hormones: result at diagnostic	Mean values of hormones: result during treatment
Sawicka-Zkowska et al., 2013 (20)	Cross-sectional	74 Caucasian survivors patients (42 boys) after treatment for acute leukemia (n = 64) and lymphomas (non-Hodgkin lymphoma; n = 10) Mean age: 15.5 ± 2.6	Acute leukemia and non-Hodgkin lymphoma	51 nonobese patients (34 boys) hospitalized in the department due to reasons other than neoplastic diseases Mean age: 14.8 ± 3.6	Leptin (ng/ml)	Cancer survivors: 6.64 ± 7.70 Controls: 14.48 ± 19.28 $p < 0.05$	-
Kojima et al., 2013 (3)	Cross-sectional	49 patients (27 boys) survivors of various types of cancer with a median age at diagnosis of 5.1 years (range: 0.2-14.2 years); the median present age was 10.7 years (range: 6.0-25.3 years)	Leukemias, lymphomas and solid tumor	None	Leptin (ng/ml)	Patients were stratified according to the number of metabolic syndrome components: 0: 3.6 (1.1-24.8) 1: 4.6 (1.7-19.5) 2-4: 6.2 (1.9-17.6)	-
Tavil et al., 2012 (21)	Case-control	72 (39 boys) children with acute leukemia and range of age 1.08-6 years (mean 6.96 ± 4.16, median 6 years) All patients were newly diagnosed and received only high-dose methylprednisolone during the first 7 days of therapy	Acute lymphoblastic leukemia and acute non-lymphoblastic leukemia	70 age- and sex-matched healthy children (41 boys) with an age range of 0.5-16 years (mean 6.76-4.92, median 4 years)	Leptin (ng/ml)	Controls: 5.96 ± 6.76 Cancer: 4.92 ± 3.39 $p > 0.05$	Cancer 7-day after high-dose methylprednisolone therapy: 7.16 ± 5.40 $p < 0.001$ compared with before
Kohler et al., 2011 (22)	Cross-sectional	54 patients (27 male) previously treated with mean of 5.8 years from treatment completion The mean ages at diagnosis and study entry were 5.8 ± 3.9 years and 14.0 ± 5.0 years, respectively Females mean age was 16.0 ± 4.5 years and boys mean age was 12.1 ± 4.7 years	Acute lymphoblastic leukemia	51 healthy controls (21 male) participated in the study Females mean age was 14.3 ± 5.2 years and boys mean age was 13.6 ± 4.5 years	Leptin (ng/ml)		Females survivors: 17.88 ± 18.7 Female controls: 7.8 ± 7.4 $p < 0.05$ Boys survivors: 3.18 ± 2.7 Boys controls: 3.68 ± 5.1 $p > 0.05$

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Table I (Cont.). Summary of studies and their results

Reference	Design of study	Characteristics of patients	Type of cancer	Control group	Hormone	Mean values of hormones: result at diagnostic	Mean values of hormones: result during treatment
Chow et al., 2010 (23)	Prospective cross-sectional	Children at age < 22 years Two groups were organized: a) Hematopoietic-cells transplant (HCT) group with 26 (16 boys) patients currently in remission b) Non-hematopoietic-cells transplant (non-HCT) 48 (22 boys) patients in first year complete remission after treatment with conventional chemotherapy Mean age was 15 (8-21 years) for HCT and , and 14 (8-21y years) for non-HCT	Acute lymphoblastic leukemia	None	Leptin (ng/ml)	-	At least 1 year after HCT: 3.0 (2.2-3.8) Non-HCT: 2.4 (1.2-3.5) $p > 0.05$
Petridou et al., 2010 (24)	Case-control	75 patients (0-14 years old) newly diagnosed with histologically confirmed Hodgkin lymphoma Mean age was 11.5 ± 2.97 years	Hodgkin lymphoma	75 controls matched for age (6 months) and gender were recruited among children admitted for other causes in the same hospital at the same time as cases Mean age was 11.2 ± 2.90 years	Leptin (ng/ml)	Cases: 8.2 ± 7.26 Controls: 7.5 ± 8.30 $p > 0.05$	-
Moschovi et al., 2010 (15)	Case-control	9 (5 boys) children with newly diagnosed ALL with mean age of 4.3 ± 2.1 years (2.1-7.2) in the diagnosis and 5.6 ± 2.0 years (3.2-8.5) in the last measurement in maintenance phase of chemotherapy	Acute lymphoblastic leukemia	9 healthy children matched for age and sex were used as controls	Leptin (ng/ml)	ALL diagnosis: 27.4 ± 4.2 Controls: 17.8 ± 3.4 $p < 0.001$	Last measurement in maintenance phase of chemotherapy: 17.1 ± 3.9 $p < 0.001$

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Table I (Cont.). Summary of studies and their results

Reference	Design of study	Characteristics of patients	Type of cancer	Control group	Hormone	Mean values of hormones: result at diagnostic	Mean values of hormones: result during treatment
Petridou et al., 2009 (25)	Case-control	121 patients (0-14 years old) newly diagnosed with histologically confirmed non-Hodgkin lymphoma Mean age was 8.8 ± 3.5 years	Non-Hodgkin lymphoma	121 controls matched for age (6 months) and gender were recruited, among children admitted for other causes in the same hospital at the same time as cases Mean age was 8.8 ± 3.5 years	Leptin (ng/ml)	Cancer: 6.0 ± 6.31 Controls: 5.9 ± 7.38 $p > 0.05$	-
Moschovi et al., 2008 (16)	Case-control	9 (5 boys) children with newly diagnosed ALL with mean age of 4.3 ± 2.1 years (2.1-7.2) in the diagnosis and 5.6 ± 2.0 years (3.2-8.5) in the last measurement in maintenance phase of chemotherapy	Acute lymphoblastic leukemia	9 healthy children matched for age and sex were used as controls	Ghrelin (pg/ml)	ALL diagnosis: 32.6 ± 2.9 Controls: 97.2 ± 14.4 $p < 0.001$	Last measurement in maintenance phase of chemotherapy: 50.6 ± 16.3 (+57%) $p < 0.05$
Papadia et al., 2007 (26)	Case-control	27 patients (15 boys) treated for ALL during childhood and in complete remission for at least 2 years They had an average age (± SD) of 14.0 ± 0.8 years (range: 6-21 years)	Acute lymphoblastic leukemia	17 (6 boys) healthy subjects with a comparable mean age (12.8 ± 1 years, range: 8-21 years), selected among relatives of the patients (brothers, sisters, or cousins)	Leptin (ng/ml)	Cases: 15.58 ± Controls: 10.78 ± 2.0 $p < 0.05$ Obs: expressed in mean ± SD	-

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Table I (Cont.). Summary of studies and their results

Reference	Design of study	Characteristics of patients	Type of cancer	Control group	Hormone	Mean values of hormones: result at diagnostic	Mean values of hormones: result during treatment
Yaris et al., 2005 (27)	Case-control	20 patients (12 boys, 13 with ALL and seven with non-Hodgkin lymphoma) and mean age 132 ± 45 (range; 64-218) months The follow-up times from diagnosis and the end of therapy were 60 ± 22 and 25 ± 11 months, respectively	Acute lymphoblastic leukemia and non-Hodgkin lymphoma	20 (11 male) healthy children aged 68-216 months (mean: 134.8 ± 36.5) were selected from the children referred to outpatients clinics of the Department of Pediatrics for suspected disease and were found to be normal	Leptin (ng/mL)	Cases: 10.3 ± 5.4 Controls: 15.7 ± 6.6 $p < 0.05$	-
Wex et al., 2002 (28)	Longitudinal	38 patients were evaluated in the day of diagnosis and in complete hematologic remission at day 33 Median age was 6.0 years; range: 1.2-21.9 years	Acute lymphoblastic leukemia	13 healthy children (median age: 7 years; range: 3-13 years)	Leptin (ng/ml)	Cancer on the day of diagnosis: 0.92 ± 0.79 Healthy donors: 3.01 ± 2.27 ng/ml $p < 0.05$	Average leptin concentrations on day 33 of chemotherapy treatment: 2.6 ± 2.4 $p < 0.01$
Mayer et al., 2000 (29)	Cross-sectional	Patients were divided in two groups: - 39 patients (23 boys) who had been treated for non-high risk ALL and who fulfilled the following criteria: a) prolonged first remission for at least 3 years; and b) age between 10 and 20 years at the time of this study - Additionally, 25 patients (15 boys) received comparable chemotherapy and, in addition, fractionated cranial irradiation for prophylaxis	Acute lymphoblastic leukemia	None	Leptin (ng/ml)	Non-irradiation group: 0.38 ± 0.53 Irradiation group: 0.48 ± 0.25 $p > 0.10$	-

DISCUSSION

This review confirms that there is a large discrepancy between studies in relation to the concentrations of these hormones in cancer patients compared to controls, and between different treatment protocols. Many studies evaluated hormones in cancer survivors, not necessarily with active disease, and this may have contributed to the variety of findings. Survival rates after childhood cancer have improved markedly, and, today, more than 80% of patients with a pediatric malignancy will become five-year survivors (30). With the improved survival rates, long-term treatment-related effects are being observed more frequently, and need to be addressed. Obesity is one such late effect, which increases the long-term risk of death from cardiovascular diseases. This condition likely has a significant association with appetite hormones.

An interesting aspect of the studies included in this systematic review is that very few studies have evaluated ghrelin. Ghrelin is a key regulator of nutrient sensing, meal initiation, and appetite (31). Additionally, studies have reported that ghrelin exhibits proliferative properties in cancer (32). Interestingly, the articles that included the evaluation of this hormone dosed total ghrelin, not its fractions (acylated and non-acylated). There is a debate about the usefulness of total ghrelin as a biomarker of appetite. For some authors, total ghrelin measurements do not accurately reflect specific biological actions of ghrelin. Ghrelin circulates in both acylated and unacylated forms; the unacylated form's levels are 2.5 times higher than the acylated form's (33). It is felt that acylation at serine-3 is essential for the biological activity of ghrelin. However, unacylated ghrelin is able to antagonize the metabolic but not the neuroendocrine response elicited by acylated ghrelin (34). More information on the relationships of acylated and unacylated ghrelin in patients with cancer is called for.

Of the studies included in the systematic review, only two evaluated ghrelin concentrations in the pediatric population with cancer (16,19), and both measured total ghrelin. Levels of ghrelin in children with ALL were lower than in controls, and in the maintenance phase of chemotherapy there was a significant increase in the circulating levels of the hormone (16). In acute leukemia, there is inflammation and serum hyperlipidemia, and both may suppress ghrelin at diagnosis (35). Leukemia causes a more intensive inflammatory process than solid tumors; so, gut hormones may behave differently in ALL. Trivin et al. (19) observed that the hypothalamic involvement in patients with craniopharyngioma decreased levels of ghrelin, and this reduction was more significant the greater was the involvement. In the particular setting of craniopharyngioma, the destruction, or functional impairment, of the hypothalamus is probably responsible for the failure to integrate neuronal, hormonal and metabolic signals from the body, leading to changed feeding behavior (36).

Leptin is proportional to total body fat mass and, communicating primarily with the hypothalamus, has a role in satiety and energy use (18). Recently, leptin has been shown to play a regulatory role for differentiation within the myeloid and erythroid cell lineage, whereas results of its regulatory effects on lymphocytes and related tumor cells have been contradictory (28). Higher serum leptin levels have been associated with body fatness in ALL survivors (37). In the current systematic review, the results in leptin concentrations were quite discrepant between studies. This may be due, in part, to the fact that leptin levels are affected by several variables, including gender, pubertal stage, weight, diet and the analytical method (38). Small variations are expected in the values assayed by different methodology. Large variability is probably due to different pubertal stages and BMIs in the studies (39,40).

Most of the studies included in the review evaluated children and adolescents with ALL or survivors of hematological malignancies. Leukemia is the most common malignancy in children (9,41). It is a heterogeneous group of diseases in which there is a substitution of normal medullary and blood elements by immature cells (blasts), and accumulation of these cells in other tissues (42). Because more than 80% of children with ALL survive to adulthood, the late effects of therapy must be considered (23,43). In survivors, overnutrition may be one of the risk factors for type II diabetes mellitus, hypertension, and cardiovascular disease. This is a particular problem for cancer survivors, who already have the additional risk for cardiovascular disease due to potential cardiotoxic effects of chemotherapy or radiotherapy (44). The role of leptin in hematological malignancies has been explored, not just as an appetite hormone, but also as a stimulus for proinflammatory cytokines, hematopoiesis and lymphopoiesis (25), promoting atherogenesis. It may indeed be an independent risk factor for cardiovascular disease.

According to Srivastava et al. (18), leptin is proportional to total body fat mass and communicates primarily with the hypothalamus, promoting satiety and influencing energy usage. However, studies have failed to find a direct relationship between leptin levels and anthropometric parameters of body fat (45,46). Petridou et al. have shown that elevated serum adiponectin, but not leptin levels, might be independently associated with both Hodgkin's and non-Hodgkin's lymphoma incidence, as well as with poor prognosis, in children (24,25). In young adult survivors of childhood cancer, adiponectin might be associated with insulin resistance (47). The differences between studies do not allow us to characterize leptin changes in children with cancer in this review. More studies are needed to investigate the role and associations of appetite hormones in children and adolescents with cancer, in order to better understand the pathophysiology of nutritional findings, and even to establish different patterns of response in different types of cancer.

In conclusion, changes in the responses of the ghrelin and leptin hormones in children and adolescents with cancer are quite diverse, probably due to the different types of cancer observed, different treatments performed and biological characteristics of this age group. Because of growing interest in the effectiveness of strategies to minimize cardiometabolic risk in the childhood cancer population, further research is necessary to better understand the behavior of these hormones during the disease and its possible relations with the nutritional status and the prognosis of the patients.

REFERENCES

1. Brinksma A, Huizinga G, Sulkers E, Kamps W, Roodbol P, Tissing W. Malnutrition in childhood cancer patients: A review on its prevalence and possible causes. Crit Rev Oncol Hematol 2012;83(2):249-75.
2. Mostoufi-Moab S, Seidel K, Leisenring WM, Armstrong GT, Oeffinger KC, Stovall M, et al. Endocrine abnormalities in aging survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. J Clin Oncol 2016;34(27):3240-7.
3. Kojima C, Kubota M, Nagai A, Adachi S, Watanabe K-I, Nakahata T. Adipocytokines in childhood cancer survivors and correlation with metabolic syndrome components. Int J Endocrinol 2016;2016:6349134.
4. Murphy AJ, White M, Viani K, Mosby TT. Evaluation of the nutrition screening tool for childhood cancer (SCAN). Clin Nutr 2016;35(1):219-24.
5. Metayer C, Milne E, Clavel J, Infante-Rivard C, Petridou E, Taylor M, et al. The Childhood Leukemia International Consortium. Cancer Epidemiol 2013;37(3):336-47.
6. Murphy MFG, Bithell JF, Stiller CA, Kendall GM, O'Neill KA. Childhood and adult cancers: Contrasts and commonalities. Maturitas 2013;76(1):95-8.
7. Ezeoke CC, Morley JE. Pathophysiology of anorexia in the cancer cachexia syndrome. J Cachexia Sarcopenia Muscle 2015;6(4):287-302.
8. Cummings DE. Ghrelin and the short- and long-term regulation of appetite and body weight. Physiol Behav 2006;89(1):71-84.
9. Karaman S, Ercan O, Bolayirh M, Celkan T, Apak H, Özkan A, et al. Late effects of childhood ALL treatment on body mass index and serum leptin levels. J Pediatr Endocrinol Metab 2010;23:669-74.
10. Kerenidi T, Lada M, Tsaroucha A, Georgoulias P, Mystridou P, Gourgoulianis KI. Clinical significance of serum adipokines levels in lung cancer. Med Oncol 2013;30:507.
11. Ozsoy S, Besirli A, Unal D, Abdulrezzak U, Orhan O. The association between depression, weight loss and leptin/ghrelin levels in male patients with head and neck cancer undergoing radiotherapy. Gen Hosp Psychiatry 2015;37(1):31-5.
12. Takahashi M, Terashima M, Takagane A, Oyama K, Fujiwara H, Wakabayashi G. Ghrelin and leptin levels in cachectic patients with cancer of the digestive organs. Int J Clin Oncol 2009;14:315-20.
13. Mariani S, Basciani S, Giona F, Lubrano C, Ulisse S, Gnessi L. Leptin modification in chronic myeloid leukemia patients treated with imatinib: An emerging effect of targeted therapy. Leuk Res Reports 2013;2(2):58-60.
14. Park SH, Jung MH, Chung NG, Suh B-K, Lee BC. Serum ghrelin and leptin concentrations in children with cancer: Comparisons with normal children. Korean J Pediatr Vol 2007;50(9):905-11.
15. Moschovi M, Katsibardi K, Chrousos G, Moschovi M, Trimis G, Vounatsou M. Serial plasma concentrations of adiponectin, leptin, and resistin during therapy in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2010;32(1)e8-13.
16. Moschovi M, Trimis G, Vounatsou M, Katsibardi K, Margeli A, Dimitriadi F, et al. Serial plasma concentrations of PYY and ghrelin during chemotherapy in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2008;30(10):733-7.
17. Moher D, Liberati A, Tetzlaff J, Altman DG. Academia and clinic annals of internal medicine preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. Annu Intern Med 2009;151(4):264-9.
18. Srivastava R, Batra A, Tyagi A, Dhawan D, Ramakrishnan L, Bakhshi S. Adiponectin correlates with obesity: A study of 159 childhood acute leukemia survivors from India. Indian J Cancer 2015;52(2):195-7.
19. Trivin C, Busiah K, Mahlaoui N, Recasens C, Souberbielle J-C, Zerah M, et al. Childhood craniopharyngioma: Greater hypothalamic involvement before surgery is associated with higher homeostasis model insulin resistance index. BMC Pediatr 2009;9(24):1471-2431.
20. Sawicka-Zkowska M, Krawczuk-Rybak M, Muszynska-Roslan K, Panasiuk A, Latoch E, Konstantynowicz J. Does Q223R polymorphism of leptin receptor influence on anthropometric parameters and bone density in childhood cancer survivors? Int J Endocrinol 2013;2013:805312.
21. Gunay Balta A, Tavil B, Balta G, Lay Ergun E, Ozkasap S, Tuncer M, et al. Leptin promoter G-2548A genotypes and associated serum leptin levels in childhood acute leukemia at diagnosis and under high-dose steroid therapy. Leuk Lymphoma 2012;53(4):648-53.
22. Kohler JA, Moon RJ, Wright S, Willows E, Davies JH. Increased adiposity and altered adipocyte function in female survivors of childhood acute lymphoblastic leukaemia treated without cranial radiation. Horm Res Paediatr 2011;75(6):433-40.
23. Chow EJ, Simmons JH, Roth CL, Baker KS, Hoffmeister PA, Sanders JE, et al. Increased cardiometabolic traits in pediatric survivors of acute lymphoblastic leukemia treated with total body irradiation. Biol Blood Marrow Transpl 2010;16(12):1674-81.
24. Petridou ET, Dessypris N, Panagopoulou P, Sergentanis TN, Mentis AFA, Pourtsidis A, et al. Adipocytokines in relation to Hodgkin lymphoma in children. Pediatr Blood Cancer 2010;54:311-5.
25. Petridou ET, Sergentanis TN, Dessypris N, Vlachantoni IT, Tseleni-Balafouta S, Pourtsidis A, et al. Serum adiponectin as a predictor of childhood non-Hodgkin's lymphoma: A nationwide case-control study. J Clin Oncol 2009;27(20):5049-55.
26. Papadia C, Naves LA, Costa SSS, Vaz JAR, Domingues L, Casulari LA. Incidence of obesity does not appear to be increased after treatment of acute lymphoblastic leukemia in Brazilian children: Role of leptin, insulin, and IGF-1. Horm Res 2007;68:164-70.
27. Yaris N, Sözen E, Erduran E, Ökten A, Örem A, Çakirbay H. Bone mineral metabolism and its relationship to leptin levels in survivors of childhood leukemia and lymphoma. Pediatr Hematol Oncol 2005;22(6):489-98.
28. Wex H, Ponelis E, Wex T, Dressendörfer R, Mittler U, Vorwerka P. Plasma leptin and leptin receptor expression in childhood acute lymphoblastic leukemia. Int J Hematol 2002;76:446-52.
29. Mayer EI, Reuter M, Dopfer RE, Ranke MB. Energy expenditure, energy intake and prevalence of obesity after therapy for acute lymphoblastic leukemia during childhood. Horm Res 2000;53(4):193-9.
30. Follin C, Gabery S, Petersen A, Sundgren PC, Bjorkman-Burtcher I, Latt J, et al. Associations between metabolic risk factors and the hypothalamic volume in childhood leukemia survivors treated with cranial radiotherapy. PLoS One 2016;11(1):1-13.
31. Pradhan G, Samson SL, Sun Y. Ghrelin: Much more than a hunger hormone. Curr Opin Clin Nutr Metab Care 2013;16(6):619-24.
32. Majchrzak K, Szyszko K, Pawłowski K, Motyl T, Król M. A role of ghrelin in cancerogenesis. Pol J Vet Sci 2012;15(1):189-97.
33. Kojima M, Hosoda H, Matsuo H, Kangawa K. Ghrelin: Discovery of the natural endogenous ligand for the growth hormone secretagogue receptor. Trends Endocrinol Metab 2001;12(3):118-22.
34. Broglio F, Gottero C, Prodam F, Gauna C, Muccioli G, Papotti M, et al. Non-acylated ghrelin counteracts the metabolic but not the neuroendocrine response to acylated ghrelin in humans. J Clin Endocrinol Metab 2004;89(6):3062-5.
35. Lambert M, Delvin EE, Paradis G, O'Loughlin J, Hanley JA, Levy E. C-reactive protein and features of the metabolic syndrome in a population-based sample of children and adolescents. Clin Chem 2004;50(10):1762-8.
36. Müller HL, Emser A, Faldum A, Bruhnken G, Etavard-Gorris N, Gebhardt U, et al. Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma. J Clin Endocrinol Metab 2004;8:3298-305.
37. Tonorezos ES, Vega GL, Sklar CA, Chou JF, Moskowitz CS, Mo Q, et al. Adipokines, body fatness, and insulin resistance among survivors of childhood leukemia. Pediatr Blood Cancer 2012;58(1):31-6.
38. Wilasco MIA, Goldani HAS, Dornelles CTL, Maurer RL, Kieling CO, Porowski M, et al. Ghrelin, leptin and insulin in healthy children: Relationship with anthropometry, gender, and age distribution. Regul Pept 2012;173(1-3):21-6.
39. Bjarnason R, Boguszewski M, Dahlgren J, Gelander L, Kriström B, Rosberg S, et al. Leptin levels are strongly correlated with those of GH-binding protein in prepubertal children. Eur J Endocrinol 1997;137(1):68-73.
40. García-Mayor RV, Andrade MA, Ríos M, Lage M, Diéguez C, Casanueva FF. Serum leptin levels in normal children: Relationship to age, gender, body mass index, pituitary-gonadal. J Clin Endocrinol Metab 1997;82(9):2849-55.
41. Wiemels J. Perspectives on the causes of childhood leukemia. Chem Biol Interact 2012;196(3):59-67.
42. Sanches FLFZ, Nitsch TM, Vilela MMS, Sgarbieri VC. Comparison of biochemical and immunological profile of pediatric patients with acute myeloid leukemia in relation to healthy individuals. J Pediatr (Rio J) 2015;91(5):478-84.
43. Orgel E, Genkinger JM, Aggarwal D, Sung L, Nieder M. Association of body mass index and survival in pediatric meta-analysis. Am J Clin Nutr 2016;103(3):808-17.
44. Brinksma A, Roodbol PF, Sulkers E, Kamps WA, De Bont ESJM, Boot AM, et al. Changes in nutritional status in childhood cancer patients: A prospective cohort study. Clin Nutr 2015;34(1):66-73.
45. Sawicka-Zkowska M, Krawczuk-Rybak M, Muszynska-Roslan K, Panasiuk A, Latoch E, Konstantynowicz J. Does Q223R polymorphism of leptin receptor influence on anthropometric parameters and bone density in childhood cancer survivors? Int J Endocrinol 2013;2013:1-9.
46. Komsu-Ornek Z, Demirel F, Dursun A, Ermis B, Etem I, Piskin E, et al. Leptin receptor gene Gln223Arg polymorphism is not associated with obesity and metabolic syndrome in Turkish children. Turk J Pediatr 2012;54(1):20-4.
47. Latoch E, Muszynska-roslan K, Panas A, Panasiuk A, Sawicka-zukowska M, Zelazowska-rutkowska B, et al. Adipokines and insulin resistance in young adult survivors of childhood cancer. Int J Endocrinol 2016;2016:6349134.

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ARÁN

Nutrición Hospitalaria

Revisión

Efectos del estado nutricional en la enfermedad de la esclerosis múltiple: revisión sistemática

Effects of nutritional status on the multiple sclerosis disease: systematic review

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Resumen

Objetivo: revisar la literatura científica existente sobre los efectos del estado nutricional en la esclerosis múltiple.

Método: revisión sistemática de la literatura científica recogida en las bases de datos Medline (PubMed), Scopus, Cochrane Library y Web of Science, hasta noviembre de 2016. Ecuación de búsqueda: ("Multiple Sclerosis"[Mesh] OR "Multiple Sclerosis"[Title/Abstract] OR "Disseminated Sclerosis"[Title/Abstract] OR "Multiple Sclerosis Acute Fulminating"[Title/Abstract]) AND ("Nutritional Status"[Mesh] OR "Nutritional Status"[Title/Abstract] OR "Nutrition Status"[Title/Abstract]). La calidad de los artículos se evaluó mediante el cuestionario STROBE. Se completó la búsqueda con la consulta a expertos y la revisión de la bibliografía de los artículos seleccionados.

Resultado: de las 160 referencias recuperadas, tras aplicar los criterios de inclusión y exclusión, se seleccionaron para la revisión 29 artículos. La gran mayoría de los estudios determinaron los niveles de vitamina D. Otros centraron su búsqueda en averiguar qué déficits de nutrientes podrían estar relacionados con el desarrollo de la esclerosis múltiple.

Conclusiones: la vitamina D puede influir en la mejora de la esclerosis múltiple. La luz solar y la actividad física serían factores importantes, junto con el estado nutricional, en el curso de dicha enfermedad. Sería necesaria la generación de nuevos trabajos específicos que profundizaran en el tema para averiguar más acerca de la relación existente entre el estado nutricional y la esclerosis múltiple.

Palabras clave:

Esclerosis múltiple. Estado nutricional. Revisión sistemática; Vitamina D. 25 hidroxivitamina D.

Abstract

Objective: To review the available scientific literature about the effects of nutritional status on the multiple sclerosis disease.

Methods: A systematic review of the scientific literature in the Medline (PubMed), Scopus, Cochrane Library and Web of Science databases through November 2016. Search equation: ("Multiple Sclerosis"[Mesh] OR "Multiple Sclerosis"[Title/Abstract] OR "Disseminated Sclerosis"[Title/Abstract] OR "Multiple Sclerosis Acute Fulminating"[Title/Abstract]) AND ("Nutritional Status"[Mesh] OR "Nutritional Status"[Title/Abstract] OR "Nutrition Status"[Title/Abstract]). The quality of the selected articles was discussed using the STROBE questionnaire. The search was completed through experts inquiry and additional review of the bibliographic references included in the selected papers. The concordance between authors (Kappa index) had to be higher than 80% for inclusion in this review.

Results: Of the 160 references recovered, after applying inclusion and exclusion criteria, 29 articles were selected for review. Concordance between evaluators was 100.00%. The most studies established vitamin D levels. Others focused their research on finding out which nutrient deficits might be related to the multiple sclerosis development.

Conclusions: Vitamin D may influence multiple sclerosis improvement. Sunlight and physical activity would be important factors, with nutritional status, in the course of this disease. It is necessary to produce new specific works that will delve into the subject to find out more about the relationship between nutritional status and multiple sclerosis.

Key words:

Multiple sclerosis. Nutritional status. Vitamin D. 25 hidroxyvitamin D.

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INTRODUCCIÓN

Entre las enfermedades más comunes del sistema nervioso central (SNC) se encuentra la esclerosis múltiple (EM), la cual afecta en torno a dos millones de personas en todo el mundo (1) y es, además, la enfermedad neurológica degenerativa más común en adultos jóvenes (2) y con mayor prevalencia en mujeres (3).

La EM puede presentarse de diversas formas, según las manifestaciones clínicas y el pronóstico de la enfermedad, pudiendo ser remitente-recurrente (forma más común), progresiva primaria o progresiva secundaria (4).

A pesar de que el origen de la EM es aún desconocido, en esta patología se ven implicados un conjunto de procesos inflamatorios e inmunológicos crónicos que provocan una desmielinización y, con ello, el daño axonal (5). Swui-Ling y cols. (4) sugieren que su desarrollo es debido a factores genéticos, ambientales, nutricionales e inmunológicos.

Si bien es imprescindible una correcta alimentación en cualquier enfermedad, no es hasta el año 1950 que el neurólogo Swank establece una relación entre la dieta y la EM (6). A pesar de ello, aún a día de hoy, el tratamiento de la EM no incluye la combinación de fármacos con recomendaciones dietéticas o cambios en el estilo de vida, lo cual puede ser debido a la falta de información (7).

En consecuencia, el objetivo del presente estudio consistió en revisar la literatura científica existente sobre los efectos del estado nutricional en la esclerosis múltiple.

MATERIAL Y MÉTODOS

DISEÑO Y FUENTE DE OBTENCIÓN DE DATOS

Se trata de un estudio descriptivo transversal de los documentos recuperados en la revisión bibliográfica mediante técnica sistemática.

Todos los datos utilizados se obtuvieron de la consulta directa y acceso, vía internet, a la literatura científica indizada en las siguientes bases de datos:

- Medlars Online International Literature (Medline), via PubMed.
- The Cochrane Library.
- Scopus.
- Web of Science, Institute for Scientific Information (ISI).

TRATAMIENTO DE LA INFORMACIÓN

Se estudiaron los artículos publicados en cualquier país, por cualquier institución o investigador individual y en cualquier idioma, publicados desde el inicio de la indización de cada una de las fuentes primarias.

Del estudio del Thesaurus, Medical Subject Headings (MeSH), desarrollado por la U.S. National Library of Medicine se consideró adecuado el uso de los términos esclerosis múltiple *("Multiple Sclerosis")* y estado nutricional *("Nutritional Status")*, tanto como descriptores como en "términos de búsqueda" en los campos de título y resumen. No se han utilizado ni calificadores de materia *(Subheadings),* ni *Entry Term*.

La ecuación de búsqueda se desarrolló para su empleo en la base de datos Medline, vía PubMed, mediante la utilización de los conectores booleanos: ("Multiple Sclerosis"[Mesh] OR "Multiple Sclerosis"[Title/Abstract] OR "Disseminated Sclerosis"[Title/Abstract] OR "Multiple Sclerosis Acute Fulminating"[Title/Abstract]) AND ("Nutritional Status"[Mesh] OR "Nutritional Status"[Title/Abstract] OR "Nutrition Status"[Title/Abstract])

Posteriormente, esta ecuación fue adaptada a las otras bases de datos anteriormente mencionadas, pudiéndose reproducir, en cualquier momento, en la base de datos correspondiente.

La búsqueda se realizó desde la primera fecha disponible, de acuerdo a las características de cada base de datos, hasta noviembre de 2016 (momento de la última actualización).

SELECCIÓN FINAL DE LOS ARTÍCULOS

La elección final de los documentos se realizó según el cumplimiento de los criterios de inclusión y exclusión.

- *Criterios de inclusión:* se aceptaron solo artículos originales publicados en revistas indizadas y con proceso de revisión por pares. Para recoger los artículos de máxima actualidad se decidió revisar los artículos originales a partir del año 2000, ya que ello supone, aproximadamente, el doble de la vida media, según índice de Burton Kebler, para las publicaciones en el ámbito de las ciencias de la nutrición (8).
- *Criterios de exclusión:* se rechazaron aquellos artículos que no aportaban una relación entre el estado nutricional y la esclerosis múltiple.

Adicionalmente, como búsqueda secundaria y para reducir los posibles sesgos de publicación, se examinó el listado bibliográfico de los artículos seleccionados en la búsqueda principal con el objeto de identificar estudios no detectados en la revisión electrónica.

La selección de los artículos pertinentes se realizó de forma independiente por dos autores: IRE y JSV. Para dar por válida la inclusión de los estudios se estableció que la valoración de la concordancia entre estos autores (índice Kappa) debía ser superior al 80%. Siempre que se cumpliera esta condición, las posibles discordancias se solucionaron mediante la consulta a la autora CWB y posterior consenso entre todos los autores (9).

Para valorar la calidad de los artículos seleccionados se utilizaron las directrices para la publicación de estudios observacionales STROBE *(Strengthening the Reporting of Observational studies in Epidemiology)* (10), que contiene un listado de 22 variables que deben describirse en la publicación de estos estudios. Para cada artículo seleccionado se asignó un punto por cada ítem presente (en caso de no ser aplicable, no puntuaba). Cuando un ítem estaba compuesto por varios puntos, estos se evaluaron de forma independiente, dándole el mismo valor a cada uno de ellos, y posteriormente se realizó un promedio (siendo este el resultado

final de ese ítem), de tal forma que en ningún caso se pudiera superar la puntuación de un punto por ítem.

El control de la información extraída de los estudios revisados se realizó mediante dobles tablas que permitían la detección de los errores y la corrección mediante nueva consulta de los originales.

Todos los datos relevantes de cada trabajo se resumieron en una tabla, recogiéndose las siguientes variables: primer autor y año de publicación, población a estudio, intervención realizada, periodo en el que se realizó la intervención y principales hallazgos.

RESULTADOS

Con los criterios de búsqueda descritos se recuperaron 160 referencias de las que, tras eliminar los artículos duplicados y aplicar los criterios de inclusión y exclusión (Fig. 1), fue posible recuperar a texto completo 29 artículos (3,11-38) (Tabla I), procedentes de Medline (n = 4; 14%), Scopus (n = 9; 31%), ISI - Web of Science (n = 1; 3%) y los listados bibliográficos de los artículos relevantes recuperados (n = 15; 52%). El acuerdo sobre la pertinencia de los estudios seleccionados fue del 100%. Al evaluar la calidad de los artículos aceptados para la revisión mediante el cuestionario STROBE (10), las puntuaciones oscilaban entre 6,5 y 15,1, con mediana igual a 11,6 (Tabla II).

La mayoría de trabajos fueron estudios de casos y controles (14; 48%) (11,14-16,18,21,23,24,28,30-33,35). Sin embargo, también existen, entre otros, estudios de cohortes (6; 21%) (22,25,34,36-38) y transversales (6; 21%) (13,17,19,20,27,29).

El cálculo del coeficiente Kappa dio una medida del acuerdo en la selección de los artículos entre los evaluadores del 96,00% ($p < 0,001$).

La obsolescencia de estos artículos, medida por la mediana, fue de seis años (índice de Burton Kebler). De los 29 artículos recuperados, 28 estaban escritos en inglés (3,11-16,18-38) y solo uno en castellano (17).

Los años con mayor número de trabajos publicados fueron 2013 (16-19) y 2014 (12-15), con cuatro publicaciones cada uno (41%).

El origen de los artículos fue muy diverso; procedían de Estados Unidos (20,27,32,34,36) en cinco casos, Irán (13,16,19,24) en cuatro casos, Turquía (3,12,35) y Noruega (11,31,38) en tres casos, Suecia (14,21), Países Bajos (28,29) y Australia (25,30) en dos casos e India (18), Suráfrica (33), España (17) y Polonia (15) en un caso. En cuatro artículos no se especificó el país donde se realizó el estudio (22,23,26,37). En ningún trabajo se indicó el ámbito donde se desarrolló la intervención (urbana o rural).

Los artículos estudiaron un número muy heterogéneo de sujetos (desde n = 11 [16] hasta n = 121.701 [22]). Respecto a la distribución por sexo, se observó que primaba el sexo femenino, ya que en cuatro estudios solo se incluía a mujeres (22,34,36,37) y en 22, la población de estas era mayor que la de hombres (3,12-21,23-26,28,29,31-33,35,38). En tres estudios no se especificaba el sexo de la población (11,27,30). La edad media observada fue de entre 8,7 ± 33,0 (16) y 50,52 ± 11,67 (17) años.

El periodo de intervención oscila entre una semana (17) y 20 años (34), y para conocer el estado nutricional se utilizaron muestras de sangre (14,18-21,23-27,29,32,35) o cuestionarios de frecuencia alimentaria (3,12,13,15,22,31,34,36,37). En cuatro casos se emplearon ambas técnicas (28,30,33,38).

La intervención aplicada fue muy similar en todos los estudios, ya que el objetivo de 14 de 29 era determinar, sobre todo, los niveles de 25-hidroxivitamina D (25[OH]) (14,18-21,23-30,32). Otros estudios centraron su búsqueda en averiguar qué déficits de nutrientes podrían estar relacionados con el desarrollo de la EM. De hecho, once artículos (3,12,13,15,22,31,33,34,36-38) trabajaron con cuestionarios dietéticos para obtener estos datos. Akbulut y cols. (12), Zabay y cols. (17) y Saka y cols. (3) indagaron sobre las posibles repercusiones que pudieran tener las medidas antropométricas sobre la enfermedad. Tres estudios tuvieron en cuenta también la exposición a la luz solar para obtener sus conclusiones (28,30,31).

CONCENTRACIÓN DE 25-HIDROXIVITAMINA D Y EM

Respecto a los resultados observados, se puede apreciar que existe una relación inversa entre los niveles de 25(OH) y la EM, es decir, un déficit de vitamina D favorece el desarrollo de la enfermedad.

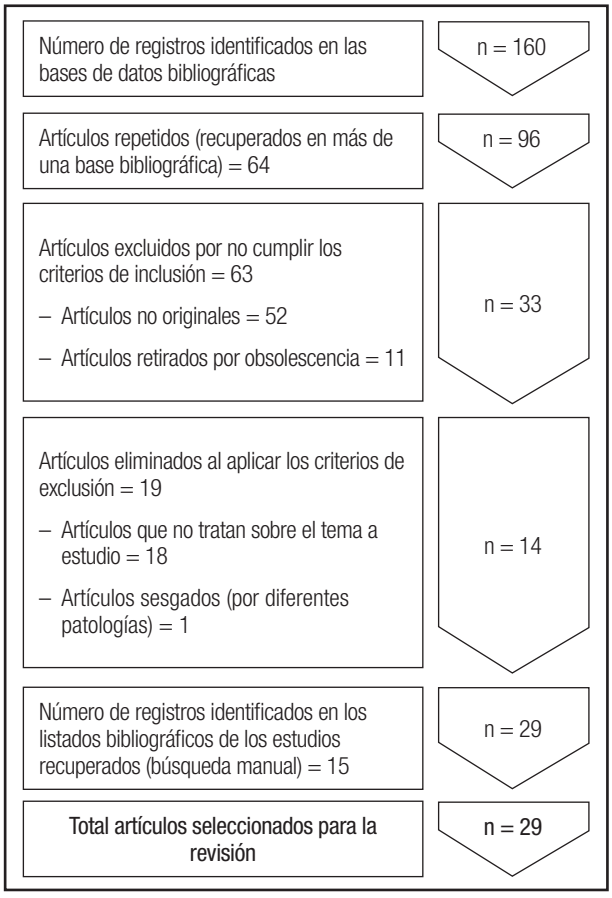

Figura 1.

Diagrama de selección de artículos incluidos en la revisión.

Tabla I. Características de los 29 estudios (evaluados) sobre la esclerosis múltiple y el estado nutricional

Autor, año	Población	Localidad	Periodo	Diseño	Intervención	Principales hallazgos
Røsjø y cols. 2015 (11)	n: 92 pacientes con EM más controles Sexo: no consta Rango edad: 18-55 años	Noruega	24 meses	Casos y controles	Administración aleatorizada de omega-3 y placebo para seguimiento y posterior examen de relación entre vitamina D e interferón-β1a a través de la actividad de resonancia magnética y de imagen (MRI)	Los niveles de vitamina D no tienen gran influencia en los efectos del tratamiento con interferón-β1a
Akbulut y cols. 2014 (12)	n: 63 pacientes EM Sexo: H22/M41 Edad media F: 35,1 ± 8,90 Edad media M: 34,6 ± 8,19	Ankara, Turquía	4 meses	Descriptivo	Determinación de las medidas antropométricas y evaluación a través de un cuestionario de frecuencia de alimentos	Una nutrición adecuada y equilibrada es importante para mejorar la calidad de vida de pacientes con EM El objetivo es aumentar los niveles plasmáticos de ácidos grasos esenciales, antioxidantes, ácido fólico y vitamina B12
Bitarafan y cols. 2014 (13)	n: 101 pacientes EM Sexo: H25/M76 Rango edad: 20-40 años Edad media F: 31,82 ± 5,96 Edad media M: 30,24 ± 7,37	Teherán, Irán	2 años	Transversal	Cumplimentación durante 3 días de un registro dietético de 24 horas	Reconocer y corregir la baja ingesta de nutrientes en los pacientes con EM, con especial consideración en el ácido fólico, magnesio y vitamina D puede mejorar el síndrome de fatiga en pacientes con EM
Ueda y cols. 2014 (14)	n: 459 pacientes EM Sexo: H110/M349 Edad media: no consta n: 663 controles Sexo: H164/M499 Edad media: no consta	Suecia	No consta	Casos y controles	Medición de los niveles de vitamina D en muestras de sangre neonatales almacenadas y en la ingesta diaria de productos que la contengan	No se encontró asociación entre los niveles de 25-hidroxivitamina D (25[OH]) neonatales y el riesgo de EM
Socha y cols. 2014 (15)	n: 101 pacientes EM Sexo: H37/M64 Rango edad: 18-58 años Edad media: 40,86 ± 10,2 n: 63 controles Sexo: H20/M43 Rango edad: 19-65 años Edad media: 41,12 ± 14,1	Bialystok, Polonia	No consta	Casos y controles	Cuestionario de frecuencia de alimentos	La concentración de selenio (Se), actividad glutation peroxidasa (GSH-Px) y el estado total de antioxidantes fueron más bajos en pacientes con EM que en el grupo control Buenos hábitos alimentarios tienen una significante influencia sobre el estado del Se

(Continúa en la siguiente página)

[Nutr Hosp 2018;35(1):211-223]

Tabla I (Cont.). Características de los 29 estudios (evaluados) sobre la esclerosis múltiple y el estado nutricional

Autor, año	Población	Localidad	Periodo	Diseño	Intervención	Principales hallazgos
Naghashpour y cols. 2013 (16)	n: 11 pacientes EM con riboflavina Sexo: H3/M8 Edad media: 8,7 ± 33.0 n: 18 pacientes EM con placebo Sexo: H8/M10 Edad media: 10,6 ± 30,6	Ahvaz, Irán	6 meses	Casos y controles	Administración de forma aleatoria de suplementos de riboflavina y placebo a pacientes con EM	Los suplementos de riboflavina dan lugar a una reducción no significativa en la escala expandida del estado de discapacidad (EDSS) en comparación con el placebo Esta diferencia no está asociada con los niveles de homocisteína
Zabay y cols. 2013 (17)	n total: 142 pacientes EM Sexo: H29,6%/M70,4% Edad media: 50,52 ± 11,67	Barcelona, Lleida y Reus (España)	1 semana	Observacional, transversal y descriptivo	Recolección de datos a través de la historia clínica del paciente y de una exploración específica con datos demográficos y clínicos	La desnutrición es un problema importante en la población y se debe trabajar más para intervenir en situaciones de riesgo o en estados nutricionales alterados Múltiples factores contribuyen a la desnutrición en la EM y estos deberían valorarse en un futuro
Pandit y cols. 2013 (18)	n: 110 pacientes EM Sexo: H20%/M80% Edad media: 35,4 ± 9,6 n: 108 controles Sexo: H21%/M79% Edad media: 36,1 ± 10,3	Mangalore, India	No consta	Casos y controles	Determinación de niveles de 25-hidroxivitamina D (25[OH]) y del IMC	Niveles altos de 25(OH) están asociados a un menor riesgo de EM No se observa relación entre EM y obesidad
Ashtari y cols. 2013 (19)	n: 200 pacientes EM Sexo: H46/M154 Rango edad: 18-50 años	Isfahan, Irán	7 meses	Transversal	Medida de la depresión y fatiga mediante el Inventario de Depresión de Beck para la Atención Primaria (BDI-II) y la escala de gravedad de la fatiga (FFS) respectivamente Medición de niveles de 25-hidroxivitamina D (25[OH])	Niveles bajos de vitamina D están asociados a síntomas depresivos en pacientes con EM, no habiendo por el contrario correlación entre síntomas de fatiga y vitamina D
Amezcua y cols. 2012 (20)	n: 80 pacientes EM blancos Sexo: H21/M59 Edad media: 46,5 años n: 80 pacientes EM hispanos Sexo: H33/M47 Edad media: 39,4 años	California	1 año	Transversal	Toma de muestras de sangre para determinar los niveles de 25(OH)	Los niveles de 25(OH) difieren en función de la etnia La hipovitaminosis D persiste en pacientes hispanos tanto en verano como en invierno mientras que en pacientes blancos los niveles son menores en invierno

(Continúa en la siguiente página)

Tabla I (Cont.). Características de los 29 estudios (evaluados) sobre la esclerosis múltiple y el estado nutricional

Autor, año	Población	Localidad	Periodo	Diseño	Intervención	Principales hallazgos
Salzer y cols. 2012 (21)	n1: 192 pacientes EM Sexo: H15/M177 Rango edad: 19-66 años n1: 384 controles Sexo: H30/M354 Rango edad: no consta n2: 37 madres de niños con EM Rango edad: 13-32 años n2: 185 madres de niños sanos Rango edad: no consta	Suecia	9 años	Casos y controles	Tomas de muestras de sangre para medir los niveles de 25(OH) D	Los niveles obtenidos de 25(OH) D son mayores en los meses de verano que en los de invierno, asociándose niveles altos de 25(OH) D a un menor riesgo de EM La vitamina D actúa como factor protector de la EM sobre todo en adultos jóvenes (< 20 años) y durante el periodo final del embarazo y la infancia
Saka y cols. 2012 (3)	n total: 37 pacientes EM Sexo: H15/M22 Rango edad: 20-55 años Edad media: 33,3 ± 9,72	Ankara, Turquía	3 meses	Descriptivo	Seguimiento a través de un registro dietético y un cuestionario de frecuencia de alimentos durante 3 días y determinación del IMC	Estado nutricional pobre (valores de vitamina D y vitamina B12 por debajo de los valores de referencia) y alto IMC en pacientes con EM
Mirzaei y cols. 2011 (22)	n1: 121.701 Sexo: mujeres Rango edad: 30-55 años n2: 116.430 Sexo: mujeres Rango edad: 25-42 años	No consta	No consta	Cohortes	Cumplimentación de un cuestionario semicuantitativo de frecuencia alimentaria durante el periodo de embarazo	Una ingesta elevada de leche y vitamina D durante el embarazo reduce el riesgo de padecer EM en la descendencia
Gelfand y cols. 2011 (23)	n: 339 pacientes afroamericanos EM Sexo: H149/F190 Edad media: 41,9 años n: 342 controles afroamericanos Sexo: H185/F157 Edad media: 43,7 años	No consta	11 años	Casos y controles	Toma de muestras de sangre para determinar los niveles de 25(OH)	Los niveles de 25-hidroxivitamina D fueron más bajos en los afroamericanos con EM que en los controles Esta observación puede deberse a diferencias en el clima y en la geografía
Shaygannejad y cols. 2010 (24)	n: 50 pacientes EM Sexo: H8/M42 Rango edad: 15-55 años n: 50 controles Sexo: H8/M42 Rango edad: 15-55 años	Isfahan, Irán	1 año	Casos y controles	Toma de muestras de sangre para determinar los niveles de 25(OH)	El déficit de vitamina D es un factor desencadenante de la EM y es necesario detectar qué factores lo causan, como problemas dietéticos o genéticos

(Continúa en la siguiente página)

[Nutr Hosp 2018;35(1):211-223]

Tabla I (Cont.). Características de los 29 estudios (evaluados) sobre la esclerosis múltiple y el estado nutricional

Autor, año	Población	Localidad	Periodo	Diseño	Intervención	Principales hallazgos
Simpson y cols. 2010 (25)	n: 145 pacientes EM Sexo: H36/M109 Rango edad: 21-76 años	Southern Tasmania, Australia	3 años	Cohorte prospectivo longitudinal	Entrevista a pacientes sobre su estilo de vida, determinación de los niveles de 25(OH) D y registro diario durante una semana de posibles cambios en síntomas neurológicos	Los niveles de 25(OH) D detectados fueron mayores durante el mes de verano Así, estos niveles se relacionan con una mayor densidad de mielina y con una disminución de daños por recaídas
Smolders y cols. 2009 (26)	n: 29 pacientes EM Sexo: H10/M19 Rango edad: 23-39 años	No consta	6 meses	Descriptivo	Determinación de la concentración de 25-hidroxivitamina D (25[OH]) y cultivo celular para valorar la actividad de las células T	La vitamina D es un importante promotor de la regulación de las células T en la EM Debe mantenerse un estado de la vitamina D saludable en estos pacientes
Newhook y cols. 2009 (27)	G1: 50 mujeres embarazadas G2: 51 recién nacidos G3: 48 niños Sexo: no consta Edad media: no consta	Terranova y Labrador, Canadá	7 meses	Transversal	Medición de los niveles de 25-hidroxivitamina D (25[OH])	La hipovitaminosis D en mujeres embarazadas, recién nacidos y niños puede tener importantes consecuencias negativas para la salud
Kragt y cols. 2009 (28)	n: 101 pacientes EM Sexo: H32/M69 Edad media: 45,8 años n: 107 controles Sexo: H58/M49 Edad media: 44,2 años	Ámsterdam, Países bajos	6 meses	Casos y controles	Toma de muestras de sangre y cumplimentación de cuestionarios de frecuencia alimentaria y exposición al sol para medir los niveles de 25(OH) y 1,25(OH)2 D	No se han encontrado diferencias entre los niveles en suero de 25(OH) y 1,25(OH)2 D entre el total de pacientes con EM y controles; sin embargo, niveles altos de 25(OH) están inversamente asociados con el riesgo de EM en mujeres
Smolders y cols. 2008 (29)	n: 267 pacientes EM Sexo: H66/M201 Edad media: no consta	Países bajos	2 años	Transversal	Toma de muestras de sangre para determinar niveles de 25(OH) D y 1,25-hidroxivitamina D (1,25[OH]2 D)	Bajos niveles de 25(OH) y 1,25(OH)2 D están asociados con una progresión de la EM, siendo los suplementos de vitamina D importantes para controlarla
Van Der Mei y cols. 2007 (30)	n: 136 pacientes EM Sexo: No consta Media edad: 43,5 años n: 272 controles Sexo: No consta Edad media: 43,6 años	Tasmania, Australia	No consta	Casos y controles	Medición de la concentración de 25-hidroxivitamina D (25[OH]), de la exposición solar y registro dietético de la ingesta de vitamina D	Entre los casos de EM, el aumento de la discapacidad está fuertemente asociado con bajos niveles de 25 (OH) y con una exposición solar reducida Se recomiendan una detección activa de niveles insuficientes de vitamina D y una intervención para restaurar dichos niveles como parte del tratamiento en pacientes con EM

(Continúa en la siguiente página)

Tabla I (Cont.). Características de los 29 estudios (evaluados) sobre la esclerosis múltiple y el estado nutricional

Autor, año	Población	Localidad	Periodo	Diseño	Intervención	Principales hallazgos
Kampman y cols. 2007 (31)	n: 152 pacientes EM Sexo: 64% mujeres Edad media: no consta n: 402 controles Sexo: 67% mujeres Edad media: no consta	Troms y Finnmark, Noruega	No consta	Casos y controles	Cumplimentación de cuestionarios sobre la frecuencia de exposición al sol y sobre hábitos alimentarios	La dieta y el clima interactúan para reducir el riesgo de padecer EM de forma que la luz solar y el aceite de hígado de pescado tienen efecto protector frente a la enfermedad
Munger y cols. 2006 (32)	n: 257 pacientes EM (148 raza blanca, 77 raza negra, 32 hispanos) Sexo: H174/F83 Edad media: no consta n: 514 controles (296 raza blanca, 154 raza negra, 64 hispanos) Sexo: H348/F166 Edad media: no consta	Estados Unidos	12 años	Casos y controles	Análisis de muestras de sangre almacenadas para determinar niveles de 25(OH)	En la raza blanca, el riesgo de padecer EM disminuye considerablemente con niveles elevados de 25(OH) En la raza negra e hispanos, cuyos niveles de 25(OH) son menores que en blancos, no se ha encontrado asociación entre la EM y los niveles de 25(OH)
Van Rensburg y cols. 2006 (33)	n: 35 pacientes EM Sexo: H90%/M10% Edad media: no consta n: 30 controles Sexo: H3/M27 Edad media: no consta	Provincia Occidental del Cabo, Suráfrica	6 meses	Casos y controles	Comparación de parámetros de la sangre entre pacientes con EM y controles y seguimiento a través de un régimen nutricional: "Raphah Regimen"	Es probable influenciar el curso de la EM proporcionando los nutrientes necesarios en cantidades adecuadas para regenerar la mielina Niveles altos de hierro suponen una edad de diagnóstico de la enfermedad más tardía
Munger y cols. 2004 (34)	n1: 92.253 Sexo: mujeres Rango edad: 30-55 años n2: 95.310 Sexo: mujeres Rango edad: 25-42 años	Estados Unidos	20 años 10 años	Cohortes	Cumplimentación de cuestionarios semicuantitativos de frecuencia alimentaria cada 4 años	El total de la vitamina D obtenida está inversamente asociado al riesgo de EM Estos niveles de vitamina D son más importantes en mujeres habitantes en lugares donde el sol en invierno es insuficiente
Besler y cols. 2002 (35)	n: 24 pacientes EM Sexo: H16/M8 Edad media: 35,0 ± 7,3 n: 24 controles Sexo: H16/M8 Edad media: 36,8 ± 4,1	Ankara, Turquía	No consta	Casos y controles	Tomas de muestras de sangre para medir los niveles de vitaminas antioxidantes: alfa tocoferol, beta-carotenos, retinol y ácido ascórbico	Hay un estrés oxidativo en pacientes con EM que se relaciona con bajos niveles de vitaminas antioxidantes Estas vitaminas tienen un papel importante en el control de los efectos que producen las especies reactivas de oxígeno

(Continúa en la siguiente página)

Tabla I (Cont.). Características de los 29 estudios (evaluados) sobre la esclerosis múltiple y el estado nutricional

Autor, año	Población	Localidad	Periodo	Diseño	Intervención	Principales hallazgos
Zhang y cols. 2001 (36)	n1: 81.683 Sexo: mujeres Rango edad: 38-63 años n2: 95.056 Sexo: mujeres Rango edad: 27-44 años	Boston, Massachusetts	12 años 6 años	Cohortes	Cumplimentación de cuestionarios semicuantitativos de frecuencia alimentaria para determinar niveles de vitamina A, C y E	No hay evidencia de que el consumo elevado de carotenos, vitamina C, vitamina E, frutas y verduras esté asociado con un menor riesgo de EM
Zhang y cols. 2000 (37)	n1: 92.422 Sexo: mujeres Rango edad: 30-55 años n2: 95.389 Sexo: mujeres Rango edad: 25-42 años	No consta	14 años 4 años	Cohortes	Cumplimentación de un cuestionario semicuantitativo de frecuencia alimentaria para obtener información sobre la dieta y el tipo de grasas o aceites consumidos	No hay evidencias de que el consumo elevado de grasas saturadas o una baja ingesta de ácidos grasos poliinsaturados estén asociados a un aumento en el riesgo de EM
Nordvik y cols. 2000 (38)	n: 16 pacientes EM Sexo: H4/M12 Rango edad: 22-37 años	Trondheim, Noruega	2 años	Cohorte	Tomas de muestras de sangre y cumplimentación de un cuestionario de frecuencia alimentaria Administración de aceite de pescado, suplementos de vitamina B y vitamina C	Las recomendaciones dietéticas y los suplementos de ácidos grasos ω-3 reducen las exacerbaciones de la enfermedad y mejoran las funciones en pacientes con EM recientemente diagnosticados

Numerosos estudios son los que confirman estos resultados (18,19,21,22,24,26-30,34).

Por el contrario, Rosjo y cols. (11) y Ueda y cols. (14) difieren de las conclusiones anteriores, sin observar relación causal directa entre bajos niveles de vitamina D y la aparición de la EM. Así, Zabay y cols. (17) señalan que existen múltiples factores que contribuyen a la aparición de EM y el déficit de 25(OH) podría deberse a la disminución de la exposición solar, a la desnutrición o a dificultades de la ingesta, y no como causa de la EM. En esta línea, Munger y cols. (32) no encontraron asociación entre la EM y los niveles de 25(OH).

Según tres estudios (20,23,32), la raza o etnia son también factores desencadenantes de la enfermedad ya que los niveles de 25(OH) son mayores en la población de raza blanca que en hispanos o población de raza negra. Munger y cols. (32), sin embargo, no han logrado encontrar dicha asociación entre la EM y pacientes hispanos o de raza negra.

Niveles adecuados de vitamina D durante el embarazo y la infancia son decisivos para el desarrollo de la enfermedad (21,22,17). Mirzaei y cols. (22) destacan también la importancia del consumo de leche durante la gestación.

NUTRICIÓN Y EM

Akbulut y cols. (12) y Zabay y cols. (17) destacan la importancia de intervenir para conseguir una nutrición adecuada y equilibrada y así mejorar la calidad de vida de pacientes con EM.

Besler y cols. (35) hablan de un estrés oxidativo en pacientes con EM que se relaciona con bajos niveles de vitaminas antioxidantes. Estos resultados son respaldados por otros dos estudios (12,15) que destacan la importancia de niveles adecuados de antioxidantes. Por el contrario, Zhang y cols. (36) no encuentran relación entre el consumo elevado de carotenos, vitamina C, vitamina E, frutas y verduras y el desarrollo de la enfermedad. Entre otros resultados, destacan niveles adecuados de selenio (15), hierro (33), ácido fólico (12) y vitamina B12 (3,12) para un buen curso de la enfermedad.

Hay diversidad de opinión respecto a la relación entre la EM y el consumo de ácidos grasos saturados. Dos estudios (12,38) encuentran la importancia de la ingesta de ácidos grasos esenciales con la EM y Saka y cols. (3) relacionan los valores elevados de índice de masa corporal (IMC) con el desarrollo de la enfermedad. Por el contrario, otros dos estudios no encuentran dicha relación (18,37).

CLIMA Y EM

Cinco de 29 estudios relacionan los niveles de 25(OH) con la exposición a la luz solar y encuentran que estos niveles son más elevados durante los meses de verano que en invierno (20,21,23,25,30).

Kampman y cols. (31) destacan la importancia de la interacción entre la dieta y el clima para reducir el riesgo de padecer EM, de forma que la luz solar y el aceite de hígado de pescado tienen un efecto protector frente a la enfermedad.

Tabla II. Análisis de la calidad metodológica de los estudios a través de los 22 ítems de valoración de la guía STROBE (10)

Referencia	Puntuación de los 22 ítems																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Total	%
Saka (3)	0,5	1	1	0	1	0	0	1	0	0	1	0,2	0	0,3	1	0,3	1	1	1	0	0	0	10,3	46,8
Pandit (18)	1	1	1	1	1	0,5	0	1	0	0	1	0,2	0	0	1	0,6	0	1	1	0	0	1	12,3	55,9
Van Rensburg (33)	0,5	1	1	0	1	0,5	0	1	0	1	0	0	0	0	1	0,6	0	1	1	1	0	1	11,6	52,7
Newhook (27)	1	1	1	1	1	0,5	1	1	0	0	1	0	0,3	0	1	0	NA	1	0	0	0	1	11,8	56,2
Socha (15)	1	1	1	0	1	0,5	0	1	0	0	0	0	0	0	1	0,3	0	1	0	0	0	1	8,8	40,0
Zabay (17)	1	1	1	1	1	0,5	1	1	0	0	0	0,2	0,6	0,3	1	0	1	0	1	0	0	0	11,6	52,7
Ashtari (19)	0,5	1	1	0	1	0,5	0	1	0	0	1	0	0,3	0,3	1	0	0	1	1	1	0	1	11,6	52,7
Smolders (26)	0,5	1	1	0	0	0	1	1	0	0	0	0,2	0	0	1	0	0	1	0	0	0	0	6,7	30,5
Van Der Mei (30)	1	1	1	0	1	1	1	1	0	1	0	0,4	0	0,3	1	0,3	NA	1	1	0	0	1	13,0	61,9
Røsjø (11)	0,5	1	0	1	1	0,5	0	1	0	0	0	0,4	0	0,3	1	0,6	0	1	1	1	0	0	10,3	46,8
Naghashpoor (16)	1	1	1	1	1	0,5	1	1	0	0	1	0,4	1	0,3	1	0	0	1	1	0	0	1	14,2	64,5
Ueda (14)	1	1	1	1	1	1	0	1	0	0	0	0,3	0	0,3	1	0,3	0	1	1	0	0	1	11,9	54,1
Bitarafan (13)	1	1	1	0	1	0,5	0	1	0	0	1	0,2	0,3	0,3	1	0	0	1	0	0	0	0	9,3	42,3
Akbulut (12)	0,5	1	1	0	0	0	0	1	0	0	1	0,2	0,3	0,3	1	0	1	1	0	0	0	0	8,3	37,7
Simpson (25)	1	1	1	1	1	0,5	1	1	0	1	0	0,4	0,3	0	1	0	1	1	0	0	1	1	14,2	64,5
Salzer (21)	1	1	1	1	1	1	0	1	0	1	0	0,2	1	0,3	1	0,3	0	1	1	0	0	1	13,8	62,7
Besler (35)	1	1	1	0	0	0	0	1	0	0	0	0,2	0	0	1	0,3	NA	1	0	0	0	0	6,5	31,0
Nordvik (38)	0,5	1	1	1	0	0,5	0	1	0	0	0	0	0,6	0,3	1	0	0	1	1	0	0	0	8,9	40,5
Kampman (31)	1	1	1	0	1	0,5	0	1	0	1	0	0,4	0	0	1	0,6	1	1	0	0	0	0	10,5	47,7
Zhang (36)	1	1	1	0	0	0,5	0	1	0	1	1	0,2	0	0	1	1	NA	1	1	0	0	1	11,7	55,7
Smolders (29)	1	1	1	0	0	0	0	1	0	0	1	0,4	0	0	1	0,6	1	1	0	0	0	0	9,0	41,0
Munger (32)	1	1	1	1	1	0,5	0	1	0	1	0	0,2	0	0	1	1	NA	1	1	0	0	0	11,7	55,7
Kragt (28)	1	1	1	1	1	0,5	1	1	0	1	0	0,4	0,6	0	1	0,6	1	1	1	0	0	1	15,1	68,6
Amezcua (20)	1	1	1	0	1	0	0	1	0	0	1	0,2	0	0,3	1	0	NA	1	1	0	0	1	10,5	50,0
Shaygannejad (24)	1	1	1	0	1	0	0	1	0	0	1	0,2	0	0	1	0	0	1	0	0	0	1	9,2	43,8
Gelfand (23)	1	1	1	1	1	0,5	0	1	0	1	0	0,2	0	0	1	0,3	NA	1	1	0	0	1	12,0	57,1
Mirzaei (22)	0,5	1	1	1	0	0	0	1	0	0	1	0,4	0	0	1	0,3	NA	1	1	1	0	1	11,2	53,3
Zhang (37)	1	1	1	1	1	0,5	1	1	1	1	0	0,4	0	0	1	0,6	NA	1	0	0	0	1	13,5	64,3
Munger (34)	1	1	1	1	1	1	0	1	0	0	1	0,6	0	0,3	1	0,3	1	1	1	0	0	1	14,2	64,5

0 = no cumple el ítem ni ninguna de sus partes; 1 = cumple el ítem en su totalidad; 0 a 1 = cumple parcialmente el ítem; NA = no aplica.

DISCUSIÓN

Durante la revisión de los diferentes artículos se ha podido comprobar que el estudio de la relación existente entre la EM y el estado nutricional es un tema poco tratado y que, por tanto, actualmente no se conocen resultados concluyentes. Sin embargo, algunos autores coinciden en que la EM es una enfermedad estrechamente relacionada con los niveles de vitamina D y un déficit de estos ocasiona un empeoramiento de dicha enfermedad. Es probable a su vez que la luz solar tenga un papel importante en ello, pues es la encargada de producir, mediante la transformación cutánea de 7-dehidrocolesterol, vitamina D, siendo esta la mayor fuente de dicha vitamina en el organismo (39).

El estudio de la actualidad/obsolescencia del tema escogido presenta una adecuada vigencia e interés, ya que del total de documentos recuperados, el 60% de los artículos fueron publicados en los últimos siete años; datos similares se encuentran en los trabajos previamente publicados en el entorno de las ciencias de la salud (40). Para respaldar estos datos, las principales revistas iberoamericanas hablan de un índice de Burton Kebler de unos siete años para la ciencia de la nutrición (41), acorde con el valor calculado en esta revisión (mediana igual a seis años).

No todos los conocimientos provenientes de los artículos científicos publicados tienen el mismo impacto o valor sobre la toma de decisiones en materia de salud. Es decir, dependiendo de la calidad metodológica de las investigaciones, el acercamiento a la veracidad científica será variable y esto se va a reflejar en las recomendaciones sobre la problemática clínica (42). Los ensayos clínicos (EC) controlados y aleatorizados son los que aportan una mayor evidencia científica; sin embargo, en la búsqueda realizada por las diferentes bases de datos no fue posible recuperar este tipo de estudios, sino que la máxima evidencia científica encontrada fueron estudios de casos y controles. El hecho de no haber encontrado EC puede ser debido a que es un tema actual en el cual se ha profundizado muy poco.

No es de extrañar que Estados Unidos haya sido el lugar de procedencia de los artículos más común en la búsqueda, ya que junto a China son los dos países con mayor producción científica. Con ocho de las diez mejores universidades del mundo, Estados Unidos sigue siendo el líder mundial en lo que respecta a la ciencia y la innovación (43). Igualmente, el inglés es el idioma elegido para la publicación de la mayoría de los artículos ya que hacerlo en otra lengua distinta resulta negativo para el factor de impacto y las citaciones (44). Además, el número de revistas anglófonas contenidas en las bases de datos actualmente es muy elevado (43).

Los datos recogidos demuestran que la población de interés para el desarrollo del estudio no supera en general los 55 años. Esto hace pensar que los estudios se centran, por una parte, en la infancia, para valorar si los indicadores nutricionales medidos en ella y las posibles intervenciones influencian el curso de la enfermedad, o en adultos no ancianos, donde la EM se caracterizará por unos determinados signos y síntomas. El hecho de que no se incluya a la población anciana puede ser debido a que la enfermedad afecta fundamentalmente a adultos jóvenes.

Los artículos seleccionados para la revisión también muestran que los estudios se han formado con muestras poblacionales donde el número de mujeres incluidas es mayor que el de hombres. Indudablemente, es normal esta selección pues se sabe que la EM tiene mayor prevalencia en mujeres; sin embargo, esto nos conduce a plantearnos lo siguiente: la menopausia es un estado irremediable en la mujer adulta en el que se presentan una serie de patologías entre las que se encuentra la osteoporosis. Por ello, llegado el momento, se indica a las mujeres que refuercen el consumo de calcio y que lo combinen junto a la administración de vitamina D debido a que esta favorece la fijación del calcio en los huesos. Es probable que, de forma no intencionada, las mujeres con EM a las que se les ha introducido dicha vitamina en la dieta presenten una mejoría notoria respecto a su calidad de vida, pues, como han afirmado la mayoría de artículos incluidos en la revisión, la vitamina D está inversamente relacionada con el desarrollo de la EM.

La información que puede obtenerse a través de la base de datos de ISI-Web of Science (ISI-WoS) puede ser de gran utilidad para orientar los esfuerzos en materia de investigación científica, ya sea a nivel personal, institucional o nacional (45). Sin embargo, a pesar de ser la base de datos de donde se recuperaron inicialmente muchos trabajos (n = 71), solamente uno fue finalmente seleccionado. Esto podría ser debido a la inexistencia de indización (la consulta mediante "*Topic*" se realiza en formato texto interrogando el título, resumen y palabras clave) y a la imposibilidad de limitar la búsqueda por el tipo de artículo o por especie (46).

ISI-WoS publica solamente información de revistas con presencia internacional, dejando fuera mucha producción académica importante de regiones específicas (45). Esto podría explicar el porqué de no haber recuperado la información pertinente sobre temas locales con esta base de datos, pues se buscaba en un tema muy concreto y poco estudiado como es la relación de la nutrición y la EM.

Muchos de los artículos incluidos en esta revisión hablan de que un buen estado de salud es imprescindible para evitar el desarrollo de la enfermedad (3,12,13,17,33,38). Así, es importante tener en cuenta el IMC y la nutrición, que deben ser adecuados para tener una salud y calidad de vida óptimas. Sin embargo, esto se sabe que es importante para evitar el desarrollo de cualquier enfermedad y que una desnutrición severa afecta negativamente al desarrollo de cualquier patología, entre ellas la EM. No obstante, no ha habido ningún estudio que haya relacionado la actividad física con este tema y, teniendo en cuenta que un buen estado de salud se consigue compaginando dieta y ejercicio, esto podría considerarse una posible limitación que debería tenerse en cuenta en posteriores estudios.

El hecho de que numerosos autores hayan concluido que llevar un estilo de vida saludable e incorporar en la dieta todos los nutrientes necesarios o detectar el sobrepeso es lo correcto, es algo racional pues es la base para impedir el desarrollo de muchas enfermedades. Sin embargo, muchos artículos mencionan a la vitamina D como posible elemento capaz de evitar o mejorar el curso de la enfermedad. Esto no puede ser coincidencia y hace pensar que, aunque la etiología de la EM sea

aún desconocida, dicha vitamina debe tener un papel inmunomodulador importante que evita la pérdida de mielina en fibras nerviosas. Así, Salzer y cols. (21), Mirzaei y cols. (22) y Newhook y cols. (27) destacan la importancia de evitar la hipovitaminosis D ya durante la gestación. Ahora bien, también hay estudios (17) que inciden en la necesidad de valorar diversos factores, como desnutrición, exposición solar o dificultades en la ingesta, a la hora de predecir la asociación entre 25(OH) y la EM, y quizá estas causas estén actuando como variables confusoras a la hora de apreciar relación causal.

Los niveles de antioxidantes también son estudiados en ciertos artículos que les atribuyen una importancia especial como posibles paliadores de la EM (12,35).

A día de hoy, se sabe que la luz solar es un importante activador de la síntesis de la vitamina D. Por ello, algunos autores (20,21,23,25,30) han estudiado la relación existente entre el sol, dicha vitamina y la EM y destacan la importancia de compaginar el clima con la dieta. Los niveles totales de vitamina D en el organismo provienen de los alimentos, aunque muy pocos la contienen, o de la síntesis cutánea, que es la mayor fuente del organismo, como se ha comentado anteriormente. Por tanto, si las hipótesis hasta ahora formuladas involucran a la vitamina D como posible elemento clave en la EM, de forma indirecta, el sol se presenta también como un factor importante en este tema. Esto explica el hecho de que países con escasas horas de luz durante ciertas épocas del año sean, al igual que la raza negra, por la cantidad de melatonina que contiene la piel (39), más propensos al desarrollo de la enfermedad.

LIMITACIONES A ESTE ESTUDIO

En la presente revisión, se han recuperado artículos que han llevado a cabo largos periodos de intervención, lo que indudablemente resulta en parte beneficioso por un aporte mayor de la información; sin embargo, al ser los resultados muy actuales, estos no han podido ser ampliamente discutidos por los expertos. Por otra parte, los largos periodos de estudio pueden ocasionar pérdidas de pacientes y, por lo tanto, estas deberían haber sido controladas mediante el cálculo del número necesario a tratar.

En esta revisión prima la heterogeneidad de los artículos estudiados, por lo que no se han podido extraer conclusiones firmes sobre la relación existente entre el estado nutricional y la EM. Por consiguiente, su principal limitación es precisamente esta: la falta de ensayos clínicos diseñados para detectar estos problemas que se encuentran muchas veces como comentarios asociados, observaciones no buscadas y, sin embargo, encontradas por los autores, por lo que el rigor del ensayo no las contempla (47).

Por todo lo anteriormente expuesto, se puede concluir que la vitamina D puede influir en la mejora de la EM. La luz solar y la actividad física serían factores importantes, junto al estado nutricional, en el curso de dicha enfermedad.

Se considera necesario que futuros ensayos clínicos centren su estudio en indagar más en este tema y que contemplen las limitaciones descritas anteriormente.

BIBLIOGRAFÍA

1. Anderson DW, Ellenberg JH, Leventhal CM, Reingold SC, Rodríguez M, Silberberg DH. Revised estimate of the prevalence of multiple sclerosis in the United States. Ann Neurol 1992;31(3):333-6.
2. Compston A. Genetic susceptibility to multiple sclerosis. In: Compston A, McDonald I, Noseworthy J, Lassmann H, Miller D, Smith K, et al. (eds.). McAlpine's Multiple Sclerosis (3rd ed.). Londres: Churchill Livingstone; 1998, pp. 104-44.
3. Saka M, Saka M, Koseler E, Metin S, Bilen S, Aslanyavrusu M, et al. Nutritional status and anthropometric measurements of patients with multiple sclerosis. Saudi Med J 2012;33(2):160-6.
4. Ho SL, Alappat L, Awad AB. Vitamin D and multiple sclerosis. Food Sci Nutr 2012;52(11):980-7.
5. Shaygannejad V, Golabchi K, Haghighi S, Dehghan H, Moshayedi A. A comparative study of 25 (OH) vitamin D serum levels in patients with multiple sclerosis and control group in Isfahan, Iran. Int J Prev Med 2010;1(3):195-201.
6. Pozuelo-Moyano B, Benito-León J. Dieta y esclerosis múltiple. Rev Neurol 2014;58(10):455-64.
7. Riccio P, Rossano R, Larocca M, Trotta V, Mennella I, Vitaglione P, et al. Anti-inflammatory nutritional intervention in patients with relapsing-remitting and primary-progressive multiple sclerosis: A pilot study. Exp Biol Med 2016; 241(6):620-35.
8. Tomás-Casterá V, Sanz-Valero J, Juan-Quilis V. Estudio bibliométrico de la producción científica y de consumo de las revistas sobre nutrición indizadas en la red SciELO. Nutr Hosp 2013;28(3):969-70.
9. Wanden-Berghe C, Sanz-Valero J. Systematic reviews in nutrition: Standardized methodology. Br J Nutr 2012;107(2):3-7.
10. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Van-denbroucke JP, et al. Declaración de la Iniciativa STROBE (Strengthening the Reporting of Observational studies in Epidemiology): directrices para la comunicación de studios observacionales. Gac Sanit 2008;22(2):144-50.
11. Røsjø E, Myhr KM, Løken-Amsrud KI, Bakke SJ, Beiske AG, Bjerve KS, et al. Vitamin D status and effect of interferon-β1a treatment on MRI activity and serum inflammation markers in relapsing-remitting multiple sclerosis. J Neuroimmunol 2015;280:21-8.
12. Akbulut G, Orhan G, Gurkas E, Sanlier N, Gezmen-Karadag M, Sucullu Y, et al. Determination of nutritional status via food frequency consumption (FFQ) and serum proteins and anemia parameters in multiple sclerosis (MS) patients. GMJ 2014;25:128-31.
13. Bitarafan S, Harirchian MH, Nafissi S, Sahraian MA, Togha M, Siassi F, et al. Dietary intake of nutrients and its correlation with fatigue in multiple sclerosis patients. Iran J Neurol 2014;13(1):28-32.
14. Ueda P, Rafatnia F, Bäärnhielm M, Fröbom R, Korzunowicz G, Lönnerbro R, et al. Neonatal vitamin D status and risk of multiple sclerosis. Ann Neurol 2014;76(3):338-46. DOI: 10.1002/ana.24210
15. Socha K, Kochanowicz J, Karpińska E, Soroczyńska J, Jakoniuk M, Mariak Z, et al. Dietary habits and selenium, glutathione peroxidase and total antioxidant status in the serum of patients with relapsing-remitting multiple sclerosis. Nutr J 2014;13(62):1-6.
16. Naghashpour M, Majdinasab N, Shakerinejad G, Kouchak M, Haghighizadeh MH, Jarvandi F, et al. Riboflavin supplementation to patients with multiple sclerosis does not improve disability status nor is riboflavin supplementation correlated to homocysteine. Int J Vitam Nutr Res 2013;83(5):281-90.
17. Zabay C, Sánchez S, Casalilla M. Prevalencia de desnutrición en afectados de esclerosis múltiple que reciben tratamiento rehabilitador en los hospitales de día de la Fundació Esclerosi Múltiple. Rev Cient Soc Esp Enferm Neurol 2013;38(1):42-7.
18. Pandit L, Ramagopalan SV, Malli C, D'Cunha A, Kunder R, Shetty R. Association of vitamin D and multiple sclerosis in India. Mult Scler 2013;19(12):1592-6.
19. Ashtari F, Ajalli M, Shaygannejad V, Akbari M, Hovsepian S. The relation between Vitamin D status with fatigue and depressive symptoms of multiple sclerosis. J Res Med Sci 2013;18(3):193-7.
20. Amezcua L, Chung RH, Conti DV, Langer-Gould AM. Vitamin D levels in Hispanics with multiple sclerosis. J Neurol 2012;259(12):2565-70.
21. Salzer J, Hallmans G, Nyström M, Stenlund H, Wadell G, Sundström P. Vitamin D as a protective factor in multiple sclerosis. Neurology 2012;79(21):2140-5.
22. Mirzaei F, Michels KB, Munger K, O'Reilly E, Chitnis T, Forman MR, et al. Gestational vitamin D and the risk of multiple sclerosis in offspring. Ann Neurol 2011;70(1):30-40.
23. Gelfand JM, Cree BA, McElroy J, Oksenberg J, Green R, Mowry EM, et al. Vitamin D in African Americans with multiple sclerosis. Neurology 2011;76(21):1824-30.

24. Shaygannejad V, Golabchi K, Haghighi S, Dehghan H, Moshayedi A. A comparative study of 25 (OH) vitamin D serum levels in patients with multiple sclerosis and control group in Isfahan, Iran. Int J Prev Med 2010;1(3):195-201.
25. Simpson S Jr, Taylor B, Blizzard L, Ponsonby AL, Pittas F, Tremlett H, et al. Higher 25-hydroxyvitamin D is associated with lower relapse risk in multiple sclerosis. Ann Neurol 2010;68(2):193-203.
26. Smolders J, Thewissen M, Peelen E, Menheere P, Tervaert JW, Damoiseaux J, et al. Vitamin D status is positively correlated with regulatory T cell function in patients with multiple sclerosis. PLoS One 2009;4(8):1-8.
27. Newhook LA, Sloka S, Grant M, Randell E, Kovacs CS, Twells LK. Vitamin D insufficiency common in newborns, children and pregnant women living in Newfoundland and Labrador, Canada. Matern Child Nutr 2009;5(2):186-91.
28. Kragt J, Van Amerongen B, Killestein J, Dijkstra C, Uitdehaag B, Polman Ch, et al. Higher levels of 25-hydroxyvitamin D are associated with a lower incidence of multiple sclerosis only in women. Mult Scler 2009;15(1):9-15.
29. Smolders J, Menheere P, Kessels A, Damoiseaux J, Hupperts R. Association of vitamin D metabolite levels with relapse rate and disability in multiple sclerosis. Mult Scler 2008;14(9):1220-4.
30. Van der Mei IA, Ponsonby AL, Dwyer T, Blizzard L, Taylor BV, Kilpatrick T, et al. Vitamin D levels in people with multiple sclerosis and community controls in Tasmania, Australia. J Neurol 2007;254(5):581-90.
31. Kampman MT, Wilsgaard T, Mellgren SI. Outdoor activities and diet in childhood and adolescence relate to MS risk above the Arctic Circle. J Neurol 2007;254(4):471-7.
32. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 2006;296(23):2832-8.
33. Van Rensburg SJ, Kotze MJ, Hon D, Haug P, Kuyler J, Hendricks M, et al. Iron and the folate-vitamin B12-methylation pathway in multiple sclerosis. Metab Brain Dis 2006;21(2-3):121-37.
34. Munger KL, Zhang SM, O'Reilly E, Hernán MA, Olek MJ, Willett WC, et al. Vitamin D intake and incidence of multiple sclerosis. Neurology 2004;62(1):60-5.
35. Besler HT, Comoğlu S, Okçu Z. Serum levels of antioxidant vitamins and lipid peroxidation in multiple sclerosis. Nutr Neurosci 2002;5(3):215-20.
36. Zhang SM, Hernán MA, Olek MJ, Spiegelman D, Willett WC, Ascherio A. Intakes of carotenoids, vitamin C, and vitamin E and MS risk among two large cohorts of women. Neurology 2001;57(1):75-80.
37. Zhang SM, Willett WC, Hernán MA, Olek MJ, Ascherio A. Dietary fat in relation to risk of multiple sclerosis among two large cohorts of women. Am J Epidemiol 2000;152(11):1056-64.
38. Nordvik I, Myhr KM, Nyland H, Bjerve KS. Effect of dietary advice and n-3 supplementation in newly diagnosed MS patients. Acta Neurol Scand 2000;102(3):143-9.
39. Valero MA, Hawkins F. Metabolismo, fuentes endógenas y exógenas de vitamina D. REEMO 2007;16(4):63-70.
40. Sanz-Valero J, Wanden-Berghe C. Análisis bibliométrico de la producción científica, indizada en MEDLINE, sobre los servicios de salud proporcionados por las unidades de hospitalización a domicilio. Hosp Domic 2017;1(1):21-34.
41. Tomás-Caterá V, Sanz-Valero J, Juan-Quilis V. Estudio bibliométrico de la producción científica y de consumo de las revistas sobre nutrición indizadas en la red SciELO. Nutr Hosp 2013;28(3):969-70.
42. Manterola C, Zavando D; Grupo MINCIR. Cómo interpretar los "niveles de evidencia" en los diferentes escenarios clínicos. Rev Chil Cir 2009;61(6):582-95.
43. Sanz-Valero J, Gil Á, Wanden-Berghe C, Martínez de Victoria E; CDC-Nut SENPE. Análisis bibliométrico y temático de la producción científica sobre ácidos grasos omega-3 indizada en las bases de datos internacionales sobre ciencias de la salud. Nutr Hosp 2012;27(2):41-8.
44. Franco-López A, Sanz-Valero J, Culebras JM. Publicar en castellano, o en cualquier otro idioma que no sea inglés, negativo para el factor de impacto y citaciones. JONNPR 2016;1(2):65-70.
45. Cortés J. Web of Science: termómetro de la producción internacional de conocimiento - Ventajas y limitaciones. Culcyt 2008;5(29):5-15.
46. Domingo-Pueyo A, Sanz-Valero J, Wanden-Berghe C. Efectos sobre la salud de la exposición laboral al cromo y sus compuestos: revisión sistemática. Arch Prev Riesgos Labor 2014;17(3):142-53.
47. Wanden-Berghe C, Sanz-Valero J, García de Lorenzo A, Martín-Peña G, Cervera M, Luengo L, et al. Efectos adversos de la nutrición parenteral en pacientes oncológicos; revisión sistemática. Nutr Hosp 2012;27(2):409-18.

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ARÁN

Nutrición Hospitalaria

Revisión

Soporte nutricional y nutrición parenteral en el paciente oncológico: informe de consenso de un grupo de expertos

Nutritional support and parenteral nutrition in the oncological patient: an expert group consensus report

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Resumen

Introducción: la malnutrición es un problema médico frecuente de los pacientes oncológicos que impacta de forma negativa en la calidad de vida.

Objetivo: analizar y dar respuesta a diferentes cuestiones a la hora de afrontar el manejo nutricional de un paciente oncológico en la práctica clínica.

Métodos: un grupo multidisciplinar de expertos en Oncología Médica, Farmacia y Nutrición elaboró una lista de temas relacionados con el estado nutricional del paciente oncológico que fueron agrupados en tres bloques: soporte nutricional; nutrición parenteral (NP); y nutrición parenteral domiciliaria (NPD) en el paciente oncológico. Se realizó una revisión de la literatura que incluyó artículos publicados en español, inglés y francés hasta febrero de 2017. El documento se estructuró como un cuestionario con aquellas preguntas que, según el criterio del panel, podrían generar mayor controversia o duda.

Resultados: de las 18 cuestiones abordadas, 9 versaron sobre el soporte nutricional: 5 relacionadas con la NP y 4 trataron sobre la NPD. Dentro de las recomendaciones del panel destacar que, en el paciente oncológico, la NP está indicada principalmente cuando no es posible el uso del tubo digestivo y/o la alimentación oral y/o nutrición enteral no es suficiente o posible. Además, el objetivo de la NPD es mejorar o mantener, el estado de nutrición de un paciente en el ámbito domiciliario.

Conclusiones: esta revisión constituye una herramienta para oncólogos y especialistas responsables del manejo nutricional del paciente con cáncer.

Palabras clave:

Nutrición. Soporte nutricional. Nutrición enteral. Nutrición parenteral. Nutrición parenteral domiciliaria. Cáncer.

Abstract

Background: Malnutrition is a frequent medical problem of cancer patients that negatively impacts their quality of life.

Objective: To analyze and respond to different issues related to the nutritional management of cancer patients in the clinical setting.

Methods: A multidisciplinary group of experts in Medical Oncology, Pharmacy, and Nutrition developed a list of topics related to the nutritional status of cancer patients, which were grouped into three blocks: Nutritional support; Parenteral nutrition (PN); and Home PN (HPN) in cancer patients. A literature search, which included articles published in Spanish, English, and French until February 2017, was carried out. The document was organized as a questionnaire with those questions that, according to the panel's criteria, could generate greater controversy or doubt.

Results: Of the 18 questions addressed, 9 focused on nutritional support: 5 were related to PN and 4 about HPN. Among the different recommendations, the panel emphasized that in the cancer patient, PN is indicated mainly when it is not possible to use the digestive tract and/or oral feeding and/or enteral nutrition is not sufficient or possible. Additionally, the objective of the HPN is to improve or maintain the nutritional status of a patient at home.

Conclusions: This document seeks to lay down a set of recommendations and to identify key issues that may be useful for the nutritional management of cancer patients.

Key words:

Nutrition. Nutritional support. Enteral Nutrition. Parenteral Nutrition. Home parenteral Nutrition. Cancer.

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INTRODUCCIÓN

Los pacientes con cáncer suelen presentar deficiencias nutricionales importantes que a menudo afectan significativamente a su calidad de vida. De hecho, la proporción de pacientes que, en el momento del diagnóstico, presentan pérdida de peso oscilan entre un 15 y un 40% en función del tipo de cáncer. Sin embargo, la incidencia de desnutrición aumenta conforme evoluciona la enfermedad hasta afectar a un 80% de los pacientes (1-3).

La presencia de desnutrición afecta negativamente a la evolución de los pacientes cancerosos, aumentando la incidencia de infecciones, el tiempo de estancia hospitalaria y el riesgo de muerte (3,4). Sin embargo, la información centrada en el paciente sobre las recomendaciones nutricionales a implementar es limitada, por lo que siguen existiendo una serie de dudas en relación al manejo nutricional del paciente con cáncer en la práctica clínica habitual.

El objetivo de este manuscrito es dar respuesta a las preguntas que los oncólogos se plantean a la hora de afrontar el manejo nutricional y establecer recomendaciones basadas en el consenso para proporcionar a los especialistas responsables del manejo de pacientes oncológicos un marco de referencia basado en la evidencia científica disponible y la experiencia clínica del grupo.

MÉTODOS

Un grupo multidisciplinar formado por especialistas de las áreas de Oncología Médica, Farmacia y Nutrición trabajando en colaboración, ha elaborado un documento de consenso sobre diferentes aspectos que afectan al estado nutricional del paciente oncológico. En esta primera reunión, el panel seleccionó y consensuó una primera lista de temas relacionados con el estado nutricional del paciente oncológico. Los diferentes bloques que centraron la atención del panel fueron: a) el soporte nutricional en el paciente oncológico; b) nutrición parenteral (NP) en el paciente oncológico; y c) nutrición parenteral domiciliaria (NPD) en el paciente oncológico. Los coordinadores del consenso elaboraron una primera lista de temas que se distribuyó a todos los expertos. Posteriormente, evaluaron los comentarios del panel y se realizaron las modificaciones necesarias en una reunión virtual celebrada en noviembre de 2016 en la que se definió la lista definitiva de preguntas.

Se realizó una revisión de la literatura en la base de datos MEDLINE mediante el proveedor PubMed que incluyó los diferentes artículos publicados en español, inglés y francés hasta abril de 2017. Esta búsqueda bibliográfica se complementó con las listas de referencias obtenidas de los artículos seleccionados, las bases de datos de organizaciones y de las sociedades de Oncología y Nutrición y las guías de práctica clínica de referencia.

El documento se estructuró como un cuestionario que incluyó aquellas preguntas que, desde el punto de vista de los miembros del panel, podrían generar mayor controversia o duda. Los coordinadores presentaron un primer documento que fue revisado por los miembros del grupo de expertos, evaluaron los comentarios del panel y modificaron el borrador cuando lo consideraron necesario. Las revisiones subsiguientes se basaron en la retroalimentación de los otros autores hasta que se alcanzó un consenso y el texto final fue validado (Fig. 1).

RESULTADOS

1. ¿CUÁL ES LA INCIDENCIA DE MALNUTRICIÓN SEGÚN LOS DISTINTOS TIPOS DE ENFERMEDAD NEOPLÁSICA Y TRATAMIENTOS ONCOLÓGICOS?

La incidencia es variable según el tipo de tumor y estadio. Por tipo de tumor, su prevalencia es de un 86% en cáncer de páncreas, de un 48-61% en linfomas de mal pronóstico y cáncer colorrectal, hasta el 46% en tumores urológicos y pulmonares; y 30-40% en linfoma de buen pronóstico, cáncer de mama y sarcomas (3-5). Por estadio, la malnutrición está presente hasta en el 15-20% de estadios iniciales, 80% en enfermedad avanzada y 80-90% en pacientes terminales (3-5).

El estudio español NUPAC (6), diseñado para determinar la prevalencia de la malnutrición en cáncer avanzado, confirmó un 52% de malnutrición moderada o grave, 57,7% en cáncer esofágico, 50% en gástrico, 47,1% en laríngeo y 17,6% en cáncer de

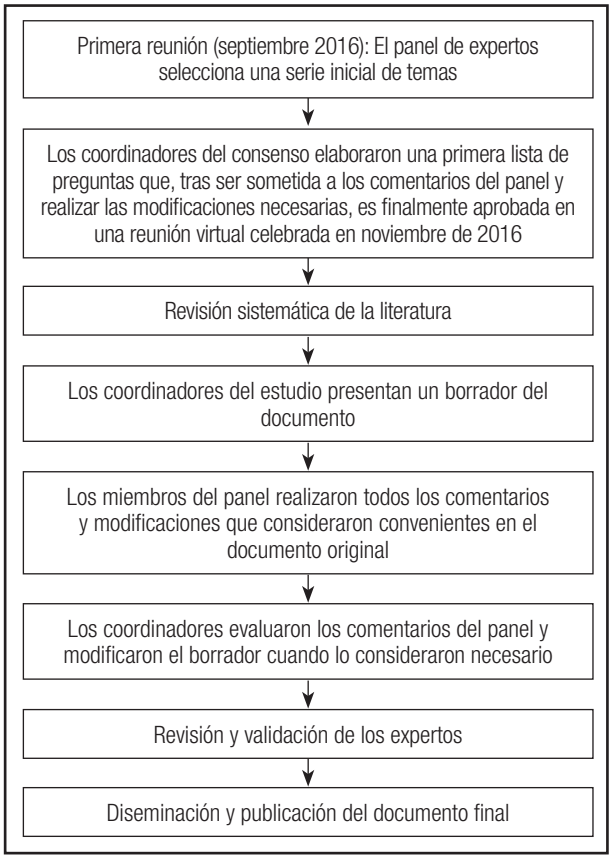

Figura 1.
Diagrama de flujo del proceso de consenso.

próstata. Se observó una escasa concienciación de los médicos implicados y pocos pacientes con diagnóstico nutricional (6).

El estudio PREDyCES® encontró una asociación entre desnutrición y enfermedad, situación emocional reactiva, anorexia, exploraciones complementarias, dietas restrictivas impuestas por la enfermedad, cirugía, tratamientos con quimioterapia/radioterapia y, por último, con la alimentación. La desnutrición repercutía en la estancia hospitalaria y en costes, con un aumento medio de estancia de 3-4 días de los pacientes desnutridos en comparación con los bien nutridos y un incremento de los costes asociados a la hospitalización de un 20-25% (7).

2. ¿CÓMO INFLUYE EL PROCESO ONCOLÓGICO EN EL ESTADO NUTRICIONAL DEL PACIENTE?

Existen múltiples causas asociadas con la desnutrición en pacientes con cáncer (Tabla I).

3. ¿CÓMO INFLUYE EL ESTADO NUTRICIONAL DEL PACIENTE EN LA EVOLUCIÓN DEL PROCESO ONCOLÓGICO?

La caquexia asociada al cáncer produce: a) deterioro de la imagen corporal, el estado funcional y la calidad de vida, con mayor riesgo de toxicidad por los tratamientos oncológicos; b) pérdida de masa muscular con riesgo de insuficiencia cardiaca, respiratoria y úlceras de decúbito; c) retardo en la cicatrización que favorece las fístulas y dehiscencias; y d) deterioro del sistema inmune lo que favorece las infecciones y la disminución de las enzimas digestivas con riesgo de malabsorción (8). Además, la caquexia y desnutrición tiene un impacto pronóstico negativo y se asocia hasta con el 30% de las muertes por cáncer (1-3,9,10). En pacientes terminales, los síntomas anorexia, pérdida de peso, xerostomía y disfagia fueron considerados predictores negativos de supervivencia (1-3,9,10).

Una revisión retrospectiva multicéntrica del Eastern Cooperative Oncology Group (ECOG) observó que la pérdida de peso mayor del 5% previo al diagnóstico e inicio de tratamiento del cáncer, era predictora de mortalidad temprana independientemente del estadio, la histología y el estado general (11).

Tabla I. Diferentes causas asociadas con la desnutrición en pacientes con cáncer

Causas asociadas con desnutrición
– El tumor: • Alteraciones mecánicas y funcionales especialmente en tumores otorrinolaringológicos (ORL) y digestivos • La liberación de hormonas catabólicas, citoquinas y factores movilizadores que favorecen el hipermetabolismo y la caquexia
– El paciente: • Hábitos personales, deterioro físico, anorexia y factores psicológicos
– El tratamiento: • Efectos secundarios de la cirugía, la radioterapia, la quimioterapia y la inmunoterapia. La mucositis, emesis y diarrea dificultan la ingesta y favorecen la malabsorción y pérdida de nutrientes
– El equipo sanitario: • Falta de valoración nutricional, escaso conocimiento y entrenamiento para detectar la desnutrición, retardo en iniciar nutriciones enterales y parenterales adaptadas y adecuadas
– Las autoridades sanitarias: • Ausencia de planificación de profesionales • Déficit en unidades de nutrición y dietistas en los organigramas de los hospitales y en las unidades multidisciplinares que atienden a pacientes con cáncer en la red pública y que garanticen la adecuada asistencia nutricional en los mismos

4. ¿CÓMO PODEMOS DETECTAR LA DESNUTRICIÓN EN EL PACIENTE ONCOLÓGICO?

Se recomienda realizar una valoración nutricional en todos los pacientes con cáncer al diagnóstico y durante el tratamiento con el fin de detectar aquellos pacientes malnutridos o en riesgo nutricional y llevar a cabo una intervención precoz dado que el diagnóstico tardío puede dificultar la recuperación y ganancia de peso (12).

El primer paso para detectar la desnutrición es mediante el uso rutinario de herramientas de cribado nutricional. Que estén ligados a protocolos de actuación posterior.

Las guías de la Sociedad Europea de Nutrición Clínica y Metabolismo (ESPEN) publicadas en 2017 (13), recomiendan evaluar periódicamente la ingesta de nutrientes, los cambios en el peso y el índice de masa corporal (IMC), desde el diagnóstico del cáncer y repetir la evaluación en función de la estabilidad de la situación clínica.

Existen numerosas herramientas de cribado nutricional; las más usadas serían: para paciente hospitalizado: Nutritional Risk Screening 2002 (NRS 2002), para la población en general: el Malnutrition Universal Screening Tool (MUST), para paciente anciano el Mini Nutritional Assessment (MNA) y el Malnutrition Screening Tool (MST), ha sido validado en pacientes oncológicos hospitalizados y ambulatorios en tratamiento con quimioterapia y radioterapia.

En las Guías Clínicas Multidisciplinares sobre el manejo de la nutrición del paciente con cáncer, publicada en España en 2008 (14), donde participaron la SEOM (Sociedad Española de Oncología Médica), SEOR (Sociedad Española de Oncología Radioterápica) y la SENPE (Sociedad Española de Nutrición Enteral y Parenteral), se consensuó hacer uso del MST como cribado nutricional, para los pacientes adultos con cáncer, por su sencillez, fiabilidad y validez.

El MST se compone de dos preguntas: una relacionada con la pérdida de peso y la otra con la ingesta/apetito. Clasifica a los

pacientes en dos grupos: con riesgo de desnutrición (resultado ≥ 2) y sin riesgo de desnutrición (resultado < 2).

Una vez detectado el riesgo de desnutrición se precisa de una valoración nutricional completa posterior. La valoración nutricional "gold standard" en el paciente oncológico es la VGS-GP (Valoración Global Subjetiva Generada por el Paciente) (15). Debe realizarla personal entrenado si hay unidades de nutrición por un especialista en Nutrición y, si no las hay, por un profesional bien formado. Esta tiene en cuenta la pérdida de peso, datos de la historia clínica como es el diagnóstico, tratamientos actuales y medicación recibida, y analíticos como la albúmina y prealbúmina. También se involucra al propio paciente quien completa la parte referente a los síntomas presentes, el tipo de alimentación y actividad cotidiana que realiza. Requiere de una exploración física exhaustiva para detectar disminución de masa muscular, grasa y presencia de edemas. Esta clasifica al paciente en A: normonutrido; B: riesgo nutricional o desnutrición moderada; y C: desnutrición grave.

5. ¿QUÉ PARÁMETROS (CLÍNICOS, ANALÍTICOS Y ANTROPOMÉTRICOS) SE DEBEN TENER EN CUENTA PARA VALORAR EL ESTADO NUTRICIONAL INICIAL Y DURANTE EL SEGUIMIENTO DEL PACIENTE ONCOLÓGICO?

No existe un único parámetro que nos informe sobre el estado nutricional, sino la combinación de varios (clínicos, analíticos, antropométricos y funcionales).

Parámetros *clínicos* como la localización del tumor y tratamiento realizado: existe mayor riesgo nutricional en localizaciones digestivas, así como tratamientos concomitantes. Sintomatología presente: se debe interrogar al paciente sobre la situación actual, detectando signos de riesgo nutricional que favorecen la pérdida ponderal o dificultan la ingesta y absorción de nutrientes, como, la presencia de anorexia, astenia, disminución de la actividad física, náuseas o emesis, diarrea, esteatorrea o estreñimiento, disgeusia, dolor, depresión o problemas socioeconómicos que dificulten el acceso a la comida.

Las guías ESPEN (13) recomiendan una valoración de la masa muscular y de las reservas de grasa que puede realizarse mediante absorciometría dual de rayos X (DEXA) o análisis de bioimpedancia (BIA), así como una evaluación del rendimiento físico utilizando diversas escalas como la ECOG, Karnofsky, dinamometría, velocidad de la marcha, etc. (13).

Los parámetros *analíticos* más asociados con el estado nutricional son la albúmina y la prealbúmina. Sin embargo, deben evaluarse en el contexto global puesto que pueden verse alterados por otros problemas intercurrentes y comunes en pacientes con cáncer (infecciones, enfermedades hepáticas, renales, deshidratación, anasarca, etc.).

Las guías ESPEN recomiendan, para medir la inflamación sistémica, el uso de la proteína C reactiva (PCR) sérica y la albúmina (13).

Entre los parámetros *antropométricos* la disminución de peso significativa, > 10% durante 6 meses o 5% durante 3 meses se considera el indicador más fiable de déficit nutricional. Otro indicador antropométrico accesible es la medida de la circunferencia braquial (como método para evaluar la pérdida de masa muscular) que si es < 20 cm o disminuye > 2 cm entre 2 determinaciones sugiere desnutrición. Existen otros más precisos que requieren equipamientos específicos y habitualmente no disponibles.

6. ¿CUÁLES SON LOS OBJETIVOS E INDICACIONES DE LOS DISTINTOS TIPOS DE SOPORTE NUTRICIONAL ESPECIALIZADO EN EL PACIENTE ONCOLÓGICO?

El soporte nutricional se clasifica según su agresividad y complejidad, y se incluyen (13-15):

- Recomendaciones nutricionales y consejo higiénico-dietético.
- Nutrición artificial:
  - Nutrición enteral oral, suplementación (SNO).
  - Nutrición enteral por sonda.
  - NP.

La elección depende de la situación actual del paciente: diagnóstico oncológico, tratamiento oncoespecífico, pronóstico, estado nutricional, requerimientos nutricionales y de la duración del soporte nutricional (13-15). El algoritmo de soporte nutricional se muestra en la figura 2.

Si la ingesta de alimentos por vía oral es insuficiente a pesar del consejo nutricional y los suplementos nutricionales orales, se recomienda iniciar nutrición enteral, para la que, según la previsión de duración del soporte y de situaciones del paciente, se escogerá el tipo de sonda y la forma de colocarla (13-16). Si el aporte enteral no es suficiente o posible, se indicará NP (13-15).

Se indica soporte nutricional en pacientes con cáncer cuando existe desnutrición, se espera que el paciente no pueda ingerir alimentos durante una semana o más o si su ingesta es inferior al 60% de sus necesidades durante más de 10 días (Grado de recomendación C) (13).

7. ¿CUÁLES SON LOS REQUERIMIENTOS NUTRICIONALES EN EL PACIENTE ONCOLÓGICO?

Los requerimientos energéticos de los pacientes oncológicos, en principio, y si no se realizan medidas individualizadas (calorimetría indirecta), se deben considerar semejantes a los de las personas sanas (25-30 Kcal/kg/día) (13).

Debemos tener en cuenta que esta aproximación se suele sobreestimar en las personas obesas y subestimar en las extremamente delgadas, al igual que algunas ecuaciones predictivas, como Harris-Benedict.

En cuanto a los requerimientos proteicos deberían ser de entre 1 (mínimo) y 1,2-1,5 g/kg/día y en el caso de existir catabolismo

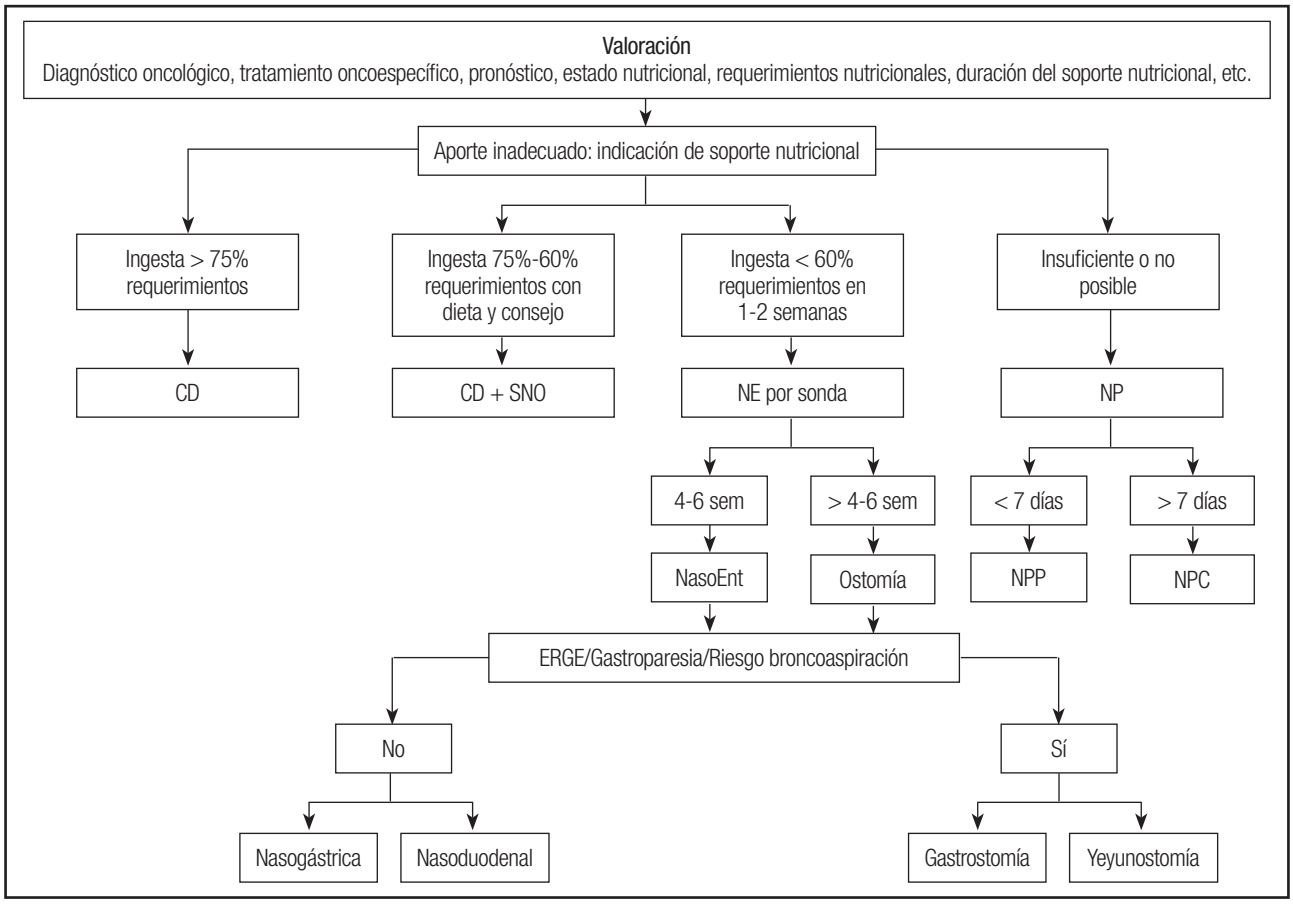

Figura 2.

Algoritmo de soporte nutricional. Adaptado de Hernández y cols. (14) (CD: consejo dietético; SON: suplementos nutricionales orales; NE: nutrición enteral; NP: nutrición parenteral; sem: semana; NasoEnt: nasoenteral; NPP: nutrición parenteral periférica; NPC: nutrición parenteral central; ERGE: enfermedad por reflujo gastroesofágico).

proteico podría aumentarse a 2 g/kg/día (13). En pacientes con insuficiencia renal aguda o crónica el suministro de proteínas no debe superar 1,0 o 1,2 g/kg/d, respectivamente. La relación entre el gasto energético y los requerimientos nitrogenados se recomienda entre 130-100 Kcal/g N (14,15,17).

La relación de lípidos/hidratos de carbono ideal vendrá determinada por los antecedentes patológicos o la situación clínica de cada paciente (17,18). Conviene que esta relación se desplace a favor de los lípidos siempre que exista resistencia insulínica, oxidación aumentada de la glucosa y pérdida de peso (18).

Otro aspecto a tener en cuenta son las necesidades hídricas y de sodio de los pacientes, que deberemos recortar por debajo de la normalidad (30 ml/kg/día para el agua y 1 mmol/kg/día para el sodio) en el caso de carcinomatosis peritoneal si aparece obstrucción o ascitis para evitar la sobrecarga o tercer espacio (13).

Respecto al resto de componentes, sobre todo vitaminas y oligoelementos no se recomienda suplementar en cantidades mayores a las dosis diarias recomendadas (DDR) si no existen déficits específicos (13).

8. ¿EXISTEN NUTRIENTES ESPECÍFICOS QUE INFLUYEN SOBRE LA EVOLUCIÓN DEL PROCESO ONCOLÓGICO?

Los nutrientes específicos o "farmaconutrientes" son sustratos nutricionales que además de su valor nutricional tienen otros efectos beneficiosos para el organismo. Se utilizan con el objetivo de modular el curso de la enfermedad. Por ejemplo, los ácidos grasos omega 3, la arginina o la glutamina (19).

Respecto a los nutrientes específicos proteicos, la glutamina (oral y parenteral) es el más investigado en las últimas décadas junto con la arginina, pero existen pocos estudios exclusivos para pacientes oncológicos y los resultados no son concluyentes (13,15,17,18). Sin embargo, en las recomendaciones de la ESPEN, se indica la preferencia de dietas inmunomoduladoras (enriquecidas en arginina, n-3, nucleótidos, con o sin glutamina) en la cirugía del cáncer de cabeza y cuello (20). Es más, los resultados de una revisión sistemática han mostrado que la administración de nutrición enteral enriquecida con arginina condujo a una reducción significativa, tanto de la incidencia de fístulas como de la estancia hospitalaria, en pacientes sometidos a cirugía de cáncer de cabeza y cuello (21).

Más recientes son los estudios con HMB (hidroxi-metil-butrirato, derivado de la leucina), utilizado como agente anti-catabólico para frenar la degradación proteica, pero tampoco los resultados, hasta la fecha, aconsejan extender su uso (13).

Con los lípidos, aunque bioquímicamente se conoce el beneficio de los ácidos grasos omega 3 respecto a los omega 6 en cuanto al descenso de la actividad proinflamatoria, tampoco existen estudios clínicos en pacientes oncológicos que lo demuestren, excepto en el caso de los pacientes oncológicos perioperatorios donde la respuesta inflamatoria es mucho más clara sobre todo en cáncer de cabeza y cuello y si centramos el tratamiento en los 5-7 días del perioperatorio (13,15). Las fórmulas comercializadas para estos usos suelen estar suplementadas a la vez con nucleótidos y arginina.

El ácido graso omega 3, derivado del aceite de pescado, ácido eicosapentanoico (EPA), ha sido también probado como agente anticaquéctico principalmente, aunque la falta de adhesión al tratamiento suele asociarse con el fracaso de los resultados de la administración en cápsulas (13).

En los últimos años se han llevado a cabo muchos estudios sobre vitamina D y cáncer, relacionando niveles bajos e incidencia y/o pronóstico del mismo, fundamentalmente en el caso del cáncer de colon; pero la verdad es que, a fecha de hoy, se desconoce cómo puede influir la normalización de dichos niveles en el pronóstico del cáncer (13).

9. ¿CUÁNDO ESTÁ INDICADA UNA NUTRICIÓN PARENTERAL EN UN PACIENTE ONCOLÓGICO?

La NP como modalidad de soporte nutricional específico en el paciente oncológico está indicada principalmente cuando no es posible el uso del tubo digestivo y/o la alimentación oral y/o nutrición enteral no es suficiente o posible (13-16,22):

- *Por contraindicación de acceso al tubo digestivo:* ante una perforación, obstrucción intestinal o quilotórax.
- *Por imposibilidad de acceso al tubo digestivo:* como ocurre en las fístulas enterocutáneas altas de alto débito en las que no se dispone de sondas para colocar distalmente a las mismas, en el íleo paralítico, hemorragia digestiva o ante insuficiente superficie absortiva por cirugía oncológica amplia.
- *Por tubo digestivo ineficaz:* como sucede en el síndrome de intestino corto, fístulas de alto débito e insuficiencia intestinal por enteritis rádica.
- *Por bajo aporte oral y/o enteral:* Cuando es inferior al 60% de las necesidades nutricionales durante más de 1-2 semanas y se prevé una mejora del estado nutricional y de calidad de vida, puede hacerse uso de la NP complementaria a la vía oral y/o enteral.

En pacientes incurables/paliativos el soporte nutricional debe realizarse cuando el beneficio esperado sea superior al riesgo potencial. Cuando la supervivencia estimada es superior a 1-3 meses, y en caso de insuficiencia intestinal, se puede ofrecer una NP, en caso de ser la vía oral/enteral insuficientes y existir expectativas de mejoría en la calidad de vida y funcionalidad del paciente y con un deseo expreso de este (13).

10. ¿CUÁLES SON LAS INDICACIONES DE NUTRICIÓN PARENTERAL COMPLEMENTARIA EN EL PACIENTE ONCOLÓGICO?

La NP complementaria a un soporte oral o enteral insuficiente estaría indicada en aquellos casos en los que se prevea una clara mejoría del estado nutricional o de la calidad de vida del paciente oncológico (13,15,23).

No se ha demostrado que la NP mejore el estado nutricional del paciente oncológico con anorexia y tracto intestinal funcionante y por ello, se debe dar siempre prioridad a la vía digestiva (13,23). No obstante, la NP complementaria podría indicarse en aquellos pacientes en los que no se puedan cubrir un 60% de sus necesidades energéticas mediante la vía digestiva durante un periodo de 1 o 2 semanas (13).

La composición de la nutrición dependerá de la complementación necesaria en cada paciente (13,15). Puede ser necesaria una suplementación completa o solo con alguno de sus componentes habituales (volumen, nitrógeno, glucosa, lípidos, micronutrientes). Puede elaborarse a la carta en el servicio de farmacia hospitalario o utilizar algún preparado comercial existente.

Cuando se puede realizar un adecuado aporte de nutrientes por vía oral o enteral no debe llevarse a cabo por vía parenteral ya que en este caso la NP no es efectiva y probablemente sí sea perjudicial (Grado de recomendación A). Se debería emplear una NP complementaria cuando el aporte enteral es insuficiente para cubrir la diferencia entre las necesidades calculadas y el aporte oral/enteral (Grado de recomendación C). Se recomienda NP en pacientes con mucositis o enteritis rádica grave a largo plazo (Grado de recomendación C) (24).

11. ¿CUÁLES SON LAS DIFERENTES VÍAS DE ADMINISTRACIÓN DE LA NUTRICIÓN PARENTERAL EN EL PACIENTE ONCOLÓGICO?

Las vías de administración de NP en el paciente oncológico son las mismas que en el resto de los pacientes. La selección de las diferentes vías disponibles dependerá del tiempo que se requiera el soporte, la frecuencia de utilización (intermitente o diaria), la actividad y el estilo de vida del paciente, los antecedentes quirúrgicos que afecten la zona de inserción, las características psicosociales y de la capacidad de cuidados del paciente (Tabla II).

La NP complementaria puede realizarse por vía periférica o central mediante catéteres temporales o permanentes en el caso de que se prevea una duración de más de 15 días. También puede utilizarse la vía subcutánea en caso de aporte complementario de suero o algún micronutriente como el magnesio.

Tabla II. Diferentes vías de administración de la nutrición parenteral en el paciente oncológico. Adaptado de Derenski y cols. (25)

Tipos de acceso	Características
Acceso periférico	Se utilizará si no se dispone de un acceso central y se prevea una duración a corto plazo (inferior a 7-10 días). Se inserta de manera percutánea vía periférica. Es barato, de sencillo manejo y con poca incidencia de infección asociada a catéter. Los inconvenientes son que la osmolaridad de la mezcla que no debe superar los 800 mOsm/L y que debe rotarse cada 48-72 h por la incidencia de flebitis
Acceso central	La elección dependerá del tipo de paciente, del manejo y la disponibilidad en cada centro. Pueden ser de cuatro tipos
Catéter central percutáneo (vía central)	Lo implanta un médico en subclavia, yugular o femoral es económico y fácilmente sustituible. Solo se usa para soporte parenteral a corto plazo, requiere sutura para su fijación y tiene una alta incidencia de infección asociada a catéter
Catéter central insertado vía periférica (PICC)	Tiene la ventaja de que puede ser implantado por diplomados en enfermería. Admite cualquier composición y osmolaridad de la mezcla. Puede ser algo más complicado el manejo para el paciente con acceso cubital en caso de soporte domiciliario
Tunelizado tipo Hickman	Se implanta en subclavia o yugular en quirófano por radiólogos vasculares o cirujanos y se extrae de manera simple. Es preferible el de una sola luz ya que minimiza la posibilidad de infección. Es fácilmente manejable por el paciente en caso de soporte domiciliario por lo que es el más recomendable en esos casos. Tiene el inconveniente cosmético de que es visible desde el exterior
Reservorio o Porth-a-cath	Se compone de un reservorio subcutáneo o puerto que es radiopaco y fabricado generalmente en titanio y de una membrana de silicona autosellante muy resistente. Se implanta en subclavia o yugular en quirófano por radiólogos vasculares o cirujanos, la imagen corporal no se altera ya que es subcutáneo y además carece de elementos exteriores que puedan dañarse. Es el preferido en los pacientes oncológicos quienes requieren un acceso vascular repetido o continuo para la administración de quimioterapia, sangre o medicamentos. El inconveniente es que para el paciente con soporte domiciliario necesita una aguja especial denominada *gripper* o *hubber* que debe cambiarse semanalmente

12. ¿QUIÉN DEBE/PUEDE REALIZAR EL SEGUIMIENTO NUTRICIONAL DEL PACIENTE ONCOLÓGICO (SERVICIO DE NUTRICIÓN, ONCÓLOGO, MÉDICO DE ATENCIÓN PRIMARIA, ETC.)?

El seguimiento nutricional del paciente oncológico debe ser multidisciplinar y adaptado a las características de cada centro.

El cribado nutricional debe estar incluido en la rutina de los cuidados del paciente oncológico y debe ser sencillo de realizar por cualquier miembro del equipo terapéutico ya sea por los diplomados en enfermería o médicos (13).

Una valoración nutricional simple con una historia clínica nutricional rápida, una antropometría que incluya el índice de masa corporal (IMC) y una determinación analítica básica que incorpore cifras de albúmina debe de ser factible para el oncólogo. Lo ideal es que el oncólogo tenga la suficiente formación en nutrición para derivar al paciente en riesgo nutricional o ya desnutrido al especialista en nutrición.

En el ambiente hospitalario debe haber una estrecha colaboración entre el servicio de oncología y la unidad de nutrición. El que exista una consulta de nutrición en oncología es una situación deseable.

En el paciente ambulatorio también se debe contar con la colaboración del médico de atención primaria para detectar los problemas nutricionales y derivar al especialista en nutrición cuando sea necesario.

El seguimiento del paciente oncológico con NPD también es multidisciplinar y requiere revisiones clínicas, analíticas inicialmente mensuales y luego trimestrales por la unidad de nutrición, así como controles analíticos básicos periódicos por el médico de atención primaria.

13. ¿CUÁNDO ESTÁ INDICADA LA RETIRADA DE UNA NUTRICIÓN PARENTERAL EN UN PACIENTE ONCOLÓGICO?

La retirada de la NP deberá atender el alcance de los objetivos planteados en cada caso además de las siguientes consideraciones:

– *Recuperación de la funcionalidad del tubo digestivo.* Se debe monitorizar la transición de la terapia nutricional evaluando la recuperación funcional digestiva que permita incorporar al plan de atención nutricional con nutrición enteral, suplementación oral y/o alimentación natural (26). La transición se realizará de forma progresiva para lo cual se considerará por un lado su tolerancia y la cobertura de requerimientos de forma exclusiva por vía digestiva para poder retirar definitivamente la NP.

– *Por complicaciones graves asociadas***.** La aparición de infección asociada a catéter o complicaciones mecánicas como rotura de catéter, obstrucción, trombosis, etc. que no permitan mantener un acceso venoso adecuado, si bien no son complicaciones de la NP en sí, constituyen una limitación para la utilización de la misma como medida de soporte nutricional y obligan a plantear su retirada (27,28).
– *En situación* premortem *de los pacientes terminales en programa de NP.* En los pacientes con enfermedad neoplásica avanzada, fallo intestinal crónico y una expectativa de vida mayor de 1-3 meses, la NPD puede mejorar la calidad de vida y prolongar la supervivencia (29-32). Sin embargo, cuando la situación clínica del paciente empeora y la muerte del paciente es inminente se deberá suspender la NP y aplicar medidas de confort ya que el soporte nutricional no ofrece beneficios en la mayoría de los casos (13,33).

14. ¿CUÁLES SON LOS OBJETIVOS DE LA NUTRICIÓN PARENTERAL DOMICILIARIA EN UN PACIENTE ONCOLÓGICO?

Según la ESPEN, los objetivos generales del soporte nutricional en el paciente oncológico, NPD en este caso, son: mantener o mejorar el aporte nutricional, atenuar las alteraciones metabólicas, mantener o mejorar la masa muscular y la capacidad funcional, reducir las interrupciones del tratamiento oncológico programado y mejorar la calidad de vida de los pacientes (13).

Los objetivos específicos de la NPD en los pacientes con cáncer son prevenir y tratar la malnutrición y/o la caquexia, mejorar el cumplimiento del tratamiento oncológico programado, reduciendo sus interrupciones, disminuir los efectos adversos del tratamiento y mejorar la calidad de vida de los pacientes (Grado de recomendación C) (13,24).

Se recomienda que antes del alta hospitalaria los pacientes estén estables metabólicamente, hayan recibido un entrenamiento centrado en el paciente con una aproximación multidisciplinar, se les den las recomendaciones por escrito, tengan acceso a recursos materiales seguros necesarios para la NPD, sean capaces física y emocionalmente de manejarla y tengan un entorno adecuado en sus domicilios (Nivel de evidencia muy débil, Grado de recomendación fuerte) (34,35).

Así mismo, para indicar NPD, la duración prevista de la misma debe ser superior a 4 semanas, la expectativa de vida superior a 3 meses y el paciente debe aceptarlo mediante firma del consentimiento informado; el entorno familiar debe estar formado, capacitado y motivado para colaborar con el manejo de la NPD y debe haber un mínimo de condiciones higiénicas en su domicilio. En cuanto al sistema, debe haber un equipo multidisciplinar con experiencia en NPD y un equipo médico-enfermero de apoyo a domicilio (36).

15. ¿CUÁLES SON LAS COMPLICACIONES DE LA NUTRICIÓN PARENTERAL DOMICILIARIA EN EL PACIENTE ONCOLÓGICO?

Las complicaciones asociadas con la NPD pueden ser las mismas que aparecen cuando este tipo de nutrición se prescribe a corto plazo, pero existen otras complicaciones específicamente relacionadas con la administración prolongada de la NP. Se observan 4 grandes grupos de complicaciones que incluyen mecánicas, infecciosas, metabólicas y psicosociales (37,38) (Tabla III).

Tabla III. Complicaciones de la nutrición parenteral domiciliaria (NPD) en el paciente oncológico. Adaptado de Cuerda Compés MC (37) y Cuerda C et al. (38)

Tipos de complicaciones	
Mecánicas	Estas complicaciones están relacionadas con la colocación y sobre todo con el mantenimiento del catéter. En el caso de la NPD, se deben destacar por su frecuencia la oclusión del catéter y la trombosis venosa (39)
Infecciosas	Son las complicaciones más frecuentemente observadas en los pacientes con NPD fundamentalmente la bacteriemia y/o sepsis asociada al catéter (40)
Metabólicas	Pueden manifestarse de forma aguda, como es el caso de la hiperglucemia/hipoglucemia, las alteraciones hidroelectrolíticas y el síndrome de realimentación o a largo plazo como consecuencia de los efectos de la NPT sobre el hígado y el hueso. La enfermedad hepática se presenta en forma de esteatosis, colestasis intrahepática, barro biliar o colelitiasis. Para prevenir esta complicación, ESPEN recomienda no aportar más de 1 g/kg de grasas, ajustar el aporte calórico e infundir la NP de forma cíclica (Grado de recomendación B) (41). La enfermedad metabólica ósea se caracteriza por la presencia de osteomalacia, osteoporosis, dolor o fracturas óseas. En esta entidad están implicados factores relacionados con la NP como son la hipercalciuria, la toxicidad por aluminio, el déficit o toxicidad de vitamina D y la sobrecarga proteica (41)
Psicosociales	La NPD puede influir en la calidad de vida del paciente (42)

ESPEN: Sociedad Europea de Nutrición Parenteral y Enteral; NPT: nutrición parenteral total; NP: nutrición parenteral.

16. ¿CUÁL ES EL SEGUIMIENTO NUTRICIONAL RECOMENDADO EN UN PACIENTE ONCOLÓGICO QUE RECIBE NUTRICIÓN PARENTERAL DOMICILIARIA?

Los pacientes con NPD requieren un seguimiento estrecho e individualizado con el objetivo de evaluar la eficacia y seguridad del tratamiento, así como poder detectar y resolver las complicaciones asociadas a esta modalidad terapéutica (43,44). Este seguimiento será realizado por el equipo de profesionales que hayan indicado la NPD, habitualmente la unidad de Nutrición del hospital de referencia, en coordinación con los equipos médicos implicados en el control de la evolución del enfermo (45).

Se debe realizar por parte del paciente un control diario de parámetros clínicos como la temperatura, diuresis, vómitos, deposición, ingesta oral y punto de inserción del catéter (43,45).

Según ESPEN, en cada visita a la unidad de nutrición se realizará una evaluación antropométrica y analítica que incluya evolución ponderal, electrolitos, función hepática, creatinina, glucosa, triglicéridos, hemograma, hierro, albumina y PCR con una periodicidad de 3 meses en pacientes estables y de 1-2 meses cuando exista inestabilidad clínica. También se recomienda solicitar una determinación de oligoelementos y vitaminas (A, D, E, B12, ácido fólico) semestralmente y medir la densidad mineral ósea mediante DEXA cada año (Grado de recomendación C) (41).

17. ¿QUÉ FUENTES DE INFORMACIÓN EXISTEN PARA MEJORAR EL CONOCIMIENTO DE LA IMPORTANCIA DEL SOPORTE NUTRICIONAL EN LOS PACIENTES ONCOLÓGICOS?

Las fuentes de información son muchas y variadas. Recientemente, se ha publicado una actualización de la Pirámide de Haynes, uno de los líderes naturales del Evidence-Based Medicine Working Group, que sintetiza en 5 estratos los recursos de información en base a su utilidad y propiedades en la toma de decisiones en la atención sanitaria (46,47).

Nos puede servir de guía teniendo en cuenta que cuanto más arriba se obtenga la información estará más elaborada y existe un mayor riesgo de estar menos actualizada:

1. *Estudios:* originales publicados en revistas médicas indexadas a las que se accede directamente a través de las bases de datos (PubMed, EMBASE, WoS, etc.). Existen unas 194 revistas de oncología y 13 específicas de nutrición clinica algunos ejemplos de estas últimas son: *Clinical Nutrition, Nutrition Clinical Practices, Journal Parenteral and Enteral Nutrition* y Nutrition.
2. *Síntesis* (systematic reviews): recoge las revisiones sistemáticas: Cochrane Library y otras de calidad.
3. *Sinopsis* (systematically derived recommendations): revisiones críticas de artículos, boletines e informes de evaluación.
4. *Sumarios* (synthesised summaries for clinical reference): incluye las guías de práctica clínica basadas en la evidencia con temas actualizados y valorados críticamente. Por ejemplo: Up To Date, Clinical Evidence, Dynamed, BMJ Best Practice.
5. *Sistemas:* hace referencia a los sistemas de ayuda a la toma de decisiones clínicas.

CONCLUSIONES

Este consenso destaca diferentes elementos claves que ayudaran a los médicos a normalizar el manejo del estado nutricional del paciente oncológico en la práctica clínica, estableciendo pautas comunes de indicación, monitorización, requerimientos nutricionales y vías de acceso a la NP.

1. Las alteraciones del estado nutricional en el paciente oncológico son frecuentes e impactan negativamente en el pronóstico del proceso tumoral.
2. El panel de expertos recomienda hacer uso de un cribado nutricional rutinario, al diagnóstico y a lo largo de la enfermedad para detectar el riesgo de desnutrición y, si este es positivo, realizar posteriormente una valoración nutricional completa para poder diagnosticar la desnutrición.
3. Actualmente existen diferentes herramientas y métodos de cribado que nos permiten detectar el riesgo nutricional. El cribado validado a nivel ambulatorio y de hospitalización en el paciente oncológico es el MST. Parámetros antropométricos, como la disminución de peso significativa, y analíticos, como la albúmina valorada juntamente con la PCR, pueden aportar información del estado nutricional.
4. Las necesidades nutricionales de los pacientes oncológicos, salvo en aquellos casos en donde se requieran medidas individualizadas, han de considerarse semejantes a las personas sanas (25-30 Kcal/kg/día).
5. En el paciente oncológico, la NP total está indicada cuando no es posible el uso del tubo digestivo y/o la alimentación oral y/o nutrición enteral no es suficiente o posible.
6. La NP complementaria a un soporte oral o enteral insuficiente estaría indicada cuando se prevea una clara mejoría del estado nutricional o de la calidad de vida del paciente oncológico.
7. El seguimiento nutricional del paciente oncológico debe ser multidisciplinar y adaptado a las características de cada centro.
8. El objetivo de la NPD es mejorar o mantener, en el ámbito domiciliario, el estado de nutrición de un paciente y estaría indicada en pacientes cuyo sistema digestivo no garantice recibir los nutrientes necesarios para cubrir sus requerimientos nutricionales.
9. La NPD requiere una evaluación periódica y conocimientos en la técnica y su manejo.

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BIBLIOGRAFÍA

1. Gupta D, Lis CG, Granick J, Grutsch JF, Vashi PG, Lammersfeld CA. Malnutrition was associated with poor quality of life in colorectal cancer: a retrospective analysis. J Clin Epidemiol 2006;59(7):704-9.
2. Rosania R, Chiapponi C, Malfertheiner P, Venerito M. Nutrition in Patients with Gastric Cancer: An Update. Gastrointest Tumors 2016;2(4):178-87.
3. Escortell Sánchez R, Reig García-Galbis M. Nutrición enteral en el estado nutricional del cáncer; revisión sistemática. Nutr Hosp 2015; 32(4):1408-16.
4. Chow R, Bruera E, Chiu L, Chow S, Chiu N, Lam H, et al. Enteral and parenteral nutrition in cancer patients: a systematic review and meta-analysis. Ann Palliat Med 2016;5(1):30-41.
5. Belda-Iniesta C, De Castro Carpeño J, Casado Saenz E, Gonzalez Barón M. Malnutrición y enfermedad neoplásica. En: Gómez Candela C, Sastre A, editores. Soporte nutricional en la Enfermedad Oncológica. Madrid: You&Us; 2004. pp. 3.
6. Segura A, Pardo J, Jara C, Zugazabeitia L, Carulla J, de Las Peñas R, et al. An epidemiological evaluation of the prevalence of malnutrition in Spanish patients with locally advanced or metastatic cancer. Clin Nutr 2005;24(5):801-14.
7. Planas M, Álvarez-Hernández J, León-Sanz M, Celaya-Pérez S, Araujo K, García de Lorenzo A; PREDyCES® researchers. Prevalence of hospital malnutrition in cancer patients: a sub-analysis of the PREDyCES® study. Support Care Cancer 2016;24(1):429-35.
8. Tisdale MJ. The 'cancer cachectic factor'. Support Care Cancer 2003;11(2):73-8.
9. Bachmann J, Heiligensetzer M, Krakowski-Roosen H, Büchler MW, Friess H, Martignoni ME. Cachexia worsens prognosis in patients with resectable pancreatic cancer. J Gastrointest Surg 2008;12(7):1193-201.
10. Fearon KC, Baracos VE. Cachexia in pancreatic cancer: new treatment options and measures of success. HPB (Oxford) 2010;12(5):323-4.
11. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med 1980;69 (4):491-7.
12. Valenzuela-Landaeta K, Rojas P, Basfi-fer K. Evaluación nutricional del paciente con cáncer. Nutr Hosp 2012;27(2):516-23.
13. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr 2017;36(1):11-48.
14. Hernandez J, Muñoz D, Planas M, Rodriguez I, Rovira P, Segui MA. Documento de consenso. En Sociedad Española de Oncología Médica (SEOM), Sociedad Española de Nutrición Enteral y Parenteral (SENPE), Sociedad Española de Oncología Radioterápica (SEOR). Guía multidisciplinar sobre el manejo de la nutrición en el paciente con cáncer. España 2008; pp. 63-7.
15. August DA, Huhmann MB; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. JPEN J Parenter Enteral Nutr 2009;33(5):472-500.
16. Joaquín Ortiz CL. Análisis de las guías clínicas en Oncología. Nutr Hosp 2016;33(Supl. 1):40-9.
17. Bozzetti F, Meyenfeldt von MF. Nutrition support in different clinical situations: Nutrition support in cancer patients. En: Lubos Sobotka, editor in chief. Basics in Clinical Nutrition. Fourth Edition. Prague: ESPEN; 2011. GALEN; 2011. pp. 573- 83.
18. Planas M, Fernández-Ortega JF, Abilés J; Spanish Society of Intensive Care-Medicine and Coronary Units-Spanish Society of Parenteral and Enteral Nutrition (SEMICYUC-SENPE). Actualización. Consenso SEMICYUC-SENPE: Paciente onco-hematológico. Med Intensiva 2011;35(Supl 1):53-6.
19. García-de-Lorenzo, director. Diccionario LID. Metabolismo y Nutrición. 1ª ed. Madrid: LID Editorial Empresas, S.L.; 2007.
20. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P; DGEM (German Society for Nutritional Medicine), Jauch KW, Kemen M, Hiesmayr JM, Horbach T, Kuse ER, Vestweber KH; ESPEN (European Society for Parenteral andEnteral Nutrition). ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation. Clin Nutr 2006;25(2):224-44.
21. Vidal-Casariego A, Calleja-Fernández A, Villar-Taibo R, Kyriakos G, Ballesteros-Pomar MD. Efficacy of arginine-enriched enteral formulas in the reduction of surgical complications in head and neck cancer: a systematic review and meta-analysis. Clin Nutr 2014;33(6):951-7.
22. Palma Milla S, Lisbona Catalan A, Gómez Candela C. Nutrición Parenteral en el paciente oncológico. Revisión. Nutrición Clínica en Medicina 2015;9(2):173-87.
23. Yan X, Zhou FX, Lan T, Xu H, Yang XX, Xie CH, et al. Optimal postoperative nutrition support for patients with gastrointestinal malignancy: A systematic review and meta-analysis. Clin Nutr 2017;36(3):710-21. DOI: 10.1016/j.clnu.2016.06.011.
24. Bozzetti F, Arends J, Lundhom K, Micklewright A, Zurcher G, Muscaritoli M. ESPEN guidelines on parenteral nutrition: non-surgical oncology. Clin Nutr 2009;28:445-54.
25. Derenski K, Catlin J, Allen L. Parenteral Nutrition Basics for the Clinician Caring for the Adult Patient. Nutr Clin Pract 2016;31(5):578-95.
26. Ukleja A, Freeman KL, Gilbert K, Kochevar M, Kraft MD, Russell MK, et al; Task Force on Standards for Nutrition Support: Adult Hospitalized Patients, and the American Society for Parenteral and Enteral Nutrition Board of Directors. Standards for nutrition support: adult hospitalized patients. Nutr Clin Pract 2010;25(4):403-14.
27. Wanden-Berghe C, Sanz-Valero J, García de Lorenzo A, Martín-Peña G, Cervera M, Luengo LM, et al; Grupo CDC-Nut SENPE. Efectos adversos de la nutrición parenteral en pacientes oncológicos; revisión sistemática. Nutr Hosp 2012;27(2):409-18.
28. Mirtillo JM. Visión general de la nutrición parenteral. En: Core Curriculum en Apoyo Nutriconal. Una aproximación basada en casos clínicos. Unidad 2. Gottschilich MM (eds). Madrid: Drug Farma SL (ed). 2008. pp. 107-19.
29. Preiser JC, Schneider SM. ESPEN disease-specific guideline framework. Clin Nutr 2011;30:549-52.
30. Amano K, Morita T, Baba M, Kawasaki M, Nakajima S, Uemura M, et al. Effect of nutritional support on terminally ill patients with cancer in a palliative care unit. Am J Hosp Palliat Care 2013;30:730-3.
31. Lundholm K, Daneryd P, Bosaeus I, Körner U, Lindholm E. Palliative nutritional intervention in addition to cyclooxygenase and erythropoietin treatment for patients with malignant disease: effects on survival, metabolism, and founction. Cancer 2004;100:1967-77.
32. Bozzetti F, Cozzaglio L, Biganzoli E, Chiavenna G, De Cicco M, Donati D, et al. Quality of life and length of survival in advanced cancer patients on home parenteral nutrition. Clin Nutr 2002;21:281-8.
33. Prevost V, Grach M-C. Nutritional support and quality of life in cancer patients undergoing palliative care. European Journal of Cancer Care 2012;21:581-90.
34. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al; Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr 2016;35(2):247-307.
35. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al; Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN. Corrigendum to "ESPEN guidelines on chronic intestinal failure in adults" [Clin Nutr 35 (2) (2016) 247-307]. Clin Nutr 2017;36(2):619.
36. Cuerda Compés MC, Gómez Enterría P, Laborda González L, Moreno Villares JM, Ordóñez González J, Pedrón Giner C, et al. Guía de Nutrición Parenteral Domiciliaria en el Sistema Nacional de Salud. Ministerio de Sanidad y Política Social. Madrid; 2009. Disponible en: https://www.msssi.gob.es/profesionales/prestacionesSanitarias/publicaciones/GuiaNPD.htm Último acceso 28 de mayo 2017.
37. Cuerda Compés MC. Complicaciones de la nutrición parenteral domiciliaria. Nutr Hosp Suplementos 2009;2(1):25-9.
38. Cuerda C, Bretón I, García Peris P. Complicaciones de la nutrición parenteral domiciliaria. Nutr Clin Med 2013;VII(1):1-10.
39. Steiger E. Consensus statements regarding optimal management of home parenteral nutrition (HPN) access. JPEN 2006;30:S94-5.
40. Centers for Disease Control and Prevention. Guidelines for the prevention of intravascular catheter-related infections. MMWR 2002;51(No. RR-10):1-29.
41. Staun M, Pironi L, Bozzetti F, Baxter J, Forbes A, Joly F, et al. ESPEN Guidelines on Parenteral Nutrition: Home Parenteral Nutrition (HPN) in adult patients. Clin Nutr 2009;28:467-79.
42. Howard L, Ashley C. Management of complications in patients receiving home parenteral nutrition. Gastroenterology 2003;124:1651-61.
43. ASPEN Board of Directors and the Standars for Specialized Nutrition Support Task Force. Standars for specialized nutrition support: home care patients. NCP 2005;20:579-90.
44. Kovacevich DS, Marsha EO. Consideration for home nutrition support. En: ASPEN Nutrition Support Practice Manual 2005. pp. 371-407.
45. Gomez Enterria P, Laborda Gonzalez L. preparación, métodos y pautas de administración de la nutrición parenteral domiciliaria. Seguimiento de los pacientes. Educación a pacientes y cuidadores. Nutr Hosp Suplementos 2009;2(1):18-24.
46. Alper DS, Haynes RB. EBHC pyramid 5.0 for accessing preappraised evidence and guinace. Evid Based Med 2016;21(4):123-5.
47. DiCenso A, Bayley L, Haynes B, Accessing preappraised evidence: fine-tuning the 5S model into a 6S model. ACP Journal Club 2009;151(3):2-3.

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ARÁN

Nutrición Hospitalaria

Artículo Especial

Declaración de Sant Joan d'Alacant en defensa del Acceso Abierto a las publicaciones científicas, del grupo de editores de revistas españolas sobre ciencias de la salud (GERECS)

Sant Joan d'Alacant declaration in defense of Open Access to scientific publications, by the group of editors of Spanish journals on health sciences (GERECS)

Noviembre de 2017

El concepto de Acceso Abierto (*Open Access*, OA) no solo tiene que ver con la accesibilidad al documento científico, sino también con los permisos de reutilización más o menos restrictivos en función de los derechos reservados para su distribución. A partir de esta idea, surgieron numerosas iniciativas, con o sin ánimo de lucro, con el fin de facilitar el acceso universal a través de internet a las publicaciones científicas.

Proyectos como *Scientific Electronic Library Online* (SciELO, 1998), *The Scholarly Publishing and Academic Resources Coalition* (SPARC, 1998), PubMed Central (PMC, 2000), *The Public Library of Science* (PLOS, 2000) o BioMed Central (BMC, 2001), fueron pioneros de una revolución que haría replantear las estrategias comerciales de la edición científica. Otros como Dialnet (2001), Red de Revistas Científicas de América Latina y el Caribe, España y Portugal (Redalyc, 2003) y el *Directory of Open Access Journals* (DOAJ, 2003), también extenderían el movimiento del acceso abierto y ayudaron al proceso de globalización del conocimiento en las comunidades científicas del ámbito iberoamericano.

Las primeras Declaraciones que sentaron las bases del futuro desarrollo del acceso abierto fueron: la *Budapest Open Access Initiative* (2002), *Berlin Declaration on Open Access to Knowledge in the Sciences and Humanities* (2003) y *Bethesda Statement on Open Access Publishing* (2003), esta última considerada como la declaración de principios para las ciencias de la salud.

Por otro lado, se han promovido manifiestos, impulsados generalmente en reuniones de editores de revistas científicas que proponían algunas recomendaciones para el correcto desarrollo del acceso abierto a la ciencia. En España se podría citar la Declaración de la Alhambra (2010), que aportó recomendaciones para las políticas y plan de acción para el desarrollo del acceso abierto en el sur de Europa. Más reciente y en el ámbito latinoamericano, se elaboró la Declaración de la reunión de Consorcios de Iberoamérica y el Caribe (2017), que entre sus recomendaciones discute la desviación del concepto de *Open Access* por la creciente aparición de revistas de pago por publicación con precios a veces abusivos (APC, *article processing charges*) con la etiqueta de *Open Access*.

La pasada conferencia de Ámsterdam, «*Open Science – From Vision to Action*» (2016) formuló dos importantes objetivos paneuropeos a alcanzar en el año 2020:

- Acceso abierto completo para todas las publicaciones científicas.
- Un nuevo enfoque orientado hacia la reutilización óptima de los datos de investigación.

Para alcanzar estos objetivos, se propuso la aplicación de nuevos sistemas de evaluación y recompensa de los trabajos científicos, y la generación de políticas de buenas prácticas.

En esta línea, los ministros de ciencia de las naciones de la Unión Europea acordaron, en la sesión celebrada el 27 de mayo de 2016, el documento *The transition towards an Open Science system - Council conclusions*, recomendando que las publicaciones resultantes de la investigación financiadas con fondos públicos estén disponibles de forma gratuita en el año 2020, para lo cual, cada país deberá implementar su propia política de publicación.

Este acuerdo subraya que el principio para la reutilización óptima de los datos de investigación debería ser «lo más abierto posible, tan cerrado como sea necesario» y hace hincapié en que las oportunidades para la reutilización óptima de los datos de investigación solo pueden realizarse si los datos son consistentes con los principios FAIR (*findable, accessible, interoperable and re-usable*) dentro de un entorno seguro y confiable.

Así, la *European Open Science Policy Platform*, en su tercera reunión de marzo de 2017, adoptaba las siguientes recomendaciones:

- Las comunidades interesadas, los Estados miembros y la Comisión Europea deberían evaluar e identificar conjuntamente cómo se debe alcanzar el mandato de *Open Access* para 2020.
- El progreso hacia un OA completo debe tener en cuenta la rapidez con la que cambia el sistema de publicación y cómo las comunicaciones académicas crecen en riqueza y variedad.
- No hay una solución única, aunque el objetivo final para todas las disciplinas pueda ser el mismo. Las cuestiones relacionadas con el cumplimiento, incluidos los incentivos y

Declaración de Sant Joan d'Alacant en defensa del Acceso Abierto a las publicaciones científicas, del grupo de editores de revistas españolas sobre ciencias de la salud (GERECS). Nutr Hosp 2018;35:234-236

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la observancia, deberían proponerse, aclararse y armonizarse de una manera que sea sensible a todas las disciplinas.
- Las opciones de las condiciones de pago por la publicación deben ser claras y de fácil localización en las condiciones establecidas por cada revista.
- A partir de 2020 la Comisión Europea debe avanzar hacia una definición más amplia de OA, que incorpore toda la gama de formatos y aplicaciones emergentes como resultado de la investigación científica.

Teniendo en cuenta todo lo anteriormente mencionado, conscientes de los futuros cambios que tendrán que asumir los editores de las revistas españolas sobre ciencias de la salud, estos proponen las siguientes *recomendaciones y peticiones:*

1. Adherirse a los criterios emanados de la reunión de marzo de 2017 de la *European Open Science Policy Platform*.
2. Alentar a nuestras instituciones a que respalden la Expresión de Interés OA2020 (https://oa2020.org/) y, en consecuencia, firmen sus principios.
3. Instar a las agencias de investigación a nivel nacional a poner en marcha políticas científicas que requieran a sus investigadores que depositen sus publicaciones en repositorios institucionales.
4. Teniendo en cuenta el compromiso social de las revistas en OA con la accesibilidad del conocimiento, incluyendo a la ciudadanía, se solicita el reconocimiento como mérito académico/profesional la publicación en revistas de acceso abierto que estén indizadas en plataformas comprometidas con la excelencia, como SciELO, Redalyc o DOAJ.

Asimismo, en línea con la Declaración de San Francisco de Evaluación de la Investigación (*San Francisco Declaration on Research Assesment*, DORA, 2012), los editores de revistas de ciencias de la salud consideran necesario apoyar la adopción de las siguientes prácticas:

1. Reducir el énfasis del índice de impacto, u otras métricas basadas en indicadores sobre la revista en que fue publicado, como una herramienta de promoción personal.
2. Promover nuevos indicadores relacionados con el contenido científico del artículo en lugar de métricas sobre la revista en que fue publicado.

En Sant Joan d'Alacant, a 25 de noviembre de 2017

Nota: "Este documento se publica simultáneamente en las revistas que han suscrito la Declaración de Sant Joan d'Alacant del Grupo de Editores de Revistas Españolas sobre Ciencias de la Salud (GERECS) el día 25 de noviembre de 2017".

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Nota Clínica

3-hydroxy-3-methylglutaryl-CoA lyase deficiency: a case report and literature review

Deficiencia de la 3-hidroxi-3-metilglutaril-CoA liasa: un caso clínico y revisión de la literatura

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Abstract

Introduction: 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency is an autosomal recessive disorder that usually presents in the neonatal period with vomiting, metabolic acidosis, hypoglycemia and absent ketonuria. Few cases are reported in the literature, and optimal dietary management and long term outcome are not fully understood.

Case report: We report a 2 year old girl with HMG-CoA-lyase deficiency who had limited fasting tolerance on a low protein diet, with several recurrent hospital admissions with severe hypoketotic hypoglycaemia and metabolic acidosis. We also review the dietary management and outcome of other reported cases in the literature.

Discussion: In order to define optimal dietary treatment, it is important to collect higher numbers of case studies with detailed dietary management, fasting times and outcome.

Key words:

3-hydroxy-3-methylglutaryl-CoA lyase deficiency. Leucine. Protein. Hypoglycemia. Metabolic acidosis.

Resumen

Introducción: la deficiencia de la 3-hidroxi-3-metilglutaril-CoA (HMG-CoA) liasa es un desorden autosómico recesivo que normalmente se presenta en la infancia con vómitos, acidosis metabólica, hipoglicemia y sin cetonuria. Se han publicado pocos casos en la literatura científica sobre el mejor tratamiento dietético para el adecuado desarrollo de los pacientes a largo plazo, por lo que esta deficiencia no es bien conocida.

Caso clínico: presentamos una niña de 2 años con deficiencia de la 3-hidroxi-3-metilglutaril-CoA (HMG-CoA) liasa. Recibiendo una dieta baja en proteína con una tolerancia de ayuno limitada con episodios recurrentes de admisión hospitalaria con hipoglicemia hipoketótica y acidosis metabólica. También hemos revisado el tratamiento dietético y el desarrollo de otros casos publicados en la literatura científica.

Discusión: es importante recoger más casos clínicos describiendo el tratamiento dietético seguido, el tiempo máximo de ayuno y el desarrollo de los pacientes con el objetivo de definir el mejor tratamiento.

Palabras clave:

Deficiencia de la 3-hidroxi-3-metilglutaril-CoA (HMG-CoA) liasa. Leucina. Proteína. Hipoglicemia. Acidosis metabólica.

Conflicts of interest: Anita MacDonald has received research funding and honoraria from Nutricia, Vitaflo, Biomarin and Lactalis International. She is a member of the following advisory boards: European Nutritionist Expert Panel (Biomarin), Sapropterin Advisory Board (Biomarin), ELEMENT (Danone-Nutricia), and Arla and Applied Pharma Research. Anne Daly has undertaken evaluation work for the nutritional companies - Vitaflo Ltd, Nutricia Ltd and Metax. Alex Pinto has received an educational grant from Cambrooke Therapeutics and grants from Vitaflo, Merck Serono and Biomarin to attend scientific meetings. Steve Kitchen received sponsorship from Sobi, Nutricia and Vitaflo to attend meetings. All the other authors do not declare any conflict of interest.

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INTRODUCTION

3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency (3-hydroxy-3-methylglutaric aciduria), an autosomal recessive disorder, is caused by several mutations in the HMG-CoA Lyase gene (1,2). It was first described in 1976 (3). It is associated with mitochondrial HMG-CoA lyase enzyme deficiency, which has an important role in the ketogenic pathway and is the last step in leucine catabolism (1,4-6) leading to inadequate ketone body synthesis (7) and accumulation of toxic metabolites (4) of leucine catabolism (Fig. 1). It occurs in 1 in 100,000 live neonates (1), although this may be an underestimate due to sudden infant death and misdiagnosis with Reye's syndrome. It is more common in Saudi Arabia, Portugal, Spain and Pakistan (1) with a high incidence of parental consanguineous marriage reported in documented cases (4,8-11). It is suggested that HMG-CoA-lyase deficiency should be added to newborn screening panels (12), although further studies are necessary to demonstrate its effectiveness.

Although there is considerable heterogeneity, patients usually present in the first year of life (7,8,13,14) with vomiting, hypotonia, metabolic acidosis, hypoketotic hypoglycaemia (7,15), and hepatomegaly, and it is usually triggered by illness or fasting. In acute episodes, hypothermia, lethargy, apnoea, coma and even death may ensue if untreated (7,14-17). Pancreatitis (15,18) and cardiomyopathy (1,14,19) are less common long term complications. There is increased excretion of the following urinary organic acids: 3-hydroxy-3-methylglutaric acid, 3-methyl-glutaric acid, 3-methyl-glutaconic acid and 3-hydroxy-isovaleric acid (6,14,20). Abnormal liver function tests, raised lactate and hyperammonaemia may occur. Most children have normal developmental progress with appropriate treatment (1,5,21), but recurrent metabolic decompensation may result in neurological deficit including stroke-like episodes (22). On treatment, urinary organic acids improve but still remain abnormal (23).

The primary aim of management is rigorous emergency management, with high carbohydrate intake during infection and avoidance of extended fasts (16-18), with dietary protein and possibly fat restriction. In early childhood, metabolic decompensation is rapid with acidosis a common feature requiring intravenous administration of glucose and sodium bicarbonate if acidosis is severe (4,7). There are few published case studies and optimal dietary management is not clearly established. Carnitine supplementation is prescribed if serum levels are low.

In this paper we present the dietary management of a 2 year old girl with HMG-CoA-lyase deficiency cared for by Royal Stoke Hospital and Birmingham Children's Hospital, UK. The parents gave consent for this case to be published. We also review the dietary management of published case reports of HMG-CoA-lyase deficiency. A comprehensive search was conducted up until December, 2016 using PubMed, ScienceDirect, Scopus and Google Scholar. Search terms were as follows: '3-hydroxy 3-methylglutaric aciduria', '3-hydroxy-3-methylglutaryl-CoA lyase deficiency', 'HMG-aciduria and diet', 'HMG-CoA lyase deficiency and diet'.

CASE REPORT

A female infant of Pakistani origin was born at 37 weeks gestation via normal delivery following a pregnancy complicated by maternal gestational diabetes, significant morning sickness and fatigue. Her birth weight was 2.8 kg and parents were distant cousins. At 4 months of age she had developed colic and intermittent vomiting commonly after feeding.

At 5 months of age, she was admitted to hospital with rapid breathing after a short history of vomiting. On admission she was hypotonic, pale and unresponsive and parents reported her urine has an unusual odour. She had severe non ketotic hypoglycaemia (glucose: < 0.6 mmol/L), very low blood ketones, and metabolic acidosis (pH 7.17; pCO_2: 4.63 kPa; HCO_3: 13.1 mmol/L), requiring intravenous infusion with glucose and *Trometamol* respectively. Her free fatty acids (FFA) were 2821 umol/L, 3-hydroxybutyrate < 50 umol/L (in normoglycaemia reference range is FFA, 600 umol/L and 3-hydroxybutyrate, < 300 umol/L), and FFA/3-hydroxybutyrate ratio > 50 (reference range < 2.0). Lactate was moderately elevated (3.1 mmol/L). She was ventilated and subsequently extubated the following day. She was hypothermic (35.4 °C) with a

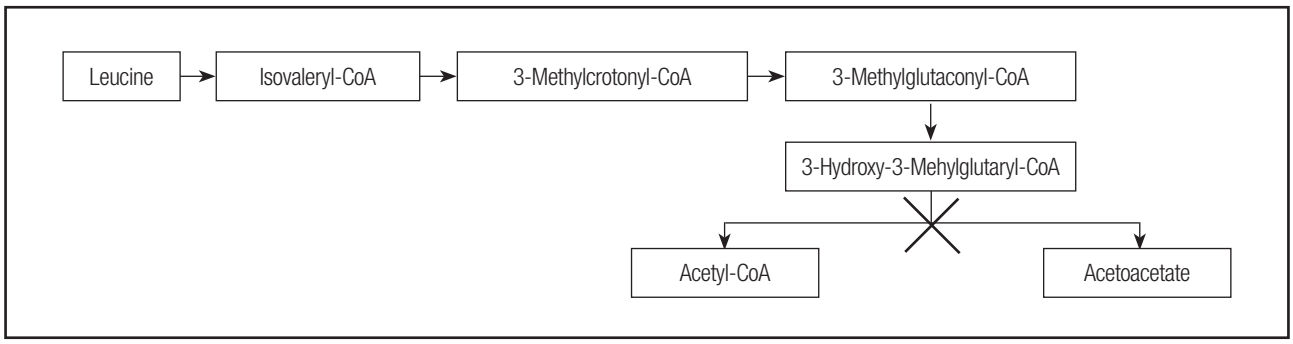

Figure 1.

The leucine catabolic pathway in patients with HMG-CoA lyase deficiency.

stable cardiovascular status. The hyperammonaemia (535 µmol/L) normalised with dextrose. She required a blood transfusion for anaemia (Hb, 55 g/L). Initially her INR level was 1.6, associated with a degree of liver dysfunction, and she was given vitamin K. Her weight was < 9th percentile. There were no clinical signs of infection and respiratory distress. Her metabolic investigations were consistent with HMG-CoA-lyase deficiency showing grossly increased urine 3-hydroxyisovalerate, 3-methylglutaconate, 3-hydroxy-3-methylglutarate (HMG) and methylcrotonylglycine. There was a marked dicarboxylic aciduria (particularly glutarate, adipate, octenedioate, suberate, sebacate, 3-hydroxysebacate and 5-hydroxyhexanoate. There was also grossly increased plasma hydroxy-C5 carnitine 1.31 umol/L (reference range ≤ 0.08). The plasma free carnitine was 13 umol/L (reference range 13 to 52 umol/L). DNA analysis was not performed.

She commenced continuous 24 hour nasogastric (NG) low protein feeds which consisted of a combination of standard infant formula and protein-free infant formula (*Energivit®*, Nutricia®) providing: protein, 1.5 g/kg/day; energy, 120 kcal/kg/day; and fat, 6.3 g/kg/day. Fat intake remained unrestricted. The percentage of energy provided by protein, fat and carbohydrate was 5%, 47% and 48% respectively. Her emergency feeding plan consisted of 10% glucose polymer with a maximum fasting time of 3 hours. Carnitine (100 mg/kg/day) supplements were prescribed. She was discharged home on a feeding plan of 3 to 4 hourly feeds but her oral feeding was poor and she struggled to achieve prescribed feed volumes. She began 'top up' bolus NG tube feeds at the age of 8 months to ensure a minimal feed target was met. Assessment of her fasting tolerance (Table I) at 10 months indicated a maximum safe fasting time of only 7 hours with free fatty acids elevated to 1327 µmol/L at 7 hours. Her blood ketone levels were < 50 µmol/l throughout the fast, which is consistent with a ketone synthesis defect.

By 11 months of age she had required 11 hospitalizations, presenting mainly with recurrent vomiting, metabolic acidosis and hyperammonaemia without obvious contributing factors, although she had commenced histamine H2 receptor antagonists (*ranitidine*) and *gaviscon*. In 3 of the admissions, she required intraosseous cannulation due to poor venous access in order to correct acidosis and hypoglycaemia. Some of the hypoglycaemic attacks were attributed to poor adherence with the feeding plan as there were a number of family social issues. At 11 months of age, due to the persistant metabolic instability and feeding difficulties, she commenced overnight continuous nasogastric tube feeds with two to three hourly feeds day-time feeds. She remains on 1.5 g/kg/day natural protein without leucine-free L-amino acid supplementation. Her enteral feeds were based on a standard infant formula (to meet natural protein requirements), supplemented with a protein-free infant formula and low protein solids. She had a percutaneous endoscopic gastrostomy (PEG) insertion at 13 months of age.

Since commencement of overnight feeding, she has had two further hospital admissions; one due to PEG insertion and one associated with gastroenteritis. She is 2 years old and her developmental progress is within normal limits. Her weight is between the 25-50th percentile and her length is on the 25th percentile.

DISCUSSION

This is a report of a young child with HMG-CoA lyase deficiency with limited fasting tolerance who developed severe and repeated hypoglycaemia without obvious contributing factors. At the age of 10 months, her metabolic response to a fasting time of 7 hours was associated with increased free fatty acids (suggesting increased fatty acid oxidation) despite normal blood glucose (Table I). This led to the introduction of overnight continuous tube feeding without further reported reoccurrence of unexplained hypoglycaemia following 13 months follow-up. Earlier reports (9,15,20,24,25) have described death and serious morbidity in acute crisis which underlines the need for prompt diagnosis and attentive treatment.

There is limited published evidence about the safe fasting times in HMG-CoA-lyase deficiency. It has been suggested that it may be reasonable to continue a night feed until the age of 1 year, but

Table I. Fasting tolerance test result for case study at the age of 10 months

	Plasma glucose µmol/L	Plasma lactate µmol/L	Free fatty acids µmol/L	3-hydroxybutyrate µmol/L
Baseline	5.6	2.2	323	< 50
1 hour	5.6	1.2	450	< 50
2 hours	5.0	2.1	596	< 50
3 hours	4.9	1.6	408	< 50
4 hours	4.9	2.5	675	< 50
5 hours	4.9	2.0	946	< 50
6 hours	4.8	6.0	N/A	N/A
7 hours	5.1	3.2	1,327	< 50
7.5 hours	N/A	N/A	N/A	N/A
8 hours	N/A	N/A	N/A	N/A

for older children overnight fasting (10 to 12 hours) is considered safe (26). However, a boy (24) with HMG-CoA-lyase deficiency who was diagnosed in the neonatal period and had been carefully treated with a low protein and fat restriction, died unexpectedly at 13 months of age in his sleep. His maximum nocturnal fasting time was 8 hours. Necropsy indicated no signs of infection. His death was attributed to fasting hypoketotic hypoglycaemia. François et al. (20) assessed the response to fasting in a 8 month old child with HMG-CoA lyase deficiency. When the first post fasting bood samples were analysed at 11 hours, high free fatty acid concentrations (approximately 1,000 µmol/L), with a blood glucose of 3 were observed. The authors suggested overnight feeding may be beneficial.

There is little evidence to support optimal dietary treatment and recommendations have varied for protein, leucine and fat restrictions (4,6,9,15,24,27). Commonly, dietary treatments are combined so the importance of each dietary component is not well established. More case reports have prescribed dietary protein restriction with less emphasis on the ketone body and fatty acid metabolism defect (Table II).

The severity of protein restriction is variable, with some advocating a moderate protein restriction only (6,26,28,29) and others recommending a leucine restriction as low as 50 mg/kg/day (30). Many case studies report a leucine intake of 50 to 150 mg/kg/day, i.e. equivalent to approximately 0.5 to 1.5 g/kg/day of natural protein (6,10,24,25,29,31-33). Leupold et al. (29) showed a 5-fold increase in urinary metabolites when natural protein increased from 1.8g to 2.5 g/kg/day (29). In one case study, a five-fold increase in 3-hydroxy-3 methylglutaric acid was observed following one meat meal (10). Dasouki et al. (1987) reported that urinary organic acids improved on a diet providing only 87 mg/kg/day of leucine and 2 g/kg/day total protein (presumably supplemented with leucine free amino acids but unreported) and 25% of energy as fat. In a child with HMG-CoA-lyase deficiency, a 750 mg (100 mg/kg/day) leucine load led to increase in leucine metabolites (6). Estimated safe leucine requirements for children and adults are 54 mg/kg/d and 40 mg/kg/d, respectively (34).

Leucine has an important role in protein synthesis (34) and any over restriction may potentially result in weight loss (35) and triglyceride lipolysis (36), subsequently leading to amino acid imbalance and metabolic decompensation. This is a potential risk if the glucose based emergency feeds are used excessively. The use of leucine-free L-amino acids is not well reported in HMG-CoA-lyase deficiency. They should only be necessary if WHO safe levels of protein intake are not met by natural protein restriction and only a few reports (10,29,31,37) describe their use. Shilkin et al. (10) reported one patient who refused the prescribed leucine free formula and so followed a self-restricted protein diet only.

Our case study, similar to other case reports (4,31) was not on a restricted fat intake but some fat restriction may have been beneficial. Defects in fatty acid catabolism may play an important role in metabolic decompensation. Some case reports limit fat intake to 20 to 30% of total energy intake (6,10,29). In one report, excretion of leucine metabolites increased significantly (3-hydroxy-3-methylglutaric acid, 3-methyl-glutaconic acid, 3-methyl-glutataric acid and 3-hydroxyisovaleric acid) when fat intake was increased from 15 g to 40 g/day in 2 children with HMG-CoA-lyase deficiency (6). Walter et al. (25) showed in a 9 month old infant, that progressive fat restriction (3.1 g/kg/day to 1.7 g/kg/day) lowered urinary excretion of 3-hydroxy-3-methylglutaric acid and 3-methyl-glutaconic acid despite a dietary leucine increase from 50 up to 150 mg/kg/d.

Uncooked cornstarch may have a role in the management of HMG-CoA lyase deficiency by helping extend fasting tolerance but there are only 2 case reports that describe its use. Gibson et al. (1990) reported a clinically stable 13 month old male who was given 1.5 g of uncooked cornstarch before sleeping, together with a low protein and modest fat restriction. In another case report (38), a 3 month old child with severe hypoglycaemia was prescribed a leucine restricted diet together with uncooked cornstarch (dose unavailable). She had a fasting tolerance of 18 hours at 12 months of age and dietary treatment stopped when she was 4 years old. The use of uncooked cornstarch warrants further investigation in this condition.

Patients with HMG-CoA lyase deficiency may develop hypoglycaemia and metabolic acidosis very quickly during fasting or intercurrent illness (20), leading to coma and sudden death (4,7,17,24). Thompson et al. (1990) showed in 6-year-old twins with HMG-CoA-lyase deficiency that protein mobilization and leucine oxidation play important roles during infection but not during fasting. During infection, leucine turnover, oxidation and plasma concentrations markedly increase leading to an elevation in urinary organic acids; but during fasting, fatty acid catabolism was considered to lead to a higher production of leucine metabolites. Although glucose polymer emergency feeds should be initiated on the first sign of illness, our case study commonly failed to tolerate these feeds, leading to a potential delay in starting intravenous glucose and bicarbonate to correct metabolic acidosis (7). There may be a role for commencing home NG tube feeding with emergency feeds on the first sign of illness to ensure adequate and continuous supply of glucose and fluid intake.

CONCLUSIONS

Overall there is limited clinical experience with the management of patients with HMG-CoA lyase deficiency and published case studies suggest a wide clinical heterogeneity. The optimal dietary treatment remains undefined and the rigorousness of therapy is likely to be influenced by the severity of each case. This case study exhibited limited nocturnal fasting tolerance and poor metabolic control when treated with a low protein diet only. Establishing disorder severity at an early stage of management is essential to optimise clinical outcome. Evaluating fasting tolerance immediately post diagnosis will help establish the requisite for night feeding in individual cases. With all rare disorders requiring dietary management it is important to monitor clinical progress, document dietary intake and biochemical markers carefully in order to systematically evaluate the role of nutritional intervention. It is necessary to collect higher numbers of case studies with detailed dietary management, fasting times and outcome in order to improve future treatment.

Table II. Characteristics of patients with HMG-CoA-lyase deficiency

					Diagnosis		Diet				
Patient	**Ref**	**Gender**	**Country of origin**	**Consanguinity**	**Age of diagnosis**	**Clinical symptoms**	**Dietary prescription**	**Leucine/Protein prescription**	**Amino acid formula**	**Fasting tolerance**	**Outcome**
Current case study		F	UK (Pakistani origin)	Yes	5 months	Coma, metabolic acidosis, non ketotic hypoglycemia, hyperammonaemia, hyper-lactatemia	Nocturnal nasogastric feeds	Low protein (1.5 g/kg/day)	No	≤ 7 hours	Age 2 years: normal growth and development
1	(15)	F	N/A	No	5 years	Acidosis, intractable vomiting, abdominal tenderness, acute pancreatitis	High CHO Low fat	Low leucine	No	-	6 yrs: growth, development, and school performance are normal
2	(24)	M	N/A	N/A	46 hours	Metabolic acidosis, hypoglycemia, hyperammonaemia, hyper- lactatemia and altered hepatic enzymes	Low fat (5 g/kg/day) High CHO (22 g/kg/day) High fluid (180 ml/kg/day)	Low protein (1.5-2 g/kg/day)	No	< 8 hours	13 months: died suddenly in his sleep without any sign
3[¥]	(4,27)	F	United Arab Emirates	Yes	3 days	Slow respirations, hypothermia, abdominal distention, palpable liver,metabolic acidosis. Elevated transaminases, ammonia, lactic acid pyruvic acid and LDH. Prothrombin time increased; fibrinogen decreased	Low fat (25% of total calories)	Low leucine (87 mg/kg/day) Moderate protein (2 g/kg/day)	No	-	15 months: normal growth and development
4	(4, 29)	F	Portugal	N/A	5 months	Head circumference > 90th percentile, mild metabolic acidosis and mild hypoglycemia	-	Low leucine (80-100 mg/kg/day) Low protein	Leucine free formula	-	3 years: severely delayed development, only walks with support

(Continue in the next page)

Table II (Cont.). Characteristics of patients with HMG-CoA-lyase deficiency

					Diagnosis		Diet				
Patient	**Ref**	**Gender**	**Country of origin**	**Consanguinity**	**Age of diagnosis**	**Clinical symptoms**	**Dietary prescription**	**Leucine/Protein prescription**	**Amino acid formula**	**Fasting tolerance**	**Outcome**
5	(37)	F	China		4 years	Status epilepticus, hypoglycemia, and severe metabolic acidosis	2100-2200 kcal/d Lipid (24%) CHO (63%)	Leucine (1,000 mg/day) Protein (1.5-2 g/kg/day)	Leucine free formula with maltodextrin	Avoidance of starvation	13 years: no episodes of metabolic decompensation or hypoglycemia during follow-up
6¥	(9)	F	Saudi Arabia	Yes	4 days	Severe lactic acidosis, hypoglycaemia and coma	Low fat (30%)	Low leucine (87 mg/kg/day)	No	-	3 yrs: normal developmental assessment, mild changes in MRI of brain
7¥	(9)	F	Saudi Arabia	Yes	40 days	Lethargy, mild spastic quadriparesis with exaggerated reflexes	Low fat (20%)	Low leucine (80 mg/kg/day)		-	3 years: normal developmental assessment
8¥	(9)	F	Saudi Arabia	Yes, one girl and 5 maternal aunts died neonatally with the same disease	24 hours	Devastating metabolic acidosis, hypoglycemia, lactate 20 mmol/l	Low fat (30%)	Low leucine (87 mg/kg/day)	Low Leucine Formula	-	9 months: developmental delay
9¥*	(9)	M	Saudi Arabia	Yes	2 months	Due to previously sibling death	Low fat (30%)	Low leucine (80 mg/kg/day)	No	-	21 months: normal developmental assessment
10	(4,10)	M	Australia	Yes	7 months	Diarrhea, vomiting, drowsiness, apnoea attacks, cyanosis, hypoglycemia, metabolic acidosis	High CHO	Low protein	Leucine free formula	-	4.6 years: well and developing satisfactorily
11*	(4,39)	M	Morocco		Prenatal	--	Breast milk + oral glucose	Leucine (50 mg/kg)	No	-	2.5 years: growing and psychomotor development normal
12	(4,11,25)	F	Pakistan	Yes	9 months	Respiratory infection, vomiting, metabolic acidosis	Fat (1.7 g/kg/day)	Leucine (150 mg/kg/day) Protein (1.2 g/kg)	No	-	6 yrs: died from illness and diarrheoa

(Continue in the next page)

Table II (Cont.). Characteristics of patients with HMG-CoA-lyase deficiency

					Diagnosis		Diet				
Patient	**Ref**	**Gender**	**Country of origin**	**Consanguinity**	**Age of diagnosis**	**Clinical symptoms**	**Dietary prescription**	**Leucine/Protein prescription**	**Amino acid formula**	**Fasting tolerance**	**Outcome**
13	(38)	F	Chile		3 months	Seizures, severe hypoglycaemia, metabolic acidosis, hepatomegaly and encephalopathy	CHO (74%) Fat (17%)	Protein (1 g/kg)	No	-	13 years: well nourished, static mild intellectual impairment, deafness and retinitis pigmentosa
14[++]	(4,6)	M	USA	No	8 months	Vomiting, lethargy, tachypnea	Low fat	Low protein	No	-	> 2 years: Developing normally
15[++]	(4,6)	F	USA	No	11 months	Vomiting, lethargy, tachypnea	Low fat	Low protein	No	-	> 2 years: Developing normally
16[+]	(4,31)	M	Pakistan	Yes	4 months	Poor head control, a divergent squint and roving eye movement	-	Natural protein (1 g/kg)	Leucine free formula	-	1.6 years: Developing normally, good health
17[+]	(4,31)	F	Pakistan	Yes	4 months	Diagnosed after diagnosis	-	Natural protein (1 g/kg)	Leucine free formula	-	1.6 years: Developing normally, good health
18	(4,33)	F	Chile	N/A	3 months	Vomiting, rapid onset of coma, profound hypoglycaemia, hepatomegaly	-	Leucine (120 mg/kg) Protein (2 g/kg)	No	-	1.5 years: Progressing well
19	(4,32)	M	USA	No	14 months	Lethargy, cold, vomiting, hypoglycemia	-	Low leucine	MSUD formula	-	2 years: Normal physical development, slightly delayed mental development

*[+]twins. *Siblings. [++]Double first cousins. [¥]Carnitine supplementation (100 mg/kg/day).*

REFERENCES

1. Pié J, Lopez-Vinas E, Puisac B, Menao S, Pié A, Casale C, et al. Molecular genetics of HMG-CoA lyase deficiency. Mol Genet Metab 2007;92(3):198-209.
2. Wysocki S, Hähnel R. 3-Hydroxy-3-methylglutaric aciduria: 3-hydroxy-3-methylglutaryl-coenzyme A lyase levels in leucocytes. Clin Chim Acta 1976;73(2):373-5.
3. Faull KF, Bolton PD, Halpern B, Hammond J, Danks DM. The urinary organic acid profile associated with 3-hydroxy-3-methylglutaric aciduria. Clin Chim Acta 1976;73(3):553-9.
4. Gibson KM, Breuer J, Nyhan WL. 3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency: review of 18 reported patients. Eur J Pediatr 1988;148(3):180-6.
5. Reimão S, Morgado C, Almeida I, Silva M, Real HC, Campos J. 3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency: Initial presentation in a young adult. J Inherit Metab Dis 2009;32(1):49-52.
6. Norman E, Denton M, Berry H. Gas-chromatographic/mass spectrometric detection of 3-hydroxy-3-methylglutaryl-CoA lyase deficiency in double first cousins. Clinical Chemistry 1982;28(1):137-40.
7. Puisac B, Pié A, Teresa E, Ramos FJ, Bueno G, Pie J, et al. HMG-CoA lyase deficiency: INTECH Open Access Publisher; 2011.
8. Yalçınkaya C, Dinçer A, Gündüz E, Fıçıcıoğlu C, Koçer N, Aydın A. MRI and MRS in HMG-CoA lyase deficiency. Pediatr Neurol 1999;20(5):375-80.
9. Ozand P, Al Aqeel A, Gascon G, Brismar J, Thomas E, Gleispach H. 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) lyase deficiency in Saudi Arabia. J Inherit Metab Dis 1991;14(2):174-88.
10. Shilkin R, Wilson G, Owles E. 3–HYDROXY-3-METHYLGLUTARYL COENZYME A LYASE DEFICIENCY. Acta Paediatr 1981;70(2):265-8.
11. Leonard J, Seakins J, Griffin N. β-hydroxy-β-methylglutaricaciduria presenting as Reye's syndrome. Lancet 1979;313(8117):680.
12. Cipriano LE, Rupar CA, Zaric GS. The cost-effectiveness of expanding newborn screening for up to 21 inherited metabolic disorders using tandem mass spectrometry: Results from a decision-analytic model. Value Health 2007;10(2):83-97.
13. Thompson G, Chalmers R, Halliday D. The contribution of protein catabolism to metabolic decompensation in 3-hydroxy-3-methylglutaric aciduria. Eur J Pediatr 1990;149(5):346-50.
14. da Rosa MS, Seminotti B, Ribeiro CAJ, Parmeggiani B, Grings M, Wajner M, et al. 3-Hydroxy-3-methylglutaric and 3-methylglutaric acids impair redox status and energy production and transfer in rat heart: relevance for the pathophysiology of cardiac dysfunction in 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency. Free Radic Res 2016;50(9):997-1010.
15. Wilson W, Cass M, Søvik O, Gibson K, Sweetman L. A child with acute pancreatitis and recurrent hypoglycemia due to 3-hydroxy-3-methylglutaryl-CoA lyase deficiency. Eur J Pediatr 1984;142(4):289-91.
16. Vaidyanathan K, Narayanan M, Vasudevan D. Organic acidurias: an updated review. Indian J Clin Biochem 2011;26(4):319-25.
17. Wysocki S, Hähnel R. 3-Hydroxy-3-methylglutaryl-coenzyme a lyase deficiency: a review. J Inherit Metab Dis 1986;9(3):225-33.
18. Leung AA, Chan AK, Ezekowitz JA, Leung AK. A case of dilated cardiomyopathy associated with 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG CoA) lyase deficiency. Case Rep Med 2009;2009.
19. Gibson K, Cassidy S, Seaver L, Wanders R, Kennaway N, Mitchell G, et al. Fatal cardiomyopathy associated with 3-hydroxy-3-methylglutaryl-CoA lyase deficiency. Journal of inherited metabolic disease. 1994;17(3):291-4.
20. Francois B, Bachmann C, Schutgens RB. Glucose metabolism in a child with 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency. J Inherit Metab Dis 1981;4(1):163-4.
21. Bakker H, Wanders R, Schutgens R, Abeling N, Gennip A. 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency: absence of clinical symptoms due to a self-imposed dietary fat and protein restriction. J Inherit Metab Dis 1993;16(6):1061-2.
22. Huemer M, Muehl A, Wandl-Vergesslich K, Strobl W, Wanders R, Stoeckler-Ipsiroglu S. Stroke-like encephalopathy in an infant with 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency. Eur J Pediatr 1998;157(9):743-6.
23. Bischof F, Nägele T, Wanders RJ, Trefz FK, Melms A. 3-hydroxy-3-methylglutaryl-CoA lyase deficiency in an adult with leukoencephalopathy. Ann Neurol 2004;56(5):727-30.
24. Ribes A, Briones P, Vilaseca M, Baraibar R, Gairi J. Sudden death in an infant with 3-hydroxy-3-methylglutaryl-CoA lyase deficiency. J Inherit Metab Dis 1990;13(5):752-3.
25. Walter J, Clayton P, Leonard J. 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency. J Inherit Metab Dis 1986;9(3):287-8.
26. Dixon M. Emergency regimens. Clinical paediatric dietetics. 3rd ed. Oxford: Blackwell. 2007 pp. 375-8.
27. Dasouki M, Buchanan D, Mercer N, Gibson K, Thoene J. 3-Hydroxy-3-methylglutaric aciduria: response to carnitine therapy and fat and leucine restriction. J Inherit Metab Dis 1987;10(2):142-6.
28. Zafeiriou DI, Vargiami E, Mayapetek E, Augoustidou-Savvopoulou P, Mitchell GA. 3-Hydroxy-3-methylglutaryl coenzyme a lyase deficiency with reversible white matter changes after treatment. Pediatric Neurology 2007;37(1):47-50.
29. Leupold D, Bojasch M, Jakobs C. 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency in an infant with macrocephaly and mild metabolic acidosis. Eur J Pediatr 1982;138(1):73-6.
30. Ketel A, Ket J, Schutgens RB, Duran M, Wadman S. Clinical and biochemical observations on a child with a deficiency of 3-hydroxy-3-methylglutaryl coenzyme A lyase. J Inherit Metab Dis 1980;3(1):89-90.
31. Stacey T, De Sousa C, Tracey B, Whitelaw A, Mistry J, Timbrell P, et al. Dizygotic twins with 3-hydroxy-3-methylglutaric aciduria; unusual presentation, family studies and dietary management. Eur J Pediatr 1985;144(2):177-81.
32. Gibson K, Breuer J, Kaiser K, Nyhan W, McCoy E, Ferreira P, et al. 3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency: report of five new patients. J Inherit Metab Dis 1988;11(1):76-87.
33. Hammond J, Wilcken B. 3-Hydroxy-3-methylglutaric, 3-methylglutaconic and 3-methylglutaric acids can be non-specific indicators of metabolic disease. Organic Acidurias: Springer; 1984. p. 117-8.
34. Joint W. Protein and amino acid requirements in human nutrition. World Health Organ Tech Rep Ser 2007(935):1.
35. Zhu X, Krasnow SM, Roth-Carter QR, Levasseur PR, Braun TP, Grossberg AJ, et al. Hypothalamic signaling in anorexia induced by indispensable amino acid deficiency. Am J Physiol Endocrinol Metab 2012;303(12):E1446-E58.
36. Cheng Y, Meng Q, Wang C, Li H, Huang Z, Chen S, et al. Leucine deprivation decreases fat mass by stimulation of lipolysis in white adipose tissue and upregulation of uncoupling protein 1 (UCP1) in brown adipose tissue. Diabetes 2010;59(1):17-25.
37. Tong L-X, Weng C-Y, Liu S-Y, Chu S-Y. Dietary therapy for a patient affected with 3-hydroxy-3-methylglutaric aciduria. Tzu Chi Medical Journal 2014;26(3):146-7.
38. Jones KJ, Wilcken B, Kilham H. The long-term evolution of a case of 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency associated with deafness and retinitis pigmentosa. J Inherit Metab Dis 1997;20(6):833-4.
39. Duran M, Schutgens RB, Ketel A, Heymans H, Berntssen MW, Ketting D, et al. 3-Hydroxy-3-methylglutaryl coenzyme A lyase deficiency: Postnatal management following prenatal diagnosis by analysis of maternal urine. J Pediatr 1979;95(6):1004-7.

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ARÁN

Nutrición Hospitalaria

Nota Clínica

Anorexia nerviosa como causa de fallo hepático agudo. A propósito de un caso

Anorexia nervosa as a cause of acute liver failure. Report of a case

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Palabras clave:

Anorexia nerviosa.
Fallo hepático.
Autofagia hepatica.
Malnutrición.
Nutrición enteral.

Resumen

Caso clínico: presentamos una paciente de 33 años con anorexia nerviosa de 15 años de evolución con uno de los pocos casos reportados de fallo hepático agudo severo secundario a la desnutrición.

Discursión: tras el soporte nutricional protocolizado para evitar el síndrome de realimentación y un adecuado manejo multidisciplinar, la paciente evoluciona favorablemente logrando normalizar los electrolitos, la función hepática y las alteraciones en la coagulación.

Key words:

Anorexia nervosa.
Hepatic failure.
Hepatic autophagy.
Malnutrition. Enteral nutrition.

Abstract

Case report: We present a 33 years old patient with anorexia nervosa of 15 years of evolution with one of the few reported cases of severe acute liver failure secondary to malnutrition.

Discurssion: After the protocolized nutritional support to avoid the refeeding syndrome and a multidisciplinary approach, the patient progresses favorably normalizing electrolytes, liver function and coagulation disorders.

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INTRODUCCIÓN

La anorexia nerviosa es un trastorno de la conducta alimentaria caracterizado por una pérdida de peso voluntaria, una distorsión de la imagen corporal y un temor intenso a la ganancia ponderal (1). Se asocia a múltiples complicaciones médicas, como problemas cardiovasculares, desórdenes endocrinos, electrolíticos, anormalidades hematopoyéticas, amenorrea y osteoporosis (1). La tasa de mortalidad ronda un 5%, siendo los suicidios y los problemas cardiovasculares derivados de la malnutrición las dos principales causas de muerte.

Se constata que un 40% de casos de anorexia nerviosa se complican con una afectación hepática (2). Sin embargo, el fallo hepático suele ser moderado y se restablece precozmente con la recuperación del estado nutricional (2,3).

Presentamos uno de los pocos casos reportados de fallo hepático agudo secundario a anorexia nerviosa con desnutrición grave.

CASO CLÍNICO

Se trata de una mujer de 33 años con historia de anorexia nerviosa (AN) tipo purgativo de 15 años de evolución. Inició la enfermedad a los 14 años con múltiples reingresos que han precisado estancia en UCI en varias ocasiones. Como tratamiento habitual destaca lorazepam, escitalopram, levetiracetam, calcio, vitamina D, potasio, omeprazol y trazodona.

La paciente ingresa desde el Servicio de Urgencias por caquexia extrema e hipoglucemia. Al ingreso destaca una ictericia conjuntival, bradipsiquia y bradilalia. *Exploración física:* TA 99/75 mmHg, SatO2 (FiO_2 21%) 95%, temperatura 36,7 °C; ACP: rítmica sin soplos, murmullo vesicular conservado sin ruidos sobreañadidos; abdomen: blando y depresible, no doloroso, sin signos de peritonismo, no se palpan masas ni megalias, no signos de ascitis; miembros inferiores: no edemas ni signos de trombosis venosa profunda. Respecto a los datos antropométricos objetivamos: circunferencia braquial 13,4 cm (percentil < 1), talón-rodilla 49,8 cm, circunferencia de la pantorrilla 19,8 cm, pliegue tricipital 1,8 mm (percentil < 1), pliegue escapular 2,6 mm, peso 26,8 kg (27,7 kg hace 2 semanas referido), talla 160 cm e índice de masa corporal: 10.

Se cursa ingreso involuntario por parte de psiquiatría dada la negativa inicial de la paciente para el inicio de medidas terapéuticas.

En la analítica inicial presenta GPT 1421 U/L y bilirrubina total 6,4 mg/dL, además de importantes alteraciones en la coagulación (Índice de Quick 32%, tiempo de protrombina 27,3 segundos) y síntomas de encefalopatía. Durante las siguientes 48 horas se produce un empeoramiento de función hepática hasta alcanzar valores de bilirrubina total 7,13 mg/dL, GPT 2012 U/L, objetivándose a su vez alteraciones iónicas (hiponatremia, hipopotasemia, hipomagnesemia e hipofosfatemia).

Se descartan mediante pruebas analíticas y de imagen (ecografía abdominal) y valoración por Medicina Digestiva otras causas de hepatopatía, objetivándose resultados negativos para tóxicos en orina, autoanticuerpos (ac. mitocondriales, ac. músculo liso, ac. LKM, ac. células parietales, ac. anticitoplasma de neutrófilo) y serologías víricas (VHA, VHB, VHC, VIH, VHS I y II, Epstein Barr).

Con el fin de evitar el síndrome de realimentación, y dada la necesidad de controlar el volumen calórico y de macro/micronutrientes, se inicia nutrición enteral por sonda nasogástrica junto con dieta oral absoluta al segundo día de ingreso comenzando con nutrición enteral (fórmula normocalórica normoproteica con fibra) a 336 Kcal al día (21 ml/h, 13 Kcal/kg) aumentando progresivamente (4º día a 43 ml/h, 26 Kcal/kg; 5º día a 50 ml/h, 30 Kcal/kg; 7º día a 55 ml/h, 33 Kcal/kg; 10º día a 65 ml/h, 39 Kcal/kg; 12º día a 90 ml/h, 54 Kcal/kg) hasta alcanzar 1440 Kcal. Se reinicia nutrición oral (yogurt y pieza de fruta) junto con sonda el día 11 de ingreso sin complicaciones. Los desórdenes electrolíticos se resolvieron con suplementos orales y administración intravenosa.

La paciente mejora progresivamente los parámetros hepáticos hasta conseguir, el día 14, corregir la función hepática (Figs. 1 y 2), los trastornos electrolíticos y las alteraciones en la coagulación (Tabla I) con un peso al alta de 27,7 kg (+ 0,9 kg respecto al ingreso).

Durante todo el ingreso los servicios de psiquiatría y medicina digestiva evalúan diariamente a la paciente. Dada la estabilización y la buena evolución clínica, se contacta con el Institut de Transtorns Alimentaris "ITA", y se decide el día 21 de ingreso traslado a su centro para seguimiento.

DISCUSIÓN

Hasta en un 60% de las pacientes con anorexia nerviosa se presenta elevación de las enzimas hepáticas previa a la realimentación (5). Los marcadores de daño hepático por encima de las 200 U/L son menos comunes y mucho más infrecuente es encontrar en estos casos un fallo hepático severo (4).

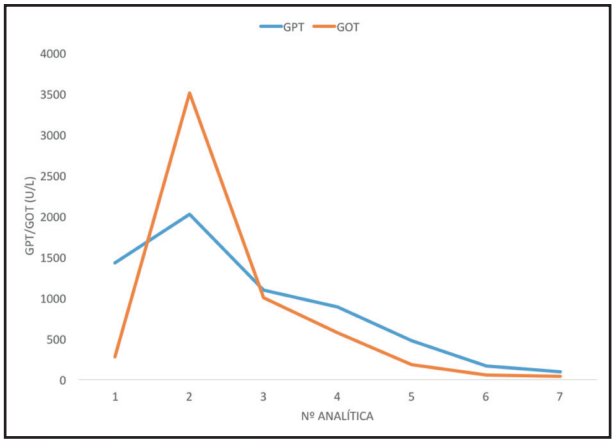

Figura 1.

Evolución de la función hepática GPT/GOT.

Tabla I. Evolución de los trastornos electrolíticos y alteraciones de la coagulación

	Analítica nº 1	Analítica nº 2	Analítica nº 3	Analítica nº 4	Analítica nº 5	Analítica nº 6	Analítica nº 7	Analítica nº 8
Índice de Quick (%)	32	50	58	76	80	100	83	--
Tiempo de protrombina (seg)	27,3	19,9	16,7	13,8	13,3	11,1	13	--
Potasio	3,7	4,2	3,6	4,3	4,7	4,4	4,5	4,9
Magnesio	1,8	2	2,6	1,8	1,9	1,7	1,7	2
Fósforo	1,9	4,1	0,5	2,2	3,5	3,3	3,9	4,8
Sodio	131	127	129	132	135	133	135	131

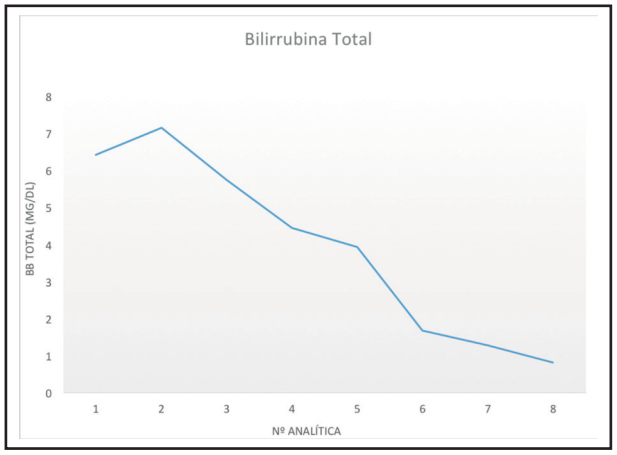

Figura 2.

Evolución de la función hepática.

Aunque el mecanismo de daño hepático en la anorexia nerviosa es desconocido, la elevación de los niveles de transaminasas así como la afectación de la función hepática se han relacionado con la presencia de una deshidratación global secundaria a hipovolemia e hipotensión, así como con la hipoxemia secundaria a la hipoperfusión (3), un incremento del estrés oxidativo y un exceso de depósito de grasa (5).

Ratou y cols. describen las biopsias de 12 pacientes con anorexia nerviosa y fallo hepático. Los hepatocitos de 4 pacientes mostraron numerosos autofagolisosomas, un sello morfológico de la autofagia en microscopía electrónica. Por el contrario, las mitocondrias, el retículo endoplásmico y los núcleos eran normales en la mayoría de las células. Según estos autores, la anorexia nerviosa con un estado nutricional extremadamente pobre debe agregarse a la lista de afecciones que causan insuficiencia hepática aguda. Sus hallazgos demuestran que la autofagia inducida por el hambre en el hígado humano puede estar involucrada en la muerte de células hepáticas durante la anorexia nerviosa, a pesar de que otros mecanismos de daño de las células hepáticas también podrían estar implicados (6).

La autofagia hepática es, por tanto, una complicación muy poco frecuente que se puede producir en casos extremos de anorexia (5).

Gracias a los casos reportados y a la negatividad del resto de etiologías más frecuentes de fallo hepático agudo pudimos evitar la realización de la biopsia a nuestra paciente y lograr la resolución del cuadro centrándonos en su enfermedad de base.

Dada la complejidad de estos pacientes es necesario un equipo multidisciplinar, siendo primordial garantizar una mejora en su estado nutricional y de salud, evitar complicaciones potencialmente mortales como es el síndrome de realimentación, y asegurar una normalización en la función hepática.

BIBLIOGRAFÍA

1. Chanhyok S-C , Nobuaki I, Manabu T, Megumi M, Akira T, Yasuhiro T. Hypoglycemic coma in a patient with anorexia nervosa coincident with acute exacerbation of liver injury induced by oral intake of nutrients. Inter Med 2010;49:1553-6.
2. Furuta S, Ozawa Y, Maejima K, Kitahora T, Hasegawa K, Kuroda S, et al. Anorexia nervosa with severe liver dysfunction and subsequent critical complications. Intern Med 1999;38:575-9.
3. Bridet L, Martin JJ, Nuno JL. Acute liver damage and anorexia nervosa: a case report. Turk J Gastroenterol 2014;25:205-8.
4. Kheloufi M, Boulanger CM, Durand F, Rautou PE. Liver autophagy in anorexia nervosa and acute liver injury. Biomed Res Int 2014;2014:701064. DOI: 10.1155/2014/701064.
5. Pelegrina Cortés B, Guillén Sacoto MA, Palma Milla S, Lisbona Catalán A, Martín Fuentes M, Gómez-Candela C. About a very extreme malnutrition case in a female patient with long-term non-treated restrictive anorexia nervosa. Nutr Hosp 2014;30(3):690-4.
6. Rautou PE, Cazals-Hatem D, Moreau R, Francoz C, Feldmann G, Lebrec D, et al. Acute liver cell damage in patients with anorexia nervosa: a possible role starvation-induced hepatocyte autophagy. Gastroenterology 2008;135:840-8.

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Crítica de Libros

TRATADO DE NUTRICIÓN

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Desde que en el año 2005 el profesor Ángel Gil publicó la primera edición del Tratado de Nutrición, este texto ha pasado a ser la obra capital escrita en lengua española sobre la ciencia de la Nutrición en su más amplio sentido. Su inmediato éxito científico, junto con la inquietud del profesor Gil, hizo que en el 2010 se publicara la 2ª edición que, al igual que la primera, tuvo una enorme difusión entre los profesionales de la salud especialmente interesados en la Nutrición, tanto en la universidad donde es un texto de consulta obligada entre profesores y estudiantes de los grados de Nutrición y Dietética, Medicina, Farmacia, Bioquímica y Biología Molecular, Ciencia y Tecnología de los Alimentos, etc. como en los profesionales de la Medicina, ya que se abordan todos los aspectos clínicos relacionados con la nutrición y para todas las edades.

En el año 2017 se publica la 3ª edición con los mismos objetivos que las dos anteriores y aumentando su calidad científica, puesto que en esta ocasión consta de 5 tomos, con 14 coordinadores y más de 350 autores.

El Tomo I está destinado a los conocimientos de los procesos de digestión, absorción, y destino metabólico de los macro y micronutrientes, así como las funciones de cada uno de ellos. El Tomo II, de nueva creación, aborda los conocimientos de lo que actualmente se denomina "Nutrición molecular y genómica nutricional", e incluye capítulos sobre Nutrigenética, Nutriepigenética, Nutriproteómica, y Nutrimetabololómica. En el Tomo III se estudia la composición y el valor nutritivo de los grupos de alimentos clásicos, así como de los nuevos compuestos bioactivos y los alimentos funcionales; también se aborda el conocimiento actual sobre los alimentos transgénicos, y los aspectos relacionados con la higiene y seguridad alimentaria. En el Tomo IV se han actualizado los conocimientos sobre las ingestas dietéticas de referencia y las guías dietéticas basadas en los índices de calidad de la dieta; se estudian asimismo las estrategias nutricionales de intervención en salud pública, la educación nutricional, la importancia de los primeros mil días de vida en la salud del adulto, el proceso de comunicación en nutrición y salud, y la relación entre gastronomía, cocina y alimentación. El Tomo V, dedicado al estudio de la nutrición y enfermedad, ha incorporado las guías actuales de las sociedades Europea y Americana de Nutrición Enteral y Parenteral (ESPEN y ASPEN), Americana de Cuidados Críticos, así como de las guías existentes en España tanto de adultos como pediátricas.

La posibilidad de acceso a través de su versión electrónica en un sitio web específico permite la visualización de su contenido, especialmente útil en lo referente a imágenes, muchas de ellas animadas. Ello hace que sea texto enormemente didáctico.

La edición de Editorial Panamericana es excelente, tanto en el texto como en la calidad de las tablas y figuras, lo cual facilita enormemente su lectura.

Por todo ello, solo cabe felicitar al profesor Gil y a los coordinadores por este libro altamente recomendable para todos los profesionales relacionados con la Nutrición: investigadores de base, investigadores clínicos, médicos, docentes universitarios, etc.

Jaime Dalmau

Director-Editor de *Acta Pediátrica Española*

José Manuel Moreno

Director-Editor de *Nutrición Hospitalaria*