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Nutrición Hospitalaria

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Running por tu esperma; beneficios del ejercicio físico en la calidad seminal

Running for your sperm; benefits of physical exercise on seminal quality

editorial

La inactividad física y el aporte calórico excesivo son los determinantes principales de la obesidad, el problema de salud pública más importante en los países desarrollados y en vías de desarrollo, afectando a prácticamente todas las edades y grupos socioeconómicos y acarreando graves consecuencias sanitarias, sociales y económicas (1).

En el varón, una de las comorbilidades más frecuentemente asociadas a la obesidad es el hipogonadismo, síndrome clínico que resulta de la incapacidad para producir concentraciones fisiológicas de testosterona, cantidades normales de esperma, o ambos (2).

Hasta el 50% de los varones obesos presentan niveles reducidos de testosterona sérica, incrementándose dicha prevalencia al 70-80% en la obesidad mórbida. La obesidad, asimismo, ejerce un profundo efecto negativo sobre la fertilidad masculina, asociándose a reducciones en la concentración espermática, en el volumen eyaculado y en la movilidad de los espermatozoides (3).

La pérdida de peso es la piedra angular en el tratamiento del hipogonadismo asociado a obesidad, con resultados francamente positivos en la restauración hormonal (fundamentalmente con cirugía bariátrica), pero los resultados en cuanto a parámetros seminales y fertilidad son contradictorios (4).

Diversos estudios, sin embargo, muestran que el ejercicio físico puede ser una efectiva medida terapéutica para mejorar la calidad seminal en la obesidad (5).

El trabajo de Rosety y cols. (6) en este número de la revista aporta evidencias adicionales al respecto. En este estudio, se aleatorizó a 90 varones obesos sedentarios jóvenes a ejercicio físico aeróbico moderado (correr en un tapiz rodante) o a un grupo control sin ejercicio físico. En el grupo de intervención se produjo un incremento discreto en los niveles de testosterona, pero lo más llamativo fue que mejoró la calidad seminal, con un aumento significativo en la concentración, motilidad y morfología de los espermatozoides.

Estos hallazgos coinciden con los de dos recientes ensayos clínicos aleatorizados. En el primero de ellos, el ejercicio físico (continuo de intensidad moderada, continuo de alta intensidad o interválico de alta intensidad) mejoró parámetros de calidad seminal, estrés oxidativo e inflamación y mejoró la integridad del ADN espermático (7). En el segundo, el ejercicio físico aeróbico moderado atenuó los marcadores seminales de inflamación y estrés oxidativo, y aumentó el sistema de defensa antioxidante. Asimismo, produjo una mejoría significativa en los parámetros seminales, la integridad de ADN seminal y, lo que es más importante, aumentó las tasas de embarazo (8).

Subrayemos, sin embargo, que no todo ejercicio físico parece ser beneficioso para la calidad espermática. Solamente el ejercicio físico de intensidad moderada se ha correlacionado con mejoras en los parámetros seminales, mientras que el ejercicio físico intenso (≈80% del VO_2 máximo) ha demostrado tener efectos deletéreos sobre calidad seminal. Una peor calidad seminal se ha encontrado en deportistas de élite sometidos a un programa de actividad física extremo y a elevados niveles de estrés. Asimismo, la realización de ciertas actividades deportivas donde hay un aumento significativo en la temperatura escrotal (ciclismo, equitación, deportes de motor) o donde se utilizan ropas ajustadas a nivel testicular, se ha relacionado con parámetros seminales más deteriorados (9).

Estudios futuros deberán evaluar el tipo y la intensidad del ejercicio físico más adecuado para mejorar la calidad seminal, qué pacientes se benefician en mayor grado y cómo de duradero es el efecto. Igualmente,

editorial

dichos estudios deberían centrarse en resultados finales robustos, como tasas de embarazo, en sustitución de marcadores subrogados seminales.

Mientras tanto, en consonancia con la mayoría de las guías publicadas, se debería recomendar al paciente obeso la realización de una actividad aeróbica de intensidad moderada de al menos 30 minutos de duración durante al menos 5 días a la semana (un total de 150 minutos semanales), lo cual ha demostrado reducir la incidencia de diabetes mellitus tipo 2, hipertensión arterial y dislipemia, y además previene la aparición de enfermedad cardiovascular (10).

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Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

Factores predictores de hipertrigliceridemia en pacientes hospitalizados con nutrición parenteral total

Predictive factors of hypertriglyceridemia in inhospital patients during total parenteral nutrition

María Julia Ocón Bretón[1], Ana Isabel Ilundain González[1], Jara Altemir Trallero[2], Ana Agudo Tabuenca[1] y José Antonio Gimeno Orna[1]

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Resumen

Introducción: la nutrición parenteral total (NPT) es una modalidad de soporte nutricional indicada en aquellas situaciones donde el enfermo no puede cubrir sus requerimientos nutricionales por vía enteral. A pesar de ser una terapia segura y eficaz, no está exenta de complicaciones, entre las que cabe destacar, por su frecuencia, la hipertrigliceridemia. La etiología de esta complicación metabólica es compleja y multifactorial.

Objetivos: el objetivo de este trabajo fue determinar los factores de riesgo asociados al desarrollo de hipertrigliceridemia en pacientes adultos hospitalizados no críticos que reciben NPT a corto plazo y evaluar el efecto que una emulsión lipídica enriquecida en ácidos grasos poliinsaturados omega-3 ejerce sobre esta complicación metabólica.

Material y métodos: estudio observacional retrospectivo de cohortes donde se ha incluido a pacientes hospitalizados adultos no críticos que precisaron NPT durante un periodo superior a siete días. Se consideró la presencia de hipertrigliceridemia cuando los niveles plasmáticos de triglicéridos fueron superiores a 200 mg/dl. Las emulsiones lipídicas empleadas fueron una mezcla al 50% de triglicéridos de cadena larga (LCT) y de cadena media (MCT) o una combinación al 40% LCT/50% MCT/10% omega-3. Se recogieron variables clínicas, nutricionales y bioquímicas. Las determinaciones analíticas se realizaron antes del comienzo de la NPT y semanalmente hasta su retirada. Los factores predictores de la aparición de hipertrigliceridemia fueron identificados mediante modelos de regresión logística multivariante.

Resultados: fueron incluidos 101 pacientes (61,4% varones), de los cuales el 33% desarrolló hipertrigliceridemia. En el análisis multivariante los factores de riesgo independientes asociados a la presencia de hipertrigliceridemia fueron los niveles plasmáticos iniciales de triglicéridos, el índice de masa corporal (IMC) y un aporte de glucosa en la NPT superior a 3,1 g/kg/día. La infusión de una emulsión lipídica enriquecida con ácidos grasos omega-3 se asoció con un descenso no significativo del riesgo de aparición de hipertrigliceridemia.

Conclusión: la situación clínica metabólica del paciente y la dosis de hidratos de carbono en la NPT resultan fundamentales en el desarrollo de la hipertrigliceridemia relacionada con la NPT. La administración de una emulsión lipídica enriquecida en ácidos grasos omega-3 es segura, aunque no se asoció a un efecto protector significativo sobre el riesgo de aparición de esta complicación metabólica.

Palabras clave:

Hipertrigliceridemia. Nutrición parental total. Ácidos grasos omega-3. Emulsión lipídica. Índice de masa corporal.

Abstract

Introduction: Total parenteral nutrition (TPN) is a kind of nutritional support indicated for patients whose clinical situation makes it impossible to cover their nutritional requirements enterally. Despite the fact that TPN is a safe and effective therapy, some complications have been described. One of the most frequent is hypertriglyceridemia. The etiology of this metabolic complication is complex and multifactorial.

Objetive: The aim of this work was to determine risk factors associated with the development of hypertrilgyceridemia in adult inhospital non critical patients who carry TPN for a short term. A secondary aim was to evaluate the effect that a lipid emulsion fortified with omega-3 poliunsaturated fatty acids causes on this metabolic complication.

Material and methods: This is an observational retrospective cohort study, in which adult inhospital non critical patients have been included. Only those who needed TPN during more than seven days were included. Hypertriglyceridemia was defined as plasma triglycerides levels higher than 200 mg/dl. The lipid emulsions were composed whether by a combination of 50% long-chain (LCT) and medium-chain (MCT) triglycerides or 40% LCT/50% MCT/10% omega-3. Clinical, nutritonal and biochemical parameters were included. Analitical samples were obtained before starting TPN, and weekly until withdrawal. Multivariate logistic regression analysis was used to identify predictive factors of the appearance of hypertriglyceridemia.

Results: One hundred and one patients were included (61.4% male). Thirty-three per cent of them developed hypertriglyceridemia. In the multivariate analysis the independent risk factors associated with the presence of hypertriglyceridemia were the initial plasmatic triglycerides levels, the body mass index (BMI) and an input of glucose in the TPN higher than 3.1 g/kg/day. The infusion of a lipid emulsion fortified with 3-omega fatty acids was associated with a nonsignificant reduction of the risk of appearance of hypertriglyceridemia.

Conclusion: The patient's clinical metabolic situation, as well as the load of carbohydrates in the TPN are essential for the development of the TPN-associated hypertriglyceridemia. The administration of a lipid emulsion fortified with omega-3 fatty acids is safe, even though it was not associated with a significant protective effect over the risk of appearance of this metabolic complication.

Key words:

Hypertriglyceridemia. Total parenteral nutrition. 3-omega fatty acids. Lipid emulsion. Body mass index.

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INTRODUCCIÓN

La nutrición parenteral total (NPT) es una terapia nutricional que permite mantener el estado nutricional en aquellos pacientes que no pueden cubrir sus requerimientos nutricionales por vía oral/enteral al no poder utilizar con total seguridad el tracto gastrointestinal (1). Este tipo de soporte nutricional puede asociarse con el desarrollo de complicaciones metabólicas debidas principalmente a las características y a la cantidad de nutrientes administrados y/o al tipo de paciente candidato a recibir este tratamiento nutricional (2). Habitualmente, los pacientes con indicación de NPT suelen presentar un proceso inflamatorio agudo que genera un estado catabólico en el cual queda comprometido el metabolismo proteico, lipídico y de los hidratos de carbono (3).

La hipertrigliceridemia es una frecuente complicación metabólica relacionada con la administración de la NPT cuya incidencia se encuentra entre el 6% y el 60% de los casos (4,5). Aunque no existe un consenso universal para definir esta situación metabólica, la mayor parte de los autores consideran la existencia de hipertrigliceridemia asociada a la NPT cuando los valores plasmáticos de triglicéridos son superiores a 200 mg/dl (4,6,7).

A pesar de que en la actualidad no ha sido establecida cuál es la relevancia clínica de la hipertrigliceridemia, existe una evidencia creciente que demuestra que esta complicación metabólica puede asociarse con un aumento de la morbilidad por complicaciones infecciosas y prolongar la estancia hospitalaria (6).

La etiología de la hipertrigliceridemia es compleja y multifactorial y estaría relacionada con una alteración del aclaramiento plasmático de los lípidos, bien por un aporte excesivo de grasa o glucosa en la NPT o bien por una disminución de la actividad de la lipoproteinlipasa (LPL) (8). Se han descrito diferentes factores de riesgo asociados con el desarrollo de hipertrigliceridemia entre los que cabe destacar la sepsis, la insuficiencia renal, la pancreatitis, la hiperglucemia, la obesidad y la administración de ciertos fármacos como el propofol, la heparina y los corticoides (9-11).

La composición de los ácidos grasos presentes en la emulsión lipídica también podría influir en la etiopatogenia de la hipertrigliceridemia. Se ha observado que las emulsiones lipídicas que contienen ácidos grasos poliinsaturados (PUFA) omega-3 poseen un aclaramiento plasmático lipídico más rápido que el aceite de soja, de oliva o la mezcla LCT/MCT (12). Algunos autores han documentado que la sustitución o la adición de aceite de pescado rico en PUFA omega-3 en la emulsión lipídica puede asociarse con una reducción de los niveles plasmáticos de triglicéridos fundamentalmente en niños que reciben NPT a largo plazo (13-15). Se han encontrado resultados contradictorios con respecto a la implicación de estas emulsiones lipídicas enriquecidas en aceite de pescado en el perfil lipídico de los pacientes adultos que reciben NPT a corto plazo (16-18).

El objetivo de nuestro trabajo fue determinar los factores predictores de hipertrigliceridemia en pacientes adultos hospitalizados no críticos que reciben NPT a corto plazo y evaluar el efecto que ejerce una emulsión lipídica enriquecida con ácidos grasos omega-3 en la hipertrigliceridemia asociada a la NPT.

MATERIAL Y MÉTODOS

DISEÑO DEL ESTUDIO

Se realizó un estudio observacional de cohortes retrospectivo en el cual fueron analizados pacientes ingresados en un hospital de tercer nivel que recibieron NPT durante el periodo de junio de 2012 hasta febrero de 2014. Se incluyó a pacientes mayores de 18 años con incapacidad para cubrir sus requerimientos nutricionales por vía oral y/o enteral y que precisaron NPT durante al menos una semana. Se consideraron criterios de exclusión los pacientes críticos hospitalizados en la Unidad de Cuidados Intensivos, el embarazo y la administración concomitante de nutrición enteral.

SOPORTE NUTRICIONAL

La NPT estaba compuesta por una mezcla ternaria de macronutrientes junto con vitaminas, minerales y oligoelementos. El único fármaco que se aditivó a la bolsa fue la insulina. La NPT se infundió a través de un catéter venoso central a un ritmo constante, controlado mediante una bomba de perfusión, durante 24 horas.

El aporte calórico suministrado fue de 25-30 kcal/kg/día con unos requerimientos proteicos de 1,1-1,5 proteínas/kg y una ratio hidratos de carbono/grasas desde 70/30 hasta 60/40. La NPT fue prescrita de forma individualizada para cada paciente y su composición se modificó de acuerdo a la situación clínica y a los parámetros de laboratorio.

Las bolsas de NPT fueron elaboradas y suministradas por el servicio Nutriservice® del laboratorio B. Braun y en la campana de flujo laminar del Servicio de Farmacia del hospital se aditivaron diariamente las vitaminas y los oligoelementos.

Todos los pacientes recibieron los mismos productos usados en su elaboración: glucosa a diferentes concentraciones, una solución de aminoácidos de estrés (Aminoplasmal PO), vitaminas (Cernevit; Baxter Clintec, Maurepas, France) y oligoelementos (Addamel; Fresenius Kabi, Halden, Noruega). Las emulsiones lipídicas infundidas fueron una mezcla al 50% de LCT y MCT (Lipofundina LCT/MCT 20%) o una mezcla basada en el 50% de MCT, 40% de LCT y 10% de aceite de pescado omega-3 (Lipoplus 20%). La composición de ambas emulsiones lipídicas se describe en la tabla I. La indicación del tipo de emulsión lipídica dependió de la duración prevista de la NPT y del grado de estrés metabólico. Se empleó la emulsión lipídica enriquecida en omega-3 en aquellos pacientes donde se preveía que la NPT iba a ser infundida durante un periodo prolongado de tiempo o cuando existía una mayor gravedad o severidad de la situación clínica.

VARIABLES CLÍNICAS

Se recogieron las variables edad, sexo, motivo de indicación de la NPT y consumo de fármacos y tóxicos (corticoides, heparina, ciclosporina, tacrolimus, alcohol y tabaco). Así mismo, se analizó

Tabla I. Composición de las emulsiones lipídicas empleadas en la NPT

Contenido por 1.000 ml de emulsión	Lipoplus 20%	Lipofundina MCT/LCT 20%
Aceite de soja (LCT)	80 g	100 g
Aceite de coco (MCT)	100 g	100 g
Aceite de pescado	20 g	0 g
Fosfolípidos	12 g	12 g
Glicerol	25 g	25 g
α-tocoferol	190 mg	190 mg
Fitosteroles	ND	278 mg
Relación ω_6/ω_3	2,7	7

la existencia de algunas enfermedades subyacentes: pancreatitis aguda, insuficiencia renal (filtrado glomerular < 60 ml/min), fístula enterocutánea de alto débito (pérdidas digestivas superiores a 500 ml/día), diabetes mellitus y obesidad (IMC > 30 kg/m^2).

Los pacientes fueron evaluados hasta ser dados de alta del hospital y se registraron la duración de la estancia hospitalaria, las complicaciones infecciosas (bacteriemia por catéter, infección del tracto urinario, neumonía e infección de la herida quirúrgica) y la mortalidad.

VARIABLES NUTRICIONALES

Se analizaron la talla, el peso actual y el peso habitual y se calculó el índice de masa corporal (IMC) con la formula peso/talla^2. Se realizó un cribado nutricional mediante el cuestionario *Nutritional Screenig Risk* (NRS-2002).

Como variables específicas relacionadas con los componentes de la NPT se evaluaron los gramos medios de los tres macronutrientes, así como el aporte calórico total. Estos valores medios se calcularon en relación al peso y se analizaron como gglucosa/kg/día, glípidos/kg/día, gn$_2$/kg/día y kcal/kg/día. También se evaluó el tipo de grasas infundidas (LCT/MCT o LCT/MCT/omega-3).

Se clasificó el aporte calórico de la bolsa de NPT como alto o bajo en kcal/kg (con un punto de corte en 27), alto o bajo en lípidos (con un punto de corte en 0,9 g/kg) y alto o bajo en HC (con un punto de corte en 3,1 g/kg). La duración de la infusión de la NPT se consideró prolongada cuando superó los once días. Se seleccionaron estos valores por aproximarse a las medianas de la distribución de la muestra de los pacientes incluidos en el estudio.

VARIABLES BIOQUÍMICAS

En todos los pacientes se realizó una extracción de una muestra de sangre venosa antes del inicio de la NPT y semanalmente hasta que la NPT fue retirada. Las muestras fueron recogidas a las 8:00 a.m., sin detener la NPT durante el periodo nocturno. Los principales parámetros bioquímicos plasmáticos determinados fueron: triglicéridos, colesterol total, LDL-colesterol (que se calculó mediante la fórmula de Friedwald cuando los triglicéridos fueron inferiores a 400 mg/dl [LDLc = colesterol total - triglicéridos/5 – HDLc]), HDL-colesterol, glucosa, HbA1c e insulina. Se calculó la resistencia insulínica mediante el índice HOMA *(Homeostasis Model Assessment)* = glucosa (mg/dl) x insulina (µU/ml)/405.

Otros parámetros analizados fueron el filtrado glomerular (según la formula MDRD4-IDMS), la urea, la creatinina, las enzimas hepáticas, el hemograma, el fibrinógeno y la ferritina. Como marcadores proteicos se determinaron la albúmina, la prealbúmina, la transferrina, las proteínas totales y la proteína C reactiva (PCR) ultrasensible.

VARIABLES DEPENDIENTES

Se consideró hipertrigliceridemia cuando los niveles plasmáticos de triglicéridos fueron superiores a 200 mg/dl al finalizar la infusión de NPT. Se definió incremento de triglicéridos (IT) según la siguiente formula: IT (%) = ([triglicéridos finales-triglicéridos iniciales]/triglicéridos iniciales) x 100.

ANÁLISIS ESTADÍSTICO

Las variables cuantitativas se describieron mediante media y desviación estándar (DE) y las cualitativas, con distribución de frecuencias. Se realizó una trasformación logarítmica de los triglicéridos dada su desviación manifiesta de la normalidad en su distribución. Se compararon las características de los pacientes mediante prueba no paramétrica de Mann-Whitney (cuantitativas) o Chi cuadrado (cualitativas). El análisis del cambio durante el seguimiento en las variables cuantitativas se ejecutó mediante t de Student para datos emparejados y con el test de McNemar en las variables cualitativas.

El riesgo de cada variable sobre la aparición del pronóstico de interés se evaluó mediante regresión logística uni y multivariante. Mediante procedimiento de exclusión secuencial se seleccionaron los mejores modelos predictivos. Se consideraron significativas las asociaciones con $p < 0,05$. El análisis estadístico de los datos se realizó con el programa SPSS versión 22.0 para Windows.

RESULTADOS

Fueron incluidos 101 pacientes (61,4% varones y 36,8% mujeres) con una edad media de 65 (DE 15) años y un IMC medio de 24,5 (desviación estándar [DE] 4,7) kg/m^2. Un 25,7% de los pacientes presentaron diabetes mellitus.

El aporte calórico medio diario administrado en la NPT fue de 26,8 (DE 4) kcal/kg/día, distribuido como 3,1 (DE 0,5) gde glucosa/kg/día, 0,89 (DE 0,18) gde grasas/kg/día y 0,2 (DE 0,03) gde N_2/kg/día. Se indicó una emulsión lipídica enriquecida en ácidos grasos omega-3 en el 53,5% de los pacientes. La duración media de la administración de la NPT fue de 14,3 (DE 8) días, con una mediana de once días. En la tabla II se detallan las características demográficas, clínicas y nutricionales de la población estudiada.

Las principales indicaciones de NPT fueron las complicaciones postoperatorias de cirugía mayor abdominal (46%), seguidas de la mucositis asociada a quimioterapia y/o radioterapia (13%) y del preoperatorio en pacientes con desnutrición severa (11%).

Tabla II. Características generales de la población analizada

Características	Valor
Edad, años	65 (DE 15)
Sexo, varón, nº (%)	62 (61,4)
IMC, kg/m^2	24,5 (DE 4,7)
Riesgo nutricional (NRS > 3), nº (%)	99 (99%)
Insulinorresistencia (HOMA > 4,8), nº (%)	42 (51,9)
Enfermedades subyacentes, nº (%)	
Diabetes	26 (25,7)
Insuficiencia renal	7 (6,9)
Obesidad	9 (8,9)
Fístula enterocutánea	7 (6,9)
Pancreatitis aguda	4 (3,9)
Consumo de tóxicos, nº (%)	
Alcohol	13 (13,1)
Tabaco	19 (19,4)
Consumo de fármacos, nº (%)	
Corticoides	12 (11,9)
Heparina	82 (82%)
Ciclosporina	0 (0%)
Tacrolimus	0 (0%)
Contenido de la NPT	
Aporte calórico/kg peso, kcal/kg/día	26,8 (DE 4)
Grasas, g/día	59,1 (DE 10,8)
Grasas/kg peso, g/kg/día	0,89 (DE 0,18)
Glucosa, g/día	205,9 (DE 32)
Glucosa/kg peso, g/kg/día	3,1 (DE 0,5)
Nitrógeno, g/día	14,3 (DE 2,6)
Nitrógeno/kg peso, g/kg/día	0,2 (DE 0,03)
LCT/MCT/omega-3, nº (%)	54 (53,5)

La estancia media hospitalaria fue de 39,1 (DE 28,5) días. Cincuenta y seis (57,7%) pacientes desarrollaron complicaciones infecciosas, que estuvieron relacionadas con la herida quirúrgica en 32 casos (32,7%), y diez pacientes (9,9%) fallecieron.

Al finalizar el estudio se constató una incidencia de hipertrigliceridemia del 33,3%. Se observó un incremento significativo en los niveles de triglicéridos entre el inicio y el final de la infusión de NPT (logaritmo triglicéridos 4,89 ± 0,57 *vs.* 5,1 ± 0,48; p = 0,007), con un incremento porcentual del 37,6%.

Los pacientes a los que se les objetivo hipertrigliceridemia al final de la administración de NPT se caracterizaron por presentar de forma significativa valores iniciales más elevados de triglicéridos (logaritmo triglicéridos 5,1 ± 0,6 *vs.* 4,7 ± 0,4; p = 0,001) y un incremento porcentual más marcado en los niveles de triglicéridos (75,1 ± 98,3% *vs.* 20,1 ± 65,6%; p = 0,003). No se encontraron diferencias significativas en el resto de las variables clínicas, analíticas o en los componentes de la NPT, aunque unos valores iniciales más elevados de colesterol total (126,2 ± 39,7 *vs.* 112 ± 38,5; p = 0,077) y un aporte superior a 3,1 gde glucosa/kg/día en la bolsa de NPT (62,5% *vs.* 43,5%; p = 0,082) quedaron en el límite de la significación estadística (Tabla III).

En el análisis univariante, las variables que alcanzaron *odds ratios* (OR) significativas para el desarrollo de hipertrigliceridemia fueron los valores iniciales de triglicéridos (OR = 4,91; IC 95%: 1,76-13,68; p = 0,002) y el incremento porcentual en los niveles de triglicéridos (OR = 1,009; IC 95%: 1,003-1,015; p = 0,005). El IMC (OR = 1,09; IC 95%: 0,99-1,19; p = 0,076) y un aporte mayor de 3,1 g/kg/día de glucosa en la NPT (OR = 2,16; IC 95%: 0,90-5,15; p = 0,084) quedaron en los límites de la significación estadística. El empleo de la emulsión lipídica enriquecida en omega-3 se asoció de forma no significativa con un menor riesgo de hipertrigliceridemia (OR = 0,60; IC 95%: 0,25-1,41; p > 0,1).

En el análisis multivariante, el mejor modelo (R^2 = 0,331) para predecir la aparición de hipertrigliceridemia fue el compuesto (por orden de importancia pronóstica) por las variables valores iniciales de triglicéridos (OR = 5,47; IC 95%: 1,81-16,53; x^2 = 12,34; p < 0,001), IMC (OR = 1,21; IC 95%: 1,04-1,40; x^2 = 8,31; p = 0,004) y aporte de glucosa en la NPT superior a 3,1 g/kg (OR = 4,81; IC 95%: 1,38-16,76; x^2 = 6,71; p = 0,010). La infusión de la emulsión lipídica rica en aceite de pescado se asoció con un descenso no significativo del riesgo de hipertrigliceridemia (OR = 0,61; IC 95%: 0,21-1,76; x^2 = 0,81; p > 0,1) (Tabla IV).

Cuando se evaluó la asociación entre el incremento porcentual de triglicéridos y el empleo de ácidos grasos omega-3, y tras ajustar para factores de confusión como IMC y niveles iniciales de triglicéridos, los ácidos grasos omega-3 se asociaron con un incremento de un 11,25% menor de los valores de triglicéridos (b = -11,25; IC 95%: -39,3-16,90; p = 0,43).

DISCUSIÓN

La hipertrigliceridemia es una frecuente complicación metabólica asociada a la administración de NPT (8,19). En nuestro estudio se ha objetivado que la incidencia de hipertrigliceridemia

Tabla III. Características de la población a estudio según la presencia de hipertrigliceridemia

Variable	Sin hipertrigliceridemia	Con hipertrigliceridemia	p
Edad, años	66,1 (DE 15,7)	63,1 (14)	> 0,1
IMC, kg/m^2	23,9 (DE 4,5)	25,8 (DE 5,2)	> 0,1
Duración NPT, días	13,9 (7,3)	15,1 (DE 9,1)	> 0,1
kcal/kg/día	27 (DE 4,1)	26,4 (DE 4,1)	> 0,1
kcal/kg/día ≥ 27, %	45,2	56,3	> 0,1
g grasas/kg/día	0,91 (DE 0,18)	0,84 (DE 0,18)	> 0,1
g grasas/kg/día ≥ 0,9, %	44,3	38,7	> 0,1
g glucosa/kg/día	3,1 (DE 0,5)	3,1 (DE 0,5)	> 0,1
gr glucosa/kg/día > 3,1, %	43,5	62,5	0,082
Grasas omega-3, %	59,4	46,9	> 0,1
Glucosa, mg/dl	125,6 (DE 55)	139,3 (DE 64,6)	> 0,1
HbA1c, %	5,8 (DE 1)	5,8 (DE 0,8)	> 0,1
HOMA > 4,8; %	49,1	56	> 0,1
Colesterol total, mg/dl	112 (DE 38,5)	126,2 (DE 39,7)	0,077
HDL-c, mg/dl	24,7 (DE 17,9)	25,2 (DE 15)	> 0,1
Logaritmo triglicéridos inicial	4,7 (DE 0,4)	5,1 (DE 0,6)	0,001
Incremento triglicéridos, %	20,1 (DE 65,6)	75,1 (DE 98,3)	0,003
Albúmina, g/dl	2,2 (DE 0,6)	2,4 (DE 0,6)	> 0,1
Ferritina, ng/ml	791,3 (DE 2.277)	904,1 (DE 1.519,3)	> 0,1
Fibrinógeno, mg/dl	623,2 (DE 194)	664 (DE 189,2)	> 0,1
PCR, mg/dl	11,7 (DE 12)	9,2 (DE 7,7)	> 0,1
Tratamiento con heparina, %	79,4	84,4	> 0,1
Tratamiento con corticoides, %	11,1	15,6	> 0,1
Consumo alcohol, %	10,9	20	> 0,1
Complicaciones infecciosas, %	59,7	56,3	> 0,1

Tabla IV. Factores de riesgo asociados al desarrollo de hipertrigliceridemia (regresión logística)

Tipo análisis	Univariante			Multivariante		
Variable	**OR**	**IC (95%)**	**p**	**OR**	**IC (95%)**	**p**
IMC, kg/m	1,09	0,99-1,19	0,076	1,21	1,04-1,40	0,004
gglucosa/kg/día > 3,1	2,16	0,90-5,17	0,084	4,81	1,38-16,76	0,01
Grasas omega-3	0,60	0,25-1,41	> 0,1	0,61	0,21-1,76	> 0,1
Log triglicéridos inicial	4,91	1,76-13,68	0,002	5,47	1,81-16,53	< 0,001

es del 33,3%, situándose en un término medio dentro del amplio rango publicado en la literatura, que oscila entre el 6% y el 60% (4,5,9,20,21). Estas diferencias en la incidencia podrían ser atribuidas a los criterios empleados para definir la hipertrigliceridemia y a las características de los pacientes estudiados.

En un estudio multicéntrico español en el cual se analizó a 260 pacientes a los que se les infundió una NPT durante al menos siete días y se definió la hipertrigliceridemia como unos valores de triglicéridos superiores a 265 mg/dl (3 mmol/l), se observó una incidencia de hipertrigliceridemia del 26,2% (9). Cuando para definir la hipertrigliceridemia se emplea un punto de corte en los niveles plasmáticos de triglicéridos de 200 mg/dl, la incidencia de esta complicación metabólica aumenta, e incluso puede duplicarse. En otro estudio español que incluyó una población de pacientes con

un tamaño muestral y unas características demográficas, clínicas y nutricionales muy parecidas a las de nuestro estudio, la incidencia de hipertrigliceridemia duplicó la de nuestro trabajo (60,7%) (4). Por el contrario, Kao y cols. (6), en una muestra más pequeña (66 pacientes) aunque muy similar a la nuestra en cuanto a la composición nutricional y a la duración de la NPT, encontraron una incidencia de hipertrigliceridemia semejante a la de nuestro estudio (31%).

Existen algunos grupos de pacientes que presentan un riesgo más elevado de desarrollar hipertrigliceridemia, como es el caso de los enfermos con fístulas enterocutáneas de alto débito, los pacientes críticos y los enfermos con obesidad, cuya incidencia se encuentra en torno al 35% (22,23). En nuestro trabajo, debido a la limitación del tamaño muestral y al tratarse de una población bastante homogénea, compuesta fundamentalmente por enfermos perioperatorios no críticos de los cuales solo había un 9% de pacientes obesos y un 7% de enfermos con fístulas enterocutáneas, no pudimos realizar un análisis referente al tipo de enfermo.

El principal objetivo de nuestro estudio fue conocer cuáles eran los factores predictores de hipertrigliceridemia asociada a la NPT. Hemos observado que en la aparición de la hipertrigliceridemia está implicada una combinación de factores de riesgo relacionados con algún componente de la NPT y con el enfermo, sobre todo con su situación clínica metabólica. El IMC, los niveles plasmáticos de triglicéridos previos al inicio de la NPT y un aporte de glucosa superior a 3,1 g/kg/día son los principales factores predictores de hipertrigliceridemia.

Uno de los factores de riesgo clásicamente asociados con el desarrollo de hipertrigliceridemia es el elevado aporte calórico en forma de glucosa (24). En los años 80, Meguid y cols. (25) demostraron que la sustitución de un tercio de las calorías procedentes de la glucosa por grasa se asociaba con un descenso significativo de los niveles de triglicéridos. Posteriormente, Tappy y cols. (26) randomizaron a 16 pacientes a recibir una NPT normocalórica normoproteica que contenía un 75% de glucosa frente a una NPT que solo contenía el 15% de glucosa, y observaron una mayor elevación en los niveles plasmáticos de glucosa, insulina y triglicéridos y un mayor incremento de la lipogénesis *de novo* en los enfermos a los que se les había administrado la NPT que aportaba un 75% de glucosa.

El mecanismo por el cual un excesivo aporte de glucosa causa hipertrigliceridemia parece estar relacionado con una elevación en la secreción de insulina, la cual estimula la síntesis hepática de ácidos grasos, con la consiguiente producción de triglicéridos hepáticos. Por otro lado, la hiperinsulinemia inhibe a la enzima carnitina aciltransferasa, limitando la oxidación mitocondrial de los ácidos grasos. Todo ello conduce a la síntesis y liberación hepática de triglicéridos y VLDL (27,28).

Otro de los componentes de la NPT implicados en el desarrollo de la hipertrigliceridemia son las emulsiones lipídicas, fundamentalmente la dosis y el tipo de ácidos grasos infundidos (19,29). Se ha demostrado que la administración de una dosis lipídica superior a 1,5 g/kg/día se relaciona con la presencia de hipertrigliceridemia (9,30). En nuestro trabajo, un aporte de grasa superior a 0,9 g/kg/día no se asoció con el desarrollo de hipertrigliceridemia, y podría ser considerada una dosis segura para evitar la aparición de esta complicación. Estos resultados concuerdan con una revisión realizada por Miles y cols. (8), en la cual opinan que la hipertrigliceridemia en pacientes con NPT puede ser relativamente controlada limitando el aporte lipídico a 0,7-1,2 g/kg/día.

El tipo de ácidos grasos presentes en la emulsión lipídica también podría influir en la etiopatogenia de la hipertrigliceridemia (18,31,32). En nuestro trabajo hemos observado que enriquecer con un 10% de aceite de pescado la emulsión lipídica LCT/MCT se asocia con un descenso no significativo del riesgo de hipertrigliceridemia.

Aunque en niños que reciben NPT a largo plazo este tipo de emulsión lipídica podría ejercer un efecto beneficioso en la reducción de la hipertrigliceridemia asociada a la NPT (13-15), no ocurre lo mismo en los pacientes adultos a los que se les infunde NPT durante un corto periodo de tiempo, en cuyo caso los resultados encontrados son contradictorios. Simoens y cols. (12) compararon la administración durante cinco horas de una emulsión lipídica LCT/MCT/W3 con una emulsión LCT/MCT cuatro días consecutivos en ocho pacientes normolipémicos, y demostraron un aclaramiento plasmático más rápido de los triglicéridos infundidos en el grupo de pacientes que recibieron la mezcla de aceites LCT/MCT/W3. Wichmann y cols. (16) randomizaron a un amplio grupo de pacientes quirúrgicos a recibir durante cinco días una emulsión LCT/MCT/W3 o una emulsión LCT, y observaron unos niveles significativamente más bajos de triglicéridos plasmáticos en el grupo de pacientes a los que se les infundió la emulsión que contenía LCT/MCT/W3. En un metaanálisis publicado por Pradelli y cols. (17), donde analizaron 23 ensayos clínicos que incluían a 1.500 pacientes críticos o con cirugía electiva y comparaban el empleo de una NPT que contenía diferentes emulsiones lipídicas enriquecidas en ácidos grasos omega-3 (LCT/W3, LCT/MCT/W3, LCT/MCT/oliva/W3) con otras emulsiones lipídicas estándar (LCT, LCT/MCT, LCT/oliva), no se encontraron diferencias significativas en los valores de triglicéridos plasmáticos con el empleo de la emulsión enriquecida en omega-3.

Se han descrito otros factores de riesgo que predisponen al desarrollo de hipertrigliceridemia y que no se encuentran directamente relacionados con la NPT, sino que dependen de la situación clínica o metabólica del enfermo o del tratamiento empleado.

Está bien establecida la relación existente entre la obesidad y las alteraciones en el metabolismo lipídico. Kao y cols. (6) analizaron a 66 pacientes adultos que recibieron NPT durante más de siete días y cuya emulsión lipídica era LCT/MCT, la cual aportaba el 25% de las calorías totales, y demostraron una correlación significativa entre los valores iniciales de triglicéridos, el IMC y los niveles de adiponectina con el desarrollo de hipertrigliceridemia. Frazee y cols. (23) evaluaron a 287 pacientes adultos a los que se les infundió una media de 45 gde grasa en la NPT, y observaron que las concentraciones medias de triglicéridos durante la infusión de la NPT eran significativamente más bajas en los pacientes con un IMC < 16 kg/m^2 que en aquellos pacientes con un IMC > 16 kg/m^2, a pesar de la mayor tasa de infusión lipídica que recibieron los sujetos con un IMC < 16 kg/m^2. También documentaron que, tras ajustar por tasa de infusión lipídica, existía una clara correlación entre niveles de triglicéridos e IMC y entre concentraciones de triglicéridos y grasa visceral. Estos mismos autores analizaron a un grupo de pacientes

con trasplante de medula ósea y encontraron una correlación entre niveles iniciales de triglicéridos y niveles de triglicéridos durante la infusión de NPT. Por el contrario, en una población de 102 pacientes con fístulas enterocutáneas, Visschers y cols. (22) no encontraron asociación entre IMC e hipertrigliceridemia.

Muy citado ha sido el estudio prospectivo multicéntrico español publicado en 2003 por Llop y cols. (10), en el cual analizaron a 260 pacientes hospitalizados con NPT y documentaron que los niveles plasmáticos de glucosa > 180 mg/dl, la sepsis, la insuficiencia renal, la pancreatitis aguda, la administración de corticoides a dosis superiores a 0,5 mg/kg y el tratamiento con heparina a dosis superiores a 3 mg/kg/día eran factores de riesgo independientes para el desarrollo de hipertrigliceridemia en pacientes que reciben NPT.

En nuestros enfermos no se ha constatado una asociación entre las diferentes variables relacionadas con el metabolismo de los hidratos de carbono (glucemia, insulina, HbA1c, insulinorresistencia) o los marcadores indicadores de inflamación y la presencia de hipertrigliceridemia.

Entre las limitaciones de nuestro trabajo cabe destacar que, debido a la limitación del tamaño muestral, no se pudieron analizar otras situaciones clínicas ni el tratamiento farmacológico, ya que el número de pacientes con pancreatitis, insuficiencia renal, fístulas enterocutáneas y tratamiento con corticoides era escaso.

En conclusión, nuestros resultados demuestran que la incidencia de hipertrigliceridemia en pacientes adultos hospitalizados no críticos que reciben NPT es elevada. Esta complicación está más relacionada con la situación clínica metabólica del paciente que con la cantidad de lípidos infundidos en la NPT, aunque parece necesario un control estricto del aporte calórico proveniente de los hidratos de carbono. La administración a corto plazo de una emulsión lipídica enriquecida en PUFA omega-3 es segura, aunque no ejerció un efecto protector significativo sobre el riesgo de aparición de hipertrigliceridemia.

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Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

Gastrostomy *vs* nasogastric tube feeding in patients with head and neck cancer during radiotherapy alone or combined chemoradiotherapy

Gastrostomía o sonda nasogástrica en pacientes con cáncer de cabeza y cuello durante la radioterapia o tratamiento combinado con quimiorradioterapia

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Abstract

Introduction: Patients with head and neck cancer (HNC) submitted to radiotherapy alone or combined chemoradiotherapy present a high prevalence of malnutrition at baseline. Prophylactic use of gastrostomy has been suggested for these patients for delivering enteral nutrition. On the other hand, other authors have failed to demonstrate the effectiveness of this measure over nasogastric tube feeding.

Material and methods: We studied 40 patients with HNC with moderate or severe malnutrition who were offered either prophylactic percutaneous gastrostomy before starting oncologic treatment or close follow-up with nutritional counseling with the placement of a nasogastric tube when necessary.

Results: There were no significant changes throughout the study period in weight (p = 0.338), body mass index (BMI) (p = 0.314) or serum proteins (p = 0.729), and these changes showed no differences between the gastrostomy *vs* nasogastric tube feeding groups. The amount of delivered energy was above the estimated energy needs with both gastrostomy and nasogastric tube feeding, but there were no differences in the total energy provided by enteral nutrition between groups. Patients in the gastrostomy group received enteral nutrition support for a longer period of time (p = 0.007).

Conclusions: Both gastrostomy and nasogastric tube feeding are effective methods of delivering enteral nutrition in patients with HNC submitted to radiotherapy alone or combined chemoradiotherapy, with no differences between them in terms of avoiding further nutritional deterioration.

Key words:

Head and neck cancer. Malnutrition. Enteral nutrition. Gastrostomy. Nasogastric tube. Chemoradiotherapy.

Resumen

Introducción: los pacientes con cáncer de cabeza y cuello (CCC) que reciben radioterapia o tratamiento combinado con radioterapia y quimioterapia presentan una elevada prevalencia de desnutrición. El uso profiláctico de la gastrostomía se ha sugerido para el soporte nutricional enteral en estos pacientes. Sin embargo, otros autores no han demostrado un beneficio claro de esta medida frente al uso de la sonda nasogástrica.

Material y métodos: se realizó el estudio en cuarenta pacientes con CCC con desnutrición moderada o grave, a los cuales se les ofreció la gastrostomía percutánea antes de empezar el tratamiento oncológico o bien seguimiento estrecho mediante consejo nutricional y la colocación de una sonda nasogástrica en el momento necesario.

Resultados: no se encontraron cambios significativos en cuanto a peso, (p = 0,338), índice de masa corporal (p = 0,314) o proteínas séricas (p = 0,729) durante el seguimiento, y estos cambios tampoco fueron diferentes entre los pacientes con gastrostomía o con sonda nasogástrica. Las calorías recibidas fueron superiores a los requerimientos estimados en ambos grupos, pero no existieron diferencias entre ellos. Los pacientes con gastrostomía recibieron nutrición enteral durante más tiempo (p = 0,007).

Conclusiones: tanto la gastrostomía como la sonda nasogástrica son eficaces para el soporte nutricional enteral en pacientes con CCC que reciben radioterapia o tratamiento combinado con quimioterapia y radioterapia, sin mostrar diferencias en la evolución nutricional entre ambas.

Palabras clave:

Cáncer de cabeza y cuello. Desnutrición. Nutrición enteral. Gastrostomía. Sonda nasogástrica. Quimiorradioterapia.

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INTRODUCTION

The incidence of malnutrition in cancer patients has been reported to range from about 15% to 80%. Malnutrition contributes to an increased risk of toxicity, infection, and healthcare costs, as well as decreased treatment response, compliance, quality of life, and ultimately patient survival (1-3). Besides, most of the radiotherapy-related toxicities are closely associated with nutritional problems (4).

Given the deteriorating side effects of radiotherapy combined or not with chemotherapy, several trials in patients undergoing radiotherapy for head and neck cancer (HNC) showed that the nutritional intervention positively influenced weight, nutritional status, and quality of life compared to usual care (5-10). Furthermore, it has been suggested that prophylactic use of gastrostomy could be important for patients with HNC submitted to radiotherapy, combined or not with chemotherapy, with a high risk of developing mucositis and severe malnutrition (11). On the other hand, other authors have failed to demonstrate the effectiveness of prophylactic gastrostomy (12).

Early nutritional screening is a very important measure in order to identify patients with malnutrition and/or important gastrointestinal symptoms. The latter may interfere with normal eating behavior and pose the patient in a high risk of malnutrition (13), having also a higher mortality risk (14). Nutritional intervention is a very important component of the care of these patients and has to be implemented in early stages and in an individualized way, including a dietician counseling (15-17). Implementing such a protocol at our clinical setting has shown that 87% of the patients were able to meet their nutritional needs through the oral route with the use of an adapted diet and oral nutritional supplements, ameliorating protein-energy malnutrition (18).

In this study we aimed to evaluate the effects of enteral nutrition either through prophylactic gastrostomy or close follow-up with oral nutritional supplements and delayed placement of nasogastric tube in malnourished patients with HNC submitted to radiotherapy alone or combined chemoradiotherapy.

PATIENTS AND METHODS

We studied 40 patients with HNC attending the Department of Oncology with moderate or severe malnutrition before starting oncologic treatment. The protocol at our institution included the following steps, as previously reported (18): every patient with HNC attending the Department of Oncology was evaluated at baseline, and then twice a week after completion of treatment by members of the Department of Endocrinology and Nutrition. An auto-administered version of the Subjective Global Assessment (SGA) was applied to every patient at baseline (13). Patients with B o C rating (those with moderate or severe malnutrition) were offered either prophylactic percutaneous gastrostomy before starting oncologic treatment or close follow-up with nutritional counseling and oral nutritional supplements, with the placement of a nasogastric tube if necessary. The indication for the latter was the presence of severe dysphagia with a < 65% of daily intake of the total estimated daily calorie needs, even after appropriate nutritional counseling, adapted diets and oral nutritional supplements, in the follow-up. Therefore, this study was not randomized, and patients took part in the decision after explaining to them the pros and cons of each procedure. Patients with severe liver or renal failure were excluded. The Ethics Committee of the Hospital Ramón y Cajal approved the study, and informed consent was obtained from the participants.

Anthropometric parameters were measured, body mass index (BMI) was calculated, and the percentage of weight loss was also recorded. Serum albumin was measured by nephelometry. Normal ranges were 3.3-5.2 g/l, as reported by the Central Laboratory of our institution. Estimated daily calorie needs were calculated by the Harris-Benedict equation and multiplied by a factor of 1.2. The type of enteral nutrition employed in these cases was a standard polymeric or hyperproteic product as needed. Patients were followed-up until discontinuation of nutritional support.

Results are expressed as mean ± standard deviation (SD) unless otherwise stated. The Kolmogorov-Smirnov statistic was applied to continuous variables to assess normality. Logarithmic or square root transformations were applied as needed to ensure a normal distribution of the variables. Comparisons between groups were performed using the independent Student's t test or the Mann-Whitney U test, and using the χ^2 test for discontinuous variables, as needed. The analysis of baseline and final variables was performed by the paired Student's t test, the Wilcoxon test, or the General Lineal Model (GLM) repeated measures tool for the inclusion of between factors or covariates. Analyses were performed using SPSS 17 (SPSS Inc., Chicago, Illinois). $p < 0.05$ was considered as statistically significant.

RESULTS

Of the 40 included patients, seven were women and 33 were men. They had the following tumors: larynx (n = 14), oropharynx (n = 8), oral cavity (n = 8), cervical lymph node squamous metastasis with unknown primary cancer (n = 4), cavum (n = 4), and hypopharynx (n = 2). Enteral nutrition was delivered through nasogastric tube in 29 patients and percutaneous gastrostomy, in eleven patients. Baseline characteristics were similar in both groups (Table I).

When comparing patients on radiotherapy alone *vs* those with combined chemoradiotherapy (Table II), similar baseline characteristics were observed, except for the percentage of patients in stage IV, which was higher in the combined chemoradiotherapy group ($p = 0.001$).

During follow-up, there were no significant changes throughout the study period in weight ($p = 0.338$), BMI ($p = 0.314$) or serum proteins ($p = 0.729$), and these changes showed no differences between the gastrostomy and nasogastric tube feeding groups (Fig. 1). The amount of delivered energy was above the estimated energy expenditure with both gastrostomy and nasogastric tube feeding, but there were no differences in the total energy provid-

Table I. Clinical and biochemical characteristics of included patients at baseline (n = 40)

	Nasogastric tube (n = 29)			Gastrostomy (n = 11)		
Males, n (%)	23 (79.3)			10 (90.9)		
Tumor stage IV, n (%)	22 (78.6)			10 (90.9)		
Primary radical therapy, n (%)	13 (44.8)			8 (72.7)		
Combined chemoradiotherapy, n (%)	24 (82.8)			8 (72.7)		
Age (years)	63	±	14	59	±	11
Weight (kg)	62	±	10	60	±	11
Body mass index (kg/m^2)	22.5	±	3.4	22.0	±	4.9
Weight loss before starting treatment (%)	10.2	±	8.5	9.2	±	12.2
Total serum proteins (g/dl)	7.0	±	0.9	7.1	±	1.1
Serum albumin (g/dl)	3.8	±	0.5	3.4	±	0.6
Estimated energy needs (kcal/day)	1,553	±	250	1,499	±	277

Data are means ± SD or n (%). There were no statistical differences between groups after independent Student's t test, or the Mann-Whitney U test, or χ^2 test as needed.

Table II. Baseline characteristics of patients according to type of therapy (n = 40)

	Combined chemoradiotherapy (n = 32)			Radiotherapy alone (n = 8)		
Males, n (%)	28 (87.5)			5 (62.5)		
Tumor stage IV, n (%)	29 (90.6)			3 (42.9)*		
Primary radical therapy, n (%)	14 (43.8)			5 (62.5)		
Age (years)	61	±	13	66	±	14
Weight (kg)	62	±	11	60	±	9
Body mass index (kg/m^2)	22.0	±	3.8	23.3	±	3.5
Weight loss before starting treatment (%)	9.9	±	10.2	9.8	±	6.5
Total serum proteins (g/dl)	7.1	±	0.9	7.0	±	1.4
Serum albumin (g/dl)	4.0	±	0.4	3.3	±	0.2
Estimated energy needs (kcal/day)	1,547	±	264	1,498	±	230

*Data are means ± SD or n (%). *p < 0.005 between groups after independent Student's t test, or the Mann-Whitney U test, or χ^2 test as needed.*

ed by enteral nutrition between groups (Fig. 2). Patients in the gastrostomy group received enteral nutrition support for a longer period of time (p = 0.007) (Fig. 2).

There were two deaths in the gastrostomy group and one in the nasogastric tube feeding group (p = 0.178). The remaining patients were able to restore the oral route, and enteral nutrition was discontinued at the end of follow-up. No severe complications were reported associated to enteral feeding, and no infections after gastrostomy placement were encountered either.

DISCUSSION

Patients with HNC submitted to treatment with radiotherapy alone or combined chemoradiotherapy usually present a high prevalence of malnutrition at baseline as assessed by previous studies (10,19,20). Several symptoms such as anorexia, dysphagia, mouth sores, and others are significant predictors of reduced dietary intake and weight loss in these patients (21-26), and we have previously found a high prevalence of these digestive symptoms in our patients before starting nutritional support (18).

Nutritional intervention and nutritional counseling have shown to be effective in ameliorating malnutrition in patients with HNC treated with radiotherapy, showing that this intervention was more effective than oral intake *ad libitum* (7). Other authors have shown that early and intensive individualized dietary counselling by a dietician produces clinically relevant effects in terms of decreasing weight loss and malnutrition (27). We have also previously shown that an individual-basis nutritional intervention with an intensive follow-up was effective in ameliorating further weight loss (18).

On the other hand, prophylactic use of gastrostomy for enteral nutrition has been suggested to be important for patients with HNC submitted to chemoradiotherapy with high risk of developing mucositis and severe malnutrition (11,28). Besides, other authors

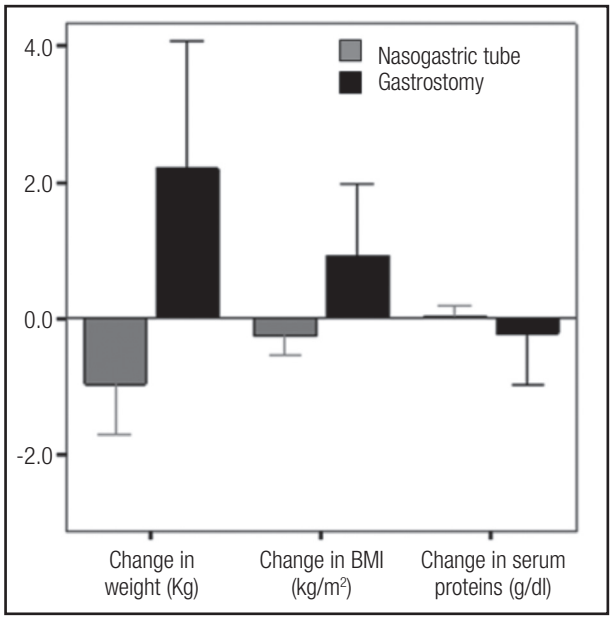

Figure 1.

Changes in weight, body mass index (BMI) and serum proteins during follow-up in patients with gastrostomy vs nasogastric tube feeding. Columns show means and error bars show standard error of means.

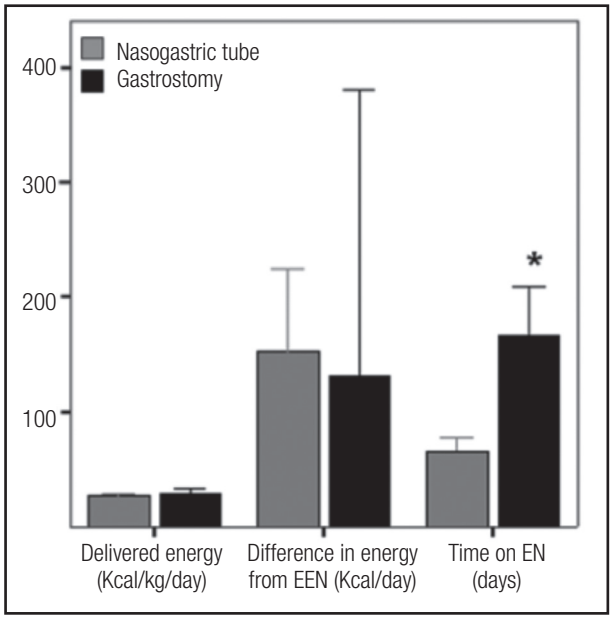

Figure 2.

Delivered energy and time interval on enteral nutrition in patients with gastrostomy *vs* nasogastric tube feeding. Columns show means and error bars show standard error of means (EEN: Estimated energy needs; EN: Enteral nutrition. *$p < 0.05$ between groups).

have failed to demonstrate the effectiveness of prophylactic gastrostomy (12). These contradictory results may respond to different nutritional status of the included patients and the type of therapy received. In this sense, a study performed in patients with locally advanced HNC undergoing definitive chemoradiotherapy showed that they obtained significant clinical benefit from the early placement of gastrostomy tubes for nutritional supplementation (29). Other study has also shown that adequate enteral nutrition by the insertion of gastrostomy tube can increase the completeness rate of concurrent chemotherapy (30).

Some recent studies have not been able to show a definite advantage for gastrostomy over nutritional counseling with the associated insertion of nasogastric tube when needed: a real clinical practice and prospective study at a tertiary hospital with 95 patients who chose to have a gastrostomy or only nutritional counselling with a therapeutic feeding tube if required showed no significant difference in the rates of delayed treatment, and only a modest less weight loss in patients with gastrostomy (31). Also, a recent network meta-analysis evaluating the comparative effects of prophylactic percutaneous gastrostomy and nasogastric tube feeding in HNC patients receiving radiotherapy or chemoradiotherapy did not show differences in tube-related complications, and both endoscopic percutaneous gastrostomy and nasogastric tube feeding were similar and superior to radiologic gastrostomy in the management of weight loss (32). Therefore, the choice between these methods for delivering enteral nutrition in patients with HNC submitted to radiotherapy alone or chemoradiotherapy needs to be further investigated in more randomized controlled trials.

A limitation of our study is that it was not a randomized one, and patients' *a priori* preferences for gastrostomy or nasogastric tube feeding may have produced some influence in the study results.

In conclusion, either gastrostomy or nasogastric tube feeding are effective methods of delivering enteral nutrition in patients with HNC submitted to radiotherapy alone or combined chemoradiotherapy, with no differences between them in terms of avoiding further nutritional deterioration.

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Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

Implementación de una vía clínica de prescripción de nutrición enteral domiciliaria de Murcia. Perfiles y características muestrales

Establishment of a clinical pathway for home enteral nutrition prescription in Murcia. Profile and sample characteristics

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Resumen

Introducción: el escenario de la nutrición enteral domiciliaria (NED) en Murcia, antes de 2010, estaba caracterizado por la gran variabilidad en la consideración del paciente subsidiario de dicha prestación, así como por el elevado consumo respecto a otras comunidades autónomas.

Objetivos: desarrollar y describir la implementación de una vía clínica de asistencia al paciente subsidiario de NED y analizar el perfil de los pacientes y las características del soporte nutricional.

Método: puesta en marcha de la vía clínica en el Área I de salud del Servicio Murciano de Salud (SMS). Diseño observacional y ambispectivo. Análisis de las muestras de NED de adultos del Área I en los años 2010 (NED1) y 2013-14 (NED2), con 345 y 457 casos, respectivamente.

Resultados: instrucción nº 4/2012 de 12 de julio, Dirección de Gerencia del SMS, que generaliza la vía clínica a todas las áreas de salud. Aunque la patología más prevalente en ambas muestras fue la neurológica, seguida de la oncológica y la digestiva, hubo diferencias significativas en la distribución. La NED1 presentó un alto porcentaje de casos de pacientes no subsidiarios de prestación. En ambas muestras, la vía más frecuente de administración fue la oral, pero con una tendencia inversa en sonda nasogástrica (SNG) y gastrostomía en NED2, donde las fórmulas específicas también se redujeron.

Conclusiones: los perfiles de la NED antes y después de la implantación de la vía clínica difieren significativamente en la patología de base, la vía de administración y el tipo de fórmula utilizada. La vía clínica ha facilitado la racionalización de la prescripción de esta prestación sanitaria.

Palabras clave:

Nutrición enteral. Soporte nutricional. Cuidados domiciliarios. Gasto en medicación.

Abstract

Introduction: Before 2010, prescribed home enteral nutrition (HEN) in Murcia was characterized by the great variability of the receptor patients, in addition to a higher use compared with other geographical areas.

Objectives: Developing and describing a clinical pathway for attending candidates for HEN, and analyzing their profile and prescription characteristics.

Methods: Establishment of a clinical pathway for HEN prescription. Bidirectional observational study of the samples of HEN in a specific area (Health Area I of the Region of Murcia) during 2010 (HEN1) and 2013-14 (HEN2).

Results: An official management statement was established, generalizing the clinical pathway for the rest of the regional areas (Instruction no. 4/2012 of July 12th). Although most prevalent diseases in both samples were neurological, followed, with a wide spread, by oncological and digestive cases, there was a significant difference regarding distribution. The HEN1 sample showed a great number of no candidate patients according to the management statement. In both samples, the most prevalent route of administration was oral, but with a trend reversal to feeding tube and gastrostomy in HEN2, where the specific formulas were also reduced.

Conclusions: The profile of HEN, before and after the deployment of the clinical pathway, changes significantly concerning the main disease, the route of administration and the formula. It has been proved that there is a need for controlling HEN for an appropriate prescription.

Key words:

Enteral nutrition. Nutritional support. Home care services. Drugs costs.

Contribuciones de autoría: MFG, JRCS, MVGZ, AAG y VJRR concibieron y diseñaron la vía clínica NED de la Región de Murcia. Todos los firmantes han participado en distintos momentos en los trabajos de campo, análisis de datos y elaboración de informes científicos llevados a cabo. JFSR y MFG elaboraron la primera versión de este manuscrito. Todos los firmantes han realizado aportaciones críticas y aprobado el texto final. El autor para la correspondencia, en nombre del resto de las personas firmantes, garantiza la precisión, transparencia y honestidad de los datos y la información contenida en el estudio, que ninguna información relevante ha sido omitida, y que todas las discrepancias entre autores han sido adecuadamente resueltas y descritas.

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INTRODUCCIÓN

La revolución de la nutrición artificial se trasladó rápidamente desde las unidades de cuidados intensivos y servicios quirúrgicos al resto de especialidades, trascendiendo finalmente el ámbito hospitalario (1,2). Así, la utilización de la nutrición enteral domiciliaria (NED) ha ido aumentando en los países occidentales en las últimas décadas, siendo difícil conocer la prevalencia real de utilización de este tratamiento, así como la comparación entre los diferentes estudios. Las causas de estas limitaciones son múltiples. Entre ellas, encontramos la falta de registros nacionales fiables en la mayoría de los países, el elevado número de centros involucrados en el seguimiento de estos pacientes, así como la falta de existencia de un acuerdo claro respecto a la definición de NED (3). Sin embargo, lo que parece indiscutible es que permite al paciente permanecer en su entorno sociofamiliar, con similares garantías de seguridad y eficacia, siempre que se programen adecuadamente el tratamiento y el seguimiento del paciente. También se debe apuntar el significativo impacto económico de la NED en los sistemas sanitarios.

El escenario de la NED en la Región de Murcia y, por ende, en el Área Sanitaria I (A1) entre los años 2007 y 2010 estaba caracterizado por dos hechos relevantes: la gran variabilidad existente en la asistencia al paciente subsidiario de esta prestación y el elevado consumo de productos dietoterápicos (4). Por un lado, la Instrucción nº 2/2007 de 5 de julio (5) del Servicio Murciano de Salud (SMS) establecía que eran los especialistas adscritos a las unidades de nutrición hospitalaria, especialistas en Endocrinología y Nutrición, Medicina Interna, Oncología, Neurología, Digestivo y Nefrología, los responsables de la indicación. Se creó, por tanto, una considerable dispersión que conducía a la falta de criterios unificados en la asistencia, el diagnóstico, la indicación y el seguimiento. Por otro lado, el consumo de dietoterápicos mostraba una tendencia al alza, al igual que sucedía en el territorio nacional, pero con cifras bastante superiores a las de la media española. En las figuras 1 y 2 se puede apreciar esta evolución. Así, en 2010, el consumo de estos productos dietéticos mediante receta fue de 192.838 unidades de venta, por un importe de casi 17 millones de euros, lo que supuso un incremento en tres años cercano al 30% en envases y el 63% en importe (4). En ese periodo de tiempo el incremento de población en el A1 fue del 5,02% (6). El A1 contaba con un padrón de 255.078, 256.725 y 257.856 habitantes en los años 2010, 2013 y 2014 respectivamente, según datos del Centro Regional de Estadística de Murcia (CREM) del Padrón Municipal de Habitantes.

Respecto al perfil de los usuarios de NED (Tablas I y II), en el A1 de la Región de Murcia la edad media fue de 78,28 ± 15,96 años en el año 2010 (4). Las principales características de esta muestra discrepaban con los datos de la mayoría de los registros de NED publicados, tanto de grupos nacionales (7-14) como internacionales (15-17).

El objetivo principal de este trabajo es desarrollar y describir el procedimiento de la implementación de la "Vía clínica de asistencia al paciente subsidiario de nutrición enteral domiciliaria en la Región de Murcia". Posteriormente, y como objetivo secundario, se persigue analizar el perfil de los pacientes con NED antes y después de la implantación de la vía clínica, así como las características del soporte nutricional.

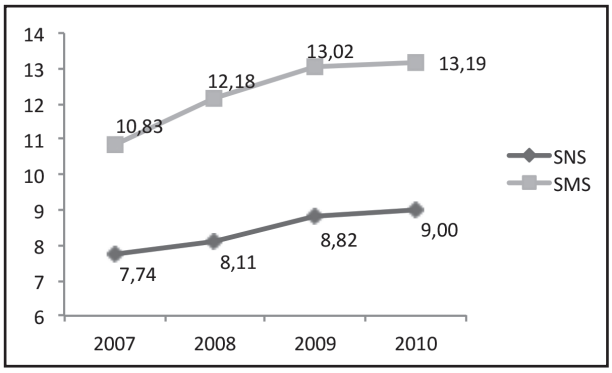

Figura 1.

Evolución de la nutrición enteral domiciliaria, unidades de venta/100 habitantes/año, en el Sistema Nacional de Salud (SNS) y el Servicio Murciano de Salud (SMS) (2007-2010) (con excepción de Cataluña y Galicia).

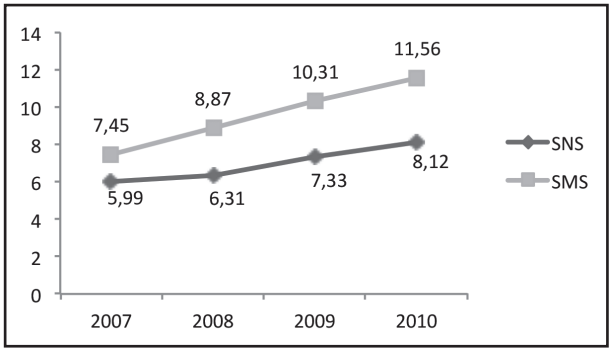

Figura 2.

Evolución del gasto en nutrición enteral domiciliaria, importe en euros/habitante/año, en el Sistema Nacional de Salud (SNS) y el Servicio Murciano de Salud (SMS) (2007-2010) (con excepción de Cataluña y Galicia).

MATERIAL Y MÉTODOS

IMPLEMENTACIÓN DE LA VÍA CLÍNICA

Tras observar los datos de la NED en la Región de Murcia entre los años 2007-2010, a finales de 2010 se puso en marcha, desde el Área de Salud I Murcia Oeste del SMS, la confección de una vía clínica que cumpliera los requisitos planteados por la Guía NED del Sistema Nacional de Salud (SNS) (18), en su versión de 2008. De este modo, el proyecto "*Implementación de una vía clínica de atención al paciente subsidiario de nutrición enteral domiciliaria en el Servicio Murciano de Salud*" fue presentado por la Unidad de Nutrición (UN) del Área I al Comité de Dietas de la Región de Murcia, donde están representados el

Tabla I. Diferencias en los perfiles de usuarios de NED antes y después de la implementación de la vía clínica

Características		NED1[a]		NED2[b]		p
Edad		78,28 ± 15,96		76,30 ± 16,87		0,092
		NED1		NED2		p
		n	%	n	%	
Sexo	Varones	166	48,1	232	50,8	0,717
	Mujeres	179	51,9	225	49,2	
Grupo de patología	Neurológica	213	61,7	359	78,6	0,000
	Oncológica	29	8,4	59	12,9	
	Digestiva	20	5,8	22	4,8	
	Otras	68	19,7	12	2,6	
	Sin dx	15	4,3	5	1,1	
Patología anexo II[c]	Pat I	15	4,3	41	9,0	0,000
	Pat II	123	35,7	358	78,3	
	Pat III	5	1,4	21	4,6	
	Pat IV	9	2,6	30	6,6	
	Criterios insuficientes	104	30,1	4	0,9	
	No AII	89	25,8	3	0,7	
Tipo de vía	Oral	296	85,8	276	60,4	0,000
	SNG	42	12,2	127	27,8	
	Gastrostomía	7	2,0	54	11,8	
Nutrición solicitada	No específica	167	48,4	188	41,1	0,000
	Específica	92	26,7	67	14,7	
	Módulo	86	24,9	202	44,2	
n		345		457		

[a]Muestra de usuarios de nutrición enteral domiciliaria (excluyendo suplementos) del Área 1 de salud del Sistema Murciano de Salud en el año 2010, antes de la implementación de la vía clínica. [b]Muestra de usuarios de nutrición enteral domiciliaria (excluyendo suplementos) del Área 1 de salud del Sistema Murciano de Salud en los año 2013-14, después de la implementación de la vía clínica. [c]Patologías recogidas en la Instrucción 4/2012 (19), por la que se establece el procedimiento a seguir para facilitar la prestación de productos dietéticos en el ámbito del sistema sanitario público de la Región de Murcia. Patología AII (con indicación en normativa regional - vía clínica) (nominal): pat I o alteraciones mecánicas de la deglución o del tránsito, que cursan con afagia o disfagia severa y precisan sonda; pat II o trastornos neuromotores que impidan la deglución o el tránsito y que precisen sonda; pat III o requerimientos especiales de energía y/o nutrientes; pat IV o situaciones clínicas cuando cursan con desnutrición; criterios insuficientes (patología indicada pero error en la vía de administración y/o la NED solicitada); y no AII o patologías no indicadas.

Servicio de Inspección de Prestaciones Asistenciales (SIPA) y el Servicio de Gestión Farmacéutica del SMS, con su consiguiente aprobación. La UN y la Subdirección de Atención Primaria (AP), ambas del Área I, coordinaron la implantación de la vía como proyecto piloto. Así, se confeccionó de forma conjunta un documento para entregar a AP en las reuniones informativas realizadas en todos los centros de salud del área. Estas reuniones tuvieron como finalidad proporcionar a los facultativos de AP los conocimientos suficientes sobre el cambio en el funcionamiento del acceso a la prestación de NED, así como de los parámetros mínimos necesarios para detectar desnutrición y necesidad de soporte nutricional. Finalmente, los documentos a cumplimentar por estos médicos para solicitar la NED a la UN fueron incluidos en el programa de historia electrónica de la red de Primaria.

PERFIL DE LA MUESTRA

Diseño observacional y ambispectivo en el que se analizaron las muestras de NED (fórmulas no específicas, específicas y módulos) de adultos del Área I en el año 2010 y en los años 2013-14, recogiendo variables relativas a la patología del paciente, la patología que justifica la NED según normativa regional, la vía de administración y el tipo de nutrición, así como variables sociodemográficas. Así, encontramos una muestra antes de la implementación de la vía clínica (NED1) relativa al año 2010 y otra posterior (NED2), compuesta por las peticiones que desde AP se realizaron al Servicio de Endocrinología y Nutrición del Hospital Clínico Universitario Virgen de la Arrixaca (HCUVA) y que fueron aceptadas para prescripción por cumplir los requisitos pertinentes a la vía clínica en los años 2013-2014.

Tabla II. Diferencias en los perfiles de usuarios de NED (excluyendo suplementos) antes y después de la implementación de la vía clínica

Características		NED10[a]		NED20[b]		p
Edad		77,76 ± 15,84		74,53 ± 17,23		,026
		NED10		NED20		p
		n	%	n	%	
Sexo	Varones	127	48,5	133	51,2	0,540
	Mujeres	135	51,5	127	48,5	
Grupo de patología	Neurológica	141	53,8	172	66,2	0,000
	Oncológica	26	9,9	52	20,0	
	Digestiva	20	7,6	22	8,5	
	Otras	62	23,7	11	4,2	
	Sin dx	13	5,0	3	1,2	
Patología anexo II[c]	Pat I	12	4,6	36	13,8	0,000
	Pat II	46	17,6	172	66,2	
	Pat III	5	1,9	20	7,7	
	Pat IV	9	3,4	29	11,2	
	Criterios insuficientes	104	39,7	0	0	
	No AII	86	32,8	3	1,2	
Tipo de vía	Oral	214	81,7	83	31,9	0,000
	SNG	41	15,6	124	47,7	
	Gastrostomía	7	2,7	53	20,4	
Nutrición solicitada	No específica	167	63,7	188	72,3	0,000
	Específica	92	35,1	67	25,8	
	Módulo	3	1,1	5	1,9	
n		262		260		

[a]Muestra de usuarios de nutrición enteral domiciliaria (excluyendo suplementos) del Área I de salud del Sistema Murciano de Salud en el año 2010, antes de la implementación de la vía clínica. [b]Muestra de usuarios de nutrición enteral domiciliaria (excluyendo suplementos) del Área I de salud del Sistema Murciano de Salud en los año 2013-14, después de la implementación de la vía clínica. [c]Patologías recogidas en la Instrucción 4/2012 (19), por la que se establece el procedimiento a seguir para facilitar la prestación de productos dietéticos en el ámbito del sistema sanitario público de la Región de Murcia. Patología AII (con indicación en normativa regional - vía clínica) (nominal): pat I o alteraciones mecánicas de la deglución o del tránsito, que cursan con afagia o disfagia severa y precisan sonda; pat II o trastornos neuromotores que impidan la deglución o el tránsito y que precisen sonda; pat III o requerimientos especiales de energía y/o nutrientes; pat IV o situaciones clínicas cuando cursan con desnutrición; criterios insuficientes (patología indicada pero error en la vía de administración y/o la NED solicitada; y no AII o patologías no indicadas.

A continuación, se presentan las variables a analizar:

- Sexo y edad.
- Patología (nominal): neurológica, oncológica, digestiva, otras enfermedades, y sin diagnóstico facilitados.
- Patología AII (con indicación en normativa regional - vía clínica) (nominal): pat I o alteraciones mecánicas de la deglución o del tránsito, que cursan con afagia o disfagia severa y precisan sonda; pat II o trastornos neuromotores que impidan la deglución o el tránsito y que precisen sonda; pat III o requerimientos especiales de energía y/o nutrientes; pat IV o situaciones clínicas cuando cursan con desnutrición; criterios insuficientes (patología indicada pero error en la vía de administración y/o la NED solicitada); y no AII o patologías no indicadas.
- Vía (nominal): oral, sonda nasogástrica (SNG) y ostomía.
- NED solicitada (nominal): fórmula no específica, fórmula específica y módulo.

Para describir los diversos parámetros, criterios clínicos y evolución de la NED, se utilizó el programa IBM SPSS Statistics 22.0. Se manejaron técnicas descriptivas para calcular frecuencias en las variables cualitativas y, en su caso, medidas centrales y de dispersión para las cuantitativas. Para los análisis entre variables se usaron técnicas de significación como la t de Student y Chi cuadrado.

La utilización de información y datos sobre consumo de productos dietoterápicos cuenta con autorización de la Dirección General de Asistencia Sanitaria. El trabajo cuenta con el informe favorable del CEIC del HCUVA, conforme a los aspectos éticos de la Declaración de Helsinki.

RESULTADOS

IMPLEMENTACIÓN DE LA VÍA CLÍNICA

En el primer semestre del año 2011 se puso en marcha la vía clínica en el Área I y se presentó en el Comité de Dietas del SMS, con representantes de los responsables de NED de todas las áreas de salud. El buen funcionamiento de la iniciativa culminó en la publicación en el BORM de la Instrucción 4/2012 (19), que establecía el procedimiento para la prestación de productos dietéticos en el ámbito sanitario público de la región. Esta instrucción generalizó la vía clínica a todas las áreas de salud. Así, los miembros de las UUNN se convertían en los únicos con potestad para la indicación de NED en el SMS. La figura 3 representa el nuevo circuito a seguir para la prescripción de NED en el SMS.

El protocolo de asistencia nutricional establecía un circuito entre AP y la UN del área sanitaria correspondiente. Cuando AP identifica a un paciente, cumplimenta un "informe de propuesta", que es enviado a la UN de referencia, donde es valorado, cumplimentando el "informe para visado" (Anexo II) y realizando la primera receta si existe indicación. El Anexo II y la primera receta se envían a AP y son remitidos al SIPA. Este, una vez visado el Anexo II, lo reenvía a AP. En ocasiones, según complejidad, será necesaria la evaluación del paciente en la UN. La Atención Especializada, a través de interconsulta, solicitará también el Anexo II a las UUNN.

PERFIL DE LA MUESTRA

En la tabla I mostramos las principales características de las muestras NED1 y NED2. El número de peticiones/pacientes ascendía a 345 en la NED1 y 457 en la NED2. En la tabla II mostramos las principales características de las muestras NED1 y NED2, tras eliminar las fórmulas espesantes NED10 y NED20 respectivamente. El número de peticiones/pacientes ascendía a 262 en la NED10 y 260 en la NED20.

DISCUSIÓN

En 1996, la creación en España, por parte del Pleno del Consejo Interterritorial del SNS, de un grupo de expertos para abordar la situación de la NED es el punto de partida de un proceso encaminado a intentar establecer unas directrices de actuación en un ámbito hasta entonces poco regularizado. Esto resultó en una orden ministerial para regular la prestación de productos dietoterápicos, la Orden de 2 de junio de 1998 (20), y una Guía de Práctica Clínica revisada en 2008 (18). Esta última revisión se realiza estando ya vigente el Real Decreto 1030/2006 de 16 de septiembre de 2006 (21), por el que se establecen la Cartera de Servicios Comunes del SNS y el procedimiento para su actualización, que deroga la orden anterior. Así pues, actualmente, para que un paciente sea subsidiario de financiación de la prestación de NED en España debe cumplir todos y cada uno de los requisitos establecidos en las mencionadas ordenanzas. La patología de base debe corresponder a alguna de las situaciones clínicas que recoge el Real Decreto 1030/2006 (21), la vía de administración es regulada por el mismo, las necesidades nutricionales no deben poder ser cubiertas con alimentos de consumo ordinario y el soporte nutricional debe suponer un beneficio en cuanto a mejora de calidad de vida o recuperación de su proceso, y que supere los riesgos que asocie. Se establece también en dicha

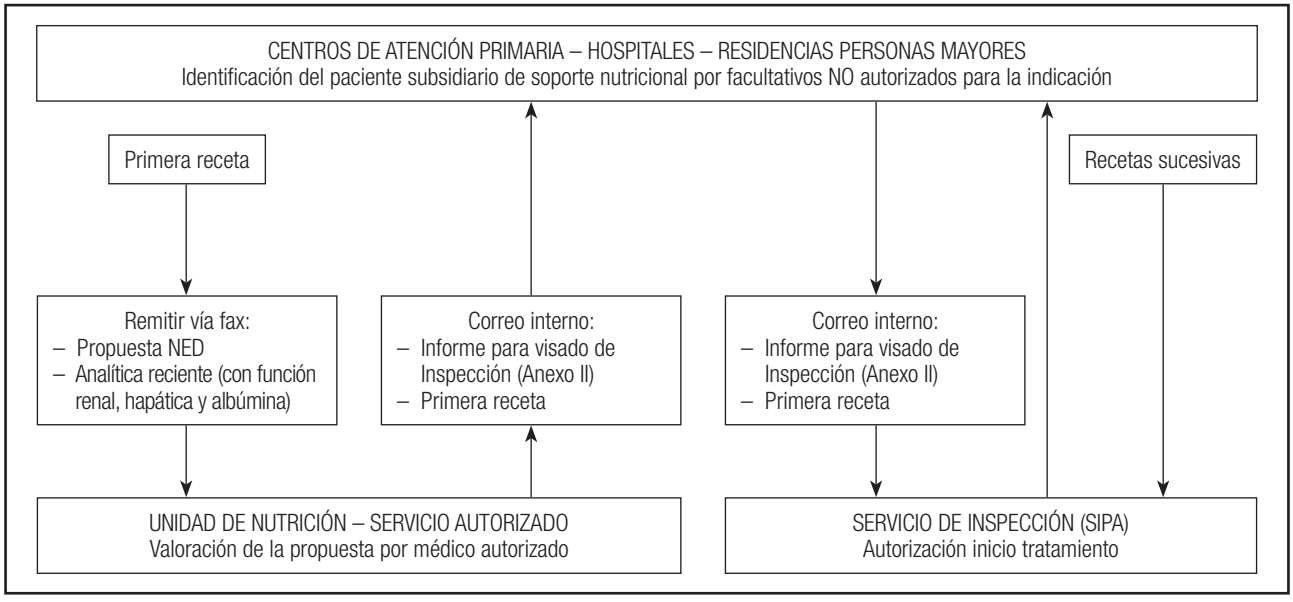

Figura 3.

Nuevo circuito para la prescripción de nutrición enteral domiciliaria en el Servicio Murciano de Salud (19).

publicación que los responsables de la indicación de los tratamientos de NED son los facultativos especialistas adscritos a la unidad de nutrición de los hospitales o aquellos que determine el Instituto Nacional de Salud o los Servicios de Salud de las CCAA en sus respectivos ámbitos de gestión y competencias, de acuerdo con los protocolos existentes para ello.

La puesta en práctica de esta legislación en las distintas CCAA presenta diferencias en cuanto a los facultativos con capacidad de realizar la indicación de la prescripción, ya que el Real Decreto 1030/2006 (21) deja abierta la posibilidad de que sean los propios Servicios de Salud de las CCAA quienes otorguen esa potestad. En la Región de Murcia, a través de la Instrucción 2/2007 (5) se estableció que la indicación de NED se podía realizar por pediatras y especialistas adscritos a las unidades de nutrición hospitalaria, especialistas en Endocrinología y Nutrición, Medicina Interna, Oncología, Neurología, Aparato Digestivo, Nefrología, facultativos pertenecientes al Plan de Cuidados Paliativos y, en el caso de las fórmulas para alergia o intolerancia a las proteínas de la leche de vaca, pediatras de AP previa realización del curso "Capacitación para el manejo de la intolerancia alimentaria y manejo de leches especiales" (modificación introducida mediante la Instrucción 1/2011 del 17 de mayo) (22).

Lo anteriormente expuesto pone de manifiesto la situación de la atención al paciente subsidiario de NED antes de la puesta en marcha de la vía clínica, objeto de este trabajo. La indicación del soporte nutricional recaía sobre las citadas especialidades, que remitían al SIPA el correspondiente informe (Anexo II) y la primera receta para su visado. El posterior seguimiento evolutivo podía llevarse a cabo tanto en Atención Especializada como en Primaria. La gran dispersión del proceso hacía imposible la existencia de criterios unificados de actuación en la atención a este tipo de patología. Por tanto, la puesta en marcha del proyecto piloto "*Implementación de una vía clínica de atención al paciente subsidiario de nutrición enteral domiciliaria en el Servicio Murciano de Salud*" culminó con el desarrollo del nuevo circuito a seguir para la prescripción de la NED en el SMS, tras la Instrucción 4/2012 (19), por la Dirección de Gerencia del SMS, que establece los facultativos competentes y el procedimiento a seguir para facilitar la prestación de productos dietéticos en el ámbito del sistema sanitario público de la región.

Con todo esto, este trabajo presenta dos realidades de la NED en Murcia. Por un lado, la existente antes de la implementación de la vía clínica desarrollada y que está representada en este trabajo por los pacientes de NED del Área I en el año 2010 (NED1), y por otro lado, la constituida por los pacientes de NED de los años 2013-2014 (NED2) de la misma área sanitaria. Al compararlas, observamos que no existen diferencias significativas en cuanto a edad y sexo. El porcentaje de ambos sexos se sitúa en torno al 50% y la edad media, por encima de los 75 años. En ambas muestras predomina la patología de base neurológica, que alcanza las dos terceras partes del total. La enfermedad oncológica parece infraestimada (8,4% en NED1 y 12,9% en NED2) en relación a cifras de otros registros. La British Association for Parenteral and Enteral Nutrition (BAPEN) (15) publica un porcentaje creciente del 25% en el año 2000, que llegó al 39% en 2010, momento en el que la neurológica alcanza el 45,7%. El grupo NADyA (7-11), sin embargo, informa de una caída de la neoplasia como enfermedad de base del 41% en 1994 al 28% en 2013, con una prevalencia de los desórdenes neurológicos que asciende hasta el 60,6%. Esta modificación podría estar motivada por la exclusión desde el año 2010 de los pacientes con soporte oral en sus bases de datos (9). En cuanto a las cifras de la República Checa de 2011, presentan el cáncer como enfermedad más prevalente entre sus pacientes con NED, alcanzando un 45%, frente a un 34% correspondiente a problemas neurológicos (16). La posible explicación a nuestro perfil es que el seguimiento de pacientes oncológicos se realiza en dos consultas monográficas de nuestra unidad y no entran a formar parte de este circuito. Esto se debe a la importancia de nutrir/renutrir a los pacientes con cáncer, entre ellos de cabeza y cuello, colocando el soporte nutricional como parte importante en el tratamiento de una grave enfermedad con elevada mortalidad (23). En la NED1 se observa un 19,7% de enfermedades distintas a la neurológica, oncológica y digestiva, frente al 2,6% de la NED2. Así mismo, el grupo sin diagnóstico cae del 4,3% en la primera al 1,1% en la segunda. Estas últimas cifras de la NED1, en relación a otros registros, podrían estar indicando la necesidad de mejora de los criterios de indicación de soporte nutricional.

Si lo que comparamos ahora son ambas muestras, en lo referente a patologías recogidas en el Anexo II (patologías financiables por el SNS) podemos apreciar que existe también una amplia diferencia entre las distribuciones. En la muestra NED1, aunque domina el grupo II de trastornos neurológicos hay un alto porcentaje de pacientes con criterios insuficientes (30,1%) y con diagnósticos no encuadrables en dicho anexo (25,8%). En la NED2, sin embargo, se observa una reducción drástica de estos dos porcentajes, al 0,9 y 0,7% respectivamente, a favor del grupo II, que alcanza el 78,3% del total.

En lo referente al tipo de vía utilizada, en ambas muestras es la oral la que encabeza el grupo, con un 85,8% en NED1 y un 60,4% en NED2. Esta caída en la segunda muestra se acompaña de un ascenso en la utilización de SNG, que se incrementa del 12,2% al 27,8%, y de la gastrostomía, que pasa del 2% al 11,8%. La comparación de estas cifras con la mayoría de los otros registros no es posible dado que en muchos de ellos se excluye la vía oral. Solamente los checos reportan un uso de esta vía del 59%, seguido de la gastrostomía, con un 29%, y de la SNG, con el 12% (16), cifras muy parecidas a las de la NED2. El registro NADyA hablaba de administración oral en un 64% en 2007; posteriormente, como hemos mencionado, solo recogen administración enteral (9).

Finalmente, cuando analizamos el tipo de fórmula solicitado, también encontramos modificaciones importantes entre NED1 y NED2. Destaca una reducción de la prescripción de fórmulas no específicas del 48,4% al 41,1% y, fundamentalmente de las específicas, del 24,9% al 14,7%, con un aumento importante de la utilización de módulos, pasando estos del 24,9% al 44,2% a expensas de espesantes principalmente. Estos cambios se podrían explicar por el trasvase de pacientes afectos de disfagia con dietas utilizadas como suplemento a módulos espesantes, así como el paso de dietas específicas a no

específicas en los casos en los que su uso no tiene suficiente evidencia científica.

Pasamos al análisis de las muestras NED10 y NED20 que excluyen los espesantes, frente a NED1 y NED2, respectivamente. Se observa una edad media menor en NED20, que puede resultar de eliminar prescripciones orales no indicadas en los pacientes muy mayores. Respecto al grupo de patología, en NED10 encontramos un aumento del grupo de *otras patologías,* con un leve descenso en las neurológicas. En NED20 se observa un aumento claro del grupo de *neoplasias*, mientras que los trastornos neurológicos descienden, especialmente los grupos *otras patologías* y *sin diagnóstico.* Al separar los espesantes, utilizados en su mayor parte en pacientes con disfagia neurológica, suben porcentualmente los otros grupos diagnósticos. Esto se aprecia de forma mucho más clara cuando la patología de base se clasifica según Anexo II; en la muestra NED10 el peso del grupo II cae, mientras que suben el grupo con *criterios insuficientes* y el de *enfermedades no indicadas en la normativa regional (vía clínica)* (19). En cambio, en la muestra NED20 la reducción en el grupo II va acompañada de un ascenso de los grupos I y IV. Los pacientes con *criterios insuficientes* o *sin diagnóstico* siguen representando apenas un 1,5% del total. En cuanto al tipo de fórmula, se aprecia un traslado de dietas específicas a no específicas en ambos casos.

Como principales limitaciones de este trabajo se encuentra la falta de inclusión de los pacientes procedentes de interconsultas de Atención Especializada y de las consultas monográficas del propio Servicio. Por otro lado, la metodología estandarizada basada en las dosis diarias definidas hubiese permitido plantear una evolución del consumo teniendo en cuenta los cambios en la presentación de la NED y/ o la población de referencia (24).

Podemos concluir que los perfiles de los pacientes con NED antes y después de la implantación de la vía clínica en el Área I difieren significativamente en la patología de base, la patología Anexo II (financiable por el SNS), la vía de administración y el tipo de fórmula utilizado. Queda clara la necesidad de centralizar la prescripción de NED para controlar la adecuada indicación, el tipo de fórmula y la vía de administración.

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Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

Adherencia y tolerancia como claves en la detención de la pérdida de peso en pacientes oncológicos sometidos a radioterapia mediante una estrategia de suplementación precoz con una fórmula enteral hipercalórica e hiperproteica específica

Adherence and tolerance as key in brake on weight loss in cancer patients with nutritional risk after intervention with a high calorie nutritional and specific hyperproteic supplement

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Resumen

Introducción: en pacientes con riesgo nutricional, la Sociedad Europea de Clínica y Metabolismo (ESPEN) y Parenteral recomienda suplementos nutricionales durante el tratamiento oncológico para prevenir la pérdida de peso involuntaria.

Objetivos: nuestro objetivo es conocer el cumplimiento, la aceptabilidad y la tolerancia de un suplemento hiperproteico, hipercalórico, rico en omega 3 en pacientes oncológicos.

Métodos: estudio unicéntrico, observacional y prospectivo en pacientes oncológicos con un suplemento nutricional hiperproteico, hipercalórico, rico en omega 3 y de bajo volumen. Fueron incluidos 30 pacientes con desnutrición o en riesgo de desnutrición. La suplementación duró seis días. Se evaluaron el cumplimiento (envases utilizado), la aceptabilidad (escala Madrid), las variables antropométricas y los acontecimientos adversos (AA) gastrointestinales.

Resultados: el 70% fueron hombres, con una edad media de 60 años (rango: 32 a 79) y con neoplasias de pulmón (43,3%), ORL (26,7%) y mama (13,3%), en estadio III-IV (56,7%), tratados con radioterapia (93,3%), quimioterapia (60%) y cirugía (16,7%). El producto fue aceptado por todos los pacientes. Se observó un cumplimiento del 100%. En dos pacientes (6,7%) se observaron AA gastrointestinales (grado II) relacionados con el suplemento; ambos sujetos presentaban patologías gastrointestinales previas. La mediana del peso, índice de masa corporal (IMC) y proteínas ingeridas aumentó durante la suplementación (0,2 kg, 0,1 kg/m^2 y 6,2 g). No se observaron diferencias respecto a la ingesta de calorías, lípidos y carbohidratos.

Conclusión: la elevada aceptación y cumplimiento del suplemento nutricional específico se asoció con la mejora nutricional de los pacientes oncológicos, pues revirtió la pérdida de peso, sin presentar problemas gastrointestinales severos ni producir desplazamiento de la ingesta.

Palabras clave:

Desnutrición relacionada con la enfermedad aguda. Suplemento nutricional. Oncología. Ácidos grasos omega 3. Nutrición oral.

Abstract

Background: In patients with nutritional risk, the European Society for Clinical Nutrition and Metabolism (ESPEN) recommends nutritional supplements during cancer treatment to prevent weight loss.

Objectives: Our goal is to determine the acceptability, compliance and tolerance of a hyperproteic, high-calorie, omega-3 enriched supplement in cancer patients.

Methods: Unicentric, prospective observational study in cancer patients with hyperproteic, high-calorie, rich in omega 3 and low volume nutritional supplement. Thirty patients with malnutrition or risk of malnutrition were included. Supplementation lasted six days. Compliance (packaging used), acceptability (Madrid scale), anthropometric variables and gastrointestinal adverse events (AEs) were evaluated.

Results: Seventy per cent were men, with an average age of 60 years (range 32-79), with lung (43.3%), ENT (26.7%) and breast neoplasms (13.3%), stage III-IV (56.7%), and treated with radiotherapy (93.3%), chemotherapy (60%) and surgery (16.7%). The product was accepted by all patients. A compliance rate of 100% was observed. Gastrointestinal AE (grade II) related to the supplement was observed in two patients (6.7%). Both subjects had previous gastrointestinal diseases. The median weight, body mass index (BMI) and protein intake increased during supplementation (0.2 kg, 0.1 kg/m^2 and 6.2 g). No differences were observed regarding calorie, fat and carbohydrates intake.

Conclusion: The high acceptance and compliance with the specific nutritional supplement was associated with an improved nutritional status for cancer patients, and reversed the weight loss without severe gastrointestinal problems, or producing intake displacement.

Key words:

The disease-related malnutrition. Dietary supplement. Oncology. Omega 3 fatty acids. Oral nutrition.

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INTRODUCCIÓN

Entre un 31 y un 87% de los pacientes (1) con cáncer presentan malnutrición en algún momento de la evolución de la enfermedad y un 15% presenta una pérdida de peso involuntaria superior al 10% en los seis meses previos al diagnóstico. La malnutrición y la pérdida de peso en pacientes con cáncer se han asociado con un peor pronóstico, un empeoramiento de la calidad de vida y un mayor riesgo de fallecer (2); sin embargo, solo un tercio de los pacientes en riesgo de malnutrición recibe soporte nutricional (3).

Las causas de la malnutrición son múltiples y están interrelacionadas en muchas ocasiones (2). Los mecanismos principales que pueden intervenir en la aparición de esta son: escaso aporte de energía y nutrientes, alteraciones de la digestión y/o absorción de nutrientes, aumento de las necesidades, alteraciones en el metabolismo de los nutrientes y aparición de caquexia tumoral. El diagnóstico de cáncer puede generar en el paciente miedo, ansiedad y depresión, así como alteraciones del manejo del estrés. Si las reacciones son desadaptativas, se puede llegar a provocar una alteración de la ingesta de alimentos que dará lugar a un deterioro progresivo en el estado nutricional y en la calidad de vida del paciente. Asimismo, la ingesta puede estar comprometida si el paciente presenta sintomatología asociada (anorexia, náuseas, vómitos, mucositis, disfagia, etc.) derivada de la propia patología o de las complicaciones de los tratamientos a los que está sometido (4).

La Sociedad Europea de Nutrición Enteral y Parenteral (ESPEN) estableció en 2006 (1), con grado de recomendación A, utilizar recomendaciones dietéticas y suplementos nutricionales durante la radio o la quimioterapia para incrementar la ingesta y prevenir la pérdida de peso asociada al tratamiento y la interrupción de la terapia.

En una revisión extensa de Colomer de 2007 (5) sobre los suplementos orales enriquecidos en ácidos grasos poliinsaturados ω-3, se destaca que estos son beneficiosos para los pacientes con cáncer avanzado y pérdida de peso, y están indicados en los tumores de páncreas y del aparato digestivo superior. Los ω-3 favorecen el aumento de peso y de apetito y contribuyen a la mejora de la calidad de vida y a la disminución de la morbilidad posquirúrgica (6,7), aunque no se ha establecido su relación con una mejoría en la supervivencia global de los pacientes con cáncer (8).

La dosis recomendada es superior a 1,5 g/día de ácido eicosapentaenoico (EPA). La tolerancia es mejor cuando los ácidos grasos poliinsaturados ω-3 forman parte de una fórmula nutricional que cuando se administran en forma de cápsulas concentradas (5), lo que podría explicarse por diferencias de absorción de los suplementos relacionadas con el vehículo utilizado. Algunos autores han indicado que formas de administración semilíquidas tendrían una mayor tasa de absorción que los suplementos encapsulados en gelatina (9). Por otra parte, los suplementos nutricionales enriquecidos en EPA también tendrían la ventaja de aportar calorías y proteínas para cubrir las necesidades nutricionales del paciente (5).

Recientemente, las Guías Clínicas de la Sociedad Americana de Nutrición Enteral y Parenteral (ASPEN) 2009 (7) recomiendan con un grado B la suplementación de ácidos grasos ω-3 en los pacientes oncológicos, pues pueden ayudar a estabilizar la pérdida de peso progresiva. Fearon y cols. (10) han demostrado cómo con suplementos enriquecidos en inmunonutrientes se puede aumentar el peso en un grupo de pacientes tumorales con muy mal pronóstico (cáncer de páncreas). No obstante, la aceptación por parte de los pacientes de estos suplementos es difícil. Por tanto, la aceptabilidad de los suplementos así como la capacidad para ingerir grandes volúmenes mantenidos durante el tiempo son puntos fundamentales en todos los protocolos de suplementación nutricional oral (10). La preferencia en el tipo de suplemento se ve afectada por una multitud de factores tales como sabor, color, olor, textura, etc. La monotonía y la fatiga en el sabor pueden conducir a una reducción en el consumo (11). Cuando el paciente presenta saciedad, disminuye el placer por comer; esto ocurre rápidamente y se relaciona más con el volumen que con el contenido energético de la comida (12,13). La utilización de suplementos de bajo volumen e hipercalóricos puede mejorar el cumplimiento y, con ello, el aporte energético y proteico total. Es un concepto similar a cuando aconsejamos "realizar varias comidas al día y en pequeñas cantidades de comida rica en energía" (14).

Nuestro objetivo es estudiar la aceptabilidad, el cumplimiento y la tolerancia de un suplemento nutricional hiperproteico, hipercalórico, rico en omega 3 y de bajo volumen en pacientes oncológicos con requerimientos aumentados que presentan desnutrición o riesgo de desnutrición (15).

MATERIAL Y MÉTODOS

El suplemento nutricional hiperproteico, hipercalórico, rico en omega 3 y de bajo volumen elegido para el estudio fue Resource® Support plus. Resource® Support plus es un alimento dietético destinado a usos médicos especiales (ADUME). Dichos productos están regulados por la Agencia Española de Seguridad Alimentaria y Nutrición. Cada envase de 125 ml aporta 251 kilocalorías, 11,5 g de proteínas, 25,4 g de carbohidratos, 3,1 g de fibra soluble (FOS:GOS), 10,9 g de grasas, nutrientes específicos para el control de la pérdida de peso en el paciente oncológico, vitaminas y minerales. Entre los nutrientes específicos se incluyen 1,9 g de ácidos grasos omega 3, 0,68 g de EPA y 0,43 g de ácido docosahexaenoico (DHA) (Tabla I).

La pauta de administración del suplemento fue de tres envases al día, de acuerdo a la dosis de EPA recomendada en este tipo de pacientes (5).

El diseño del estudio fue observacional prospectivo, longitudinal y naturalístico, no comparativo en pacientes con cáncer y desnutrición o riesgo de desnutrición. Los pacientes fueron tratados con Resource® Support plus siguiendo las condiciones estándar de uso habitual de la fórmula y bajo supervisión médica durante seis días.

El estudio se realizó en 30 pacientes oncológicos en tratamiento dietético con requerimientos aumentados que precisaban de

Tabla I. Composición nutricional

		125 ml	100 ml
Valor energético	kcal	251	201
	kJ	1.054	843
Distribución calórica	P/CHO/G/F 18/41/39/2		
Proteínas	g	11,5	9,2
Proteínas de la leche	g	11,5	9,2
Carbohidratos	g	25,4	20,3
Maltodextrinas	g	15,3	12,2
Azúcares, de los cuales	g	10,1	8,1
Sacarosa	g	1,9	1,5
Lactosa	g	0,9	0,7
Grasas	g	10,9	8,7
Ác. grasos saturados	g	1,94	1,55
Ác. grasos monoinsaturados	g	4,9	3,9
Ác. grasos poliinsaturados:	g	3,4	2,7
Ác. grasos ω3	g	1,9	1,5
EPA	g	0,68	0,54
DHA	g	0,43	0,34
Fibra alimentaria	g	3,1	2,5
FOS	g	3,1	2,5
Concentración calórica	kcal/ml 2,01		

suplementación nutricional. Antes de iniciar el tratamiento se les practicó un examen físico, un examen gastrointestinal estándar y una valoración del estado nutricional según práctica clínica habitual, a fin de establecer el estado basal de salud de los pacientes.

El estudio fue aprobado por las autoridades competentes y el Comité de Ética del Hospital Virgen de la Victoria (Málaga). A todos los pacientes se les requirió la firma de consentimiento informado para participar en el estudio.

El estudio incluyó pacientes oncológicos con indicación de suplementación nutricional de al menos cinco días, que estuvieran en pausa de su tratamiento antineoplásico o con un tratamiento no relacionado con toxicidades gastrointestinales moderadas o graves, sin enfermedades gastrointestinales graves previas ni contraindicaciones de nutrición enteral o con requerimientos de una sonda enteral. No se incluyeron pacientes que hubieran recibido suplementación nutricional estándar o específica con ácidos grasos omega 3 durante las dos semanas anteriores al estudio.

La variable principal del estudio fue la cumplimentación. La cumplimentación se evaluó mediante el número de envases retornados (tres administraciones por día).

Las variables secundarias del estudio fueron la aceptabilidad, la tolerancia del producto, las medidas antropométricas (peso, IMC, % pérdida de peso) y el registro de la ingesta del paciente. La aceptabilidad se evaluó con una escala validada de preferencia de suplementos nutricionales (escala Madrid [15]). La puntuación total se obtuvo sumando las puntuaciones de todos los elementos (preferencia mínima = 8 a máxima = 24). La tolerancia se valoró mediante los acontecimientos adversos gastrointestinales referidos por el paciente durante el seguimiento. La ingesta se evaluó durante tres días previos a la suplementación y luego de forma diaria. Los parámetros evaluados fueron energía (kcal), proteínas (g), grasas (g) y carbohidratos (g), para valorar desplazamiento de la misma.

Las variables de seguridad evaluadas fueron los AA durante el estudio, de acuerdo a los criterios *Common Terminology Criteria for Adverse Events* (CTCAE) v4.0.

TAMAÑO DE LA MUESTRA

En revisiones previas (16) se observó que el porcentaje de cumplimentación era del 78% (rango: 37-100%). Se consideró que porcentajes de cumplimentación inferiores al 50% indicarían que el producto analizado no debería ser considerado para futuros estudios.

Estos datos sugieren que rechazar una tasa de cumplimentación ≤ 50% y aceptar una tasa de cumplimentación ≥ 75% debería ser una estrategia conservadora para evaluar el suplemento nutricional estudiado. En este sentido, el tamaño de la muestra se basó en un diseño binomial de un brazo y una etapa (17). Con este diseño, si al menos 21 pacientes, de 30 reclutados, son cumplidores, los resultados abalarán la investigación de esta estrategia en siguientes estudios.

Con esta metodología hay una probabilidad del 80% de encontrar un resultado positivo si la tasa de cumplimentación real es ≥ 75% y una probabilidad del 2,5% de encontrar un falso positivo si la tasa de cumplimentación real es ≤ 50%.

METODOLOGÍA ESTADÍSTICA

Se presentaron las frecuencias absoluta y relativa para los pacientes cumplidores. Las variables de cumplimentación y aceptabilidad se estimaron mediante porcentajes y su intervalo de confianza del 95% (IC 95%), calculado mediante el método Wilson (18). La correlación entre las variables de aceptabilidad, antropométricas y nutricionales se analizó mediante la correlación no paramétrica de Spearman y su IC 95%. La evolución de las variables antropométricas y nutricionales se estudió mediante la prueba de Wilcoxon para muestras relacionadas y las medianas de la diferencia, con su IC 95%. El nivel de significación utilizado fue del 0,05 bilateral. El análisis se ha realizado con el programa estadístico R V3.0.

RESULTADOS

BASALES

En la tabla I se describen las características clínicas más importantes de los pacientes incluidos en el estudio. La mediana de

edad fue de 62 años (32 a 79). El 70% fueron hombres. Las neoplasias malignas más comunes fueron el cáncer de pulmón en 13 pacientes (43,3%), el cáncer otorrinolaringológico (ORL) en ocho pacientes (26,7%) y el cáncer de mama en cuatro pacientes (13,3%). El 56,7% de los pacientes presentaron estadios II-IV. Los tipos de tratamientos antineoplásicos recibidos fueron radioterapia (93,3%), quimioterapia (60%) y cirugía (16,7%).

La mayoría de los pacientes (90%) presentaron un diagnóstico de desnutrición moderada o en riesgo nutricional según la escala de Valoración Global Subjetiva generada por el paciente (VSG-GP).

La mediana del peso habitual fue de 72 kg, peso inicial 70,2 kg e IMC 25,6 kg/m^2. La mediana de masa de grasa fue de 18 kg, 52,6 kg de masa magra y 38 kg de agua corporal.

ANÁLISIS DE LA VARIABLE PRINCIPAL

Cumplimentación

Todos los pacientes (100%, IC 95%: 88,6-100%) cumplieron con la pauta de suplementación oral prescrita (tres veces al día). En tres pacientes se suspendió la suplementación por acontecimientos adversos (ver apartado de seguridad); sin embargo, durante el periodo en que fueron tratados cumplieron con la pauta prescrita.

El número de pacientes cumplidores, cuando consideramos como no adherentes a los pacientes discontinuados, es de 27 (90%, IC 95%: 74,4 a 96,5%), mayor que el límite de éxito predefinido en el tamaño de muestra (21 pacientes). Este resultado indica que el suplemento nutricional es una estrategia prometedora que debería ser estudiada en nuevos trabajos.

ANÁLISIS DE LAS VARIABLES SECUNDARIAS

Aceptabilidad

Todos los pacientes aceptaron el suplemento nutricional. La opinión general fue "me gusta" en un 70% (IC 95%, 52,1-83,3%) y "ni bueno ni malo" en un 30% (IC 95%, 16,6 a 47,9%) (Fig. 1).

La apariencia, el olor, el sabor, el sabor después de tragar y el dulzor también contaron con la aceptación de los pacientes

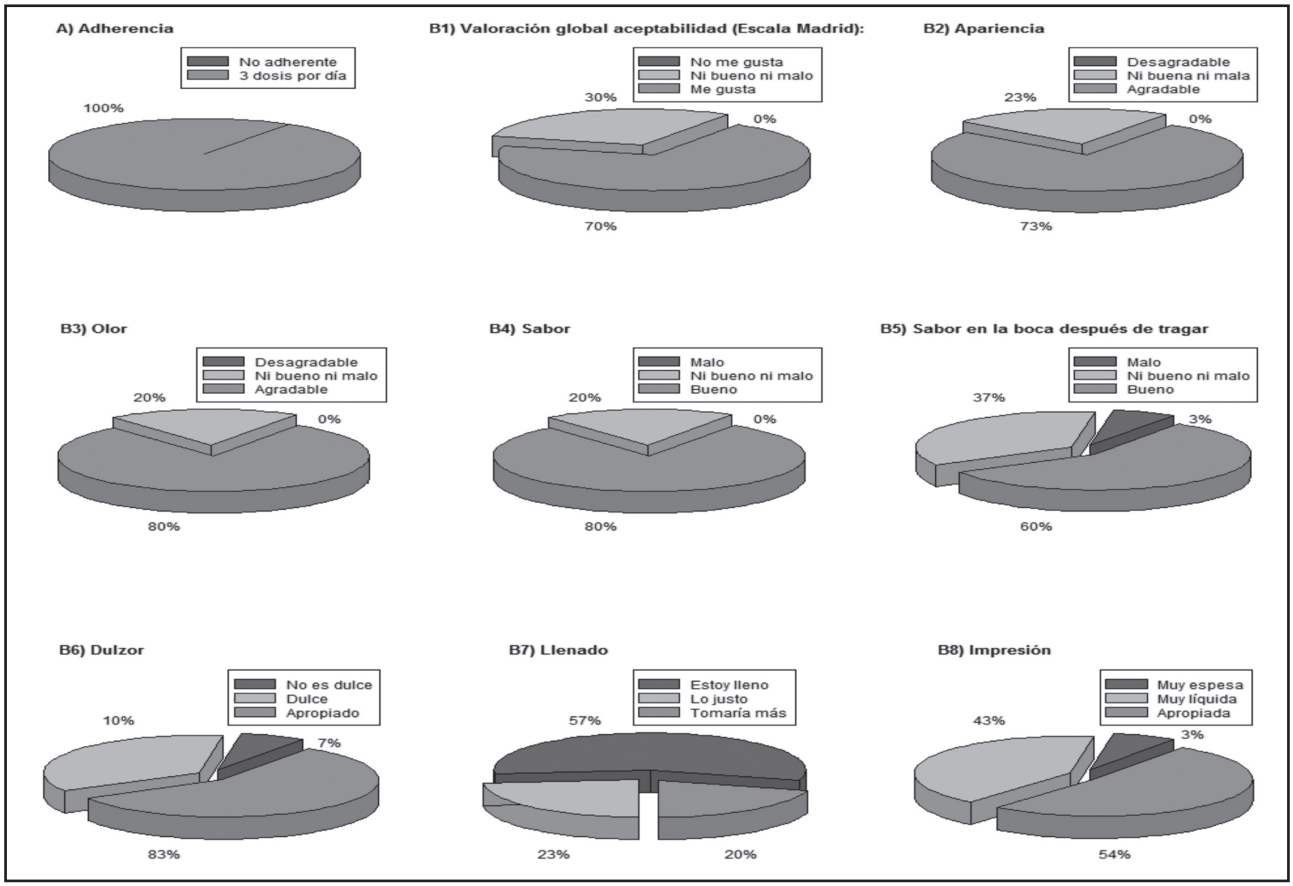

Figura 1.

Descripción de la adherencia y aceptabilidad (escala Madrid). El gráfico A describe la adherencia al tratamiento durante el estudio. Los gráficos B1 a B8 describen las puntuaciones de aceptabilidad obtenidas en la escala Madrid, para la evaluación global y para cada ítem. En el gráfico A se observa que el nivel de cumplimentación fue del 100%. En el gráfico B1 se observa que ningún paciente indicó que no le gustaba el suplemento.

(valoración positiva o no negativa en más del 90%). La saciedad y la textura fueron valoradas positivamente por el 77% y el 54% de los pacientes, respectivamente (Fig. 1).

Las puntuaciones totales de aceptabilidad en la primera y última visita del estudio tuvieron una mediana de 20,5 (rango: 15 a 24) y 20 (rango: 15 a 24). Estas dos puntuaciones mostraron una correlación muy elevada (correlación: Rho Spearman = 0,98; p < 0,001) (Fig. 2A) y no se diferenciaron estadísticamente (diferencia de medianas = 0, IC 95% 0 a 0, p = 0,655), lo que sugiere que la aceptabilidad del producto en primera toma se mantuvo relativamente constante en el resto de tomas. Por otra parte, se observó que en los pacientes discontinuados la mediana de aceptabilidad del producto fue menor que en el resto de pacientes (18,5 frente a 20,7).

Tolerancia gastrointestinal

Once pacientes (36,7%) presentaron AA gastrointestinales durante el estudio. Los más frecuentes fueron la distensión abdominal, la diarrea y las náuseas o vómitos en cinco (16,7%), cuatro (13,3%) y tres (10%) pacientes, respectivamente. Ninguno fue clasificado como grado III/IV por el investigador y solamente tres pacientes (10%) fueron considerados grado II. En estos tres pacientes se produjo la discontinuación del suplemento nutricional el segundo día (un paciente con distensión abdominal y náuseas) y el cuarto día (dos pacientes con diarrea). En dos casos (6,7%) se relacionaron los AA con la suplementación nutricional (distensión abdominal con náuseas y diarrea). Estos dos pacientes tendían a presentar una mayor ocurrencia de trastornos gastrointestinales previos a la suplementación (cáncer de colon y hernia umbilical) que el resto (p = 0,08).

Valoración antropométrica y nutricional

El peso, el IMC y la ingesta de proteínas se incrementaron significativamente tras seis días de suplementación nutricional (0,2 kg, 0,1 kg/m^2 y 6,2 g, respectivamente), lo que indica una detención de la pérdida de peso y del deterioro del estado nutricional. La ingesta de calorías y lípidos también aumentó, aunque no significativamente. Tampoco se observaron diferencias respecto a la ingesta de carbohidratos. Por tanto, los resultados no sugieren desplazamiento de la ingesta (Tabla II). Por otra parte, se observó que en los pacientes discontinuados la mediana del incremento de peso fue menor que en el resto de pacientes (0 kg frente 0,26 kg).

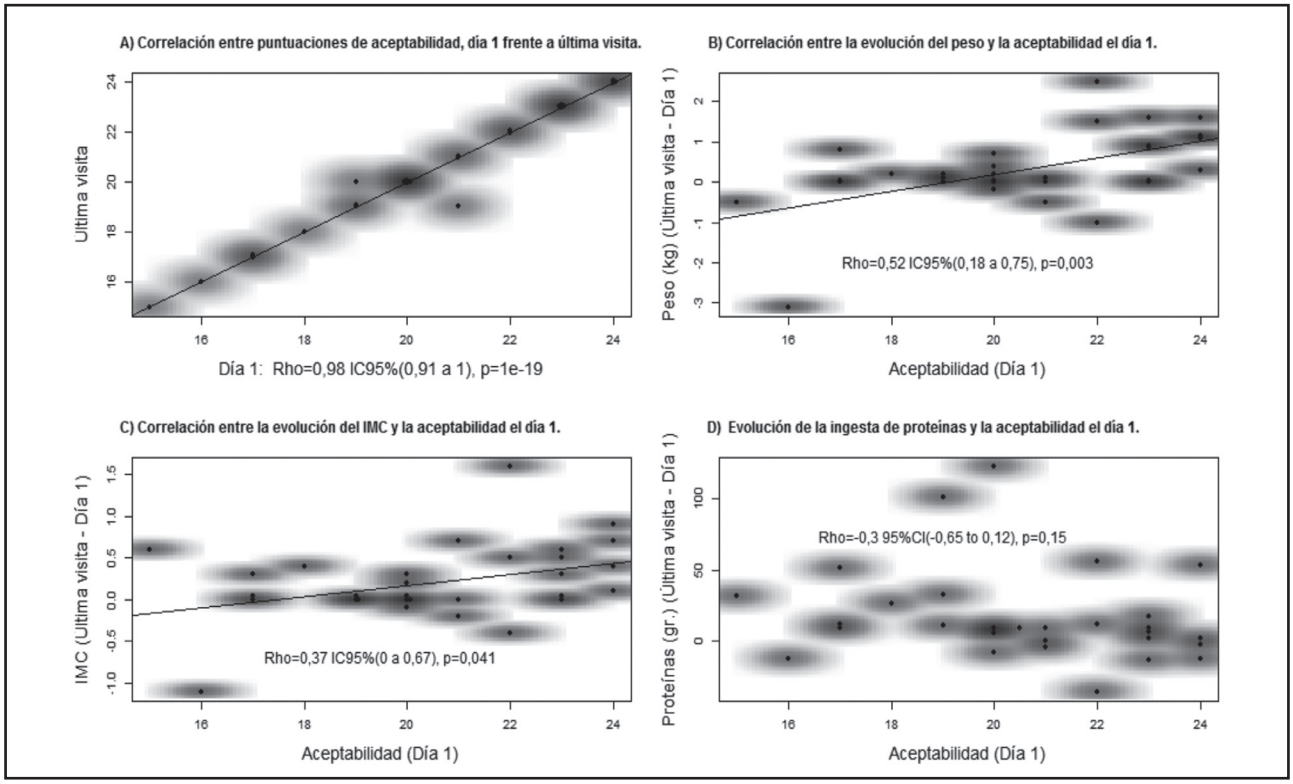

Figura 2.

Correlación entre las puntuaciones de aceptabilidad y la evolución de las variables antropométricas y de ingesta. Valores del estadístico Rho: de 0 a 0,1, ausencia total de correlación; de 0,1 a 0,25, correlación muy baja; de 0,25 a 0,5, correlación baja o moderada; de 0,5 a 0,75, correlación moderada o buena; de 0,75 a 1, correlación buena o excelente. Los valores negativos indican una correlación inversa. Se consideran correlaciones no debidas al azar las que presentan un p-valor < 0,05 (IMC: índice de masa corporal; g: gramos; IC 95: intervalo de confianza del 95%; IMC: índice de masa corporal; Rho: coeficiente de correlación de Spearman).

Tabla II. Características basales

Características basales	(n = 30)	
Edad (años), mediana (rango)	62	(32-79)
Género, n (%)		
Mujer	9	(30)
Hombre	21	(70)
Estado nutricional, n (%)		
Malnutrición severa	3	(10)
Malnutrición moderada*	27	(90)
Tipo de neoplasia, n (%)		
Maligna de pulmón	13	(43,3)
Maligna de ORL**	8	(26,7)
Maligna de mama	4	(13,3)
Linfoma no Hodking	2	(6,7)
Maligna de colon y recto	2	(6,7)
Maligna de cuello uterino	1	(3,3)
Estadio tumoral, n (%)		
II	3	(10)
III	11	(36,7)
IV	3	(10)
Tratamiento antineoplásico, n (%)		
Radioterapia	28	(93,3)
Quimioterapia	18	(60)
Cirugía	5	(16,7)
Enfermedades concomitantes, n (%)		
Metabolismo y nutrición	10	(33,3)
Vasculares	10	(33,3)
Psiquiátricos	7	(23,3)
Gastrointestinales	7	(23,3)
Peso habitual (kg), mediana (rango)	72	(49 a 100)
Peso al inicio (kg), mediana (rango)	70,2	(46,5 a 95,7)
IMC al inicio (kg), mediana (rango)	25,6	(17,5 a 35,5)
Masa de grasa (kg), mediana (rango)	18	(5,2 a 34,8)
Masa magra (kg), mediana (rango)	52,6	(35,9 a 72,8)
Agua corporal (l), mediana (rango)	38,5	(26,3 a 53,3)

*g: gramos; kg: kilogramos; IMC: índice de masa corporal; rango (máximo a mínimo). *Pacientes con malnutrición moderada o en riesgo de malnutrición. **Incluye: neoplasias de laringe (tres pacientes), orofaringe (tres pacientes) y nasofaringe (dos pacientes).*

ANÁLISIS DE SUBGRUPOS

De acuerdo al tipo de tumor, la puntuación total de aceptabilidad del suplemento nutricional en la primera visita fue de 21 (IQR: 18 a 23) para el cáncer de pulmón, 20,5 (IQR: 19 a 22) para el cáncer ORL, 20 (IQR: 18,5 a 21,5) para el cáncer de mama, 20 (IQR: 17 a 23) para el linfoma no Hodking, 22 (IQR: 20 a 24) para el cáncer de colon y recto y 20 (IQR: 20 a 20) para el cáncer de cuello uterino. La aceptabilidad del suplemento nutricional no se diferenció significativamente entre diferentes tipos de tumor.

La cumplimentación con la toma del soporte nutricional en todos los tipos de tumor fue del 100%.

Asociación entre aceptabilidad y datos antropométricos

La aceptabilidad del primer día de suplementación alimentaria correlacionó significativamente con la ganancia de peso (Rho = 0,52; $p < 0,05$) e IMC (Rho Spearman = 0,37; $p < 0,05$). No se observaron correlaciones significativas entre la aceptabilidad y el incremento de la ingesta de proteínas (Fig. 2).

Los ítems de la escala Madrid que presentaron una mayor correlación con la ganancia de peso fueron: el aspecto del suplemento (Rho = 0,46; $p < 0,05$), el sabor (Rho = 0,41; $p < 0,05$), el sabor después de tragar (Rho = 0,38; $p < 0,05$), la sensación de saciedad (Rho = 0,39; $p < 0,05$) y la valoración global del suplemento (Rho = 0,31; $p < 0,1$).

ANÁLISIS DE SEGURIDAD

Diecisiete pacientes (56,7%) presentaron AA durante el estudio. Según lo indicado previamente, en once pacientes (36,7%) fueron gastrointestinales y en diez pacientes (33,3%) se observaron no gastrointestinales. Solo en dos casos (6,7%) estos AA estuvieron relacionados con la suplementación y se trató de AA gastrointestinales (distensión abdominal con náuseas y diarrea). Todos los acontecimientos no gastrointestinales estuvieron relacionados con la enfermedad de base o el tratamiento antineoplásico (bajo recuento de linfocitos, hipoalbuminemia y hipercolesterolemia). Ningún paciente falleció durante el estudio y solo en un paciente se observó la progresión de la enfermedad.

DISCUSIÓN

Los pacientes mostraron un nivel de cumplimentación con el suplemento nutricional hiperproteico, hipercalórico, rico en omega 3 y de bajo volumen del 100% (IC 95%: 88,6 a 100%). Revisiones sistemáticas recientes han descrito niveles de cumplimentación media con suplementos nutricionales orales del 78% (rango: 37% a 100%) (16), lo que sugiere que el suplemento estudiado presenta unos niveles de cumplimentación superiores a lo observado en la mayor parte de estas publicaciones.

Los resultados de cumplimentación fueron coherentes con el elevado grado de aceptación del suplemento (ningún sujeto realizó una valoración negativa respecto a su sabor, olor, apariencia o evaluación global) y la mejora del estado nutricional de los pacientes (aumento de peso, IMC e ingesta de proteínas). No se observó desplazamiento de la dieta.

Tabla III. Evolución de las variables antropométricas y de ingesta

Variables	Periodo, mediana (IQR)		Mediana de la diferencia	
Antropométricas	*Previo***	*Suplementación***	*IC 95%*	*p-valor*
Peso (kg)	70,2 (58,9 a 80,4)	70,6 (59,2 a 80,9)	0,2 (0 a 0,7)	0,032
IMC (kg/m^2)	25,6 (23 a 27,6)	25,7 (23,1 a 27,9)	0,1 (0 a 0,4)	0,011
% pérdida peso*	2,82 (0 a 6,7)	2,4 (-1,13 a 6,02)	-0,2 (0 a -0,9)	0,036
Ingesta	*Previo*	*Suplementación*	*IC 95%*	*p-valor*
Calorías (kcal)	1.918,1 (1.574,3 a 2.335)	1.953,1 (1.647,1 a 2.431)	195,1 (-26,9 a 381,9)	0,128
Proteínas (g)	67,6 (53,6 a 80,4)	78,9 (56,2 a 94,1)	6,2 (1,1 a 19,1)	0,02
H. de carbono (g)	218,2 (188,4 a 233)	205,25 (162,5 a 284)	9,1 (-30,2 a 27,2)	0,951
Lípidos (g)	83,3 (62,3 a 119)	82,8 (72,3 a 113)	18 (-3,1 a 26,6)	0,153

*En la tabla se observa que la mediana del peso, el IMC, el % de pérdida de peso y las proteínas fueron estadísticamente diferentes ($p < 0,05$) en el periodo de suplementación respecto al periodo previo. Para peso, IMC y proteínas se observa un incremento en el periodo de suplementación. Para el % de pérdida peso se observa un decremento en el periodo de suplementación, lo que significa un aumento de peso. g: gramos; IC 95: intervalo de confianza del 95%; kcal: kilocalorías; kg: kilogramos; IMC: índice de masa corporal; IQR: rango intercuartil (percentil 25 a percentil 75). El análisis se ha realizado con la prueba de Wilcoxon para muestras relacionadas. *% pérdida de peso respecto al peso habitual: (p. habitual-p. actual)/p. habitual*100. **Los valores del periodo previo corresponden a la mediana de los tres días previos a la suplementación. Los valores en el periodo de suplementación corresponden a la última medición de este periodo.*

Por otra parte, la suplementación presentó un buen perfil de tolerabilidad en el estudio. Solo se observaron dos acontecimientos gastrointestinales relacionados. Estos pudieron ser revertidos modificando la pauta de la suplementación, sin prescribir medidas terapéuticas adicionales. Estos dos pacientes padecían trastornos gastrointestinales previos clínicamente relevantes (tributarios de tratamiento quirúrgico), lo cual sugiere que este tipo de pacientes debe tener un seguimiento especial durante la suplementación con el producto.

Nuestro estudio tuvo un periodo de tratamiento máximo de seis días. Algunos autores han relacionado un mayor tiempo de suplementación con una disminución de la aceptabilidad del suplemento (19), lo que sugeriría que esta disminución podría conllevar también un menor cumplimiento de la pauta del suplemento. Sin embargo, diferentes publicaciones (16,20) con seguimientos máximos de entre cuatro y 365 días no encontraron una relación entre la duración de la suplementación y la cumplimentación. En este sentido, nuestros resultados revelan que la adherencia al suplemento fue igual durante todo el seguimiento del estudio. Además, se observó una elevada correlación entre la aceptabilidad del suplemento al inicio y al final ($r = 0,98$).

Respecto a las diferencias con la bibliografía, la mayor parte de estudios oncológicos revisados fueron en pacientes con cánceres de cabeza y cuello y del sistema digestivo (16,21,22), mientras que los estudios no oncológicos fueron en ancianos pluripatológicos (16). Aunque el riesgo de malnutrición se ha asociado en mayor medida con este tipo de patologías (2,23,24), no se han observado diferencias en la adherencia a la suplementación entre los diferentes tipos de pacientes (e.g., ancianos, oncológicos, enfermedades respiratorias, fracturas, enfermedades renales) (16), en la línea de los resultados que observamos. También se sugiere que los pacientes oncológicos presentan un elevado cumplimiento de los tratamientos orales debido a la gravedad de su enfermedad (25). Las características que se han asociado a una buena cumplimentación con suplementos orales son: ser tratado en un marco asistencial comunitario (respecto al hospitalario [67% frente a 80%]), la elevada motivación en pacientes oncológicos (mediana de cumplimentación entre estudios del 85%, rango: 72-93% [25]), una menor edad en el momento de la suplementación y el alto contenido calórico de la suplementación con un mejor cumplimiento de la pauta de suplementación oral (16). Sin embargo, el grado de cumplimiento de nuestros resultados fue superior al cumplimiento en estudios previos realizados en el mismo marco asistencial y con población oncológica (67% y 85%).

Es destacable que la aceptabilidad del suplemento en la primera toma correlacionó significativamente con el aumento de peso en el estudio, observándose que los ítems que mostraron una mayor asociación con la ganancia de peso fueron el aspecto general de la bebida y su sabor. De acuerdo con otros estudios (11,14,26), este resultado enfatiza la importancia de factores como la presentación y la palatabilidad del suplemento en su eficacia para revertir la malnutrición del paciente, aunque nuestra hipótesis es que esta correlación observada es debida a un fenómeno de aversión condicionada al gusto (27) en el que el malestar gastrointestinal del paciente se asocia al suplemento administrado. Los tres pacientes discontinuados fueron los que presentaron acontecimientos gastrointestinales más severos y un menor grado de aceptabilidad del producto, recibieron una menor dosis del mismo y mostraron una menor ganancia de peso. Estos resultados subrayan la relación entre el malestar (o bienestar) experimentado por el paciente en el momento de la toma y su percepción del producto (27). En este sentido, existe la recomendación de que el paciente coma en un entorno muy placentero, en el cual se preste atención a la presentación de la comida (28).

Diferentes autores han indicado la importancia que tienen para la mejora de la cumplimentación las estrategias de comunicación

del equipo médico (29). En este estudio no es posible descartar que el elevado nivel de cumplimentación observado esté relacionado con las características específicas del equipo investigador. También cabe subrayar que los beneficios de la suplementación no se han comparado con otros suplementos nutricionales existentes en una misma cohorte de pacientes con cáncer. Por lo tanto, los resultados del estudio sugieren que el suplemento nutricional hiperproteico, hipercalórico, rico en omega 3 y de bajo volumen analizado presenta una elevada cumplimentación y aceptabilidad en pacientes con cáncer, aunque es necesaria la realización de futuros estudios controlados multicéntricos para valorar su eficacia en comparación con otros productos nutricionales y bajo diferentes prácticas clínicas.

CONCLUSIÓN

La aceptabilidad y cumplimentación elevadas observadas con el suplemento nutricional específico resultaron estar asociadas con la mejora del estado nutricional de los pacientes de cáncer, logrando, además, recuperar la pérdida de peso sin presentar problemas gastrointestinales severos y sin que se diera desplazamiento de la ingesta.

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Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

Índice glicémico, carga glicémica e insulina posprandial a dos fórmulas isoglucídicas con distintos edulcorantes y fibra en adultos sanos y diabéticos tipo 2

Glycemic index, glycemic load and insulin response of two formulas of isoglucose with different sweeteners and dietary fiber in healthy adults and type-2 diabetes

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Resumen

Objetivo: el objetivo de este estudio fue comparar el índice glicémico (IG), la carga glicémica (CG) y la insulina posprandial de dos fórmulas isoglucídicas con distintos edulcorantes y fibra en adultos sanos y diabéticos tipo 2 (DM2).

Metodología: en este estudio aleatorizado, cruzado y doble ciego, once sujetos sanos y seis diabéticos consumieron dos fórmulas en cuatro ocasiones (Glucerna SR® Laboratorios Abbott C.A [FG] y Enterex Diabetic®, Victus, C.A [FE], edulcoradas con fructosa y sucralosa respectivamente, con distintas fuentes de fibra), además de solución glucosada (SG) en una ocasión. Se obtuvieron muestras de sangre en ambos grupos a los tiempos 0, 15, 30, 45, 60, 90 y 120 minutos; en los diabéticos se adicionó el minuto 150 y 180 para medición de glicemias e insulina basal/posprandial de dos y tres horas.

Resultados: el área de incremento bajo la curva de glucosa (IAUC) fue menor para las fórmulas que para SG. En sanos fue de 12.857 ± 422 para FE y 11.601 ± 272 para FG ($p < 0,014$). En diabéticos resultó más disminuida para FG (28.656 ± 123) comparada con FE (29.855 ± 496) ($p < 0,01$). El IG resultó 58,07 ± 8,4 y 60,7 ± 2 para FG y FE respectivamente en controles, y 65,16 ± 0,2 y 68,06 ± 1 en diabéticos, sin diferencias; igualmente en la insulina posprandial.

Conclusiones: el IG y la CG de ambas fórmulas resultaron en un valor intermedio en los dos grupos, con perfil glicémico inferior al de SG. No se observaron diferencias en el comportamiento insulínico, evidenciando que la velocidad de absorción de los carbohidratos de estas fórmulas es prolongada, con impacto glicémico menor que el producto patrón, lo que sugiere que es aceptable su indicación en el diabético.

Palabras clave:

Fórmulas. Fibra. Edulcorantes. Diabetes.

Abstract

Objective: The aim of this study is to compare the glycemic index (GI) and glycemic load (GL) of two formulas with the same glucose content with different sweeteners and dietary fiber for diabetics in healthy adults and in patients with type-2 diabetes (DM2).

Methodology: In this randomized, double-blind crossover research, eleven healthy people and six with DM2 consumed two enteral formulas, Glucerna SR®, Laboratorios Abbott C.A. (GF) and Enterex Diabetic®, Victus C.A. (EF), sweetened with fructose y sucralose, with 1.2 and 1.3 g/100 ml of fiber source respectively (four times). Additionally, they consumed glucose solution once, obtaining blood samples at 0, 15, 30, 45, 60, 90 and 120 min for controls; in the diabetics, minutes 150 and 180 were added for measuring blood glucose, basal and postprandial insulin after two and three hours.

Results: The incremental area under the curve (IAUC) was lower for the formulas rather than for SG. In the healthy controls was 12,857 ± 422 for EF and 11,601 ± 272 for GF ($p < 0.014$). In diabetics, this curve reduced for GF (28,656 ± 123) compared to EF (29,855 ± 496) ($p < 0.01$). The IG resulted in 58.07 ± 8.4 and 60.7 ± 2 for GF and EF, respectively, in the controls, and 65.16 ± 0.2 and 68.06 ± 1 in diabetics, without significant differences, as well as in post-prandial insulin.

Conclusions: The GI and the GL of the two formulas resulted in an intermediate value in both groups, with a glycemic profile inferior to SG. No significant differences were observed regarding insulin behavior, showing that the absorption rate of carbohydrates in these formulas is slower, with a lower glycemic impact than the pattern product; thus, making its indication acceptable for the diabetic patient.

Key words:

Formulas. Fiber. Sweeteners. Diabetes.

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INTRODUCCIÓN

La incidencia de la diabetes mellitus ha alcanzado proporciones epidémicas que la han convertido en un flagelo mundial, con una estimación por la Federación Internacional de la Diabetes (FID) de 415 millones de diabéticos durante el año 2015 y una proyección de 642 millones en 2040, de los cuales 48,8 millones corresponderían a Centro y Suramérica (1).

Actualmente, la nutrición constituye la piedra angular en el manejo de la diabetes. Las directrices nutricionales han sido establecidas por la Asociación Europea para el Estudio de la Diabetes (4), la Asociación Americana de la Diabetes (ADA) (5), la Asociación Canadiense de Diabetes (6) y el Subcomité de Nutrición de Diabetes de Reino Unido (7). Al respecto, la terapia nutricional está direccionada hacia el control glicémico, constituyendo una parte crítica de las guías de tratamiento mundial, en las cuales destaca la atención dirigida tanto a la cantidad como al tipo de carbohidrato ingerido (8). En este sentido, el índice glicémico (IG) clasifica los alimentos según la calidad de los carbohidratos, midiendo su velocidad de absorción, mientras que la carga glicémica (CG) es un término más reciente que relaciona calidad y cantidad del carbohidratos (CHO) por gramos de porción habitual de consumo (8,9). Ambos permiten reducir el impacto glicémico posprandial sin la restricción total de carbohidratos en la dieta (9).

Un estudio prospectivo de Reino Unido demostró que el control glicémico estricto tiene un impacto clínico positivo a largo plazo en diabéticos, retrasando la aparición y progresión de complicaciones asociadas a la diabetes (2). Se ha reportado que las intervenciones terapéuticas que disminuyen la hiperglicemia son también capaces de reducir el riesgo de padecer de nefropatía, retinopatía y neuropatía diabética especialmente (3).

De acuerdo a directrices de la IDF, las dietas con una baja carga glicémica son beneficiosas para mejorar el control glicémico (8). Como estrategia para ayudar a mantener la euglicemia en el diabético, existen fórmulas enterales específicas para diabetes utilizadas como sustitutos calóricos nutritivos en individuos normopeso, con sobrepeso u obesos, o suplementos para desnutridos con DM2 (10).

Recientemente, ha sido ampliado el número de fórmulas nutricionales específicas para diabetes, con distintos nutrientes para facilitar el control glucémico: ácidos grasos monoinsaturados (AGM), componentes bioactivos como la fibra dietaria, fructosa (10) y edulcorantes artificiales como la sucralosa (con efectos metabólicos hipotéticamente distintos) (11).

Una revisión sistemática sobre fórmulas específicas comparadas con fórmulas estándar ha demostrado menores picos glicémicos y menor incremento en el área bajo la curva de glucosa (IAUC), sin evidencia de hipoglucemias. Además, con el uso de fórmulas estándar en estos pacientes, han sido relacionadas mayores complicaciones y requerimientos insulinémicos al intentar contrarrestar fluctuaciones glicémicas (10).

No obstante, la Sociedad de Nutrición Parenteral y Enteral (ASPEN) ha sugerido ampliar los estudios sobre el uso de fórmulas específicas para diabéticos (12). Por ello, el diseño y la aprobación de estos productos para el control glicémico en pacientes diabéticos constituye un área de creciente interés y extensa investigación (13). El estudio de indicadores de la respuesta glicémica a los alimentos generalmente se realiza en sujetos sanos, con el fin de determinar una referencia metabólica para establecer comparaciones con los diabéticos. Por tal motivo, el objetivo de este estudio fue comparar el índice glicémico, la carga glicémica y la insulina posprandial posterior a la ingesta de dos fórmulas isoglucídicas, con distintos edulcorantes y fibra dietaria, en adultos sanos y con DM2.

MATERIAL Y MÉTODOS

Fueron seleccionados 17 sujetos (once sanos y seis con DM2) que asistieron al Centro de Investigación Endocrino-metabólicas de la Facultad de Medicina de la Universidad del Zulia, bajo los siguientes criterios de inclusión y exclusión:

- *Sujetos sanos:* índice de masa corporal (IMC) normal (18,4 a 24,9 kg/m^2), ausencia de enfermedades crónicas, historia familiar de DM, sin tratamiento médico y con valores bioquímicos normales. Glicemia basal > 100 mg/dl fue criterio de exclusión.
- *Sujetos diabéticos*: fueron seleccionados hombres y mujeres de entre 45 y 60 años, con diagnóstico de DM2 de acuerdo a los criterios de la ADA (3) y uso demostrado de hipoglucemiantes orales (metformina) durante al menos dos meses anteriores a la selección e IMC de 18,5 kg/m^2 a ≤ 35 kg/m^2. Se excluyeron los individuos con DM1, cetoacidosis diabética, insuficiencia cardiaca congestiva, enfermedades gástricas renales o hepáticas, infarto de miocardio, accidente cerebrovascular y sujetos con insulinoterapia/corticosteroides o antibioticoterapia.

Los participantes firmaron el consentimiento informado, aprobado por el Comité de Ética del Centro de Investigaciones Endocrino-metabólicas de la Universidad del Zulia-Venezuela, basado en la Declaración de Helsinki (14). Para la medición de datos antropométricos se utilizó una báscula de bioimpedancia eléctrica Tanita UM-018 Digital Scales (Tokio, Japón). La altura se midió utilizando un estadiómetro modelo SECA 26SM 200 cm (Hamburgo, Alemania).

Inicialmente, la muestra del protocolo correspondía a 20 sujetos (nueve diabéticos, once sanos). Tres de los sujetos patológicos no fueron incluidos en la investigación (un sujeto se retiró voluntariamente) y dos fueron medicados con antibioticoterapia.

DISEÑO DEL ESTUDIO

El estudio aleatorizado, cruzado, controlado y doble ciego de cinco pruebas de consumo (dos para cada fórmula enteral [= 4] y uno para el producto de referencia [solución glucosada Glicolab®]) se realizó de acuerdo al protocolo de índice glicémico del 2009, con intervalos de una semana (15). Los sujetos recibieron instrucciones de actividad física a < de 90 min/semana e indicaciones dietéticas por parte de un nutricionista antes de cada visita, con inclusión de un consumo promedio mínimo de 150 g de CHO/día durante los

tres días anteriores a cada sesión en los diabéticos y > 250 g en los controles, confirmado con un registro de alimentos de 72 horas. Ningún alimento con cafeína ni leguminosas fue permitido la noche anterior. Se les solicitó evitar consumo de alcohol o tabaco.

PROCEDIMIENTO

Durante seis días distintos fueron tomadas en ayuno de diez horas muestras capilares de sangre (por duplicado) antes de iniciar cada prueba, asegurando glicemias < 100 mg/dl en los controles y de entre ≥ 60 mg/dl y < 300 mg/dl en los diabéticos. Inmediatamente después de las muestras básales, al sujeto se le dio a consumir en un periodo estandarizado < 15 minutos la fórmula asignada aleatoriamente o la solución glucosada junto con 250 ml de agua. Posteriormente, se obtuvieron muestras de sangre capilar y venosa a los tiempos 15, 30, 45, 60, 90 y 120 min (dos horas) tanto en controles como en diabéticos, adicionando en estos últimos el minuto 150 y 180 (tres horas) (15), diferencia fundamentada en que la curva glicémica es más lenta en los diabéticos que en los sujetos sanos.

FÓRMULAS EVALUADAS

Las fórmulas evaluadas fueron Glucerna SR® (FG), de Laboratorios Abbott C.A, y Enterex Diabetic® (FE), de Victus C.A. Al momento del estudio FG contenía: maltodextrina, fructosa, maltitol y sucromaltosa como fuente de carbohidratos; polisacáridos de soya y fructo-oligosacáridos (FOS) como fibra; como fuente lipídica, ácido oleico y de soya; como fuente proteica, caseinato de calcio; y suplementos de vitaminas y minerales en cantidades variables. El tamaño de la porción es de 237 ml, con un aporte calórico de 220 kcal, 11,02 g de proteínas, 8 g de grasas totales y 29,08 g de carbohidratos disponibles, de los cuales 1,8 g corresponden a fibra dietética y 1,0, a fructooligosacáridos (2,8 g).

La FE es una fórmula de presentación líquida con ingredientes como maltodextrina, caseinato de sodio, aceite de cártamo, caseinato de calcio, fibra de soya, goma arábica y goma guar, aceite de canola, vitaminas y minerales. El tamaño de ración corresponde a 8 oz líq. (237 ml), 240 calorías, 12 g de proteínas, 9 g de grasa total, 27 g de carbohidratos disponibles y 3 g de fibra dietética. El volumen final utilizado fue 408 ml de cada fórmula para la obtención de 50 g de CHO en cada caso. La solución glucosada (producto de referencia) se utilizó al 20%, aportando 220 kcal.

ANÁLISIS DE LAS MUESTRAS

Para comprobar los criterios diagnósticos, a ambos grupos se les tomó muestra de sangre en ayunas de diez horas para las determinaciones iniciales de glucosa y perfil lipídico. Después de haber desayunado, se tomó una nueva muestra posprandrial (dos horas después) en los controles para determinar glucosa e insulina, esta última también fue medida en ayunas para el grupo control. Con los métodos enzimáticos (Human GMBH, Alemania) y radioinmunoanálisis (DRG) fueron cuantificados glicemia y perfil lipídico e insulina, respectivamente.

La glicemia capilar fue determinada con glucómetros (Optium Xceed®, Abbott). El perfil lipídico incluye: colesterol total (mg/dl), colesterol- HDL (mg/dl) y triacilglicéridos (mg/dl). El colesterol-LDL (mg/dl) y el colesterol VLDL (mg/dl) fueron determinados por la fórmula de Friedewald, y el HDL-colesterol fue calculado por la adición de LDL-c y VLDL-c. La insulina se midió con el método de radioinmunoanálisis utilizando un kit comercial (DRG), con coeficientes de variación intra e interensayo de 5,1% y 7,1%, respectivamente, y con una sensibilidad de 1,2 LtIU/ml.

ANÁLISIS ESTADÍSTICO

Incremento del área bajo la curva, cálculo del índice glicémico y carga glicémica

La respuesta glicémica postprandial fue evaluada como IAUC individual (dos horas para controles) y (tres horas en diabéticos) (15), mediante el método trapezoidal, con dos IAUC para cada fórmula, utilizando el programa NCSS 2009. Con estos valores se calculó el IG, expresado como porcentaje por medio de la siguiente ecuación (15):

$$\text{Índice glicémico} = \frac{\text{AUC del alimento referencia x 100}}{\text{AUC del alimento prueba}}$$

El valor encontrado se dividió entre 1,4 para reportar los resultados tomando como base la glucosa (15).

Los valores se clasificaron en IG bajo (≤ 55), intermedio (55-69) y alto (≥ 70) (9). La carga glicémica (CG) representó una medida derivada del IG del alimento en estudio y fue calculada con la siguiente fórmula: CG = IG x CHO por porción de alimento/100 (9). Los valores resultantes han sido categorizados en CG alta > 20, CG media 11-19 y CG baja < 10 (9).

Los datos se expresan como la media y desviación estándar (DE). Previo a los análisis se evaluó la normalidad en la distribución de los datos mediante el test de Shapiro-Wilk. Junto a ello, se determinó la homogeneidad de las varianzas mediante la prueba F. Estos análisis mostraron una distribución no paramétrica de los datos. Con el fin de evaluar diferencias estadísticas entre las variables, se utilizó el test no paramétrico de U de Mann-Whitney. Se consideró significativa la diferencia cuando el valor de alfa fue inferior a 0,05. Todos los análisis se hicieron con el software SPSS 17.

RESULTADOS

CARACTERÍSTICAS DE LOS SUJETOS

La media ± DE de la edad, peso, estatura, IMC y circunferencia abdominal de los controles fue de 29,4 años ± 5,4, 62,6 kg ± 9,5, 162,9 ± 8,6, 23,4 kg/m^2 ± 1,7 y 75,8 ± 4,5, respectivamen-

te. La media ± DE de insulina basal fue de 11,9 ± 4,2 y el índice de Homa IR fue 1,6 ± 0,4. En los valores de glicemia, colesterol y triglicéridos se observó una media ± DE de 61,10 ± 22,89, 164,91 ± 18,6 y 146,7 ± 24,05, calificando a este primer grupo como sujetos sanos. En los sujetos diabéticos destacó la media ± DE de edad 54,5 ± 4,6, peso 79,7 ± 5,4, talla 1,61 ± 0,05 e IMC de 30,4 kg/m^2 ± 0,04. La media ± DE en glicemia, colesterol y triglicéridos fue de 150 ± 21,3, 209,0 ± 5,5 y 166,7 ± 18,8.

ÁREA DE INCREMENTO BAJO LA CURVA

La media y la DE del IAUC se muestra en la tabla I para las fórmulas estudiadas tanto en los sujetos sanos con una diferencia de $p < 0,0001$ entre FG y la SG, y un valor de $p < 0,014$ entre fórmulas. En los sujetos diabéticos se encontró una diferencia de $p < 0,01$ entre ambas bebidas, y entre la SG y las dos formulaciones la diferencia fue $p < 0,0001$.

RESPUESTA GLICÉMICA

El perfil glicémico posterior a la ingesta de glucosa y a las fórmulas enterales de ambos grupos se muestra en las figuras 1 y 2, así como las diferencias de tiempos entre las curvas. No se encontraron diferencias estadísticas en las concentraciones de glicemia basales para ninguno de los tratamientos. En los controles, tras la ingesta de las fórmulas, la concentración máxima de glucosa fue alcanzada a los 30 minutos ($p < 0,007$). En los sanos, la glicemia disminuyó de forma similar a las concentraciones basales en el minuto 105, destacando un descenso previo en el minuto 60 con una nueva alza para la FE en el minuto 90 ($p < 0,05$) comparada con la FG. En los diabéticos, las diferencias en la concentración de glicemia entre ambas fórmulas fueron dadas entre los 30 y 60 minutos, con un máximo incremento glicémico en el minuto 45 y alcanzando concentraciones de 178,9 mg/dl para la FG y 189,2 mg/dl para la FE ($p < 0,02$). Al término del periodo de medición (dos y tres horas), la glicemia permaneció más elevada que el nivel de ayuno ($p < 0,05$) para ambas bebidas. Cabe destacar que la curva glicémica se observó más aplanada y disminuida posterior a la ingesta de la FG en los dos grupos.

Tabla I. Comparación del área bajo la curva según el tipo de fórmula

	Área bajo la curva(mg/dl/min)		
Sujetos sanos	(SG) Glicolab®	FG	FE
Total	13.809 ± 1.359[a]	11.116 ± 987[b]	12.697 ± 1.145
Sujetos diabéticos	39.720 ± 413[c,d]	28.656 ± 123[e]	29.855 ± 496

SG: solución glucosada; FG: Glucerna SR®; FE: Enterex Diabetic®. Letras distintas indican diferencias significativas [a]: p 0,0001 con FG; [b]: p 0,014 con FE en sujetos sanos; [c,d]: 0,0001 con FG y con FE en sujetos diabéticos; [e]: p 0,01 con FE en sujetos diabéticos.

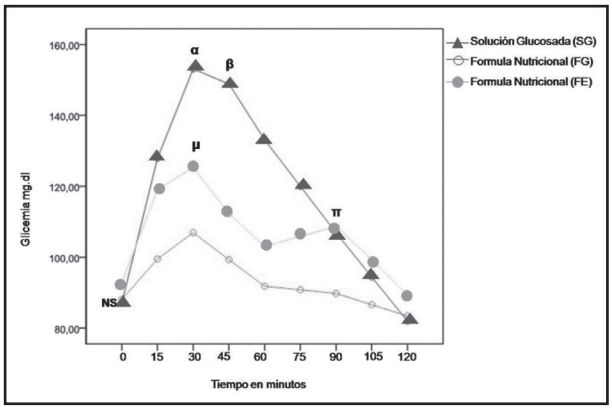

Figura 1.

Curvas de glucosa después del consumo de bebidas comerciales específicas para diabéticos Glucema SR (FG) Enterex Diabetic (FE), y solución glucosada (SG) en sujetos sanos (Diferencias significativas entre α: Glicolab (SG) y Glucema (FG) $p < 0,0001$; β: Glicolab (SG) y Enterex (FE) $p < 0,003$; μ: Glucema (FG) y Enterex (FE) $p < 0,007$; π: Glucema (FG) y Enterex (FE) $p < 0,05$).

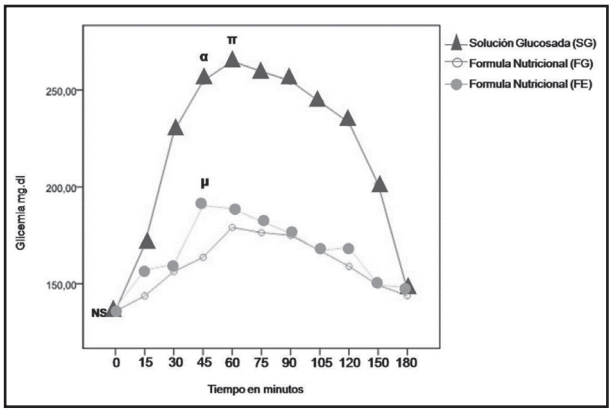

Figura 2.

Curvas de glucosa después del consumo de bebidas comerciales específicas para diabéticos Glucema SR (FG) Enterex Diabetic (FE), y solución glucosada (SG) en sujetos con diabetes tipo 2 (Diferencias significativas entre π: Glicolab (SG) y Glucema (FG) $p < 0,0001$; α: Glicolab (SG) y Enterex (FE) $p < 0,009$; μ: Glucema (FG) y Enterex (FE) $p < 0,02$).

ÍNDICE GLICÉMICO, CARGA GLICÉMICA E INSULINA POSPRANDIAL

Se expresan como la media y DE en la tabla III. El IG calculado en los controles fue de 58,0 ± 8,4 y 60,7 ± 2 mg/dl para FG y FE respectivamente, sin diferencias significativas, mientras que en los diabéticos se encontró un valor de 65,1 ± 0,2 y 68,0 ± 1 mg/dl. Se encontraron diferencias entre grupos con respecto al IG de la FE, resultando más bajo en el grupo control que en los DM2 ($p < 0,011$). Con respecto a la CG, no se encontraron diferencias por tratamientos en ningún grupo. El comportamiento insulinémico basal y posprandial de dos horas (controles) y tres horas (diabéticos) se expresa como media y DE en la tabla III, sin diferencias por tratamiento ni por grupos.

Tabla II. Comparación del índice glicémico y carga glicémica según el tipo de tratamiento

IG tamaño de la porción CHO disponibles (g) CG/glucosa			
Sanos			
FG 58,07 ± 8 FE 60,7 ± 7	237 ml 237 ml	29 g 27 g	16,8 ± 2,4 16,3 ± 1,9
Diabéticos			
FG 65,4 ± 1,2 αFE 68,1 ± 0,1	237 ml 237 ml	29 g 27 g	18,9 ± 1,2 18,3 ± 2,4

*IG: índice glicémico; CG: carga glicémica. *Letras distintas indican diferencias significativas. Diferencia de α = 0,011 para FE entre sanos y diabéticos.No se observaron diferencias significativas entre las cargas glicémicas de las fórmulas para ninguno de los grupos.*

DISCUSIÓN

Los hallazgos del presente estudio confirman que el perfil glicémico y las IAUC en sujetos sanos y diabéticos fue menor, como era de esperar, posterior al consumo de las fórmulas evaluadas en relación al producto de referencia. Se encontraron diferencias en el IAUC entre fórmulas tanto en los controles como en diabéticos, sin diferencias estadísticas entre el IG y la CG en ninguna de las dos bebidas, con un perfil glicémico más atenuado postingesta de la FG. Los valores de estos dos indicadores resultaron intermedios para las dos fórmulas en ambos grupos, y más bajos al compararlos con los valores del pan blanco reportados en las tablas de Atkinson (IG = 80-96) (16).

En esta tabla, el promedio publicado de IG (33-44) y CG (6-9) para la FG es menor que el nuestro. Sin embargo, se conoce que la variabilidad en la respuesta glicémica es elevada, incluso intraindividualmente, posiblemente también afectada por diferencias raciales, considerando que tales valores fueron determinados en sujetos de Australia, Norteamérica y Canadá, mientras que nuestra muestra es latinoamericana (15,16).

Posterior al consumo de la FG en los diabéticos, la media en el pico glicémico resultó acorde a lo recomendado por la ADA (3) en el periodo posprandial para diabéticos controlados en ayuno (< 180 mg/dl), con hemoglobina glicosilada (HbA1c) elevada. Sin embargo, el objetivo recomendado por la IDF es de 160 mg/dl (5). Nuestros resultados coinciden con investigaciones previas que señalan que el consumo de fórmulas específicas para diabetes (FED) comparado con el de fórmulas estándar (FS) atenúa la respuesta glicémica e insulinémica en DM2 (2,17,18).

De Luis afirma que la diversidad en la composición de las FED es determinante para mejorar el control glicémico, más que la cantidad total de carbohidratos únicamente. Menciona, además, que la sustitución de ácidos grasos saturados (AGS) por monoinsaturados reduce la respuesta insulinémica y glicémica (19), positivamente relacionada con los niveles de (HbA1c) y fructosamina (19). También han sido reportados requerimientos insulínicos más bajos (20) tras el consumo de fórmulas específicas para diabetes (26%) *versus* fórmulas estándar (71%), aunado a menores requerimientos por g de carbohidratos ingeridos (20). Sin embargo, nuestros resultados no mostraron diferencias en el comportamiento insulinémico posprandial (dos y tres horas) por tratamiento en ningún grupo. En una investigación, tras el consumo de la FG en sujetos sanos se halló una tendencia a reducir la primera fase en la secreción insulínica y a incrementar su sensibilidad (21). En otro estudio se encontraron menores niveles en el minuto 120 posterior a la ingesta de la fórmula FE comparada con la FG (p = 0.012), evidenciando un incremento de triglicéridos por parte esta última (p = .026) (22).

Sin embargo, la administración de estas fórmulas específicas para diabetes sigue siendo motivo de controversia, concretamente en diabéticos hospitalizados con hiperglicemia (12). No obstante, revisiones sistematizadas del soporte nutricional enteral que incluyen estas fórmulas muestran los beneficios metabólicos en DM1 y 2 (12,23). Sanz y cols. (24) afirman que la ingesta de fórmulas hipercalóricas específicas para diabéticos en adultos mayores desnutridos puede aumentar la ingesta calórica, elevando la albúmina (p < 0,001) y la hemoglobina (p = 0,026) y manteniendo el control glicémico (24).

Por otra parte, la composición nutricional de las FED contiene CHO de digestión y absorción más lenta que las fórmulas estándar (11,18). Voss y cols. (2) compararon en DM dos fórmulas con carbohidratos de absorción lenta (CDL), ácidos grasos saturados (AGS) y una FS, y reportaron que el uso de la fórmula (CDL) con AGM (w: 3) produjo una menor respuesta glicémica e

Tabla III. Comportamiento de la insulina plasmática posterior a la ingesta de las dos fórmulas específicas para diabetes

	Valores de insulina plasmática (UI/ml)		
Sujetos sanos	(SG) Glicolab® Media	FG Media	FE Media
Insulina basal Insulina posprandial	13,4 ± 2,3 20,3 ± 5,3	12,9 ± 2,1 16,1 ± 6,3	13,1 ± 1,9 17,2 ± 5,9
Sujetos diabéticos			
Insulina basal Insulina posprandial	15,2 ± 1,3 26,2 ± 3,1	14,5 ± 1,2 18,9 ± 1,8	14,2 ± 1,4 19,7 ± 1,2

*SG: solución glucosada; FG: Glucerna SR®; FE: Enterex Diabetic®. *No existieron diferencias estadísticas por tratamiento ni por grupo.*

insulinémica, con mayores niveles del péptido similar al glucagón (GLP-1) (2).

Se conoce que este péptido es secretado por las células L en el íleon terminal en respuesta a señales neuroendocrinas y a la presencia de nutrientes. Los carbohidratos digeridos lentamente pueden viajar más abajo en el intestino delgado antes de ser absorbidos y estimular un incremento plasmático tardío del GLP-1 (25). Tal es el caso de la sucromaltosa (análogo natural de la sacarosa, de menor impacto glucémico) (18,25), con incremento sostenido del GLP-1 durante cuatro horas postingesta de 50/80 g, lo que confirma su lenta absorción (25). Esto sugiere que la cantidad/calidad de los CHO podría mejorar la función de las células beta del DM2 en tiempo prolongado (2).

Por ello, la fuente y el tipo de molécula del CHO son relevantes. Devitt (18) reportó diferencias en las respuestas glucémicas postprandiales entre cuatro bebidas específicas para diabetes: la primera contiene isomaltosa; la segunda, dextrinas de tapioca; la tercera, almidón de tapioca/fructosa; y la cuarta, sucromaltosa, combinada con una maltodextrina resistente a la digestión de la amilasa en el intestino delgado, cuya respuesta glicémica fue menor frente a las otras (18). Es conocido el IG de ciertos endulzantes, entre ellos, el bajo valor de la fructosa (= 19) (16,23) y la isomaltosa (= 32) (26), cuya tasa de hidrolización es un 20-25% más lenta que en la sacarosa (= 59) (16,26). En tanto, se requieren estudios concretos sobre el IG de la sucromaltosa y de las dextrinas de tapioca.

Las fórmulas FG y FE de este estudio contienen fructosa y sucralosa respectivamente. Una investigación afirma que los edulcorantes artificiales, a pesar de no ser absorbidos a nivel intestinal (con nulo aporte calórico), pudieran inducir a la secreción de insulina pancreática a través del sistema nervioso central posterior a la degustación del sabor dulce del alimento (27). No obstante, son necesarios estudios clínicos en humanos. Referente a la fructosa, endulzante calórico (16) cuya vía metabólica no depende de insulina (28), algunos autores señalan que su metabolismo hepático puede producir niveles de glucemia más elevados, y otros explican que la producción es muy lenta por su absorción más prolongada frente a la sacarosa (28,29). Por otra parte, al comparar el IG de otros endulzantes como el maltitol IG (= 26) (16) frente al xilitol (= 7) y a la tagatosa (= 3), endulzante derivado de la lactosa, se observa que este último posee menor IG incluso que las mezclas endulzantes compuestas por polidextrosa y sorbitol, cuyo valor es = 4 (16).

El tipo y la cantidad de fibra son igualmente relevantes en la velocidad de absorción del CHO ingerido (específicamente, el tipo soluble aporta viscosidad a la formulación), con efectos sobre la motilidad intestinal, en hormonas y enzimas gastrointestinales (18). Concentraciones de fibra idénticas en productos similares han generado IG distintos; tal es el caso de dos fórmulas específicas para diabetes cuya carga de fibra es de 1,5 g/100 ml, derivada de polisacáridos de soja, inulina, goma arábica, celulosa, oligofructosa y 100% hidrolizado de goma guar, con un IG de = 40 y = 37, respectivamente (16). Índices menores (= 31) han sido reportados en fórmulas hipercalóricas con concentraciones de fibra más elevadas 2,3 g/100 ml (16). En este sentido, la fórmula FG evaluada en este estudio contiene una proporción de fibra de 1,2 g/100 ml, mientras que la FE posee 1,3 g/100 ml. Bebidas con concentraciones de 2 g/100 ml de fibra y edulcoradas con fructosa han sido estudiadas en sujetos sanos con un IG = 49 (16), valor cercano a los de nuestra investigación. Al respecto, se ha demostrado que la combinación estratégica de fibra dietaria con AGM y baja cantidad de CHO provee un mejor control al disminuir el pico glicémico y el IAUC en sanos *vs.* DM2 (2,23), como muestran nuestros resultados.

La fibra del tipo goma guar, betaglucano, psillyum, glucomannan o pectina produce un aumento particular en la viscosidad que reduce la respuesta posprandial y el IG de los alimentos (30). Recientemente, novedosas fuentes de fibra han sido evaluadas por la industria alimentaria con el fin de formular productos específicos para diabéticos, tal es el caso del mucílago de la linaza. Esta fracción de fibra soluble podría afectar potencialmente la secreción insulínica y su acción en la homeostasis de la glucosa plasmática (31).

Al respecto, Marco y cols. (32) indagaron los niveles posprandiales de glucosa e insulina, así como el IG de bebidas lácteas fortificadas con polisacáridos de soja (6%) ($p < 0,01$) y con goma de linaza ($p < 0,001$) y hallaron diferencias significativas con respecto al producto estándar. Sin embargo, no hallaron diferencias en las IAUC de insulina, en el índice insulinémico ni en la concentración máxima de esta hormona (32). Así mismo, se ha estudiado el efecto de otras semillas oleaginosas tales como el sésamo sobre la HbA1c en DM2, interesantes de indagar en ensayos de fortificación para fórmulas especializadas en el control glicémico (33).

Por otra parte, la cantidad y el tipo de proteína también podrían afectar la hiperglucemia postprandial (34), retrasando el vaciamiento gástrico (18). Efectos similares han sido reportados en diversos estudios con proteínas sobre la respuesta glicémica e insulinémica, especialmente con la proteína lactosérica (35), de la cual han sido observados cambios en la glucosa oral en sujetos sanos, sin estar afectados por el ayuno insulinémico (34,35).

Los efectos fisiológicos de proteínas séricas y caseínas pueden ser producidos por diferencias entre sus propiedades físicas. Las proteínas séricas se digieren más rápidamente que las caseínas por la coagulación de estas en el estómago, con menores tasas de digestión enzimática y menores concentraciones posprandiales de aminoácidos plasmáticos, frente a proteínas no coagulantes como el lactosuero (35). En las fórmulas evaluadas en esta investigación, la cantidad total y fuente de proteínas es similar (caseinato de calcio y sódico), por lo que diferencias del perfil glicémico no podrían atribuirse a este nutriente.

Finalmente, la mayoría de los valores de IG y CG en formulas específicas para diabetes publicados en la tabla de Atkinson han sido determinados únicamente en sujetos sanos (16). Nuestro estudio podría ser útil para futuras investigaciones al determinar ambos indicadores en DM2 particularmente para la FE. Sería interesante comparar respuestas glicémicas de otras fórmulas enterales de distintos carbohidratos de liberación prolongada sobre el efecto de saciedad y el GLP-1, así como la HbA1c en cortes longitudinales, correlacionándolo con la prevención de complicaciones micro-macrovasculares en DM1 y DM2.

CONCLUSIÓN

El creciente interés de la industria alimentaria en el diseño de fórmulas enterales para diabéticos ha permitido la incorporación de nutrientes funcionales como carbohidratos de absorción lenta (maltodextrinas resistentes), edulcorantes calóricos (fructosa) o endulzantes artificiales (sucralosa) e ingredientes bioactivos como la fibra dietaria y AGM, direccionando así novedosas investigaciones hacia su utilización en matrices alimentarias de adecuadas respuestas glicémicas. En este estudio, el IG y la CG de las dos fórmulas nutricionales resultaron en un valor intermedio sin diferencias entre grupos, con una curva glicémica más atenuada posterior al consumo de la FG. Estos resultados sugieren que la velocidad de absorción de los carbohidratos que componen ambas fórmulas es más lenta que el producto de referencia, y que el impacto glicémico de estas es menor ante la misma cantidad de carbohidratos derivados del producto patrón, infiriendo que la diversa composición de endulzantes y fibra dietaria entre ambas fórmulas no produjo efectos metabólicos distintos en el IG, CG ni en la insulinemia posprandial, lo que sugiere como aceptable su indicación en diabéticos. Sería interesante evaluar la ingesta a largo plazo y relacionarla con marcadores inflamatorios, así como con la secreción y sensibilidad insulínica en DM2.

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Trabajo Original

Paciente crítico

Effect of glutamine on liver injuries induced by intestinal ischemia-reperfusion in rats

Efecto de la glutamina en las lesiones hepáticas inducidas por isquemia-reperfusión intestinal en ratas

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Abstract

Introduction: Intestinal ischemia-reperfusion (I/R) injury may cause cell and tissue damage, reaching also other organs such as the liver. Because of the involvement of free radicals in I/R injury, treatment options with antioxidants have been studied and tested.

Objective: To evaluate the effect of glutamine (Gln) in the liver of animals with intestinal I/R injury.

Methods: We used 20 male Wistar rats divided into four groups: sham-operated (SO); glutamine + sham-operated (G+SO); intestinal ischemia-reperfusion (I/R); glutamine + intestinal ischemia-reperfusion (G+I/R). The superior mesenteric artery was clamped for 30 minutes and reperfused for 15 minutes. Gln (25 mg/kg/day) diluted in 1 ml of saline was administered intraperitoneally on the two days before I/R induction.

Results: Levels of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), lipid peroxidation (LPO) and expressions of interleukin-6 (IL-6) and nuclear factor kappa B (NF-kB) showed a significant reduction in the G+I/R group as compared with the I/R group. The activity of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and the levels of glutathione (GSH) showed an increase in the G+I/R group as compared with the I/R group.

Conclusion: Pretreatment with Gln reduced oxidative, tissue damage and showed a decrease expression of inflammatory mediators.

Key words:

DNA damage.
Inflammation.
Lipid peroxidation.
Oxidative stress.

Resumen

Introducción: las lesiones por isquemia-reperfusión (I/R) intestinales pueden causar daño celular y tisular, llegando incluso a otros órganos, como el hígado. Debido a la participación de radicales libres en la lesión I/R, se han estudiado y probado opciones de tratamiento con antioxidantes.

Objetivo: evaluar el efecto de la glutamina (Gln) en el hígado de los animales con lesión intestinal I/R.

Métodos: se utilizaron 20 ratas Wistar macho divididas en cuatro grupos: sham-operadas (SO); glutamina + sham-operadas (G+SO); isquemia-reperfusión intestinal (I/R); glutamina + isquemia-reperfusión intestinal (G+I/R). La arteria mesentérica superior se clampó durante 30 minutos y se llevó a cabo la reperfusión durante 15 minutos. Se adminsitró Gln (25 mg/kg/día) diluida en 1 ml de solución salina por vía intraperitoneal en los dos días previos a la inducción de la I/R.

Resultados: los niveles de aspartato aminotransferasa (AST), alanina aminotransferasa (ALT) y fosfatasa alcalina (FA), la peroxidación lipídica (POL) y las expresiones de interleucina-6 (IL-6) y factor nuclear kappa B (NF-kB) mostraron una reducción significativa en el grupo G+I/R en comparación con el grupo I/R. La actividad de la catalasa (CAT), la superóxido dismutasa (SOD), glutatión peroxidasa (GPx), y los niveles de glutatión (GSH) mostraron un aumento en el grupo G+I/R en comparación con el grupo I/R.

Conclusión: el tratamiento previo con Gln redujo el daño tisular oxidativo y mostró una disminución de los mediadores inflamatorios.

Palabras clave:

Daño en el DNA.
Inflamación.
Peroxidación lipídica.
Estrés oxidativo.

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INTRODUCTION

Intestinal ischemia is caused by several clinical conditions such as trauma, shock, strangulated hernia, intestinal obstruction, and small intestine transplant (1). The intestinal mucosa is injured during ischemia due to the reduction and/or obstruction of blood flow. After reintroduction of blood flow, these injuries may get worse, leading to intestinal ischemia-reperfusion (I/R) injury (2).

Several mechanisms are involved in intestinal I/R injury, such as neutrophil infiltration, intracellular adhesion molecules (ICAM-1), production of proinflammatory cytokines such as interleukin 1β and 6 (IL-1β, IL-6) and tumor necrosis factor alpha (TNF-α), exacerbated generation of reactive oxygen species (ROS), and activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) (3,4). This condition may damage the integrity of the intestinal barrier, leading to possible bacterial translocation into the bloodstream, thus triggering the onset of the systemic inflammatory response syndrome (SIRS) and the consequent physiological dysfunction of two or more systems, which is known as multiple organ dysfunction syndrome (MODS) (5-7). The liver is one of the organs that undergoes these changes because of the close relationship between intestinal function and balance of liver function. In case of bowel disease, there is imbalance of the intestinal microbiota, thus causing and worsening liver injuries (8,9).

Although some molecular aspects of the mechanism of action causing intestinal I/R injuries have not been well defined, studies have shown that inflammatory cytokines and increased ROS generation play an important role in the pathogenesis of intestinal and systemic injuries after an I/R event (10,11).

Inflammatory mediators, such as IL-6 and TNF-α, are linked to the activation of neutrophils and tissue damage resulting from I/R. Studies have demonstrated that plasma and tissue levels of these cytokines are high in intestinal I/R and MODS. These mediators may be activated by the NF-kB, which plays an important role in the control of adaptive immune responses by regulating the expression of these pro-inflammatory genes (7).

The oxidative processes resulting from the exacerbated generation of ROS may cause damage to proteins, lipids, and DNA. These processes are involved in the progression of the intestinal I/R injury and the integrity and function of other organs. Experimental studies have shown the association of oxidative damage with intestinal I/R injury in organs such as lung, liver, and kidney (7,11,12). The antioxidant system may compensate for these damages caused by ROS through enzymatic substances, such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx), and non-enzymatic substances such as glutathione (GSH). Therefore, recent studies have shown that the administration of antioxidants may contribute to reduce oxidative processes and decrease the local and systemic inflammatory process caused by the intestinal I/R injury (1,4,11,13).

Glutamine (Gln) is a hydrophilic, non-essential amino acid found on the surface of proteins, where it interacts with water. Gln is a precursor for the synthesis of nucleic acids and GSH. In addition, Gln plays a key role in the immune defense of the intestinal mucosal barrier by participating in the formation of immunoglobulins, especially IgA (14,15). Some mechanisms suggest a protective role of glutamine in the intestinal inflammatory response, namely: increased intestinal antioxidant capacity through the synthesis of GSH, reduced apoptosis, and preserved intestinal integrity, thus reducing the local and systemic inflammatory parameters (14,16).

Experimental studies have demonstrated the antioxidant role of Gln in reducing ROS generation and pro-inflammatory cytokines, as well as in preserving tissue GSH in experimental models of liver I/R (17). Fillmann et al. (2007), Marques et al. (2001), and Zhang et al. (2011) showed that pretreatment with Gln reduced oxidative and tissue damages in the gut, stomach, and liver. These authors also found a reduction in the inflammatory processes, suggesting a protective effect of Gln against free radicals (14,15,18).

In our previous study we demonstrated that pretreatment with Gln reduced intestinal lesions resulting from intestinal ischemia and reperfusion model. We observed a reduction in intestinal tissue damage, decreased oxidative damage as well as reducing inflammation mediators studied (7).

Therefore, the objective of the present study was to investigate the antioxidant and anti-inflammatory effect of Gln based on the evaluation of lipid peroxidation (LPO), DNA damage, activity of CAT, SOD, and GPx, GSH levels, and expression of IL-6 and NF-kB. Our hypothesis suggests that treatment with Gln could reduce oxidative, cell, and inflammatory damage in the liver tissue induced by an intestinal I/R experimental model.

MATERIALS AND METHODS

ANIMALS AND GLUTAMINE ADMINISTRATION

Our procedures involving animals followed the guidelines of the Research and Ethics Committee of the Research and Graduate Studies Group (GPPG), Hospital de Clínicas de Porto Alegre (HCPA), approved with the protocol number 12-0241, and the European Council Directive regarding animal experimentation (19,20).

We used 20 male Wistar rats. Their mean weight was 300 grams. The animals were divided into four groups: sham operated (SO) (n = 5), glutamine + sham operated (G+SO) (n = 5), intestinal ischemia-reperfusion (I/R) (n = 5), and glutamine + intestinal ischemia-reperfusion (G+I/R) (n = 5). The animals stayed at the Animal Experimentation Unit (UEA) of the Hospital de Clínicas de Porto Alegre. They were kept in plastic boxes lined with wood shavings and measuring 47 x 34 x 18 cm, on a 12:12-hour light/dark cycle (light from 7 am to 7 pm) and temperature between 20 and 25 °C. Water and feed were given *ad libitum*. The animals were intraperitoneally anesthetized with xylazine hydrochloride (8 mg/kg of body weight) and ketamine hydrochloride (92 mg/kg of body weight). Laparotomy and evisceration were performed to identify the superior mesenteric artery in both groups. In groups SO and G+SO (surgery simulation) the artery was not obstructed and in groups I/R and G+I/R mesenteric artery was occluded for 30 minutes using a microsurgical vascular clamp. After intestinal ischemia was achieved, the microsurgical vascular clamp was

removed and the animals were reperfused for 15 more minutes (adapted from Cho et al., 2013) (3). After this period, the liver was removed for histological analysis and other tests. Finally, the animals were killed by exsanguination under deep anesthesia (20).

Gln was administered intraperitoneally at a dose of 25 mg/kg diluted in 1 ml of saline. This dose was given once daily for 48 hours before ischemia induction (14,15).

LIVER FUNCTION TESTS BASED ON ASPARTATE AMINOTRANSFERASE (AST), ALANINE AMINOTRANSFERASE (ALT) AND ALKALINE PHOSPHATASE (ALP)

Levels of serum AST, ALT, and ALP were determined by the Biochemistry Center of the Hospital de Clínicas de Porto Alegre. To determine AST and ALT levels in the plasma, we used the commercially available enzymatic method (Boehringer Mannheim, Germany) and the results were obtained by kinetic measurement at 567 nm. Levels of ALP were measured with an automated analyzer by the enzymatic method, using p-nitrophenyl phosphate (pNPP) substrate plus water, forming p-nitrophenol, a compound measured with maximum absorption of 400 nm.

LIVER HOMOGENATE

Liver tissues were homogenized for 30 seconds in an ULTRA-TURRAX® disperser (IKA-Werke GmbH & Co. KG) at 4 °C using 1.15% KCl (5 ml/g of tissue) and phenylmethanesulfonylfluoride (PMSF) at a concentration of 100 mM. Next, the homogenates were centrifuged for ten minutes at 3,000 rpm in a refrigerated centrifuge (SORVALL Super T21, Kendro Laboratory Products, USA). The supernatant was removed and stored in microtubes. The samples were stored at -80 °C for later analyses (21).

LPO

The amount of aldehydes generated by LPO is determined by the method that measures the amount of thiobarbituric acid reacting substances (TBARS). Thiobarbituric acid was added to the samples at 0.37%, whereas trichloroacetic acid was added at 15%. The samples were incubated at 100 °C for 15 minutes and centrifuged at 3,000 rpm (1,612 x g) for ten minutes at 4 °C. Absorbency was determined by spectrophotometry at 535 nm (22).

COMET ASSAY

An alkaline comet assay was performed as described by Hartmann and Speit (1999), including some changes suggested by Picada et al. in 2003 (23,24). Blood samples (50 µl) were added to 5 ml of anticoagulant (heparin sodium 25,000 IU/ml solution - Liquemine®, Roche). Blood cell suspensions (5 µl) were added to 95 ml of 0.75% low melting point agarose (Gilco BRL) and placed on agarose pre-coated microscope slides. After solidification, the slides were placed in lysis buffer (2.5 M NaCl, 100 mM EDTA, 10 mM Tris, pH 10.0). We added 1% Triton X-100 (Sigma) and 10% dimethyl sulfoxide (DMSO) for 48 hours at 4 °C. Next, the slides were subsequently incubated in alkaline buffer (300 mM NaOH and 1 mM EDTA, pH > 13) for 20 minutes at 4 °C. An electric current of 300 mA and 25 V (0.90 V/cm) was applied for 15 minutes to perform DNA electrophoresis. Then the slides were neutralized (0.4 M Tris, pH 7.5), stained with silver, and analyzed by microscope. Images of 100 randomly selected cells (50 cells of each slide) were analyzed from each animal. The cells were also visually classified according to the size of the tail into five categories ranging from undamaged (0) to maximum damage (4), resulting in a single DNA damage score for each animal and for each group. Therefore, the damage index (DI) may range from 0 (completely intact, 100 cells x 0) to 400 (maximum damage, 100 × 4). The damage frequency (%) was calculated based on the number of tailed cells *vs* tail-less cells.

ACTIVITY OF ANTIOXIDANT ENZYMES: CAT, SOD, GPX AND GSH LEVELS

The analysis of CAT activity was based on the measurement of the reduction of hydrogen peroxide. The activity was detected spectrophotometrically at 240 nm with values expressed as pmol/mg prot (25). The analysis of SOD activity was based on the inhibition of the reaction of epinephrine with superoxide radical, which could be detected spectrophotometrically at 480 nm with values expressed as USOD/mg prot (26). GPx activity was determined based on the consumption of nicotinamide adenine dinucleotide phosphate (NADPH) in the reduction of oxidized glutathione, which could be detected spectrophotometrically at 340 nm within two minutes with the values expressed as nmol/min/mg prot (27). Measurement of GSH levels was detected spectrophotometrically at 412 nm with values expressed as µmol/mg prot, according to the method of Beutler, Duran and Kelly (28).

IMMUNOHISTOCHEMISTRY AND QUANTIFICATION OF THE EXPRESSION OF IL-6 AND NF-kB

The expression of IL-6 and NF-kB in liver tissue was determined by immunohistochemical analysis. Antigen retrieval was performed using buffer at 60 °C, and endogenous peroxidase activity was blocked by incubation in absolute methanol. The slides were incubated with rabbit polyclonal antibody (NF-kB [p65] [SC8008] - Santa Cruz Biotechnology, USA) at 1:100 and (IL-6 [SC1265] - Santa Cruz Biotechnology, USA) at 1:100 overnight at 4 °C. The slides were washed with buffer and incubated with the secondary antibody (anti-mouse IgG-HRP, anti-goat IgG-HRP, Santa Cruz Biotechnology, Santa Cruz, CA, USA) at 1:300 for 30 minutes at room temperature.

The slides were examined by a pathologist, who was unaware of the groups, using a microscope equipped with a digital analysis system including a Zeiss Axioskop 40 microscope (Oberkochen, Germany) connected by a Roper Scientific camera (Media Cybernetics, Rockville, USA) to a computer with an image capture software. The Image-Pro Plus version 4.5 software (Media Cybernetics, Rockville, USA) was used to analyze digital images. The expression was determined by multiplying the mean density of the image by the percentage of positively stained areas (brown-stained areas).

WESTERN BLOT

Western blot analysis was performed on nuclear extracts prepared from liver homogenates as previously described. The supernatant fraction was collected and stored at -80 °C in aliquots until use. Lysate proteins were fractionated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene fluoride (PVDF) membranes. The membranes were then blocked with 5% nonfat dry milk in Tris buffered saline containing 0.05% Tween 20 (TTBS) for one hour at room temperature and probed overnight at 4 °C with polyclonal anti-NF-kB (p65) (SC8008/65kDa) (Santa Cruz Biotechnology, Santa Cruz, CA, USA) at 1:200-1,000 dilution with TTBS in 5% nonfat dry milk. Anti-β-actin antibody (A5060/42kDa) (Sigma Aldrich, St Louis, MO, USA) at 1:2,000 dilution with TTBS in 5% nonfat dry milk. After washing with TTBS, the membranes were incubated for one hour at room temperature with secondary anti-mouse IgG-HRP antibody (Santa Cruz Biotechnology, Santa Cruz, CA, USA, 1:4,000). Protein detection was performed by chemiluminescence using a commercial ECL kit (Amersham Pharmacia Biotech, Little Chalfont, UK). The density of the specific bands was quantified using Scion Image software (Scion Corp., Frederick, MD, USA) (29,30).

STATISTICAL ANALYSIS

Data are expressed as means ± standard error. Statistical significance was calculated using Graphpad Instat, version 3.0 for Windows. We used one-way analysis of variance (ANOVA) and Student-Newman-Keuls for multiple analysis. Analysis of variance with robust standard errors (Welch) was used to investigate the results of the expression of IL-6 and NF-kB between the groups. Results were considered as statistically significant when the significance level was at least 5% ($p < 0.05$).

RESULTS

LIVER FUNCTION TESTS BASED ON AST, ALT AND ALP

The serum levels of AST, ALT and ALP were significantly increased in the I/R group as compared with the SO and G+SO groups, whereas there was a reduction in these levels in the I/R+G group in comparison with the I/R group (AST*, #$p < 0.001$; ALT*, $p < 0.001$, #$p < 0.05$; ALP*, #$p < 0.01$) (Table I).

LPO AND COMET ASSAY

LPO levels (Fig. 1A) showed a significant increase in the I/R group as compared with the SO and G+SO groups, whereas there was a significant decrease in LPO levels in the G+I/R group as compared with the I/R group (*, #$p < 0.001$).

The results of the comet assay showed an increase in the damage index (Fig. 1B) and damage frequency (Fig. 1C) in the I/R group as compared with the SO and G+SO groups, whereas there was a reduction in these parameters in the G+I/R group in comparison with the I/R (*$p < 0.01$, #$p < 0.05$).

ACTIVITY OF CAT, SOD, GPX AND GSH LEVELS

The activities of CAT (Fig. 2A), SOD (Fig. 2B) and GPx (Fig. 2C) decreased significantly in the I/R group when compared with the SO and G+SO groups, whereas these activities increased in the G+I/R group as compared with the I/R group (*$p < 0.01$, #$p < 0.05$).

The GSH levels (Fig. 3) showed a significant decrease in the I/R group as compared with the SO and G+SO groups, whereas there was a significant increase in the G+I/R group as compared with the I/R group (*$p < 0.01$, #$p < 0.05$).

IMMUNOHISTOCHEMISTRY AND QUANTIFICATION OF THE EXPRESSION OF IL-6 AND NF-kB

The animals of the I/R group showed strong positive staining for IL-6 (Fig. 4) and NF-kB (Fig. 6), which was visible because of the brown staining.

Table I. Effect of glutamine administration on the levels of enzymes of liver cell integrity in the blood of animals subjected to the intestinal ischemia-reperfusion model

Groups	AST	ALT	ALp
SO	101.60 ± 2.66	51.40 ± 3.24	160.20 ± 11.57
G+SO	105.33 ± 9.58	56.00 ± 4.97	159.60 ± 8.76
I/R	291.00 ± 23.57*	91.80 ± 8.62*	187.80 ± 4.82*
G+I/R	145.00 ± 12.44#	76.00 ± 3.34#	155.33 ± 4.75#

*Values are expressed as mean ± SEM. *Significant difference between the I/R group and the SO and G+SO groups. #Significant difference between the G+I/R group and the I/R group. Sham operated (SO), glutamine + sham operated (G+SO), intestinal ischemia-reperfusion (I/R), glutamine + intestinal ischemia-reperfusion (G+I/R). AST - *, # $p < 0.001$; ALT - * $p < 0.001$, # $p < 0.05$; ALP - *, # $p < 0.01$.*

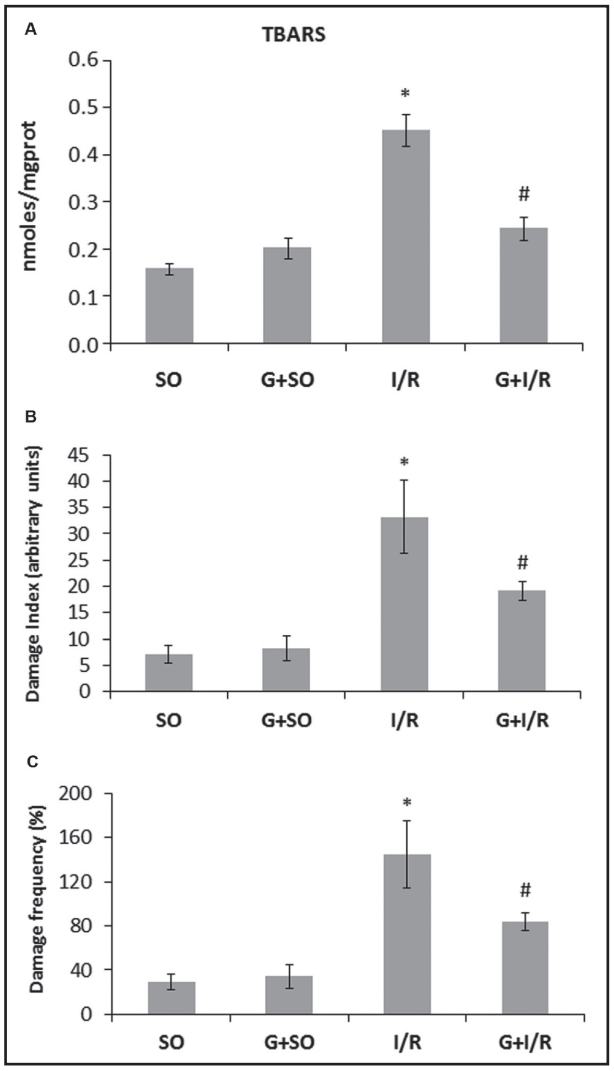

Figure 1.

Effect of glutamine administration on levels of lipid peroxidation in the liver tissue and DNA damage in the blood of animals subjected to the intestinal ischemia-reperfusion model. A. TBARS. B. Damage index. C. Damage frequency. Values are expressed as mean ± SEM. A. *Significant difference between the I/R group and the SO and G+SO groups ($p < 0.001$). #Significant difference between the G+I/R group and the I/R group. ($p < 0.001$). B and C. *Significant difference between the I/R group and the SO and G+SO groups ($p < 0.01$). #Significant difference between the G+I/R group and the I/R group ($p < 0.05$). Sham operated (SO), glutamine + sham operated (G+SO), intestinal ischemia-reperfusion (I/R), glutamine + intestinal ischemia-reperfusion (G+I/R).

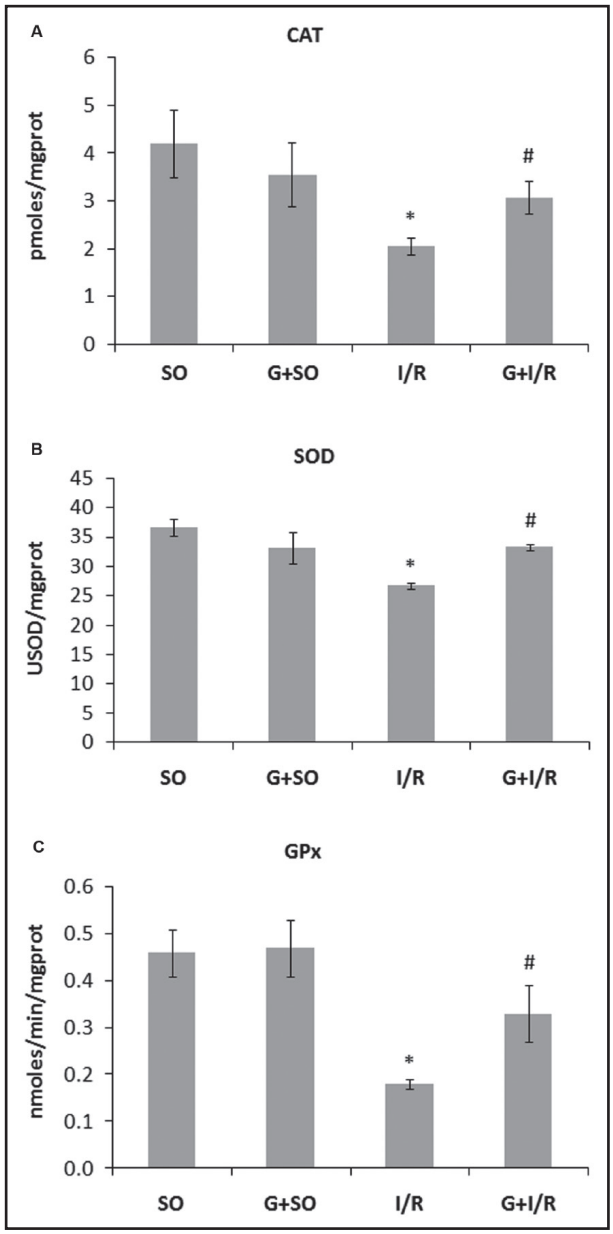

Figure 2.

Effect of glutamine administration on the CAT, SOD and GPx activity in the liver of animals subjected to the intestinal ischemia-reperfusion model. A. CAT. B. SOD. C. GPx. Values are expressed as mean ± SEM. *Significant difference between the I/R group and the SO and G+SO groups ($p < 0.01$). #Significant difference between the G+I/R group and the I/R group ($p < 0.05$). Sham operated (SO), glutamine + sham operated (G+SO), intestinal ischemia-reperfusion (I/R), glutamine + intestinal ischemia-reperfusion (G+I/R).

The SO and G+SO groups showed no positive staining. Pretreatment with Gln reduced the staining for IL-6 and NF-kB in the G+I/R group.

Similarly, the quantification of the expression of IL-6 (Fig. 4) and NF-kB (Fig. 5) showed an increase in the expression of inflammatory mediators in the I/R group as compared with the SO and G+SO groups and a significant reduction in the G+I/R as compared with the I/R group (*$p < 0.001$, #$p < 0.05$). All images were magnified 400x.

WESTERN BLOT NF-kB (p65)

The expression of nuclear factor NF-kB (p65) (Fig. 6) showed an increase in the I/R group as compared with the SO and G+SO groups, and a significant decrease in the G+I/R as compared with the I/R group (*$p < 0.01$, #$p < 0.05$).

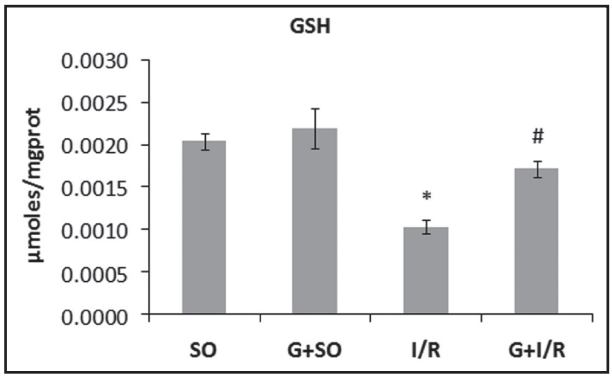

Figure 3.

Effect of glutamine administration on GSH levels in the liver of animals subjected to the intestinal ischemia-reperfusion model. Values are expressed as mean ± SEM. *Significant difference between the I/R group and the SO and G+SO groups ($p < 0.01$). #Significant difference between the G+I/R group and the I/R group ($p < 0.05$). Sham operated (SO), glutamine + sham operated (G+SO), intestinal ischemia-reperfusion (I/R), glutamine + intestinal ischemia-reperfusion (G+I/R).

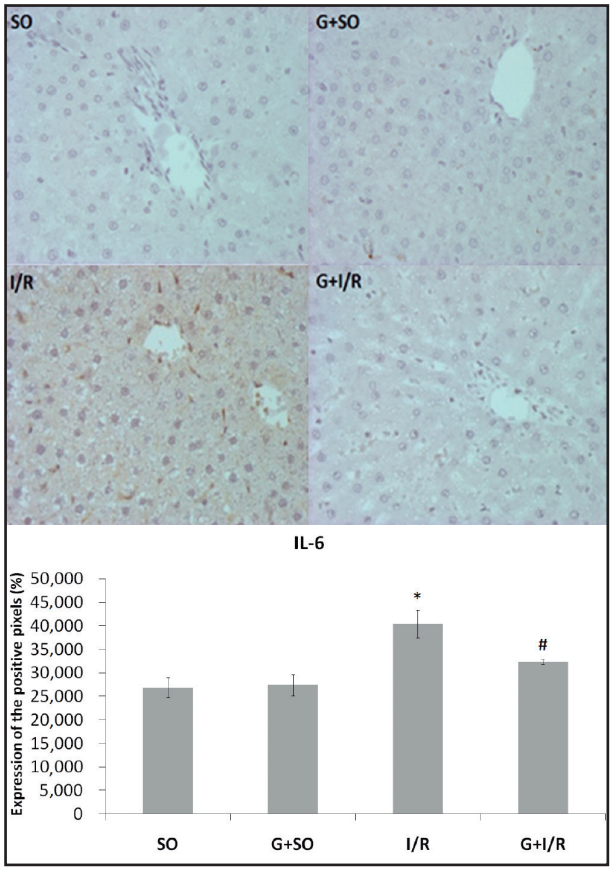

Figure 4.

Effect of glutamine administration on the immunohistochemistry and expression of IL-6 in the liver of animals subjected to the intestinal ischemia-reperfusion model. Values are expressed as mean ± SEM. *Significant difference between the I/R group and the SO and G+SO groups ($p < 0.001$). #Significant difference between the G+I/R group and the I/R group ($p < 0.001$). Sham operated (SO), glutamine + sham operated (G+SO), intestinal ischemia-reperfusion (I/R), glutamine + intestinal ischemia-reperfusion (G+I/R).

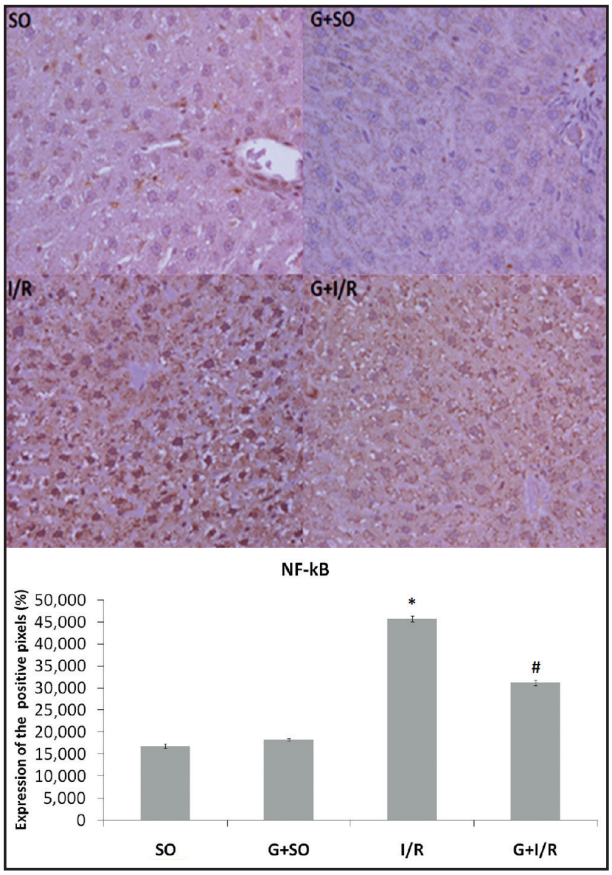

Figure 5.

Effect of glutamine administration on the immunohistochemistry and expression of NF-kB (p65) in the liver of animals subjected to the intestinal ischemia-reperfusion model. Values are expressed as mean ± SEM. *Significant difference between the I/R group and the SO and G+SO groups ($p < 0.001$). #Significant difference between the G+I/R group and the I/R group ($p < 0.001$). Sham operated (SO), glutamine + sham operated (G+SO), intestinal ischemia-reperfusion (I/R), glutamine + intestinal ischemia-reperfusion (G+I/R).

DISCUSSION

Intestinal I/R is often associated with small intestine transplant, strangulated hernia, aortic aneurysm surgery, and necrotizing enterocolitis, with high rates of mortality and morbidity in recent decades. Some studies suggest that this injury may trigger the involvement of other organs and it may be the main mechanism in the pathogenesis of MODS (6,13).

The small intestine is susceptible to ischemic injury, and the main factors involved are adhesion molecules, nitric oxide, pro-inflammatory cytokines, and reactive oxygen species. Some studies suggest that exacerbated generation of free radicals is one of the major causes of local and systemic injuries (8,9,12).

The gut-liver axis plays a key role in the deleterious effects induced by intestinal I/R because the intestinal bloodstream is connected to liver vascularization. Intestinal I/R leads to the production and subsequent release of deleterious substances, such as ROS and inflammatory mediators, which reach the liver through the portal vein causing severe liver injuries (31-33).

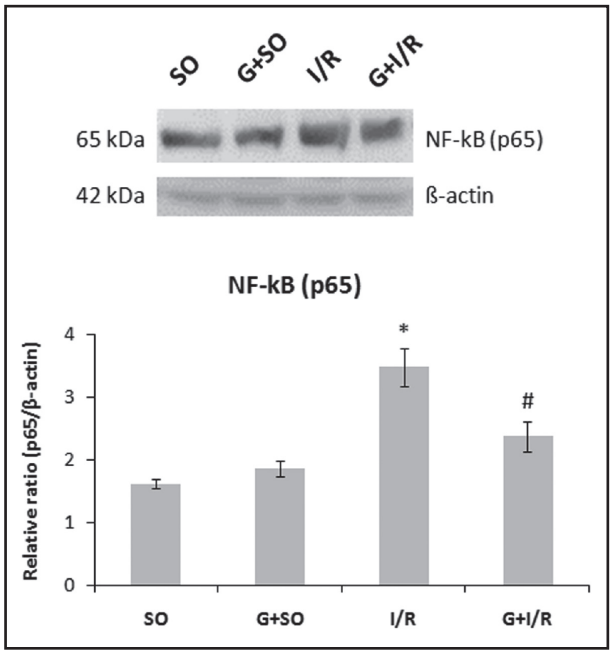

Figure 6.

Effect of glutamine administration on the expression of NF-kB (p65) by western blot analysis in the liver of animals subjected to the intestinal ischemia-reperfusion model. Values are expressed as mean ± SEM. *Significant difference between the I/R group and the SO and G+SO groups ($p < 0.01$). #Significant difference between the G+I/R group and the I/R group ($p < 0.05$). Sham operated (SO), glutamine + sham operated (G+SO), intestinal ischemia-reperfusion (I/R), glutamine + intestinal ischemia-reperfusion (G+I/R).

Gln has been studied as a possible treatment option for injuries associated with ROS and inflammatory substances because it plays an antioxidant and anti-inflammatory role, and may reduce these oxidative and inflammatory damages (7,18).

In our study, the liver damage was also evaluated based on the function of the hepatic enzymes AST, ALT, and ALP. Our results showed an increase in these enzymes in the I/R group, and pretreatment with Gln reduced these levels. Inan et al. (2012) found an increase in the activity of AST and ALT in animals subjected to an ischemia-reperfusion model. The administration of sildenafil reduced the levels of these enzymes (32).

Some studies have linked the involvement of oxidative processes, such LPO and DNA damage (34), oxidative damage, inflammatory process and DNA damage, to the progression of tissue and cell injuries caused by intestinal I/R in other organs (7,10,12). We measured the levels of LPO by TBARS and DNA damage by comet assay. We found an increase in LPO levels and DNA damage index and frequency in the I/R group; however, there was a significant decrease in terms of oxidative damage in the group pretreated with Gln, possibly due to its antioxidant activity.

Our results corroborate other studies showing similar results in the reduction of LPO levels when there is use of a substance with antioxidant effect. Shafik (2012) found an increase in the serum levels of malondialdehyde of animals with I/R. After the administration of febuxostat, these levels were reduced, thus demonstrating a possible antioxidant action of this substance (35). Cámara-Lemarroy et al. (2011) evaluated the possible antioxidant and anti-inflammatory effects of triflusal, S-adenosylmethionine and dextromethorphan, suggesting that the administration of these substances reduced the serum levels of malondialdehyde of animals with I/R (36). Oliveira et al. (2013) showed that glutamine reduced DNA damage in animals receiving cisplatin chemotherapy, a medication that affects the DNA synthesis, suggesting a protective effect of glutamine against damage of DNA bases (37,38).

The antioxidant system is a compensation mechanism for the oxidation process involving enzymatic substances, such as catalase, superoxide dismutase and glutathione peroxidase, and non-enzymatic substances, such as GSH. These substances play an important role against oxidative damage (10,11). In our study, we found a significant reduction in the activity of CAT, SOD and GPx, as well as in the levels of GSH in the I/R group, whereas there was a significant increase in the antioxidant parameters in the group pretreated with Gln.

Zhang et al. (2011) found that pretreatment with Gln was able to enhance the antioxidant capacity in an ischemia-reperfusion model. The animals treated with different doses of Gln showed an increase in SOD activity, suggesting a protective role of Gln against the oxidative damage caused by hepatic I/R-mediated liver injury (18).

Similar results were found in the study by Zhao et al. (2010), where a reduction in the activity of SOD and GPx and in the levels of glutathione in the liver of animals subjected to an intestinal I/R model was observed. The administration of sulforaphane compound (SFN), which is present in several plants, was able to increase the antioxidant capacity of the liver, suggesting a protective role against oxidative damage (39).

Intestinal I/R may lead to increased generation of free radicals and to the consequent production of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) that may be mediated by NF-kB (5,40). We measured the expression of IL-6 and NF-kB by immunohistochemistry and western blot analysis in the liver. Increased expression of inflammatory markers (IL-6 and NF-kB) was observed in the I/R group, whereas it was significantly reduced in the group pretreated with Gln, suggesting a possible anti-inflammatory effect of this amino acid.

Cho et al. (2013) evaluated the systemic inflammatory response based on the IL-6 plasma level of animals subjected to an intestinal I/R model. They found an increase in these levels in the intestinal I/R group; conversely, these levels were reduced with the administration of remifentanil, suggesting an inhibitory action on NF-kB activity thus reducing the production of IL-6 (3). Ma et al. (2014) found a positive expression of NF-kB in the liver tissue of the intestinal I/R group, whereas, when protocatechuic acid was administered, a polyphenolic compound with antioxidant and anti-inflammatory effect, there was a reduction in the expression of this inflammatory mediator (11). Similar results were found by Yao et al. (2009), showing that the treatment with carnosol, a compound with antioxidant effect, inhibited the expression of NF-kB, thereby reducing intestinal I/R-induced liver injuries (40).

In conclusion, our findings suggest that Gln inhibits LPO, restoring the activity of antioxidant enzymes, as well as reducing the

IL-6 and NF-kB expression, possibly due to its antioxidant and anti-inflammatory effect. Therefore, these results support the use of Gln to treat liver injuries caused by intestinal ischemia-reperfusion. Nevertheless, further studies should be conducted to validate its use in clinical practice.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Paciente crítico

Nitrogenous content in parenteral nutrition: a four-year experience in a general hospital. Critically-ill patient specificity

Contenido nitrogenado de la nutrición parenteral: un estudio de cuatro años en un hospital general. Especificidad en paciente crítico

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Abstract

Introduction: There have been several studies focusing on caloric intake during the last years, while protein content relevance has been underestimated. Some recent evidence has shown that protein deficiency has also an impact on patient outcomes. We have studied the nitrogen (N) content in parenteral nutrition (PN) bags administered to adult patients in a Spanish tertiary level hospital for four years.

Material and methods: Patients who received parenteral nutrition in the general ward and Intensive Care Unit (ICU) were recorded. Caloric and protein content were registered and adjusted to weight and length of stay. Data were compared among three group of patients: those in the general ward, those in the ICU and those requiring renal replacement therapy (RRT). The one-factor analysis of variance (ANOVA) test was used after checking data normality and homoscedasticity

Results: There was an increase in the mean g N/stay year after year ($p < 0.01$) from 14 to 15.5 g, with a decrease in non-protein caloric content ($p < 0.001$) from 111.6 to 101.8 kcal/g N. The range was established from 4.1 to 32.6 g. PN diets with ≥ 18 g N% ranged from 12.8% (2010) to 19.6% (2013). There were significant differences among the groups when comparing the variable g N/stay ($p < 0.0001$): 13.5 general ward *vs* 15.9 ICU patients *vs* 17.6 ICU with RRT, also when referring to adjusted weight.

Conclusions: According to most recent recommendations nitrogen has been provided in higher amounts than previously, especially in critical care patients with RRT.

Key words:

Nitrogen. Protein. Parenteral nutrition. Critical care. Renal replacement therapies. Individualized diets.

Resumen

Introducción: algunos estudios recientes sugieren que se ha dado gran importancia al aporte calórico en la nutrición parenteral (NP) del paciente adulto, infraestimando su contenido proteico. Sin embargo, se ha demostrado su relación con los resultados clínicos. Con este objetivo se ha estudiado el contenido en nitrógeno (N) de las NP administradas en un hospital terciario a lo largo de cuatro años.

Material y métodos: se recogieron datos de la NP de pacientes hospitalizados en planta, así como en la Unidad de Cuidados Intensivos (UCI). El peso del paciente, su índice de masa corporal (IMC), el contenido en nitrógeno (total y por peso), el aporte calórico no proteico y la duración de la NP fueron algunas de las variables estudiadas. Se compararon en 2013 los aportes en la planta general, en UCI y en aquellos que recibieron algún tipo de terapia renal sustitutiva (TRS). Se utilizó el análisis de varianza (ANOVA) de un factor, previa comprobación de la normalidad y homocedasticidad.

Resultados: se ha observado un aumento progresivo en aporte nitrogenado medio diario cada año ($p < 0,01$) de 14 a 15,05 g, con descenso del contenido calórico no proteico ($p < 0,001$) de 111,6 a 101,8 kcal /g N. El rango de N en bolsa fue de 4,1 a 32,6 g. Aumentó el porcentaje de bolsas con ≥ 18 g N (12,8 en 2010 *vs.* 19,6 en 2013). También hubo diferencias entre grupos de pacientes en g N/estancia ($p < 0,0001$): 13,5 plantas de hospitalización *vs.* 15,9 UCI *vs.* 17,6 UCI con TRS, igualmente si referidos a peso ajustado.

Conclusiones: En consonancia con las recomendaciones más recientes, el contenido en nitrógenos ha aumentado con los años, en especial en la NP del paciente crítico, siendo aún mayor en los sometidos a TRS.

Palabras clave:

Nitrógeno. Proteína. Nutrición parenteral. Cuidados intensivos. Técnicas de depuración extrarrenal. Dietas individualizadas.

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INTRODUCTION

There have been several recent studies focusing on caloric intake in parenteral nutrition (PN) while protein content relevance has been underestimated. Protein deficiency has also an impact on patient outcomes (1,2).

There is a clear need to identify safe amounts of nutrients for each acute disease stage in order to avoid under or overfeeding (3). In critically ill patients, undernourishment has been correlated with a higher number of infections, respiratory and immunology function impairment, as well as an increase in hospital length of stay and mortality (4). The results of a European study in 2012 including 102 patients showed a higher mortality rate on those patients who received a lower protein load, less than 1.2-1.5 g/kg/day (5). Other recent trials have shown that most critically ill patients do not reach nutritional requirements, being a low protein intake the most remarkable one (5-9), although there are some exceptions (10).

Based on our experience, we wanted to design a study to quantify the nitrogenous content in parenteral nutrition (PN) during 2010-2013 periods, comparing patients in the general ward and in the Intensive Care Unit. At the same time, we recorded the number of standardized/tailored solutions as well as insulin and glutamine addition.

MATERIAL AND METHODS

A retrospective descriptive study was performed. The pharmacist recorded daily, clinical, anthropometric and analytical information using the Nutridata® program. PN composition was also recorded. This program offers the possibility to explore data through SPSS®. Some content parameters, considered as targets, were obtained to estimate differences among different groups of patients.

Some of the analyzed variables were current weight, present weight, ideal weight (IW) and the % of weight loss/time. Body mass index (BMI) was calculated after exporting weight and height information to Excel, as well as the adjusted weight (AW = IW ± 25% of the excess or defect in weight). Current weight data are the result of the analysis done through the Process Infornut® (11), when a nutritional risk alarm arises in the filter FILNUT (12,13), during the hospital stay. If there was no opportunity to record the patient's weight, it was obtained through digital clinical records (Diraya specialized care - DAE - oncology pharmacy - Farmis Oncofarm®, reports from preanesthesia, hemodynamics, etc.). In any case, it is mandatory to fulfill patient's weight and height into the justification sheets for PN (14). Any missing information would be obtained through the visit done by a member of the nutritional team. When a new weight is recorded into Nutridata® from a patient on long-term PN, the mean weight is used as the calculator for global weight/case. When it is not feasible to get patient's height, it can be estimated from the ulna bone length. Variables such as g N/kg or the non-protein kcal/g N are calculated by the program on a daily basis. The percentage and number of PN diets and their distribution as per the different target variables were calculated using the Nutridata® database per case and day. The information regarding g N/kg is referred to the current weight in the four-year period. Enteral nutrition intake was not considered.

Three groups of patients were established: general ward, ICU, and ICU requiring renal replacement therapy (RRT). Patients on RRT are those who received PN at any time during the RRT therapy, even if it was for a short period of time.

In 2011, the Nutritional Support Team proposed a new PN protocol. It included 27 different diets ranging from standard, fat-free, cholestasis, renal o liver failure and sepsis mixtures with different nutrient content. As a novelty, it also included diets with 18 and 20 g N with a low non-protein kcal/g N ratio (highly stressed patients) (Smofkaviben® and Olimel® triple chamber bags); glutamine dipeptide (Dipeptiven®) was added in certain cases, mainly in critically ill patients. A personalized diet was defined as the one with different macronutrients and/or volume composition when compared with those in the protocol, but not different in terms of electrolytes, insulin addition or glutamine composition.

The one-way analysis of variance (ANOVA) test was used after checking data for normality and homoscedasticity.

RESULTS

Table I shows results in the three groups. The most severe and the longer the stay, the longer the length of PN use, and the higher the nitrogen load. The number of tailored formulations was higher in ICU patients requiring RRT. Table II shows yearly evolution in the study period. The number of PN bags remains similar, with a trend to higher nitrogen content and lower nitrogen/non-protein calorie ratio.

Figure 1 shows the evolution of the nitrogen intake as per weight, in the four-year period and other indicators fixed as targets. Figure 2 shows average values/stay (day) and 95% CI for nitrogen (g), non-protein kcal/g N, adjusted weight (AW) and g N/Kg AW in the three groups of patients. Patients in the ICU requiring RRT received a significantly higher nitrogen load as well as a lower N/non-protein kcal ratio.

DISCUSSION

Standard PN solutions are widely used in most hospitals. There is also the possibility of designing standardized formulations based on standard patient profiles, including different stress situations, sepsis, cholestasis, and renal or hepatic impairment. Individualized formulations could be of interest in those patients with a complex clinical situation (up to 25-40% of the cases) (15). The ready-to-use bags (triple chamber bags) have dramatically reduced the need for manual compounding, by significantly reducing manipulation and liquid transfer (16). Martínez Romero et al. (17) demonstrated that 75% of their metabolically stable patients had their needs addressed by only three standardized formulations they had designed according to case-mix. Schoenenberger

Table I. Comparison of nitrogen content in patients according to their location

2013 Total patients 365[1]	Hospitalization wards	ICUs	ICUs with RRT[2]
Cases	251	168	53
Administered bags	2,973	2,178	1,015
PN days/case	*11.84*	*12.97*	*19.15*
BMI/case	25.19 ± 5.28	27.06 ± 6.23	28.58 ± 6.6
Current weight/case (kg)	69.46 ± 15.82	75.89 ± 17.74	81.81 ± 15.33
Current weight/stay	68.68 ± 16.19	79.60 ± 18.20	85.13 ± 17.19
Ideal weight/stay	58.83 ± 7.87	61.67 ± 7.76	61.96 ± 8.64
Adjusted weight/stay	61.37 ± 8.28	66.32 ± 8.25	67.99 ± 8.13
g N/ stay (mean ± σ)	*13.56 ± 3.13*	*15.87 ± 4.19*	*17.60 ± 4.28*
% ≤ 18	94.8	72.4	52.7
% 18.1-22	4.4	20.4	33.8
% > 22	0.8	7.2	13.5
Non-prot kcal/g N/stay (mean ± σ)	*112.2 ± 20.1*	*97.3 ± 22.6*	*89.68 ± 18.4*
% ≤ 80	2.9	14.9	27.5
% 80.1-95	14.5	44.5	44.7
% > 95	82.6	40.6	27.8
g N/kg/stay (mean ± σ)*			
**/adjusted weight*	*0.223 ± 0.046*	*0.240 ± 0.059*	*0.260 ± 0.060*
Protein g equivalent	1.39	1.5	1.63
*/current weight	0.204 ± 0.052	0.205 ± 0.056	0.211 ± 0.056
*/ideal weight	0.233 ± 0.055	0.260 ± 0.068	0.288 ± 0.070
% ≥ 0.26-current-	15.6	20.4	22.8
% personalized diets	17.1	25	41.3
% protocol (% triple chamber bags)	82.9 (38)	75 (36.7)	58.7 (25.7)
PN bags with insulin (%)	8.6	22.5	31.3
Glutamine g/bag [3]	0.8	4.83	7.43

[1]Fifty-four patients stayed both in ICUs and wards; 731 bags were excluded (five homecare patients). [2]Critically ill patients requiring RRT at any time. It includes all bags with or without RRT. [3]Equivalent to 6.1; 36.6 and 56.3 ml of Dipeptiven®/bag.

et al. showed that a standardized protocol which included 20 diets helped to prepare 6,300 formulations; up to 30% of the cases were prepared from different macronutrients, although only 8% of the formulations were really individualized (18).

As our own program allowed collecting data on prescription, elaboration and dispensation, we were able to assess the protein load in our PN solutions in all three scenarios: general ward, ICU patients, and those in the ICU requiring RRT. There was an increase in the g N/stay year after year ($p < 0.01$) except from 2012 and 2013 ($p = 0.181$). The range was established from 4.1 to 32.6. PN (%) diets with ≥ 18 g N have increased every year, ranging from 12.8% (2010) to 19.6% (2013). Data from 2014 show the same trend (21.3% ≥ 18 g N). There were no yearly significant differences for mean weight or BMI per case. Nevertheless, the mean weight/stay on PN in 2013 was significantly higher ($p < 0.001$) than in the three previous years.

In Weijs paper, including 886 patients, an optimal caloric and protein intake (between 1.2 and 1.5 g/kg/day) was associated with a decrease in mortality, while only reaching the caloric targets was not sufficient to establish that association (19). In agreement with this, in a pilot study including 2,772 ICU patients a higher caloric and protein intake was associated with better clinical outcomes, especially if BMI was < 25 o ≥ 35 on admission (20). Other studies confirm these findings (21,22), suggesting that classically recommended protein intake (ESPEN) may not be sufficient.

Regarding the use of glutamine, most published studies in critically ill patients have shown beneficial effects (23), leading to diverse scientific societies to recommend glutamine use (24,25). Heyland described that very high doses administered through enteral and parenteral route (> 0.5 g/kg/day) and during the acute phase in patients with multiple organ dysfunction and shock increased mortality (26).

According to recent recommendations, we have increased the g N/stay in our PN from 14 to 15.05, with a decrease in the non-protein caloric content, from 112 to 102. This nitrogen increase has happened despite the increase on PN average duration (two days) and partly due to the increase in the number of complementary PN, but also as a result of an improvement on

Table II. Nitrogen content evolution between 2010 a 2013

Year	2010	2011	2012	2013
PN cases[1]	*411*	*419*	*409*	*365*
Mean age/case	61	61.5	62.7	59.7
Males %	62	60.6	62.1	61.4
Stays (bags)	*5,738*	*6,142*	*6,141*	*5,882*
Days/case	14.2	14.9	15.2	16.6
BMI	*25.82 ± 5.38*	*25.77 ± 5.97*	*25.91 ± 5.66*	*25.86 ± 5.49*
Current weight/case	71.28 ± 14.9	71.24 ± 16.44	71.88 ± 16.82	71.98 ± 16.37
Current weight/stay	72.44 ± 17.51	71.82 ± 18.58	71.63 ± 20.11	74.25 ± 19.56
g N/stay (mean ± σ)	14.00 ± 3.28	14.62 ± 4.21	14.89 ± 4.08	15.05 ± 4.24
% ≥ 16 g N	29.65	37.87	43.09	43.9
% ≥ 18 g N	12.8	17.2	17.4	19.6 (2014: 21.3)
% ≥ 22 g N	1.73	5.37	5.06	7.6
g N/kg-current-/stay (mean ± σ)	*0.201 ± 0.057*	*0.211 ± 0.066*	*0.218 ± 0.070*	*0.210 ± 0.059*
Protein g equivalent	1.256	1.319	1.363	1.313
% ≥ 0.26 g N/kg	15.9	21.7	25	21.3
% ≥ 0.3 g N/kg	4.7	6.9	12.2	10.1
Non-prot kcal/g N/stay (mean ± σ)	*111.6 ± 22.2*	*107.6 ± 25.1*	*106.1 ± 20.3*	*101.8 ± 25.4*
% ≤ 95 non-prot kcal/g N	24.8	36.8	37.2	41.4
% ≤ 110 non-prot kcal/g N	36.8	48.5	48.6	56.4
% >110 non-prot kcal/g N	63.2	51.5	51.4	42.9
% Personalized diets[2]	7	15.5	20.7	26.5
% Protocol (% triple chambre bags)	93 (46.5)	86.5 (44.7)	79.3 (33.7)	73.5 (31.5)
% bags with insulin	11.1	11.1	16.8	15

[1]Hospitalization wards, ICUs and homecare patients included. [2]Personalized: those different from the protocol in terms of macronutrients and/or volume, not those with added electrolytes and/or insulin or glutamine dipeptide.

the way PN is gradually initiated in patients at risk of refeeding syndrome. There was a yearly significant increase in g N/kg/stay from 0.20 to 0.22 until 2012 ($p < 0.001$). In 2013 there was a significant decrease when compared with 2012. The value reached was similar to 2011 value (0.21) and higher than 2010 value. This could be explained by the higher current weight/stay in 2013. Its equivalent in g prot/kg/d varied between 1.26 and 1.38, in accordance with ESPEN guidelines for PN (27).

The reduction in non-protein kcal/g of N turns out to be significant ($p < 0.001$ year by year, excepting 2011-2012, $p < 0.05$). An important reduction appeared in this ratio, lowered from 111.6 (2010) to 101.8 (2013). The need for personalized diets was more necessary (26.5% in 2013) when the nitrogenous content increased.

We also found a significant difference among groups when comparing the variable g N/stay (13.5 *vs* 15.9 *vs* 17.6, $p < 0.0001$). The same significance was reached for the difference in non-protein kcal/g N/stay (112 *vs* 97 *vs* 90). The increase in g N/kg/stay in ICU did not reach statistical significance when compared with hospitalization wards; however, those on RRT did ($p < 0.01$). These differences were statistically significant among the three groups when the variable g N/kg considered the IW or AW/stay ($p < 0.0001$). Patients on the general wards received 0.22 by average, while the ICU ones received 0.24. Those on RRT received 0.26 g N/kg AW, raising up to 0.29 g N when referred to the IW.

Critically ill patients, and those requiring RRT, had higher weight than those in hospital wards, received PN for a longer period, and also received higher nitrogenous content, in absolute terms and with regards to weight kg, and less non-protein calories per gram. Finally, glutamine dipeptide, as a PN component, was mainly used in these patients.

If a clinical pharmacist is fully integrated in the interdisciplinary nutrition support team, as it was in our case, in close collaboration with the Intensive Care Unit as a reference consultant, it is more feasible to adjust nutrient supplies to patient needs and, therefore, to favor quality of care in patients requiring PN.

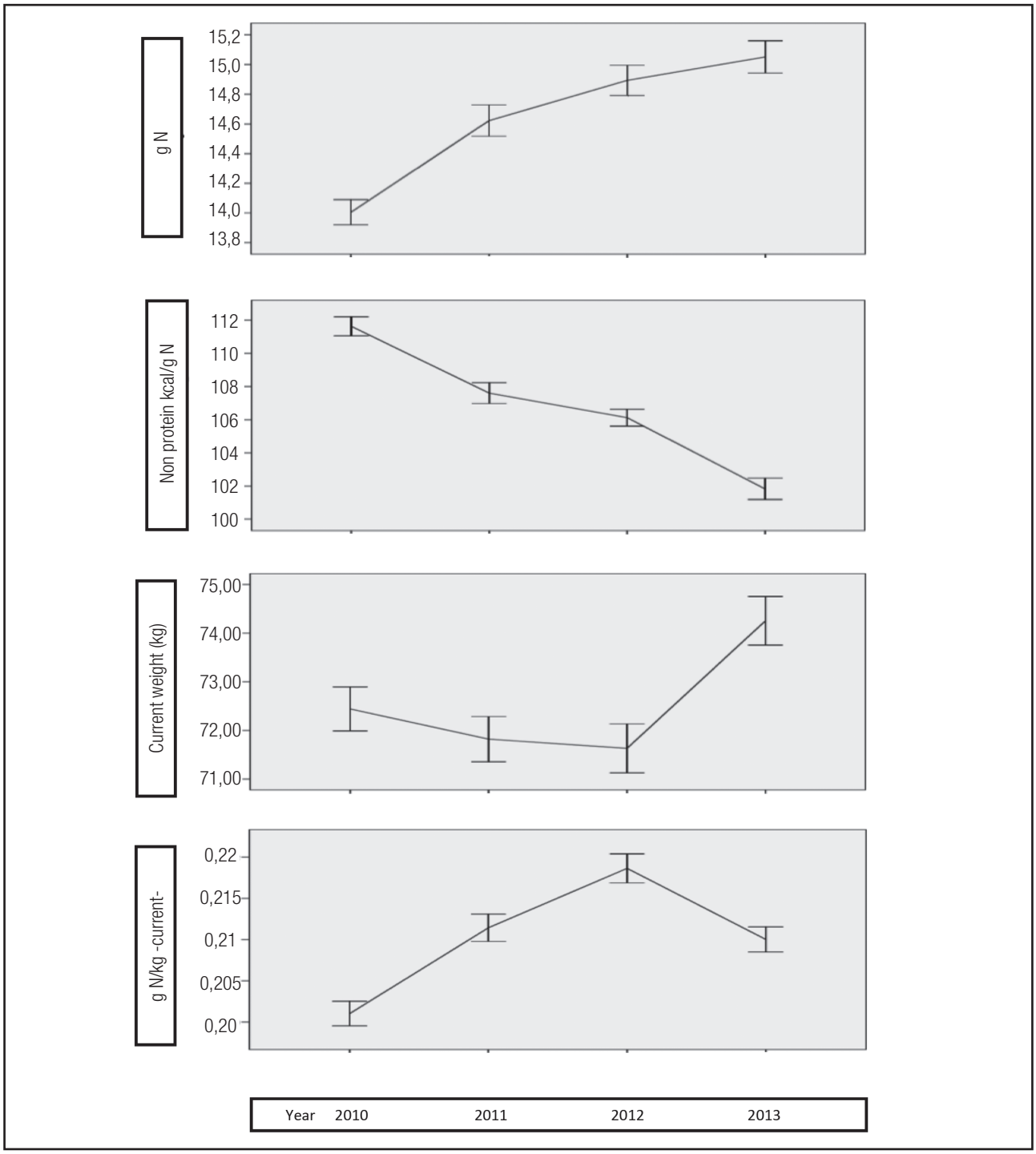

Figure 1.

Four-year evolution 2010-2013 (mean/stay with PN, CI 95%).

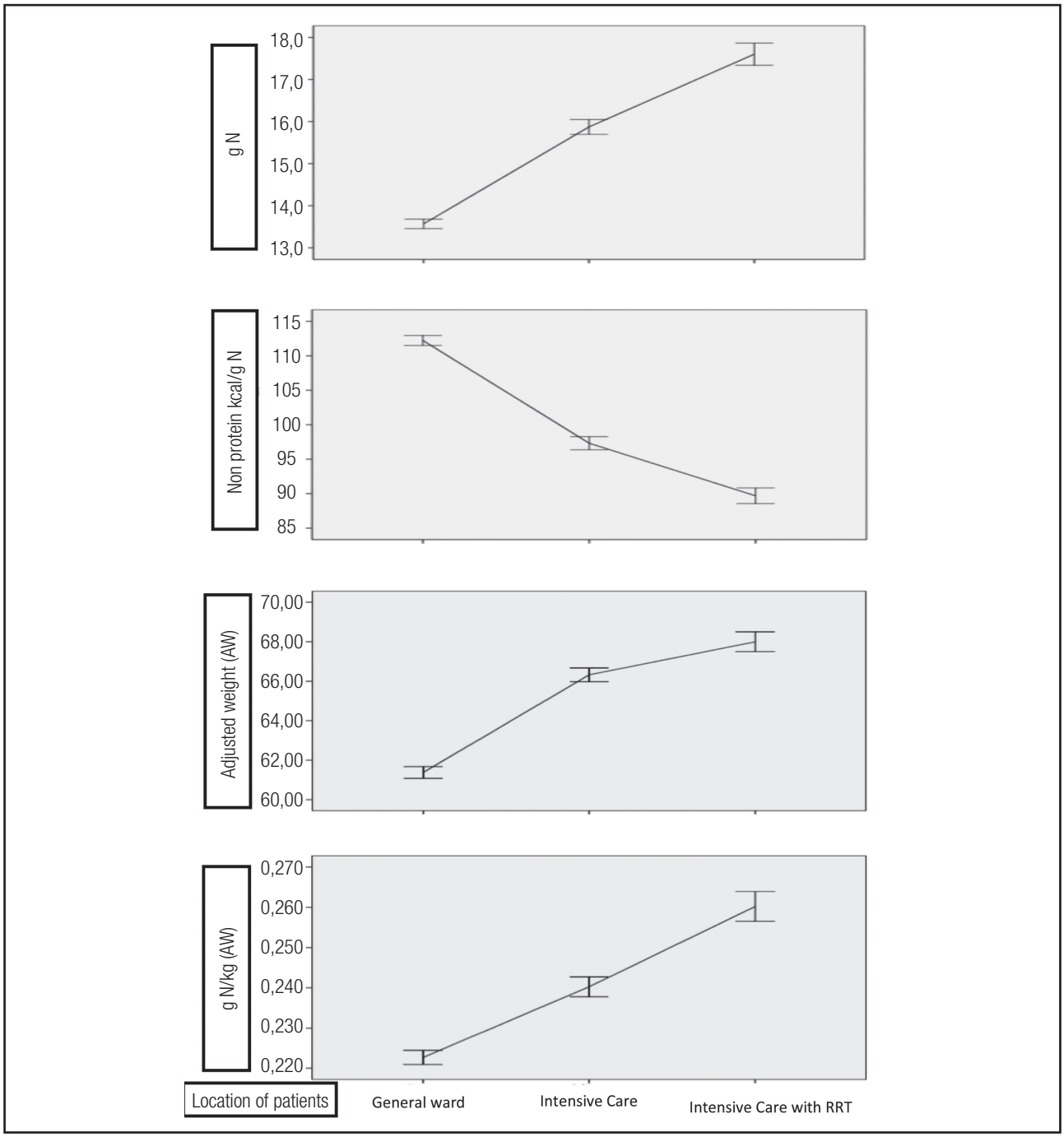

Figure 2.

Comparison during 2013: Wards/ICUs/ICUs with RRT (mean/stay with PN, CI 95%).

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Paciente crítico

Is plasma selenium correlated to transthyretin levels in critically ill patients?

¿Se correlacionan los niveles plasmáticos de selenio con los de prealbúmina en los pacientes críticos?

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Abstract

Background: Selenium is an essential trace element, but critically ill patients using total parenteral nutrition (PN) do not receive selenium because this mineral is not commonly offered. Threfore, the evaluation of plasma selenium levels is very important for treating or preventing this deficiency. Recent studies have shown that transthyretin may reflect the selenium intake and could be considered a biomarker. However, this issue is still little explored in the literature.

Objective: This study aims to investigate the correlation of transthyretin with the plasma selenium of critically ill patients receiving PN.

Method: This was a prospective cohort study with 44 patients using PN without selenium. Blood samples were carried out in 3 stages: initial, 7th and 14th day of PN. In order to evaluate the clinical condition and the inflammatory process, albumin, C-reactive protein (CRP), transthyretin, creatinine and HDL cholesterol levels were observed. To assess the selenium status, plasma selenium and glutathione peroxidase (GPx) in whole blood were measured. Descriptive analyses were performed and the ANOVA, Mann-Whitney and Spearman's coefficient tests were conducted; we assumed a significance level of 5%.

Results: A positive correlation of selenium with the GPx levels ($r = 0.46$; $p = 0.03$) was identified. During two weeks, there was a positive correlation of transthyretin with plasma selenium ($r = 0.71$; $p = 0.05$) regardless of the CRP values.

Conclusion: Transthyretin may have reflected plasma selenium, mainly because the correlation was verified after the acute phase.

Key words:

Plasma selenium.
Glutathione peroxidase.
Transthyretin.
Critically ill patients.

Resumen

Introducción: el selenio es un oligoelemento esencial. Sin embargo, los pacientes críticos con nutrición parenteral (NP) no reciben selenio de forma habitual. La evaluación de los niveles plasmáticos de selenio se vuelve imprescindible en este contexto, para prevenir las deficiencias. Algunos estudios recientes han demostrado que los niveles de prealbúmina pueden reflejar los aportes de selenio y servir como biomarcador del estado de selenio. Esta posibilidad se ha evaluado de una forma insuficiente.

Objetivo: investigar la correlación entre los niveles plasmáticos de selenio y de prealbúmina en el paciente crítico.

Método: estudio prospectivo de una cohorte de 44 pacientes que recibían NP sin selenio. Se extrajeron muestras de sangre en el momento del inicio y a los 7 y 14 días de NP. Para evaluar la situación clínica y el proceso inflamatorio, se midieron también los niveles de albúmina, proteína C reactiva (PCR), prealbúmina, creatinina y colesterol HDL. Para evaluar el estado de selenio, se midieron los niveles de selenio y de glutation peroxidasa (GPx) en sangre completa. Se realizó un análisis descriptivo así como los siguientes estudios estadísticos: ANOVA, Mann-Whitney y coeficiente de correlación de Spearman, asumiendo un nivel de significación estadística del 5%.

Resultados: se encontró una correlación positiva con los niveles de GPX ($r = 0,46$; $p = 0,03$). Durante las dos semanas de estudio, hubo correlación entre los niveles plasmático de selenio y de prealbúmina ($r = 0,71$; $p = 0,05$), con independencia de los niveles de PCR.

Conclusión: la prealbúmina puede reflejar los niveles plasmáticos de selenio, al demostrar una buena correlación tras la fase aguda de la agresión.

Palabras clave:

Selenio plasmático.
Glutation peroxidasa.
Prealbúmina.
Paciente crítico.

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INTRODUCTION

Selenium is an essential trace element with antioxidant, immunomodulatory and anti-inflammatory activity (1) in the organism. It makes up the active site of glutathione peroxidase (GPx), an enzyme that acts against the common oxidative stress in critically ill patients.

Common complications in critically ill patients, such as systemic inflammatory response syndrome (SIRS), multiple organ failure and multiple organ dysfunction (1,2) were associated with reduced plasma selenium levels and GPx. Indeed, plasma selenium and GPx were inversely correlated with the severity of disease and mortality and morbidity (1,3). Some studies have shown that low selenium concentrations may also hinder wound healing (4,5).

The oxidative stress and the inflammation process generated in the acute phase trigger a series of biochemical changes in the human body, increasing the nutritional demand of selenium, the deficiency of which could further aggravate the clinical condition. However, critically ill patients using total parenteral nutrition (PN) do not receive selenium because this mineral is not commonly offered in Brazil and others countries. Therefore, the evaluation of selenium levels is very important to treat or prevent such a deficiency in order to improve patient recovery. Although plasma selenium reflects the current selenium status and is the most widely used method for monitoring the levels of this mineral, its interpretation may be impaired during the inflammatory response (6). Thus, measurements of plasma selenium need to be carried along with parameters that reflect the inflammatory process. In clinical practice, some parameters that indicate the inflammatory response are: reduction of albumin, transthyretin and HDL cholesterol, and a concomitant increase in acute phase protein such as C-reactive protein (CRP) (7-11).

According to a recent study, transthyretin may reflect the selenium intake and could be considered a biomarker (12). The positive correlation of plasma selenium and transthyretin was reported among septic patients, but was not found in patients with systemic inflammatory response syndrome (13). Considering that, this issue is still little explored in the literature. This study aims to investigate the correlation of transthyretin with the plasma selenium of critically ill patients receiving PN.

MATERIAL AND METHODS

STUDY FEATURES

Prospective cohort study with 44 critically ill patients using PN. Blood samples were carried out in 3 stages (initial, 7th and 14th day of PN). Inclusion criteria were: hospitalization in the intensive care unit (ICU), use of total PN or PN as a primary source of nutrition and signature on the Free and Clarified Consent Form by patient or their guardian. This study was approved by the Research Ethics Committee of the School of Medical Sciences of State University of Campinas - UNICAMP (N. 538/2011). Exclusion criteria were: patients fed only oral and/or enteral nutrition and patients who had left the ICU before the first 72 hours of PN.

INDICATION AND PRESCRIPTION OF PARENTERAL NUTRITION

PN was prescribed by the physician responsible for the patient and by nutritional support team according to the European Society for Parenteral and Enteral Nutrition –ESPEN (15)-, and American Society for Parenteral and Enteral Nutrition –ASPEN (16). Since PN solutions have no selenium, the survey participants did not receive this mineral.

NUTRITIONAL ASSESSMENT STATUS

Anthropometry was performed with measurements of weight and height to calculate the body mass index (BMI), according to Lohman, Roche and Martorell (17) and the World Heatlh Organization (18). In case of confinement in bed, we opted for the method of estimating the weight (19,20) and height according to their half arm span (Mitchell and Lipschitz) (21). In case of edema, the recommendation made by Duarte and Castellani (22) was used (subtracted 1 kg when edema was only on the ankle, 3-4 kg when it was on the knee, 5-8 kg when it was on the thigh and 10-12 kg when the edema was widespread). An inextensible and inelastic measuring tape of 100 cm and 0.1 cm accuracy, a Lange Skinfold Caliper® adipometer and a stadiometer coupled to the digital scale Líder® (2 kg to 300 kg capacity) were used.

LABORATORY EVALUATION OF THE CLINICAL CONDITION

To evaluate the clinical condition and inflammatory response, standardized routine tests were performed, examining the following compounds: albumin (colorimetric -bromocresol green), C-reactive protein (CRP) (nephelometry), transthyretin (nephelometry), HDL cholesterol (enzymatic -direct colorimetric) and creatinine (kinetic Jaffé colorimetric method with compensation). The measurements were made by the specialized team of the Clinical Pathology Laboratory of Hospital das Clínicas at UNICAMP.

ASSESSMENT OF SELENIUM STATUS

To measure GPx (whole blood), a RANSEL kit (RS504)® and a RANSEL CONTROL kit (SC692)® from the Randox Laboratory (San Franscisco, USA) were used. This technique is based on the method proposed by Paglia and Valentine (23). We collected 1 ml of blood in a heparinized bottle, stored at -80 °C. Subsequently, 0.05 ml heparinized whole blood was diluted with 1 ml diluent agent, and incubated for 5 minutes and 1 ml of Drabkin's hemolyzing reagent was added. After mixing the samples, the tests were started. The RANSEL RX Daytona equipment at 340nm was used to read the samples, and the normal range of GPx (whole blood) was from 4171 to 10881 U/l. The procedure and the reading of the samples were performed by the Laboratory of Exercise Biochemistry in the Biology Institute – UNICAMP.

To dose plasma selenium, blood was collected in dry tubes (free of trace elements) and centrifuged to separate the plasma. The samples were stored at -20 °C until the time of analysis. Plasma samples were digested in pyrex glass tubes (by wet acid). After the addition of 5 ml of nitric acid 68% P.A. (Merck), the samples were kept at rest overnight. Thereafter, digestion occurred in the digestion block with an initial temperature of 50 °C, which was gradually increased until reaching a maximum of 150 °C. The purpose of this step was to eliminate organic substances and reduce selenium in the solution into selenium IV. In the next step 5 mL HCl 1.2N was added and the samples were heated for two more hours (at 100 °C). Subsequently, the solutions were diluted with deionized water to 25 mL. Selenium reading occurred through the method of atomic absorption spectrometry by generation of hydrides coupled to the quartz cell (HGQTAAS) (model Z5000, Hitachi, Tokyo, Japan) (24-26). The normal range for plasma selenium concentration was between 60-120 µg/L (27,28). The procedure and sample readings were made in the Nutrition Minerals Laboratory - from the School of Pharmaceutical Sciences, University of São Paulo - USP.

All materials used (glassworks, tips and plastics) had nitric acid bath of 30% for at least 12 hours, and were rinsed 10 consecutive times with deionized water for demineralization.

SEVERITY ASSESSMENT

To evaluate the severity, the score of the Acute Physiologic and Chronic Health Evaluation -APACHE II (29)- was used as well as the Sequential Organ Failure Assessment -SOFA (30).

STATISTICAL ANALYSIS

The data statistical treatments were made through the SAS System for Windows (Statistical Analysis System), version 9.4. SAS Institute Inc, Cary, NC, USA. Exploratory data analysis was made through summary measures (frequency, percentage, mean, standard deviation, minimum, median, and maximum). A comparison between the times and between the groups over time was performed with the ANOVA test for repeated measures with the response variables processed in ranks. Mann-Whitney test was used for comparison between groups. The correlation between the amounts of plasma selenium with numerical variables was assessed using Spearman's coefficient. The significance level was 5%.

RESULTS

The sample consisted of 44 critically ill patients with a mean age of 58.9 ± 14 years that had PN primarily for medical reasons. The primary diagnosis of patients were: gastrointestinal cancer, sepsis, trauma, acute abdomen, inflammatory, inflammatory bowel disease and pancreatitis. Table I shows the clinical characterization of the sample.

Table I. Sample description according to gender, age, PN indication, nutritional status and final outcome

Variables	n	Percentage (%)
Gender		
Male	32	72.7
Female	12	27.3
Age[a]		
< 60 years	22	50.0
≥ 60 years	22	50.0
Reasons for the use of PN		
Clinical	31	70.5
Surgical	13	29.5
Nutritional status according to BMI[b]		
Malnourished	1	4.8
Eutrophic	18	85.7
Overweight and obese	2	9.5
Final outcome		
No deaths	36	81.8
Deaths	8	18.2

BMI: body mass index: [a]In Brazil, over 60 years-old is considered elderly; [b]It was possible to measure and/or estimate weight and height of only conscious patients without generalized edema (n = 21).

Concerning evaluation of severity, the mean and standard deviation of APACHE II and SOFA were 14.9 ± 5.7 (8.0-26.0 range) and 5.7 ± 2.8 (2.0-10.0 range), respectively.

At the beginning of the study, all patients had elevated CRP levels and low selenium levels (100%). Creatinine was high (29.5%) and GPx was below normal in 50% of the evaluated cases. HDL cholesterol (85.3%), albumin (97.3%) and transthyretin (97.1%) were low in most of them. Table II shows the evolution of biochemical indicators over the three assessments.

In the first evaluation, there was positive correlation of selenium levels with the GPx ($r = 0.46$; $p = 0.03$). Throughout two weeks, there was a positive correlation between plasma selenium with transthyretin ($r = 0.71$; $p = 0.05$) and creatinine ($r = 0.67$; $p = 0.03$) (Table III, Fig. 1). There was no correlation of transthyretin with creatinine ($r = 0.42$; $p = 0.26$).

Regarding mortality, there was no statistical difference in selenium and GPx levels between the death group and the non-death group ($p > 0.05$). On the 7th day (2nd evaluation), the death group had a mean selenium concentration of 17.8 ± 4.4 µg/L and the non-death group of 24.9 ± 10.7 µg/L, a trend toward significance ($p = 0.09$) was observed. However, there was no statistically significant difference at any time of the evaluation.

Table II. Evolution of biochemical indicators of nutritional status and inflammatory profile over the three assessments

Biochemical tests	n	Normal values	Mean (SD)	Median	Minimum	Maximum
Selenium µg/L						
Baseline	44	60-120	21.6 ± 8.5	20.1	10.9	51.0
7th day of PN	30		23.2 ± 10.0	20.1	9.5	47.6
14th day of PN	16		22.2 ± 7.8	22.5	4.4	41.11
CRP mg/dL						
Baseline	37	≤ 0.3	11.6 ± 9.0	10.2	0.9	40.8
7th day of PN	24		8.3 ± 6.6	7.1	0.5	26.0
14th day of PN	12		14 ± 8.6	11.1	5.2	32.2
Transthyretin mg/dL						
Baseline	34	20 to 40	10.5 ± 5.6	10.1	1.8	35.1
7th day of PN	21		10.9 ± 4.1	10.6	3.2	16.8
14th day of PNa	9		14.8 ± 4.9	13.3	8.6	22.7
Albumin g/dL						
GPx U/l	37	3.5 to 5.2	2.3 ± 0.6	2.2	1.1	4.7
Baseline	22	4171 to 10881	4518.1 ± 1313.4	4168.3	3397.3	7384.9
7th day of PN	16		5037.4 ± 1717.5	4552.3	3397.3	8692.9
14th day of PN	7		4249.7 ± 1633.7	3713.8	3397.3	7898.7
HDL cholesterol mg/dL						
Baseline	34	≥ 40	22.6 ± 17.1	17.0	4	70
7th day of PN	20		19.7 ± 14.6	18.0	5	70
14th day of PN	9		20.9 ± 19.3	13.0	4	60
Creatinine mg/dL						
Baseline	44	< 1.2 > 0.6	1.3 ± 1.1	0.8	0.3	4.8
7th day of PN	28		1.5±1.7	0.8	0.2	6.3
14th day of PN	12		2.0±1.9	1.5	0.3	6.8

CRP: C-reactive protein; GPx: glutathione peroxidase (whole blood); [a]Statistically significant increase of transthyretin levels between the first and last dosing (p = 0.05) - ANOVA for repeated measures with the response variables processed into ranks.

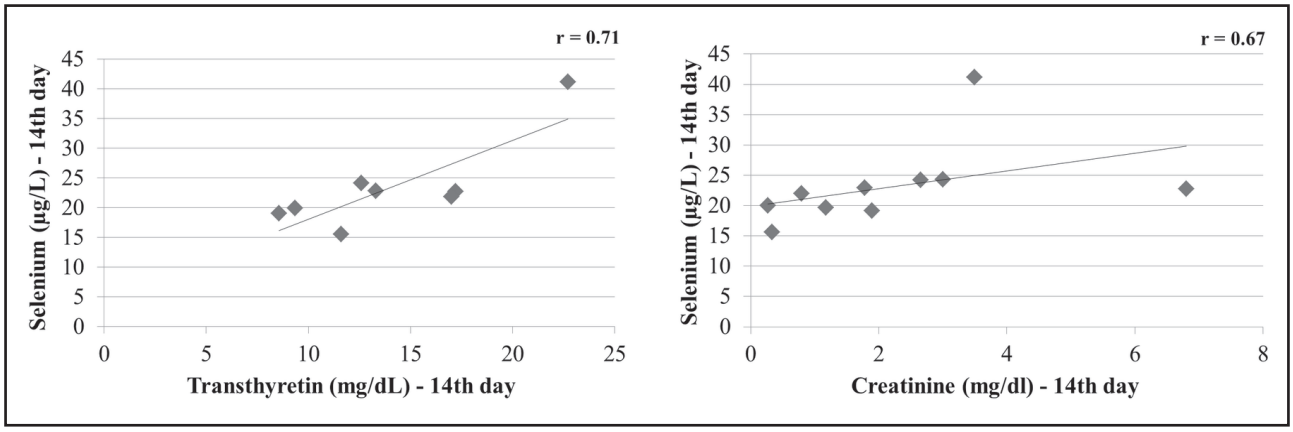

Figure 1.

Scatter plots showing correlations of bivariate plasma selenium with transthyretin and creatinine.

Table III. Correlations of plasma selenium with the other markers

Correlations	r value	p value
Initial		
Selenium x GPx	0.46	0.03*
Selenium x albumin	0.29	0.08
Selenium x transthyretin	0.13	0.47
Selenium x CRP	0.21	0.21
Selenium x BMI	0.06	0.81
Selenium x HDL cholesterol	0.18	0.30
Selenium x creatinine	0.26	0.09
7th day pf PN		
Selenium x GPx	0.13	0.64
Selenium x transthyretin	0.32	0.16
Selenium x CRP	-0.02	0.28
Selenium x HDL cholesterol	0.30	0.19
Selenium x creatinine	-0.03	0.88
14th day of PN		
Selenium x GPx	0.56	0.20
Selenium x transthyretin	0.71	0.05*
Selenium x CRP	-0.02	0.96
Selenium x HDL cholesterol	-0.21	0.64
Selenium x creatinine	0.67	0.03*

*GPx: glutathione peroxidase (whole blood); CRP: C-reactive protein; BMI: body mass index. *p < 0.05 - Spearman's correlation coefficient.*

DISCUSSION

Selenium is a trace element with antioxidant, immunomodulatory and anti-inflammatory activity, but critically ill patients using total parenteral nutrition (PN) do not receive selenium because this mineral is not commonly offered. Thus, the evaluation of selenium levels is very important to treat or prevent the deficiency. Recent studies have shown that transthyretin may reflect the selenium intake and could be considered a biomarker (6,12-14). However, this issue is still little explored in the literature. Therefore, this study aimed to investigate the correlation of transthyretin with the plasma selenium of critically ill patients receiving PN.

Mahn, Toledo and Ruz (12) suggest that transthyretin can be a biomarker of bioactive state of selenium because it responded to supplementation (SeMSeCys) offered to a group of rats that had no inflammatory process. In the study of Brodska et al., (13), there was no correlation of plasma selenium with transthyretin in patients with SIRS, however, in septic patients, selenium was correlated with transthyretin both in the supplemented group and the non-supplemented group.

In the study, the plasma selenium was below the referenced level in all patients since the first assessment. Along with this improvement (by the 14th day of evaluation), a strong positive correlation between thransthyretin and plasma selenium was observed.

It is known that, in critically ill patients, transthyretin seems to reflect the inflammatory process more than the nutritional status (32,33). Nevertheless, we did not find a negative correlation of transthyretin and of plasma selenium with CRP, which is contrary to the results observed in the Blass et al.´s (5) study.

In relation to the positive correlation of selenium with creatinine, renal failure causes selenium accumulation due to the difficulty of excretion (34). Thus, continuously low selenium levels could still be overestimated in patients with elevated creatinine. We also know that elevated levels of creatinine can influence transthyretin levels, however there was no positive correlation between transthyretin and creatinine observed in our study. Also, the strong positive correlation of transthyretin with plasma selenium, detected during the 2nd week of assessment, demonstrated that transthyretin may reflect selenium plasma. This correlation was verified after the acute inflammatory phase of the patient passed.

With regard to low levels of selenium and GPx, a positive correlation was found between the two, as observed in another study (13). GPx is a selenium-dependent enzyme that reflects the status of this mineral. It is also responsible for approximately 30% of plasma selenium measured (35,36). It is known that plasma selenium and GPx may be altered in critically ill patients due to oxidative stress (35).

Forceville et al., (37) found selenium values in patients with SIRS lower than in patients without SIRS. Manzanares et al., (38) demonstrated that the patients in critical condition without SIRS (and APACHE, less than 9) had selenium levels similar to the healthy patients group (mean and standard deviation = 72.8 ± 13.1 µg/L). Heyland et al. (39) observed that the initial plasma selenium was within normal limits in North American patients with multiple organ failure, and found no difference in the levels of selenium between the group with sepsis and the control group. It seems that in studies with critically ill patients conducted in places with selenium rich soil (as in the U.S.A.) there are no such low levels of selenium as those studies conducted in places where the soil is poor in selenium (regions of Europe and South America) (39,40). Thus, it is not yet clear whether the plasma selenium concentrations reflect the inflammatory process and/or mineral nutritional deficiencies (40).

Our study was conducted in the state of Sao Paulo (southeast Brazil), a region considered to have selenium poor soil (41,42), and actually the plasma selenium values found were similar or lower to those found in other studies (5,31,38,43). It is possible that the inflammatory response did contribute to low selenium levels, however, there was no correlation of selenium with CRP at any time. Therefore, it is presumed that the reduced levels of selenium and GPx are the consequence of both the inflammatory response as well as the intake/insufficient infusion of this trace element.

Selenium supplementation for patients using PN is recommended by ASPEN (44) (60-100 µg/day or 400 µg/day in severe cases), but it is not a practice commonly performed in Brazil and

in other countries (developed countries and developing country). We know this is one of the first studies assessing the correlation of transthyretin with plasma selenium in critically ill patients using total PN or PN as the main source of nutrition. Thus, conducting randomized clinical trials is essential to confirm the findings of our study, mainly because research with critically ill patients using PN with and without selenium is scarce.

With regard to mortality, we observed a trend of lower selenium levels in patients who died. It is possible that the assessment period (14 days) and/or the number of participants may not have been sufficient for the statistical difference to be evident. Costa et al., (31), also found, with a sample of 110 patients, no statistical difference in plasma selenium among the deceased and survivor groups. However, studies have reported a reduced risk of mortality among patients supplemented with high doses of selenium (45). In fact, the amount, the time to start and the supplementation time are still discussed, but the importance of supplementation is emphasized since this seems to prevent progression or contribute to the treatment of diseases and complications associated with these disabilities.

The main limitation of this study concerns the sample loss which occurred due to death or withdrawal of PN before the 14th day of assessment. In addition, the complexity and heterogeneity of the sample due to illness, and various clinical complications may have underestimated or overestimated selenium levels. However, both the high mortality rate and the heterogeneity of the sample are features commonly found among patients followed in the ICU.

FINAL REMARKS

Due to a positive correlation observed after the acute inflammatory phase in patients, we suggest that transthyretin may reflect plasma selenium levels. Therefore, the lower levels of it detected at the start of PN show the need for selenium monitoring and supplementation, especially in patients with low transthyretin.

STATEMENT OF AUTHORSHIP

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Nutrición Hospitalaria

Trabajo Original

Pediatría

Relationships between umbilical vein and mother iron status

Las relaciones entre la vena umbilical y el estado de hierro en la madre

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Abstract

Introduction: Iron is an essential micronutrient in the growing fetus.

Objective: The purpose of this study is to find the possible correlations that may exist between maternal and fetal iron status and newborn weight.

Material and methods: The study included 97 mothers scheduled to give birth by elective caesarean section in the central maternity of Tébessa (east of Algeria) between January and August 2014. The blood collection was sampled from the antecubital vein of the mother and the umbilical vein. The mean concentrations of parameters in maternal and fetal sides, respectively, were 10.64 ± 1.37 g/dl and 14.83 ± 1.79 g/dl for hemoglobin, 51.57 ± 20.82 µg/dl and 112.47 ± 32.34 µg/dl for serum iron, and 12.37 ± 9.58 ng/ml and 109.64 ± 58.76 ng/ml for serum ferritin. Except for ferritin, other fetal parameters were correlated with those of mothers. Birth weight was only significantly correlated with maternal hemoglobin ($r = 0.22$, $p = 0.02$) and hematocrit ($r = 0.2$, $p = 0.004$).

Conclusion: The fetal-maternal exchanges of iron were highlighted and iron status of the newborn was linked to that of the mother. The low maternal hemoglobin was associated with low newborn weight.

Key words:

Iron. Ferritin. Fetus. Newborn weight.

Resumen

Introducción: el hierro es un micronutriente esencial en el crecimiento del feto.

Objetivo: el propósito de este estudio es conocer las posibles correlaciones que puedan existir entre el estado en hierro de la madre y del feto, y el peso del recién nacido.

Material y métodos: el estudio incluyó a 97 madres programadas para dar a luz por cesárea electiva en la maternidad central de Tébessa (este de Argelia) entre enero y agosto de 2014. En la extracción de sangre se tomaron muestras de la vena antecubital de la madre y de la vena umbilical. Las concentraciones medias de los parámetros maternos y fetales, respectivamente, fueron 10,64 ± 1,37 g/dl y 14,83 ± 1,79 g/dl de hemoglobina, 51,57 ± 20,82 mg/dl y 112,47 ± 32,34 mg/dl para el hierro sérico y 12,37 ± 9,58 ng/ml y 109,64 ± 58,76 ng/ml para la ferritina sérica. A excepción de la ferritina, los otros parámetros fetales se correlacionaron con los de la madre. El peso al nacer solo se correlacionó significativamente con la hemoglobina materna ($r = 0,22$; $p = 0,02$) y el hematocrito ($r = 0,2$; $p = 0,004$).

Conclusión: se pusieron de relieve los intercambios materno-fetales de hierro y el estado de hierro en el recién nacido se mostró ligado al de la madre. La hemoglobina materna baja se asoció con un bajo peso del recién nacido.

Palabras clave:

Hierro. Ferritina. Feto. Peso del recién nacido.

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INTRODUCTION

The only source of nutrients for growth of the fetus is maternal blood (1). Iron is vital for early brain growth and function because it supports neuronal and glial energy metabolism, neurotransmitter synthesis, myelination, and development of red blood cells, blood vessels and muscles (2,3). As fetal iron results exclusively from the mother by active transport function of the placenta, the amount transferred could be reasonably assumed to be influenced by the amount of maternal iron available (4). Iron transfers from the mother to the fetus are regulated by the placenta and involve placental structure, iron transporters, and regulation of placental expression of these proteins (5).

The last trimester of pregnancy is the period of the most important weight gain and iron storage in the fetus. Amounts of iron in low birth children are lower than full-term newborns and after birth accumulated iron compared to full-term newborns. After birth, reserves acquired during pregnancy will be used during the first 4-6 months of life (6).

Iron deficiency anemia is the most common preventable nutritional deficiency during pregnancy, which have an impact on morbidity and maternal as well as perinatal complications, such as premature delivery, intrauterine growth retardation, and perinatal death (7,1). In Blida, north Algeria, prevalence of iron deficiency anemia during pregnancy in 2006 was 46.66% (8).

Published studies highlighted the relationship between the maternal and neonatal iron status, but the results remained discrepant (9,10). Challenges and concerns with routine blood sampling among healthy newborns still encountered. Studies were done to compile reference data on iron status among healthy newborns using both venous and cord blood (11,12). Understanding the relationship between maternal and fetal iron status may help exert efforts to prevent iron deficiency in pregnancy and infancy, and improve outcomes for mothers and infants.

The present study was undertaken to find the possible relationships between maternal blood parameters which determine the iron status (hemoglobin [Hb], hematocrit [Hct], serum iron, total iron binding capacity of transferrin [TIBC], saturation coefficient of transferrin [CS] and serum ferritin) and blood from the umbilical cord vein, reflecting the placental exchange.

MATERIALS AND METHODS

The study was carried out on 97 couples of mothers and newborns scheduled to give birth by prophylactic cesarean in the Central Maternity Doctor Khaldi Abed Elazziz of Tébessa (east of Algeria) between January and August 2014.

In all these cases, pure prophylactic cesarean were performed after 37 to 42 weeks of gestation in women with a pregnancy of normal development and exhibiting no significant pathology which affected the metabolism of iron in the body. These women were aged between 22 and 42 years old. Primigravida or multigravida and indications of cesarean were conditioned by a notion of prior cesarean, contracted pelvis, breech present position.

For each selected woman, we explained the purpose and the experimental protocol approved by the Ethics Committee of the University Frères Mentouri Constantine 1. All women included in this study signed informed consent.

BLOOD SAMPLES COLLECTION

Under normal operating conditions at the central maternity of Tébessa, maternal arterial samples were prohibited; maternal blood samples were then collected from antecubital vein of the arm and without tourniquet before anesthesia.

Five milliliters were collected by a sterile 5 ml syringe. Two milliliters were put in an EDTA-K3 tube (Ethylene Diamine Tetra-Acetic) for the measurement of hematocrit (Hct) and hemoglobin (Hb), and three milliliters were placed in a dry tube for the determination of serum iron, serum ferritin and total iron binding capacity of transferrin (TIBC).

The blood of the umbilical vein was collected after two minutes of umbilical cord clamping, as soon as the newborn was removed and the umbilical cord was cut at the side of the placenta; the same quantities of blood were taken for the same analysis.

The fetal and maternal blood sample tubes were placed in a cooler and transported immediately to the laboratory for analysis.

Dosages of hemoglobin and hematocrit were performed immediately on the blood. Serum was recovered after centrifugation at 1,500 rpm for 15 minutes and stored in the refrigerator in the maternity laboratory at 4 °C. After blood sampling of all subjects of the day, samples were transported in a cooler to the laboratory of the Bouguera Boulaaras Bekaria Hospital for measuring other parameters as soon as samples were received.

BIOASSAYS

The rates of hemoglobin and hematocrit were determined on an automated counter Nihon Kohden type for hematological analysis (model MEK-6400K, Nihon Kohden Corporation, Tokyo, Japan). The serum iron was estimated by a colorimetric method using ferrozine as chromogen. The total iron binding capacity of transferrin was evaluated after transferrin saturation by an iron solution and adsorption of the excess over magnesium hydroxycarbonate (Fer Ferrozine + TIBC kit, ref.: 200643, Biomaghreb, Tunisia). The saturation coefficient of transferrin was calculated from the assay of serum iron and TIBC, CS% = ([serum iron/TIBC] × 100), serum ferritin was estimated by ELFA technology (Enzyme Linked Fluorescent Assay) using a Mini VIDAS automate (Ferritine kit, ref.: 30411, Biomerieux S.A., France).

STATISTICAL ANALYSIS

Statistical analyses were performed using XL STAT version 2009.1.01 (Addinsoft 1995-2009, USA). The results of this study are presented using descriptive statistics such as arithmetic mean, standard deviation and frequency. Analyses of relations between maternal and newborn blood parameters excluded all

pairs of diabetic cases to avoid interference with their interpretation regarding iron status. The assumption of normality of data was verified by the Anderson-Darling test to use the statistical methods. Comparisons between two means were tested by t-test. Pearson's correlation was used to investigate possible association between variables. The significance level adopted was 5%.

RESULTS

AGE AND GESTITY

Our study group consisted of 97 women aged between 22 and 42 years old; the average age was 31.7 ± 4.7 years. The majority of pregnant women (61.85%) belonged to the age group of 30-39 years old. Depending on gestity, 40 women (41.23%) were primigravida, 51 (52.57%) were secundigravida, and six (6.18%) were multigravida (Table I).

No significant relationship ($p > 0.05$) was found between maternal iron status and age and gestity.

BLOOD PARAMETERS AND RELATIONSHIPS

In table II we presented the blood parameters, measured in the antecubital vein and umbilical vein, as mean ± standard deviation (SD) and extreme values. We noticed that maternal and fetal values generally fluctuated in the same way as evidenced by the similarity of standard deviations; the same remark was noticed for extreme values.

Umbilical vein values were greater than those of maternal vein; serum iron and ferritin were, respectively, two and nine times greater in newborns than in mothers.

Except for serum iron, significant linear correlations were observed between fetal hemoglobin and other fetal parameters. Respectively, Hct and TIBC were positively correlated to Hb ($r = 0.6$, $p < 0.0001$ and $r = 0.2$, $p = 0.04$). CS and serum ferritin were negatively correlated to Hb ($r = 0.28$, $p = 0.005$ and $r = 0.38$, $p < 0.0001$) (Table III).

Table IV shows correlations between Hb and other maternal parameters. Hb was only correlated positively with Hct ($r = 0.79$, $p < 0.0001$), and was negatively correlated with serum ferritin ($r = 0.33$, $p = 0.001$).

The relationships between maternal parameters and those of the umbilical vein are outlined in table V. Except for serum ferritin, fetal and mother parameters were positively correlated. The greatest correlation was seen between fetal and maternal serum iron ($r = 0.39$, $p < 0.0001$).

Birth weight (Figs. 1 and 2) was significantly related to maternal Hb ($r = 0.22$, $p = 0.02$) and Hct ($r = 0.2$, $p = 0.004$).

Table I. Distribution of women according to age and gravidity (n = 97)

	Class	Number	Frequency (%)
Age (year)	(22-29)	33	34.02
	(30-39)	60	61.85
	40 and more	4	4.12
Gestity	Primigravida	40	41.23
	Secundigravida	51	52.57
	Multigravida	6	6.18

DISCUSSION

In this study, no blood parameter of iron status was correlated with maternal age or maternal gestity; age and multiple gestity did not seem to be risk factors for iron deficiency. There were discrepancies between authors. Chandyo et al. (13) reported women with parity ≥ two had higher mean hemoglobin concentration than nulliparous ones. In others studies on risk factors of maternal anemia during pregnancy, Emamghorashi et al. (14) and Veghari et al. (15) found that multiparity, but not age, influenced maternal iron status. Multiparity and short birth interval (< two years) between pregnancies created a large demand for iron, which was needed to develop the fetus and placenta.

The measured iron status parameters were higher in fetal blood than in maternal blood.

Table II. Blood parameters in antecubital and umbilical veins (n = 97)

	Antecubital vein		Umbilical vein	
	Mean ± SD	Extreme values	Mean ± SD	Extreme values
Hb (g/dl)	10.64 ± 1.37	7.9-14.3	14.83 ± 1.79	10.80-18.90
Hct (%)	32.06 ± 4.09	18.7-41.5	43.19 ± 5.56	30.4-58.1
Serum iron (µg/dl)	51.57 ± 20.82	20.39-123	112.47 ± 32.34	52.72-191.1
TIBC (µg/dl)	460.09 ± 92.61	320-786	533.83 ± 98.57	329.0-797.0
CS (%)	12.12 ± 5.26	3.10-30.14	21.88 ± 8.27	8.46-53.32
Serum ferritin (ng/ml)	12.37 ± 9.58	2.9-71.48	109.64 ± 58.76	11.21-246.64

Hb: Hemoglobin; Hct: Hematocrit; TIBC: Total iron binding capacity of transferrin; CS: Saturation coefficient of transferrin.

Table III. Relationships between blood parameters (y) and hemoglobin (x) in the umbilical vein (n = 97)

Parameters (Y)	A	b	r	p
Hct (%)	1.856	15.67	0.6	< 0.0001
TIBC (µg/dl)	11.04	370	0.2	0.04
CS (%)	-1.304	41.22	0.28	0.005
Serum ferritin (ng/ml)	-12.64	297.1	0.38	< 0.0001
Serum iron (µg/dl)	-	-	-	0.055

Hct: Hematocrit; TIBC: Total iron binding capacity of transferrin; CS: Saturation coefficient of transferrin; a: Regression coefficient; b: Constant term; r: Pearson's correlation coefficient.

Table IV. Relationships between blood parameters (y) and hemoglobin (x) in antecubital vein (n = 97)

Parameters (Y)	A	b	r	p
Hct (%)	7.348	2.332	0.79	< 0.0001
TIBC (µg/dl)	-	-	-	0.675
CS (%)	-	-	-	0.862
Serum ferritin (ng/ml)	-12.26	2.336	0.33	0.001
Serum iron (µg/dl)	-	-	-	0.532

Hct: Hematocrit; TIBC: Total iron binding capacity of transferrin; CS: Saturation coefficient of transferrin; a: Regression coefficient; b: Constant term; r: Pearson's correlation coefficient.

Table V. Relationships between umbilical vein (y) and maternal (x) parameters (n = 97)

Parameters	A	b	r	p
Hb g/dl	0.288	11.75	0.22	0.02
Hct (%)	0.424	29.54	0.30	0.002
Serum iron (µg/dl)	0.606	79.65	0.39	< 0.0001
TIBC (µg/dl)	0.217	434.1	0.20	0.04
CS (%)	0.411	16.78	0.26	0.009
Serum ferritin (ng/ml)	-	-	-	0.763

Hb: Hemoglobin; Hct: Hematocrit; TIBC: Total iron binding capacity of transferrin; CS: Saturation coefficient of transferrin; a: Regression coefficient; b: Constant term; r: Pearson's correlation coefficient.

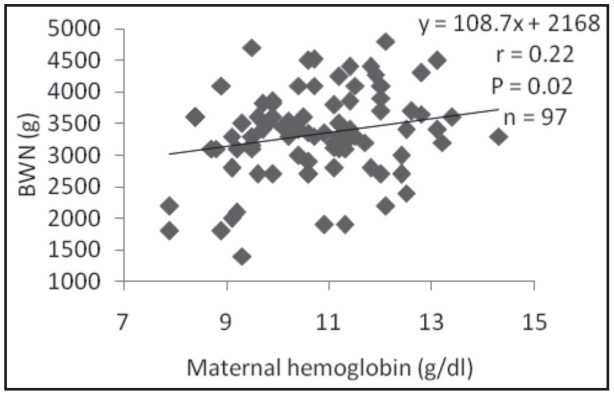

Figure 1.
Relationship between maternal hemoglobin and birth weight of newborns (BWN).

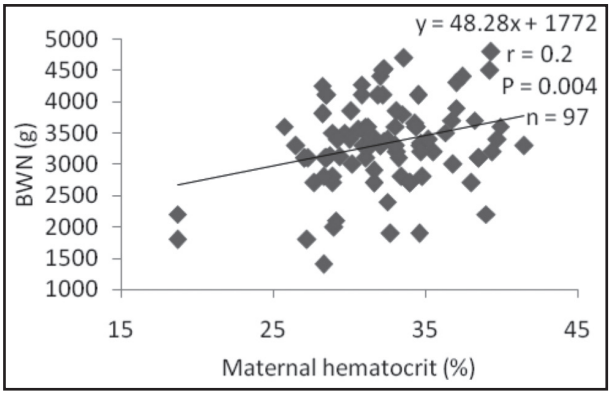

Figure 2.
Relationship between maternal hematocrit and birth weight of newborns (BWN).

This finding was also noticed by Dop et al. (16) and Sa et al. (17) in their studies on anemia in pregnancy in Togo and Brazil respectively. The relatively low values we observed in Hb and Hct in maternal blood might be due to the plasma volume expansion resulting in hemodilution during pregnancy (18,19). However, the rates of hemoglobin and hematocrit were high in infants because of the increase in the number and size of red blood cells in cord blood (20). In addition, physiological change during pregnancy altered the composition of blood, amplified the transfer of certain hematopoietic micronutrients and increased the use of some others (19).

The negative link in the umbilical vein between Hb and ferritin and with the CS suggested a competition between hemoglobin-synthesis and storage of iron as ferritin, as it was reported by Macphail et al. (21), who studied the relationship between the iron status of 103 mothers and their newborns. The TIBC varied in the same way as Hb, which complied with the role of transferrin in the supply of iron to hemoglobin. These findings were in accordance with the study of Doc et al. (16).

The large variation of the fetal iron concentration (53-191 µg/dl) did not greatly affect the level of fetal hemoglobin, with variations remaining relatively low (11-19 g/dl). Similar results were reported by Singla et al. (22), who evaluated the parameters status of maternal and fetal iron and morphology of the placenta from 69 mothers and newborns in India. We believe that a link could be observed with iron concentrations below a certain critical threshold, not encountered in our study group, which exposed the newborn to diseases due to a strong iron deficiency.

Our results indicate a significant relationship between the concentration of Hb in the umbilical vein and the antecubital vein ($r = 0.22$, $p = 0.02$). This was consistent with Shoa et al. (2), who evaluated the relationship between iron status of mother and full term neonate to term and reported a high significance ($r = 0.10$; $p \leq 0.0001$; $n = 2775$). However, Turkey et al. (23) did not a find a correlation between maternal and newborn hemoglobin. Thus, the maternal Hb affected the level of fetal Hb; as a result, a decrease in maternal Hb was likely to develop anemia in the newborn at an early age, poor cognitive and neurological development and risk of developing chronic diseases in adulthood, such as heart disease and type 2 diabetes (24,25).

In this study, significant correlations were found between newborns serum iron, TIBC and CS and those of their mothers. Adariana et al. (26) reported similar correlations. The feto-maternal relationship for serum iron was greater than other parameters ($r = 0.39$; $p < 0.0001$), and the fetal serum iron level was generally twice that of the mother. We deduced from this relationship that the fetus took over 60% of maternal iron, which passed in a counter-gradient way. A minimum iron concentration of 80 µg/dl was kept constant in the fetus, even if the mother was deficient in iron. This was possible by a regulation of iron transport proteins in the placenta ensuring an adequate supply of iron to fetal growth, even in mothers suffering from iron deficiency (27). Then the weak correlations shown between newborn and maternal parameters could not predict hematological and biochemical parameters of newborn of mildly or moderately anemic pregnant women (26).

Similarity to Shoa et al. (2) and Sa et al. (17), we observed a low rate of serum ferritin in mothers (12.37 ± 9.58) compared to newborns (109.64 ± 58.76). According to Gambling et al. (28), the concentrations of ferritin decreased significantly during pregnancy and the process was mediated by signals from the fetus whose nature was not known yet. On the other hand, like others (26,29), we did not find any feto-maternal relationship for serum ferritin. However Shoa et al. (2) reported significant weak correlations ($r = 0.07$) due probably to their large sample. Iron transmitted to the fetus came from maternal stores as ferritin. The release of iron from ferritin is still being studied and the underlying mechanism is not clearly established yet (5).

From experiments on rats, which were widely used as a model for the human placenta function, a hierarchy of use of maternal iron was observed: the fetus was a priority, maternal hematocrit came on, and maternal iron stores were the last. This had serious consequences for the mother, if the observations obtained in rats had to be transposed to humans, because the mother needed iron stores not only for herself but also for breastfeeding as well as for future pregnancies (5,30).

In this study of women with gestation in normal development, birth weight had linear relationship with maternal Hb and Hct (Figs. 1 and 2). Similar results were reported by Singla et al. (22), who also suggested a negative effect of anemia during pregnancy on different anthropometric measurements at birth. However, two studies on two different populations (US and UK) had not reported a relationship between markers of iron status (hemoglobin and mean corpuscular volume) at different stages of pregnancy and fetal growth (31,32). In contrast, another study showed that the babies of iron-deficient anemia mothers had greater head circumference and were heavier than those from non-anemic non-iron-deficient mothers (14).

The effect of maternal anemia on intra-uterine growth is attributed to chronic deprivation of oxygen to the developing fetus (33). According to Rodríguez et al. (34), various biological mechanisms had been proposed to explain the ways in which iron deficiency, including in its most severe form, may adversely affect fetal growth. Maternal and fetal stress could result from increasing concentrations of noradrenaline generated by iron deficiency or hypoxia resulting from anemia. Excess of noradrenaline rises vagal activity, hence hyperinsulinemia, which may result in fetal weight increase.

Maternal and fetal stress, in turn, activated the production of the corticotropin-releasing hormone that stimulated fetal cortisol. Accordingly, the longitudinal growth of the fetus might be affected by the action of cortisol (35). Animal studies supported this hypothesis. The stress caused by iron deficiency was shown by the increase in cortisol levels due to iron-free diet in rats (36-38). Another plausible hypothesis of the effect of iron deficiency on fetal growth was that erythrocytes and the fetal-placental unit could suffer oxidative damage caused by iron deficiency. Finally, possible maternal infections could increase with iron deficiency, and might enable the production of the corticotropin-releasing hormone (35).

CONCLUSION

In the present study, we observed that age and gestity were not a risk factor for iron deficiency in pregnant women.

Hemoglobin, hematocrit, serum iron, total iron binding capacity of transferrin and saturation coefficient of transferrin in the fetus were in a linear relationship with those in the mother. Accordingly, any deficiency in these components of the status of iron or alteration in their metabolic regulation was likely to develop pathologies related to the optimal intake of iron in the newborn which could be complicated in adulthood.

Birth weight was affected by the rate of hemoglobin and maternal hematocrit. The other parameters of iron status did not seem to have much direct link with birth weight of newborns in the present study.

Much work has to be achieved with a larger population, depicting situations of high iron deficiency or excess for a better definition of the fetal-maternal relationships that may occur.

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Trabajo Original

Pediatría

Associations between insulin resistance and three B-vitamins in European adolescents: the HELENA study

Asociaciones entre la resistencia a la insulina y tres vitaminas del grupo B en adolescentes europeos: el estudio HELENA

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Abstract

Objective: To assess whether adolescents with high body mass index (BMI), or fat mass index (FMI), in combination with insulin resistance (assessed with the Homeostatic Model Assessment [HOMA] index), had also lower blood vitamin B_6, folate and vitamin B_{12} concentrations.

Methods and materials: Six hundred and fifteen adolescents from the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study, with data on B-vitamins (both intakes and status), and BMI, FMI, HOMA, were selected. Intakes were assessed by two non-consecutive 24-h recalls. B-vitamins biomarkers were measured by chromatography and immunoassay. Analysis of covariance was applied to elucidate the differences in B-vitamins between combinations of groups defined according to the median of the z-scores of markers of body composition and insulin sensitivity.

Results: When considering energy intakes and education of the mother in the model, in females, vitamin B_6 intakes were higher in the high BMI/high HOMA group than in the high BMI-low HOMA group. Similarly, vitamin B_6 intakes were higher in the high FMI/high HOMA group than in the low FMI/low HOMA group. Plasma vitamin B_{12} was significantly lower in males in the high FMI/high HOMA group than in the low FMI/low HOMA group, keeping also significant their trends throughout the groups, a fact that can be observed also for females ($p < 0.05$).

Conclusion: Adolescents with combined higher adiposity and higher HOMA insulin sensitivity showed lower vitamin B_{12} plasma concentrations. These differences do not seem to be explained by dietary vitamin B_{12} intake.

Key words:

Vitamin B_6. Folic acid. Vitamin B_{12}. Adolescent. Body mass index. Insulin resistance.

Resumen

Objetivo: evaluar si los adolescentes con mayor índice de masa corporal (IMC), o de masa grasa (IMG), en combinación con la resistencia a la insulina (medida con el Modelo de Valoración Homeostática [índice HOMA]), ingieren y tienen valores más bajos de vitamina B_6, folato y vitamina B_{12}.

Métodos y materiales: seiscientos quince adolescentes participantes en el estudio *Healthy Lifestyle in Europe by Nutrition in Adolescence* (HELENA), con valores de ingesta y concentraciones de las vitaminas B_6, folato y B_{12}, e IMC, IMG y HOMA, fueron seleccionados. Las ingestas se midieron mediante dos recuerdos de 24 horas no consecutivos. Los biomarcadores de las vitaminas fueron obtenidos mediante cromatografía e inmunoensayo. Se aplicó el análisis de la covarianza para evaluar las diferencias entre las vitaminas (ingesta y concentraciones) entre las combinaciones de los grupos definidos según las medianas de los valores z de los marcadores de la composición corporal y de la sensibilidad a la insulina.

Resultados: considerando la ingesta energética y la educación de la madre en el modelo en chicas, las ingestas de vitamin B_6 fueron mayores en el grupo de mayor IMC/mayor HOMA que en el grupo mayor IMC/menor HOMA. Del mismo modo, el grupo constituido por mayor IMG/mayor HOMA presentó mayores ingestas de esta vitamina que el grupo formado por la combinación entre menor IMG/menor HOMA. La vitamina B_{12} plasmática en chicos fue significativamente menor en el grupo formado por mayor IMG/mayor HOMA que en el grupo menor IMG/menor HOMA, manteniendo también la tendencia significativa en los grupos, lo que también se puede observar en las chicas ($p < 0.05$).

Conclusiones: los adolescentes con mayor adiposidad en combinación con una mayor sensibilidad a la insulina mostraron menores valores de vitamina B_{12} plasmática. Estas diferencias no parecen estar explicadas por diferencias en la ingesta de vitamina B_{12}.

Palabras clave:

Vitaminas B_6. Ácido fólico. Vitamina B_{12}. Adolescentes. Índice de masa corporal. Resistencia a la insulina.

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INTRODUCTION

Prevalence of overweight and obesity in European children ranges between 10 and 40 percent among European adolescents (1), while obesity is currently considered as the fifth leading risk for global deaths (2). Aside genetics, inadequate lifestyle factors like unhealthy dietary habits and/or insufficient physical activity are the main attributable causes of both overweight and obesity (3). Childhood obesity has been shown to be accompanied by low micronutrient intake and micronutrient deficiencies (4). For instance, obesity has been related to low iron intake in children and adolescents in a study developed in Israel (5), where obese children and adolescents showed a higher prevalence of iron deficiency or even iron deficiency anemia than non-obese.

The body mass index (BMI) is the most widely used height-normalized index for the screening of excess body fat, also in adolescents, but it can be criticized since it does not discriminate between lean- and fat-mass (6). Measurement of skinfolds thickness allows an estimation of subcutaneous adipose tissue deposition and, thus, the use of the fat mass index (FMI = kg fat mass/m^2) instead of the BMI for classifying obesity status in children (6). Obesity is often associated with hyperinsulinism and insulin resistance, which over time can develop into in glucose intolerance, impaired β-cell function and diabetes mellitus type 2 (7).

Vitamin B_{12} is a crucial nutrient present in animal products (8). Its main roles are linked with the cognitive function, bone health, and deoxyribonucleic acid (DNA)-replication during periods of rapid growth and development like childhood and adolescence (9,10). An optimal vitamin B_{12} status during early life stages is essential in preventing future health risks like anemia (9). Besides, vitamin B_{12} deficiency contributes to hyperhomocysteinemia, which is an independent risk factor for atherosclerotic disease (11). Sub-clinical deficiencies of vitamin B_{12} status are not uncommon during adolescence and in high risk population groups like vegans or vegetarians, elderly or low-resource people (12).

Low vitamin B_{12} status can be due to gut malabsorption syndromes, pernicious anemia (13), or secondary malabsorption produced by metformin therapy, an insulin sensitizer used for the treatment of type 2 diabetes and insulin resistance in adolescents (14,15).

A recent paper based on the HELENA study reported levels of B-related vitamins, such as B_6, folate and B_{12} (16), in which 2% of studied adolescents had low plasma vitamin B_{12} and 5% had low holotranscobalamin (HoloTC) concentrations. Besides, low concentrations of both plasma folate (PF) and red blood cells (RBC-folate) were identified in 10% of the HELENA adolescents, and low pyridoxal-phosphate (PLP) concentrations were also identified in 5% of them.

A recent Australian study with obese adolescents (13) called for investigation of the associations between vitamin B_{12} status and insulin sensitivity, including also dietary intakes. Consequently, this study aims to assess whether adolescents with higher body mass index (BMI) or fat mass index (FMI), in combination with higher insulin sensitivity (high Homeostatic Model Assessment [HOMA] index) had also lower B-vitamins concentrations.

To our knowledge, this is the first study in European adolescents assessing the association between B-vitamins intake and concentrations and insulin sensitivity, considering indicators of body composition like BMI or FMI.

METHODS AND MATERIALS

The multicenter and cross-sectional study Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA-CSS) recruited adolescents aged 12.5-17.5 years, from ten cities from nine European countries: Athens and Heraklion, in Greece; Dortmund, in Germany; Ghent, in Belgium; Lille, in France; Pécs, in Hungary; Rome, in Italy; Stockholm, in Sweden; Vienna, in Austria; and Zaragoza, in Spain. The purpose of the study was to provide complete and reliable information about the nutritional status of European adolescents (17). Inclusion criteria were: not participating simultaneously in another clinical trial and being free of any acute infection occurring < one week before inclusion (18). The total number of participants was 3,528, with an average participation rate of 67%, which can be considered as acceptable for such a demanding epidemiological study (19). In one third of the sample in each study center (1,076 adolescents), blood drawing was obtained. Participants from Heraklion and Pécs (7% of the total sample) did not provide comparable dietary data. For the purposes of this analysis, 615 adolescents were included, having complete data on BMI, skinfold thickness to calculate FMI, maternal education, vitamin B_6, folate and vitamin B_{12} intakes and biomarkers, and having the HOMA index for insulin sensitivity or resistance excluding also outliers (for biochemical measurements, outliers were considered when values were ± four standard deviations from the mean). Further details on the HELENA sampling procedures, pilot study and reliability of the data have been published elsewhere (19). Informed consent was obtained from all participants and their parents, and the protocol was approved by the Human Research Review Committees of the corresponding centers (20).

ASSESSMENT OF VITAMIN B_6, FOLATE, VITAMIN B_{12} AND ENERGY INTAKES

Vitamin and energy intakes were assessed using the computerized 24-hour recall, self-administered HELENA-Dietary Assessment Tool (HELENA-DIAT), adapted for European adolescents from the Young Adolescents' Nutrition Assessment on Computer (YANA-C) software (21). The adolescents completed the 24-hour recalls twice in a fortnight period. Trained staff were present during completion (21). Obtained data was linked to the German Food Code and Nutrient Data Base (BLS [Bundeslebensmittelschlüssel], version II.3.1, 2005), with 12,000 coded foods, and with up to 158 nutrient data points available for each food item (21). When traditional or local foods were not available in the BLS table, recipes were composed using foods from the BLS as ingredients. The Multiple Source Method (MSM) (22) was applied to calculate usual nutrient intakes removing the effect of day-to-

day within-person variation and random error in the two recalls. B-vitamins diet densities were calculated as follows: (amount of B-vitamin intake per 1,000 kcal of diet/recommendation of the corresponding B-vitamin intake based on the Institute of Medicine recommendations) *100. Recommendations for vitamin B_6 intakes are 1,300 µg in males and 1,200 µg in females; for folate, 400 µg in males and females; and for vitamin B_{12} 2.4 µg in both sexes (9).

ASSESSMENT OF VITAMIN B_6, FOLATE AND VITAMIN B_{12} BIOMARKERS CONCENTRATIONS

In schools, early in the morning, and in fasting status, 30 ml of blood were drawn according to a standardized blood collection protocol by a certified phlebotomist. More details on sample transport and quality assurance can be found elsewhere (23). For the measurement of pyridoxal 5'phosphate (PLP), biomarker of vitamin B_6, ethylene diamine tetraacetic acid (EDTA) whole blood was centrifuged at 3,500 g for 15 min. The supernatants were stored at -80 °C until analyzed. PLP was measured by high performance liquid chromatography (HPLC) (Varian Deutschland GmbH, Darmstadt, Germany; coefficient of variation [CV] = 1%) with a modified method of Kimura et al. (16,24).

For the measurement of plasma folate and plasma vitamin B_{12}, heparinized tubes were collected, placed immediately on ice, and centrifuged within 30 min (3,500 g for 15 min). The supernatant fluid was transported at a stable temperature of 4-7 °C to the central laboratory at the University of Bonn (IEL-Institut fuer Ernährungs [und Lebensmittelwissebschaften], Germany) and stored at 80 °C until assayed. After measuring hematocrit *in situ,* EDTA whole blood was used for the red blood cell folate (RBC-folate) analysis. EDTA whole blood was diluted 1:5 with freshly prepared 0.1% ascorbic acid for cell lysis and incubated for 60 min in the dark before storage at 80 °C. Plasma and RBC-folate and plasma vitamin B_{12} were measured by means of a competitive immunoassay using the Immunolite 2000 analyzer (DPC Biermann GmbH, Bad Nauheim, Germany) (CV for plasma folate = 5.4%, RBC folate = 10.7%, cobalamin = 5.0%) (23). Sera for measuring holotranscobalamin (HoloTC) were obtained by centrifuging blood collected in evacuated tubes without anticoagulant at 3,500 g for 15 min within one hour. Once send to the central laboratory, sera were aliquoted and stored at 80 °C until transport in dry ice to the biochemical lab at the Universidad Politécnica de Madrid for analysis (laboratory number 242 of the Laboratory Network of the Region of Madrid). HoloTC was measured by microparticle enzyme immunoassay (Active B_{12} Axis-Shield Ltd., Dundee, Scotland, UK) with the use of AxSym (Abbot Diagnostics, Abbott Park, IL, USA) (CV = 5.1%) (25).

Glucose was measured using enzymatic methods (Dade Behring, Schwalbach, Germany). Insulin levels were measured using an Immulite 200 analyzer (DPC Bierman GmbH, Bad Nauheim, Germany). The homeostasis model assessment (HOMA) calculation was used as a measurement of insulin resistance (glycaemia X insulin/22.5) (26).

CONFOUNDERS

Maternal education was used as proxy of socioeconomic status, obtained via self-administered questionnaire completed by the adolescents and expressed as: elementary, lower secondary, higher secondary or tertiary education. This variable was one of the most related socioeconomic factors associated with the studied vitamins (27). Total energy intake in kcal/d assessed with the 24 hours' dietary recalls software HELENA-DIAT was also used as a covariate in the analyses.

ANTHROPOMETRY

Anthropometry battery measurements were assessed following standardized and strictly controlled procedures previously described (28). Weight was measured in underwear and without shoes with an electronic scale (Type SECA 861) to the nearest 0.05 kg, and height was measured barefoot in the Frankfort plane with a telescopic height measuring instrument (Type SECA 225) to the nearest 0.1 cm. Body weight and height, together with subscapular and tricipital skinfold thicknesses, were measured in triplicate. BMI was calculated using the Quetelet formula (kg/m^2). The body fat percentage was calculated using the Slaughter's equation (29), and thereafter the fat mass index (FMI) was calculated by dividing fat mass by height squared (m^2).

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. All analyses were sex-specific. Descriptive data are presented as means and standard deviations (SD). Z-scores of BMI and FMI, and HOMA considering age and sex were used in the analyses. The Mann-Whitney test for non-parametric variables was applied to examine differences between two predefined groups, i.e., above or under the median of the z-scores for BMI, FMI, and HOMA. Thereafter, obtained categories were combined to create four subsequent groups to analyze intakes and statuses of the vitamins: low BMI (or FMI) - low HOMA (the most favorable group in terms of body composition and insulin sensitivity); low BMI (or FMI) - high HOMA; high BMI (or FMI) - low HOMA; and, finally, high BMI (or FMI) - high HOMA (the less favorable group). The Kruskal-Wallis test was applied to look at the differences in B-vitamin intakes and biomarkers among groups, with a Mann-Whitney test approach to contrast values 2 x 2. Finally, maternal education and total energy intakes were included in the analysis of covariance (ANCOVA) as covariates. All statistical tests and corresponding p values were two-sided, and $p < 0.05$ was the cut-off to consider a result as statistically significant.

RESULTS

In the whole HELENA sample males represented 45%, and this percentage is significantly lower than in our analysis, where males

represented the 47% ($p = 0.004$). In terms of maternal education, included males and females showed significantly higher maternal education levels than those who were excluded (data not shown) ($p < 0.001$). Males included in the dietary analysis had significantly lower energy intake ($p = 0.001$) than those excluded; no significant differences were observed in females. There was no statistically significant difference in biomarkers of all three vitamins between the samples included and excluded (based on the inclusion criteria and required data availability).

Table I presents the main characteristics of the sample, by sex. FMI and HOMA were significantly higher in females than in males whilst total energy intake was lower ($p < 0.05$). Table II presents adolescents' B-vitamins intakes and biomarkers by the corresponding groups based on the median z-scores of variables of interest (BMI, FMI, and HOMA). Adolescents with low BMI, HOMA and FMI z-scores consumed more B-vitamins than those with high BMI, HOMA and FMI z-scores, except in the case of males with low HOMA, who had lower folate intakes. Considering biomarkers, adolescents with lower BMI, FMI and HOMA showed higher B-vitamins levels, except in the case of males belonging to the low HOMA group, who had lower RBC-folate concentrations than their counterparts in the higher HOMA group ($p < 0.05$).

Table III shows the differences in B-vitamins both in intakes and concentrations among the groups defined by the subsequent categories of < median and > median of BMI, FMI, and HOMA z-scores considered in combination, without any additional adjustment. All in all, results showed that adolescents belonging to the less favorable groups (high BMI-or FMI-/high HOMA) had lower B-vitamins intake and concentrations, and also lower total energy intakes. However, when an analysis of the covariance was performed to introduce in the model the covariates of education of the mother and total energy intake, most of the statistically significant differences among groups disappeared.

Table IV shows similarly, the adjusted results of the table II (by energy intakes, and maternal education). In females, vitamin B_6 intakes were higher in the high BMI/high HOMA group than in the high BMI/low HOMA group ($p < 0.05$). Similarly, the high FMI/high HOMA group vitamin B_6 intakes were higher than in the low FMI/low HOMA group. Plasma vitamin B_{12} in males were significantly lower in the high FMI/high HOMA than in the low FMI/low HOMA group, keeping also significant their trends throughout the groups, which can be observed also for females ($p < 0.05$). These trends can be followed in figure 1.

DISCUSSION

To the authors' knowledge, this is the first study to examine the association between B-vitamin intakes and the corresponding biomarker concentrations and insulin resistance according to markers of body composition such as body mass index and fat mass index in European adolescents. The results suggest an association between higher adiposity together with higher insulin sensitivity and plasma vitamin B_{12} concentrations, showing the lowest vitamin B_{12} plasma concentrations in those adolescents with higher levels of adiposity combined with higher HOMA insulin sensitivity. Three B-vitamins intake and status corresponding to vitamin B_6, folate and vitamin B_{12} have been investigated in this study, and we have obtained several differences in them in different groups constituted by the combinations between BMI, FMI and HOMA categories. However, intake of vitamin B_6 and plasma vitamin B_{12} was the only for which a difference was found for categories of the mentioned groups when education of the mother and energy intake was taken into account.

The prevalence of insufficient vitamin B_{12} biomarker levels in this sample of European adolescents is low (5% based on HoloTC

Table I. Characteristics of the participants by sex

Characteristics	Males (n = 281), mean ± SD	Females (n = 334), mean ± SD	p-values
Age*	14.8 ± 1.3	14.8 ±1.2	0.71
BMI (kg/m^2)	20.9 ± 3.6	21.2 ± 3.3	0.12
FMI (kg fat mass/m^2)	12.6 ± 9.2	15.0 ± 6.8	0.03
HOMA	2.0 ± 1.2	2.2 ± 1.2	< 0.00
Energy intake (kcal/d)*	2,523 ± 816	1,892 ± 544	< 0.00
Vitamin B_6 diet density (%)*	57.2 ± 14.8	64.8 ± 16.3	< 0.00
Folate diet density (%)*	21.8 ± 5.8	24.4 ± 6.5	< 0.00
Vitamin B_{12} diet density (%)*	104.4 ± 33.5	104.0 ± 38.0	0.43
ME: Low education (n, %)	17 (6)	29 (9)	0.17
ME: Medium-low education (n, %)	60 (21)	83 (25)	
ME: Medium-high education (n, %)	92 (33)	115 (34)	
ME: High education (n, %)	112 (40)	107 (32)	

*BMI: Body mass index; FMI: Fat mass index; HOMA: Homeostasis Model Assessment; ME: Maternal education. B-vitamins diet densities were calculated as follows: (amount of B-vitamin intake per 1,000 kcal of diet/recommendation of the corresponding B-vitamin intake based on the Institute of Medicine recommendations) *100. Recommendations for vitamin B_6 intakes are 1,300 µg for males and 1,200 µg for females; for folate, 400 µg in males and females; and for vitamin B_{12}, 2.4 µg in both sexes. p-values in bold are the only significant ones, based either in Mann-Whitney test or t-test* at 0.05 level two-sided.*

Table II. B-vitamin intakes and concentrations and the groups established by the medians of the sex-specific z-scores of body mass index, fat mass index and Homeostasis Model Assessment index stratified by sex

B-vitamins	Males			Females		
	< median of BMI z-score^ (n = 140)	> median of BMI z-score^ (n = 141)		< median of BMI z-score^ (n = 167)	> median of BMI z-score^ (n = 167)	
	Mean ± SD	Mean ± SD	p-value	Mean ± SD	Mean ± SD	p-value
Intakes						
Vitamin B_6 (µg/d)	1,925 ± 608	1,725 ± 577	0.01	1,508 ± 511	1,385 ± 446	0.02
Vitamin B_6 diet density (%)	56.0 ± 13.5	58.4 ± 16.0	0.25	61.8 ± 15.3	67.9 ± 16.8	0.00
Folate (µg/d)	222 ± 73.2	206 ± 69.5	0.11	189 ± 57.2	172 ± 56.2	0.01
Folate diet density (%)	21.0 ± 4.8	22.7 ± 6.6	0.04	23.5 ± 5.6	25.4 ± 7.2	0.01
Vitamin B_{12} (µg/d)	6.6 ± 2.4	5.8 ± 2.5	0.00	4.8 ± 1.6	4.4 ± 1.7	0.00
Vitamin B_{12} diet density (%)	104.5 ± 32.6	104.4 ± 34.5	0.92	99.9 ± 30.9	108.1 ± 43.7	0.13
Status						
PLP (pmol/l)	67.3 ± 42.0	69.3 ± 47.4	0.75	63.7 ± 80.3	62.0 ± 44.4	0.58
PF (nmol/l)	18.6 ± 9.4	18.2 ± 11.4	0.29	18.8 ± 9.3	17.8 ± 10.1	0.09
RBC-folate (nmol/l)	818 ± 328	827 ± 433	0.47	772 ± 305	761 ± 311	0.67
Plasma B_{12} (pmol/l)	358 ± 143	318 ± 115	0.04	403 ± 154	355 ± 159	0.00
HoloTC (pmol/l)	66.1 ± 36.9	64.5 ± 27.4	0.64	64.8 ± 36.1	65.7 ± 36.6	0.82
	< median of FMI z-score (n = 140)	> median of FMI z-score (n = 141)		< median of FMI z-score (n = 167)	> median of FMI z-score (n = 167)	
Intakes						
Vitamin B_6 (µg/d)	1,910 ± 606	1,740 ± 585	0.01	1,466 ± 458	1,426 ± 506	0.31
Vitamin B_6 diet density (%)	54.8 ± 12.9	59.6 ± 16.3	0.03	62.1 ± 15.7	67.6 ± 16.5	0.02
Folate (µg/d)	222 ± 72.8	206 ± 70.0	0.07	185 ± 56.0	176 ± 57.7	0.10
Folate diet density (%)	20.8 ± 4.9	22.9 ± 6.4	0.01	23.6 ± 4.9	25.3 ± 7.1	0.02
Vitamin B_{12} (µg/d)	6.7 ± 2.5	5.7 ± 2.4	< 0.00	4.7 ± 1.5	4.5 ± 1.8	0.15
Vitamin B_{12} diet density (%)	104.4 ± 33.6	104.4 ± 33.6	0.95	104.4 ± 33.6	10.4.4 ± 33.6	0.13
Status						
PLP (pmol/l)	65.5 ± 41.7	71.1 ± 47.3	0.24	67.1 ± 81.4	58.4 ± 41.0	0.60
PF (nmol/l)	18.5 ± 9.5	18.3 ± 11.2	0.49	19.1 ± 10.1	17.5 ± 9.3	0.07
RBC-folate (nmol/l)	825 ± 335	820 ± 428	0.40	787 ± 311	746 ± 304	0.14
Plasma B_{12} (pmol/l)	362 ± 144	313 ± 113	0.01	403 ± 165	355 ± 147	0.01
HoloTC (pmol/l)	67.6 ± 38.4	63.0 ± 24.7	0.76	66.2 ± 38.3	64.4 ± 34.3	0.99
	< median of HOMA z-score (n = 140)	> median of HOMA z-score (n = 141)		< median of HOMA z-score (n = 167)	> median of HOMA z-score (n = 167)	
Intakes						
Vitamin B_6 (µg/d)	1,868 ± 620	1,781 ± 579	0.20	1,431 ± 459	1,461 ± 506	0.88
Vitamin B_6 diet density (%)	56.2 ± 14.2	58.1 ± 15.4	0.29	62.5 ± 15.7	67.1 ± 16.6	0.01
Folate (µg/d)	212 ± 70.4	216 ± 73.2	0.84	184 ± 57.4	178 ± 57.0	0.41
Folate diet density (%)	20.8 ± 5.1	22.9 ± 6.3	0.00	24.2 ± 6.6	24.7 ± 6.5	0.42

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Table II (Cont.). B-vitamin intakes and concentrations and the groups established by the medians of the sex-specific z-scores of body mass index, fat mass index and Homeostasis Model Assessment index stratified by sex

B-vitamins	Males			Females		
	< median of HOMA z-score (n = 140)	> median of HOMA z-score (n = 141)		< median of HOMA z-score (n = 167)	> median of HOMA z-score (n = 167)	
Intakes						
Vitamin B_{12} (µg/d)	6.5 ± 2.7	5.9 ± 2.2	0.04	4.6 ± 1.7	4.5 ± 1.7	0.65
Vitamin B_{12} diet density (%)	105.5 ± 35.0	103.3 ± 32.1	064	101.5 ± 37.4	106.4 ± 38.6	0.18
Status						
PLP (pmol/l)	67.4 ± 42.0	69.1 ± 47.3	1.0	67.5 ± 79.1	58.2 ± 46.3	0.24
PF (nmol/l)	18.9 ± 10.7	17.9 ± 10.1	0.43	19.6 ± 10.4	17.0 ± 8.9	0.00
RBC-folate (nmol/l)	815 ± 395	829 ± 373	0.74	766 ± 285	766 ± 329	0.70
Plasma B_{12} (pmol/l)	354 ± 132	322 ± 129	0.03	397 ± 160	361 ± 154	0.03
HoloTC (pmol/l)	70.1 ± 40.4	60.5 ± 20.6	0.17	67.8 ± 40.1	62.8 ± 32.1	0.33

*BMI: Body mass index; FMI: Fat mass index; HOMA: Homeostasis Model Assessment; PLP: Pyridoxal phosphate; PF: Plasma folate; RBC-folate: Red blood cell folate; HoloTC: Holotranscobalamin; SD: Standard deviation. B-vitamins diet densities were calculated as follows: (amount of B-vitamin intake per 100 kcal of diet/ recommendation of the corresponding B-vitamin intake based on the Institute of Medicine recommendations) *100. Recommendations for vitamin B_6 intakes are 1,300 µg for males and 1,200 µg for females; for folate, 400 µg in males and females; and for vitamin B12, 2.4 µg in both sexes. p-value based on Mann-Whitney non-parametric test. Statistical significance at 0.05 two-sided level. ^Sex-specific z-scores of BMI, FMI and HOMA were adjusted by age.*

Table III. Differences of B-vitamin intakes and biomarkers concentrations by resulting combination groups between z-scores of body mass index and fat mass index against z-scores of insulin resistance (HOMA) index

Males	Energy intake (mean, SD)	Vitamin B_6 (mean, SD)	Folate (mean, SD)	Vitamin B_{12} (mean, SD)	PLP (mean, SD)	PF (mean, SD)	RBC-folate (mean, SD)	Plasma B_{12} (mean, SD)	HoloTC (mean, SD)
BMI by HOMA (n)									
Low BMI-low HOMA (91)	2,659 ± 783[a]	1,910 ± 618[a]	215 ± 71	6.7 ± 2.4[ab]	65.7 ± 40.8	18.3 ± 8.7	782 ± 300	366 ± 142[a]	70.3 ± 43.5
Low BMI-high HOMA (49)	2,763 ± 893	1,953 ± 596	236 ± 77.0	6.3 ± 2.4	70.3 ± 44.4	19.1 ± 10.5	882 ± 370	342 ± 147	58.5 ± 17.6
High BMI-low HOMA (49)	2,502 ± 800	1,791 ± 552	208 ± 70.4	6.1 ± 3.1[a]	70.8 ± 44.6	20.0 ± 13.7	877 ± 525	330 ± 111	69.7 ± 34.6
High BMI-high HOMA (92)	2,273 ± 757[a]	1,689 ± 552[a]	206 ± 69.5	5.6 ± 2.1[b]	68.5 ± 49.0	17.3 ± 9.9	801 ± 373	311 ± 117[a]	61.6 ± 22.1
p-value	< 0.00	0.03	0.19	0.01	0.97	0.64	0.55	0.08	0.44
FMI by HOMA (n)									
Low-FMI-low HOMA (86)	2,660 ± 770[a]	1,903 ± 628[a]	215 ± 69.1	6.8 ± 2.5[ab]	65.5 ± 41.1	18.5 ± 9.1	778 ± 296	366 ± 141[a]	71.5 ± 44.7
Low FMI-high HOMA (54)	2,843 ± 952	1,921 ± 569	235 ± 78.1	6.4 ± 2.4	65.6 ± 43.5	18.6 ± 10.4	908 ± 385	357 ± 149.0	60.4 ± 20.7
High FMI-low HOMA (54)	2,504 ± 822	1,805 ± 605	208 ± 73.1	6.0 ± 2.9[a]	71.1 ± 44.0	19.7 ± 13.2	882 ± 525	332 ± 113	67.5 ± 30.7
High FMI-high HOMA (87)	2,223 ± 677[a]	1,704 ± 574[a]	206 ± 68.6	5.6 ± 2.0[b]	71.0 ± 49.3	17.5 ± 9.9	785 ± 361	302 ± 112[a]	60.6 ± 20.7
p-value	< 0.00	0.06	0.17	0.00	0.68	0.83	0.21	0.02	0.57

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Table III (Cont.). Differences of B-vitamin intakes and biomarkers concentrations by resulting combination groups between z-scores of body mass index and fat mass index against z-scores of insulin resistance (HOMA) index

Females	Energy intake (mean, SD)	Vitamin B_6 (mean, SD)	Folate (mean, SD)	Vitamin B_{12} (mean, SD)	PLP (mean, SD)	PF (mean, SD)	RBC-folate (mean, SD)	Plasma B_{12} (mean, SD)	HoloTC (mean, SD)
BMI by HOMA (n)									
Low BMI-low HOMA (100)	2,045 ± 483[ab]	1,511 ± 488[a]	194 ± 52.4[ab]	4.8 ± 1.6[ab]	64.7 ± 94.4[a]	19.7 ± 9.3[ab]	779 ± 290	418 ± 149[ab]	67.2 ± 33.7
Low BMI-high HOMA (67)	2,043 ± 544	1,502 ± 546	181 ± 63.4	4.8 ± 1.5	62.2 ± 54.4	17.5 ± 9.2[a]	760 ± 329	380 ± 159	61.3 ± 39.5
High BMI-low HOMA (67)	1,762 ± 449[a]	1,312 ± 386[a]	168 ± 61.5[a]	4.3 ± 1.7[a]	71.6 ± 49.1[a]	19.4 ± 11.9	747 ± 280	366 ± 172[a]	68.8 ± 48.3
High BMI-high HOMA (100)	1,727 ± 595[b]	1,433 ± 478	175 ± 52.6[b]	4.4 ± 1.7[b]	55.5 ± 39.9	16.7 ± 8.7[b]	770 ± 331	348 ± 151[b]	63.7 ± 26.6
p-value	< 0.00	0.05	0.01	0.02	0.04	0.02	0.95	0.00	0.47
FMI by HOMA (n)									
Low FMI-low HOMA (102)	1,995 ± 437[ab]	1,466 ± 417	189 ± 51.1	4.7 ± 1.5	70.0 ± 94.7	19.9 ± 10.4[a]	790.7 ± 294	421 ± 159[abc]	67.6 ± 35.4
Low FMI-high HOMA (65)	1,995 ± 554	1,467 ± 520	180 ± 64.1	4.7 ± 1.5	63.4 ± 56.1	17.8 ± 9.7	780 ± 339	374 ± 157[a]	63.9 ± 42.6
High FMI-low HOMA (65)	1,832 ± 550[a]	1,377 ± 517	175.4 ± 65.7	4.5 ± 1.9	64.2 ± 44.6	19.0 ± 10.4	728 ± 268	359 ± 156[b]	68.1 ± 46.8
High FMI-high HOMA (102)	1,764 ± 604[b]	1,457 ± 499	176 ± 52.3	4.5 ± 1.7	54.8 ± 38.3	16.6 ± 8.4[a]	757 ± 324	353 ± 142[c]	62.0 ± 23.4
p-value	< 0.00	0.64	0.24	0.54	0.35	0.02	0.51	0.01	0.57

BMI: Body mass index; HOMA: Homeostasis Model Assessment; FMI: Fat mass index; PLP: Pyridoxal phosphate; PF: Plasma folate; RBC-folate: Red blood cell folate; HoloTC: Holotranscobalamin; SD: Standard deviation. p-value based on Kruskal-Wallis non-parametric test. Statistical significance was established at 0.05 two-sided level. Superscripts letters represent those groups with statistical significant differences. Post hoc comparisons between groups have been established based on Mann-Whitney test. Statistical significance critical value established at 0.0167 two-sided level (resulting from dividing 0.05/3 comparisons with the reference category of "low BMI (or FMI)-low HOMA" which represents the more favorable option).

and 2% based on serum B_{12}) (30), and corresponds approximately to the prevalence of inadequate vitamin B_{12} intakes reported previously (2.9% in males and 6.0% in females) (8) in a larger sample of the same adolescents. In other studies performed in Australia and Canada, the percentage of adolescents identified with low or borderline B_{12} status was higher than the one reported in our European adolescents (respectively, 32.1% in obese adolescents in the study from Australia (13), or 13.7% in all children and adolescents and 20.4% only in obese children and adolescents reported in the Canadian survey (31) using the same cut-points as in the Australian study). However, these percentages of low vitamin B_{12} status refer exclusively to overweight/obese adolescents, and this could be the cause of such big differences with ours.

In our sample, 23.3% (32) of the adolescents were classified as overweight or obese. Even with these differences in rates of overweight/obesity and deficiency or not of vitamin B_{12} between our study and the Australian study (13), our results confirm the association between lower levels of vitamin B_{12} and higher HOMA and FMI. Besides, this negative association between vitamin B_{12} plasma levels and values of insulin sensitivity and body composition markers are likely reproducible for other micronutrients (total carotenoids, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein/zeaxanthin, lycopene, vitamin E, vitamin C, selenium, vitamin A, vitamin D, folate, vitamin B_{12}, and RBC-folate), as reported in a study of US adults (33).

There are no previous studies investigating the same associations in a similar population group. Nevertheless, previous studies (4,13,31) focused on obese adolescents or wide general population groups have also found that higher BMI z-scores were associated with lower vitamin B_{12} concentrations, with no significant gender effect.

There are several mechanisms which might explain this observation. For instance, adolescents have increased nutrient requirements secondary to increased growth and body size (34). Another reason is that adolescents with high BMI are thought to have diets with low micronutrient density. In our study, we found

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Table IV. Adjusted estimates of B-vitamin intakes and biomarker status by combination of body mass index, fat mass index and Homeostasis Model Assessment index

Indicators	Vitamin B_{12} intakes (µg/d)				Plasma B_{12} (pmol/l)				Holotranscobalamin (pmol/l)			
	Males		Females		Males		Females		Males		Females	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
BMI by HOMA (n)												
Low BMI-low HOMA (90, 100)	6.5	0.2	4.5	0.1	364	13.7	416	15.7	70.1	3.5	65.1	3.8
Low BMI-high HOMA (50, 67)	5.9	0.3	4.6	0.2	339	18.6	373	19.2	57.9	4.8	60.2	4.6
High BMI-low HOMA (50, 67)	6.1	0.3	4.4	0.2	330	18.6	352	19.1	69.2	4.7	69.0	4.5
High BMI-high HOMA (91, 100)	6.1	0.2	4.7	0.1	315	13.7	362	15.9	62.5	3.6	66.3	3.7
F and p-values	1.01	0.39	0.66	0.58	2.17	0.09	1.78	0.15	1.85	0.14	0.64	0.59
FMI by HOMA (n)												
Low-FMI-low HOMA (86, 101)	6.5	0.2	4.5	0.1	361[a]	13.8	426	15.3	70.5	3.5	66.5	3.7
Low FMI-high HOMA (54, 66)	5.9	0.3	4.5	0.2	355	8.5	352	19.0	59.3	4.8	63.5	4.6
High FMI-low HOMA (54, 66)	6.1	0.3	4.5	0.2	338	18.4	361	19.1	68.4	4.9	67.2	4.6
High FMI-high HOMA (87, 101)	6.1	0.2	4.8	0.1	306[a]	13.8	360	15.5	61.7	3.6	64.0	3.7
F and p-values	1.18	0.32	0.71	0.55	2.89	0.04	2.94	0.03	1.73	0.16	0.18	0.91

Indicators	Vitamin B_6 intakes (µg/d)				Pyridoxal phosphate (pmol/l)				Folate intakes (µg/d)				Plasma folate (pmol/l)				RBC-folate (pmol/l)			
	Males		Females		Males		Females		Males		Females		Males		Females		Males		Females	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
BMI by HOMA (n)																				
Low BMI-low HOMA (90, 100)	1,832	46.1	1,409	36.5	65.9	4.9	63.6	6.9	207	5.5	183	4.6	18.7	1.1	19.6	1.0	792	41.0	776	31.7
Low BMI-high HOMA (50, 67)	1,834	62.6	1,416	44.3	69.7	6.8	60.8	8.2	221	7.4	171	5.5	19.2	1.5	17.3	1.2	882	55.2	753	38.4
High BMI-low HOMA (50, 67)	1,803	62.4	1,385[a]	44.0	71.3	7.0	72.3	8.3	208	7.4	176	5.5	19.7	1.5	19.4	1.2	867	55.1	750	38.3
High BMI-high HOMA (91, 100)	1,823	46.1	1,544[a]	36.8	68.3	5.1	57.1	6.9	222	5.5	188	4.6	17.0	1.1	16.9	1.0	796	41.2	777	31.9
F and p-values	0.06	0.98	3.57	0.02	0.16	0.93	0.70	0.55	1.79	0.15	2.18	0.09	0.88	0.45	1.69	0.17	0.93	0.43	0.17	0.92
FMI by HOMA (n)																				
Low-FMI-low HOMA (86, 101)	1,817	46.4	1,393[a]	35.8	65.8	5.0	68.9	6.7	205	5.5	181	4.5	18.7	1.1	19.8	1.0	786	41.2	788	30.9
Low FMI-high HOMA (54, 66)	1,759	62.2	1,408	44.9	64.7	7.0	62.4	8.3	215	7.4	173	5.6	18.6	1.5	17.8	1.2	904	54.9	780	39.7
High FMI-low HOMA (54, 66)	1,827	61.8	1,409	44.7	71.2	6.9	64.8	8.5	211	7.3	178	5.6	19.5	1.5	19.0	1.2	878	54.5	730	39.0
High FMI-high HOMA (87, 101)	1,866	46.5	1,547[a]	36.3	71.1	5.1	55.9	6.9	225	5.5	186	4.5	17.3	1.1	16.6	1.0	782	41.5	759	31.1
F and p-values	0.61	0.61	3.68	0.01	0.31	0.82	0.59	0.62	2.30	0.08	1.22	0.30	0.53	0.66	1.91	0.13	1.63	0.18	0.50	0.68

RBC-folate: Red blood cell folate; SE: Standard error; n.s.: Not significant. Significant differences ($p < 0.05$) between groups are indicated by the same superscripts letters. F tests the effect of the model.

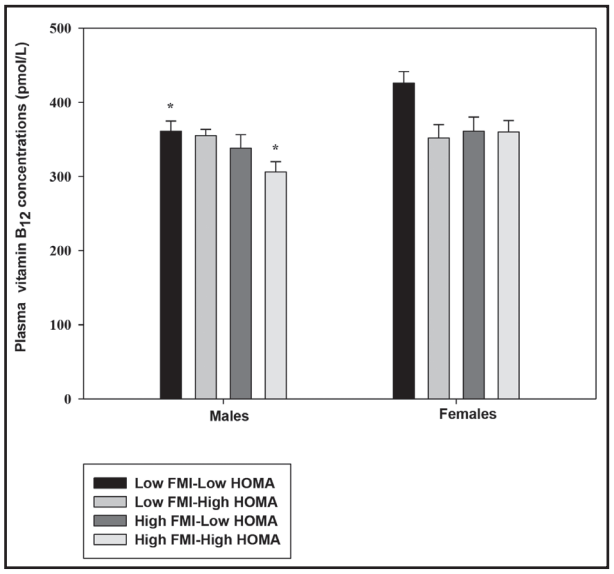

Figure 1.

Plasma vitamin B_{12} concentrations (pmol/L) according to the combination between categories of FMI and HOMA by sex.

lower B-vitamins intake in adolescents with higher BMI while they have higher B-vitamins density diets. This can be explained by the fact that in the HELENA study, adolescents with higher BMI reported lower total energy diets likely affected by underreporting (35). Another reason could be that obese adolescents may have repeated short-term restrictive diets (34); this could be the case in our study (35), because adolescents with high BMI and high FMI were those with lower total energy intakes.

There were several differences between groups constituted by the combination of body composition markers and HOMA insulin sensitivity in terms of B-vitamins biomarkers concentrations. However, only adolescents belonging to the most favorable group in terms of combination between FMI and HOMA (lower FMI combined with lower HOMA) have higher plasma vitamin B_{12} concentrations, as it had been already shown by another study (13). However, the previous study did not include the analyses of B-vitamins dietary intake, as it has being shown in our study. This fact cannot be explained by higher vitamin B_{12} intakes but it might be due to lower vitamin B_{12} density diets in comparison to those adolescents belonging to the less favorable combination groups, as shown in table II, likely resulting from the restrictive diets or underreporting behaviors previously mentioned. Besides, while we have obtained statistically significant differences for vitamin B_6 intake regarding BMI and FMI based on the median categories combined with the categories of HOMA, this was not the case for vitamin B_{12}. This is of lots of interest owing to the fact that plasma vitamin B_{12} is supposed to reflect changes in day-to-day diet rather than HoloTC, which is more efficient in predicting long-term diet changes (9), for which no difference among categories has been found.

Given that there seems not to be a plausible effect of adiposity and insulin resistance on plasma vitamin B_{12} concentrations, linked to vitamin B_{12} intake, we should consider the hypothesis that low vitamin B_{12} concentrations could influence insulin resistance. A recent genome-wide analysis (36) suggested that increased DNA methylation is associated with increased BMI in adults, and vitamin B_{12} is a determinant for DNA methylation.

Also, in a recent review about the transmission of obesity-adiposity and related disorders from the mother to the newborns (37), it is mentioned that in rural areas from India, with mothers consuming mainly vegetarian diets, the most insulin-resistant children were born to mothers who had low vitamin B_{12} but high folate levels, suggesting that a balance between these two vitamins is essential. This might be a consequence from the fact that folate together with vitamins B_{12} and B_6, among others, regulate maternal 1-carbon metabolism, which influences cellular growth and differentiation by helping synthesis of nucleic acids. However, this explanation is not helpful to understand our results, owing to the differences in the characteristics of the population group and because our sample showed higher prevalence of folate deficiency than the vitamin B_{12} one (30).

Other study (38) showed the importance of levels of homocysteine in insulin resistance with an improvement of it with a lowering homocysteine by folate + vitamin B_{12} treatment and a correlation of 0.60 between homocysteine levels and insulin resistance, as was also shown by similar studies.

Our findings might be of particular concern in case of adolescents diagnosed as obese patients because they will be prone to a further decrease in vitamin B_{12} concentrations if metformin therapy is recommended for the treatment of type 2 diabetes (15). For instance, in adults, vitamin B_{12} malabsorption was observed in approximately 20% of patients using metformin, and this was associated with a 4-24% decrease of vitamin B_{12} concentrations (39).

LIMITATIONS AND STRENGTHS

The cross-sectional design of the study represents a limitation owing to the fact that causality cannot be established. The clinical interpretation of our findings is unclear because a very low percentage of adolescents presented inadequate intakes or very low serum concentrations of vitamin B_{12}. However, the observed association between vitamin B_{12} plasma level and body composition and insulin resistance warns us about the importance of having a healthy nutritional status and elucidates the fact that overweight or obese people cannot get nutritional deficiencies. The use of harmonized and standardized procedures in a large sample of adolescents from Europe (18) should be considered as the main strength of the study, as well as the use of previously validated questionnaires and procedures (18,19). Besides, the calculation of the usual intake values based on the MSM method to prevent limitations of the 24-h recalls (22), together with the use of widely accepted micronutrient biomarkers, strengthen the reliability of the observations with any other marker or symptom (40).

CONCLUSION

Obesity is not only associated with cardiovascular conditions, cancer, dyslipidemias, etc., but also with micronutrient deficiencies which can lead to serious health problems. Among vitamins B_6, folate, and B_{12}, it seems that vitamin B_{12} is the one most consistently and negatively associated with BMI, FMI, and insulin sensitivity or resistance (HOMA) without discriminating between sexes of European adolescents.

In male and female adolescents with combined higher adiposity measured with fat mass index and higher HOMA insulin sensitivity, low vitamin B_{12} plasma concentrations were observed. These differences do not seem explained by dietary vitamin B_{12} intake. Further studies are necessary to elucidate the potential role of low vitamin B_{12} concentrations in the development of insulin resistance in adolescents in order to identify a plausible biological mechanism.

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Nutrición Hospitalaria

Trabajo Original

Pediatría

Excess weight in patients with cystic fibrosis: is it always beneficial?

Incremento de peso en pacientes con fibrosis quística: ¿es siempre beneficioso?

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Abstract

Introduction: The primary objective of this study was to find out the prevalence of overweight and obese status, as well as their association to pulmonary function, total cholesterol and vitamin D in patients with cystic fibrosis (CF).

Materials and methods: This is a multicenter descriptive and cross-sectional study. Twelve Spanish hospitals participated. 451 patients with CF were included. Adults were classified according to body mass index (BMI) and children were classified according to BMI percentiles (WHO tables). Pearson's correlation, Anova, Student's t-test and multiple linear regression were conducted.

Results: Mean age was 12.3 (range 4-57) years old, 51% were male and 18% had pancreatic sufficiency. Participants were classified in five nutritional status categories: 12% were malnourished; 57%, at nutritional risk; 24%, normally nourished; 6%, overweight; and 1%, obese. Pulmonary function in overweight or obese patients (91 ± 19%) was better than in malnourished patients (77 ± 24%) ($p = 0.017$). However, no difference was observed between those at nutritional risk (86 ± 19%) or normally nourished (90 ± 22%) groups. Overweight and obese patients had higher levels of total cholesterol ($p = 0.0049$), a greater proportion of hypercholesterolemia ($p = 0.001$), as well as lower levels of 25 OH vitamin D ($p = 0.058$).

Conclusions: Prevalence of overweight and obese was 6 and 1%. Excess weight status does not offer any benefit in pulmonary function in comparison to normally nourished patients.

Key words:

Vitamin D. Cystic fibrosis. Overweight.

Resumen

Introducción y objetivos: conocer la prevalencia de sobrepeso y obesidad, así como su asociación con la función pulmonar, el colesterol total y la vitamina D en pacientes con fibrosis quística (FQ).

Material y métodos: estudio multicéntrico descriptivo y transversal. Participaron 12 hospitales españoles. Fueron incluidos 451 pacientes con FQ, clasificados según el índice de masa corporal (IMC) en adultos y el IMC percentilado (tablas OMS) en niños. Análisis estadístico: C.Pearson, Anova, t de Student y regresión lineal múltiple.

Resultados: la mediana de edad fue 12,3 (rango 4-57) años. Un 51% eran varones y el 18%, suficientes pancreáticos (SP). El 12% estaba desnutrido; el 57%, en riesgo nutricional; el 24%, normonutrido; el 6% presentaba sobrepeso; y un 1%, obesidad. La función pulmonar en los pacientes con sobrepeso (91 ± 19%) era mejor que en los desnutridos (77 ± 24%) ($p = 0,017$), sin embargo, no se observaron diferencias con respecto a los que estaban en riesgo nutricional (86 ± 19%) o normonutridos (90 ± 22%). Los pacientes con sobrepeso tenían más elevado el colesterol total ($p = 0,0049$), mayor proporción de hipercolesterolemia ($p = 0,001$), así como niveles más bajos de 25 OH vitamina D ($p = 0,058$).

Conclusiones: la prevalencia de sobrepeso y obesidad fue del 6 y el 1%. El sobrepeso y la obesidad no ofrecen beneficio sobre la función pulmonar en comparación con los normonutridos.

Palabras clave:

Vitamina D. Fibrosis quística. Sobrepeso.

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INTRODUCTION

Advances in early diagnosis and comprehensive treatment of cystic fibrosis (CF) have caused an increase in the survival of these patients (1). One of the factors that has contributed to this phenomenon has been the improvement of the nutritional status through intensive nutritional intervention based on hypercaloric diets and nutritional supplements, as well as enteral nutrition and pancreatic enzymes for the control of steatorrhea.

On the other hand, patients with CF are not free from the prevailing sedentariness in our current society, which, combined to the improvements in medical and nutritional treatment, has led to the existence of a potential risk for excessive weight gain in some of these patients.

There are few data regarding the actual prevalence of overweight in CF. Recently published studies in Toronto and the USA indicate a prevalence of overweight between 15 and 18% (in children and adults respectively) and up to 8% for obesity (2,3).

Obesity is widely recognized as an important risk factor for the development of metabolic complications such as insulin resistance, hypertension, and dyslipidemia, which may increase the risk of cardiovascular diseases and type 2 diabetes. However, the presence of these obesity-related metabolic disturbances varies widely among obese individuals. Accordingly, a unique subset of obese individuals has been described in the medical literature that appears to be protected or more resistant to the development of metabolic abnormalities associated with obesity. These individuals, now known as "metabolically healthy but obese", despite having excessive body fatness, display a favorable metabolic profile characterized by high levels of insulin sensitivity, no hypertension, as well as normal lipid, inflammation, hormonal and immune profiles (4).

In contrast to the general population, CF patients who are overweight or obese have good pulmonary function (5). However, recent studies suggest that after certain thresholds, body mass index (BMI) is inversely correlated with pulmonary function (6). On the other hand, the effects of excess weight at the cardiovascular level are unknown in this population. For CF patients, absolute BMI should be maintained at or above 22 kg/m^2 in females and 23 kg/m^2 in males. For children, the 50th percentile is optimal (7).

The objective of our study was to establish the prevalence of overweight and obese status, as well as its association with pulmonary function, vitamin D and total cholesterol in our population of CF patients.

MATERIALS AND METHODS

This is a multicenter descriptive and cross-sectional study that was done from November 1st 2012 to April 30th 2014 during the months of November to April (when vitamin D levels were at nadirs). Clinically stable CF patients over four years old, in absence of pulmonary exacerbation, in 12 Spanish university hospitals were enrolled. Ethical approval was granted by the Ethics Committee of the Principality of Asturias, reference number (no. 45/15). Patients and guardians received written, complete and detailed information of the study, and all of them signed their informed consent for the study. All patients were treated according to published European CF guidelines (8).

Each patient was identified with a code assigned to the hospital and the case. Information was taken from the patients' medical files.

The date of birth, gender, race, the cystic fibrosis transmembrane conductance regulator (CFTR) gene genetic test, as well as whether they had been diagnosed using neonatal screening, were also recorded.

The investigators measured the morning weight and height, patients being barefoot and in underwear, using instruments with a precision of 50 g and 0.5 cm respectively, and calculated BMI. All somatometric data were classified (z-score) according to the WHO references (9). The nutritional status of each patient was classified according to the BMI in adults (≥ 18 years old) and the BMI percentile in children, as follows: malnourished (< 18.5 kg/m^2, < P10), nutritional risk (18.5-21.9 kg/m^2 for female, 18.5-22.9 for male kg/m^2; P10-p49), normally nourished (22-24.9 kg/m^2 for female, 23-24.9 kg/m^2 for male; P50-84), overweight (25-29.9 kg/m^2, P85-94) and obese (≥ 30 kg/m^2, ≥ P95). Those with growth failure were also considered as malnourished (height < P3) (8,10).

Pancreatic function was established with the determination of fecal elastase-1 (E-1) levels. Information was taken from the medical file of the patients. Those with concentrations less than 200 µg/g were considered to have pancreatic insufficiency (PI) (11).

The daily dose of vitamin D received by patients was quantified in IU/day. Vitamin D levels in the form of serum 25 OH vitamin D were measured by chemiluminescence immunoassays (CLIA) in each hospital. Levels of 25 OH vitamin D less than 30 ng/ml and 20 ng/ml were considered to be insufficient and as deficiency, respectively (12). Total cholesterol levels were quantified in mg/dl form and hypercholesterolemia was considered when levels were above 200 mg/dl. The measurements were taken while fasting.

Pulmonary function was analyzed as the forced expiratory volume in the first second of expiration (FEV1) using forced spirometry. Percentages were calculated from the absolute values expected for healthy individuals with the same age, gender and height as the patient (13).

The data collected were exported to a statistical data management program (STATA version 13.0). Basic statistical techniques for descriptive analysis were applied for the study. Pearson and Spearman correlation tests were used to analyze the joint behavior of the quantitative variables. Two-tailed t-tests were used for comparison of the averages of two groups, as well as one-factor ANOVA and Bonferroni post-hoc tests for comparison of the averages of three or more groups. For comparison of proportions, Chi-squared tests were used. To analyze the association between nutritional status, FEV1, cholesterol and 25 OH vitamin D, a linear regression analysis was conducted with multivariate adjustment (by sex, age, PI, CFTR gene, screening). If some of the variables did not meet some of the requirements of normality, non-parametric tests were applied (Mann-Whitney test). The differences

were considered as statistically significant when the probability value was $p < 0.05$.

RESULTS

DESCRIPTIVE CHARACTERISTICS

A total of 451 patients with CF aged 4-57 years old (median age [Md] 12.3 years old) were included in this study. Table I shows the main anthropometric characteristics and data of the 451 patients analyzed.

NUTRITIONAL STATUS

When analyzing the nutritional status of our patients according to BMI and height, 12% were malnourished, 57% were at nutritional risk, 24% were normally nourished, 6% were overweight and 1% were obese. If we use BMI as the only nutritional criterion, two of the patients classified as normally nourished (0.5%) and 14 of the patients classified as being at nutritional risk (3%) must be classified as malnourished given that their height was less than P3.

Patients who were overweight or obese (excess weight group) were between five and 49 years old, with a Md of 12 and an interquartile range (IQR) between ten and 16 years. Twenty-seven per cent were homozygous carriers of the DF508 mutation, 43% were heterozygous carriers and 30% were not carriers of said mutation on any of their alleles. Fifty-two per cent were males. The age, gender distribution and genetic background of the patients who were overweight or obese were similar to those of the rest of the sample. A greater proportion of pancreatic sufficient (PS) was observed, 55% *vs* 15% ($p < 0.001$), as well as a lower proportion of patients receiving vitamin D supplements, 76% *vs* 93% ($p < 0.001$).

Regarding vitamin D, 8% of patients, all of them pancreatic sufficient, did not receive daily supplementation. In those who received it, the median dose was 962 IU/day of vitamin D (IQR 800-1,600 IU/day).

NUTRITIONAL STATUS AND PULMONARY FUNCTION

In pediatric patients, an association was observed between BMI (z score) and FEV1 (%) ($r = 0.250$, $p < 0.001$) (Fig. 1). Pulmonary function in patients who were excess weight (overweight or obese) (91 ± 19%) was better than in malnourished patients (77 ± 24%) ($p = 0.017$). However, differences were not observed between excess weight and those who were at nutritional risk (86 ± 19%) or normally nourished (90 ± 22%) (Fig. 2).

The association between nutritional status and FEV1 was analyzed using a linear regression analysis. The variables that were kept in the model were: male gender; age; PS and malnutrition (Table II).

TOTAL CHOLESTEROL AND VITAMIN D IN OVERWEIGHT CF PATIENTS

Levels of total cholesterol were between 58 and 265 mg/dl, with a Md of 130 mg/dl (IQR 111-152.5 mg/dl). Only 5% of the patients had levels of total cholesterol above 200 mg/dl. Thirty-three per cent of obese patients had hypercholesterolemia; Md

Table I. Main features and anthropometric data of 451 patients analyzed

Variable	EPI 371	PS 80	Total 451
Sex (% women)	49	50	49
Age (Md [range]; year)	12.2 (4 to 56)	12.9 (5 to 57)	12.3 (4 to 57)
Group age			
< 18 years (%)	86	86	85
≥ 18 years (%)	14	14	15
CFTR mutation			
Homozygous DF508 (%)	40	0	33
Heterozygous DF508 (%)	47	65	50
No DF508 (%)	13	35	17
Newborn screening (% yes)	36	39	37
Vitamin D dose (Md [interquartile range]) (Ui/day)	1,000 (800-1,600)	756 (400-1,150)	962 (800-1,600)
BMI (Md [interquartile range])			
< 18 years (z score)	-0.43 (-0.87 to 0.05)	-0.03 (-0.48 to 1.05)	-0.37 (-0.8 to 0.12)
≥ 18 years (kg/m^2)	21.5 (19.7 to 23.3)	24.6 (19.4 to 25.6)	21.6 (19.8 to 23.7)

PS: Pancreatic sufficiency; EPI: Exocrine pancreatic insufficiency.

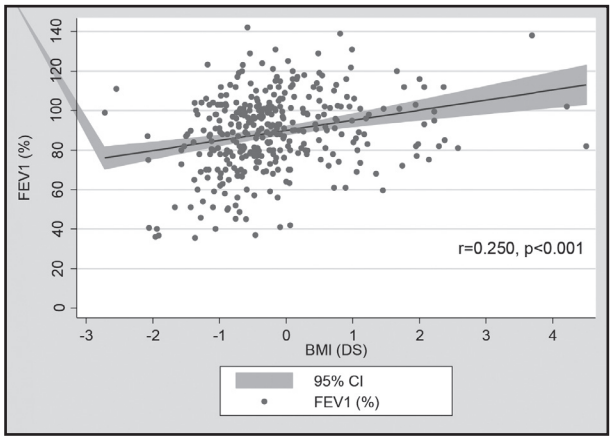

Figure 1.

Association between BMI (z score) and FEV1 (%) in childhood (< 18 years).

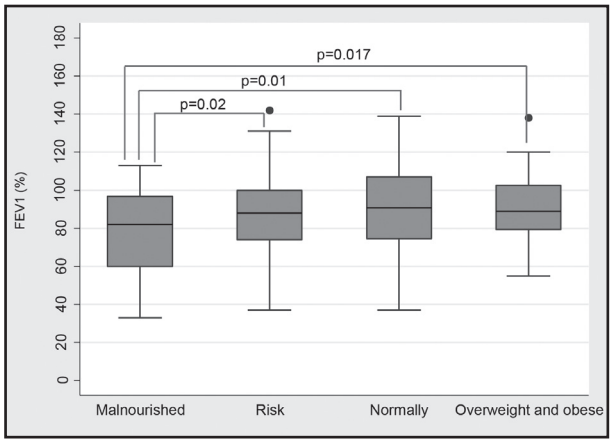

Figure 2.

Lung function of patients ranked by nutritional status.

cholesterol in this group was 169 mg/dl (IQR 153-228 mg/dl). The proportion of hypercholesterolemia was greater in adult patients 11% *vs* 3% (p = 0.003). Patients who were excess weight compared with non-overweight neither obese had elevated levels of total cholesterol: 154 ± 8 *vs* 130 ± 1 mg/dl (p = 0.0049) and a greater proportion of hypercholesterolemia 16% *vs* 3% (p = 0.001). However, those associations were not maintained in the multivariate analysis (Table III).

Levels of vitamin D were between five and 95 ng/ml with a Md of 26 ng/ml (IQR 20-33.5 ng/ml). Sixty-four per cent had insufficient levels, and 25% of these had levels lower than 20 ng/ml. In obese, the Md was 23 ng/ml (IQR 22-25 ng/ml). The patients who were excess weight compared with non-overweight neither obese had lower levels of vitamin D (24 ± 2 *vs* 28 ± 1) ng/ml (p = 0.058). Adjusting for confounding factors and modifiers such as age, exocrine pancreatic function and vitamin D dose received, the patients who were overweight maintained lower levels of 25 OH vitamin D but it was not statistically significant: b = -5.28 (CI 95% -10.51 and 0.09) (p = 0.054) ng/ml.

DISCUSSION

Obesity and weight gain have become a genuine epidemic, whose prevalence has doubled in developed countries in the last 20 years. In Spain, 30% of children between six and 12 years old are overweight, and 10% are obese (14). The phenomenon is primarily related to exogenous causes, such as an increase in energy consumed in the diet, combined with a reduction in the activities that involve energy expenditure and an increase in those of the sedentary type, and it is also associated with genetic and epigenetic factors. This tendency in lifestyle is not exclusive to the general population. It also affects patients with chronic diseases such as CF, probably with greater intensity.

In our study we observed that 7% of patients carried excess weight (6% overweight and 1% obese), about half the number of malnourished patients (12%), while the majority presented normal nutritional status. If we keep in mind the physiopathology of this disease, this prevalence seems to be elevated; however, our numbers are lower when we compare them to North American data, where prevalence reaches 23% (15% overweight and 8% obese) (3). These results could be explained by the differences in lifestyle and diet between both countries. There are also methodological

Table II. Results of multivariable linear regression for associations of subject characteristics with FEV1 % predicted

Variable	Partial β coefficient (95% CI)	p value	R2 for multivariable model
			0.25
Age	-1.3 (-1.5 to -1.0)	0.000	
Male	4.1 (0.5 to 7.6)	0.025	
Pancreatic sufficient	5.5 (0.6 to 10.3)	0.028	
Nutritional status (vs *malnourished)*			
Nutritional risk (BMI P10-49)	7.8 (2.1 to 13.5)	0.008	
Normo-nourished (BMI P50-P85)	15.0 (8.7 to 21.4)	0.000	
Overweight-obesity (BMI > P85)	13.1 (4.3 to 21.9)	0.004	

Table III. Results of multivariable linear regression for associations of subject characteristics with total cholesterol

Variable	Partial β coefficient (95% CI)	p value	R2 for multivariable model
			0.23
Age	1 (0.6 to 1.3)	0.002	
Male	-7 (-13 to -2)	0.008	
Pancreatic sufficient	29 (21 to 36)	< 0.001	
BMI > P50	7 (1 to 12)	0.028	

differences between the two analyses: in contrast to our study, the North American series only uses body mass index, without accounting for growth failure as a malnutrition criteria. Consequently, patients who are actually malnourished could be categorized incorrectly as normally nourished or overweight. Another important factor could be age, excess weight is mostly described in adults CF patients with mild phenotypes and SP.

Advances in the genetic knowledge of this disease and the implementation of neonatal screening have allowed more frequent diagnosis of patients with less aggressive phenotypes and PS. In our study, the proportion of patients with PS was greater in those who were overweight or obese (> 50%), a fact already described by Stephenson et al. (2) in a longitudinal study in adults with CF, wherein overweight status is associated with PS, advanced age, good pulmonary function and male gender. These PI patients have energy requirements that are similar to those of the general population; however, the majority of guides do not make distinctions, and specific nutritional recommendations do not exist for these types of patients. However, excess weight is not exclusively associated to milder clinical forms. In our case, more than 25% of patients who were overweight or obese were homozygous carriers of the DF508 mutation and presented exocrine pancreatic insufficiency (EPI). This circumstance was previously described by Kastner-Cole (5) in a study conducted on 3,000 pediatric and adult patients who were homozygous carriers of the DF508 mutation, in which up to 9% were observed to be overweight and 1% obese.

The positive association between nutritional status and pulmonary function is well-known in this disease. Additionally, in contrast to the general population, patients who are overweight and obese have good pulmonary function. In our analyses, we observe a positive association between BMI and FEV1, as well as the negative effect of malnutrition on pulmonary function. However, the patients who were overweight and obese did not have better pulmonary function than those who were normally nourished or at nutritional risk. Moreover, in the multivariate analysis we observed how, in those who maintained a BMI between P50 and P85, this had a superior effect on pulmonary function compared to those who were overweight or obese. Recent publications in adults suggest that the positive association between BMI and FEV1 is reversed from BMI values > 25 kg/m^2 (2,6). On the other hand, it has been observed that the parameter best associated with pulmonary function, from the nutritional point of view in these patients, is the fat-free mass index (15,16). However, given the difficulties in accessing the body composition tests, we consider that the use of BMI between P50 and P85 as a nutritional objective can be helpful in usual clinical practice.

The association between overweight and obese status and vitamin D deficiency has been described in the general population. The mechanism is not exactly known, but it is believed that it is due to the decrease in the bioavailability of vitamin D secondary to the increase in adiposity of obese patients (17). To our knowledge, to date vitamin D levels have not been analyzed in patients with CF and overweight or obese status. In our study we observe how, independently of factors that affect levels of vitamin D in this disease, such as exocrine pancreatic function, age, dose of vitamin D, and chronic inflammation (all were in absence of pulmonary exacerbation), patients with excess weight had an average of 5 ng/ml less of 25 OH vitamin D ($p = 0.054$). Given the increase in the prevalence of overweight status in this disease, we consider that this is another factor that should be kept in mind when the serum levels of this fat-soluble vitamin are analyzed.

Cholesterol levels in patients with CF are generally lower compared to the general population. In our study, only 5% had hypercholesterolemia, with endocrine pancreatic function being the variable that best determined levels of cholesterol, in such a way that PS patients had between 21 and 36 mg/dl more total cholesterol than PI patients. These differences are explained primarily because patients with PI, even when receiving enzyme supplementation, present fat malabsorption as well as greater chronic inflammation. The atherogenic lipid profile characterized by elevation of LDL cholesterol and the total cholesterol/HDL ratio has been observed in 50% of PS adult patients and up to 24% of IP patients (18). An association between BMI and LDL cholesterol in adult CF patients was recently described (19). Even though data on the HDL and LDL cholesterol fractions is not available, hypercholesterolemia values are above those published in our study, probably due to the lower age of our patients.

Microvascular complications have been described in patients who presented cystic fibrosis-related diabetes (20). However, only isolated published cases of macrovascular complications in adults with CF are known (21). Even when receiving a hypercaloric diet (22), the apparent absence of atherosclerosis is explained by the low levels of cholesterol as well as by the difficulty patients have surviving into the 5th and 6th decade of life, the age at which peak incidence of these diseases occurs in the general population. However, the increase in life expectancy, as well as overweight

and obese status, and the presence of more atherogenic lipid profiles in patients with PS, must alert us to the risk of developing metabolic problems not described to date in patients with CF.

Our study is one of the broadest published to date that analyses the prevalence of overweight and obese status in pediatric and adult patients with CF, as well as the first to analyze the association between vitamin D and excess weight in these patients. Despite the results, we are conscious of the methodological limitations of the study. The cross-sectional nature of this study does not allow us to conclude if the excess weight is the cause or the consequence. Nutritional evaluation with exclusively anthropometric data does not provide exact information on the real body composition of the patients; however, in contrast to other projects, we have included the evaluation of height to avoid under-diagnosing malnutrition. The multicentric nature, while necessary to obtain a sufficient sample size in a low prevalence disease such as CF, together with the retrospective collection of the data, may cause bias when analyzing serum levels and somatometric data, but close follow-up at specific units for this disease considerably reduces these errors. Another limitation was the small number of adults enrolled. Nowadays, half of patients of CF units are adults and up to one third are diagnosed at this age group, so the prevalence of overweight and obese as well as hypercholesterolemia may be increased in next years.

In summary, in the last few years we have observed an increase in nutritional problems due to excess weight in patients with CF. The benefits for pulmonary function, when compared to normally nourished patients, do not appear to be as significant as it was initially thought. Dietary recommendations based on hypercaloric diets must continue to be the basis of nutritional support, however, they must be personalized according to the characteristics of the patient. If we do not keep these circumstances in mind, in the near future we could face the appearance of metabolic problems not described to date in patients with CF.

CONCLUSIONS

Prevalence of overweight and obese was 6 and 1% respectively. Excess weight status does not offer any benefit in pulmonary function in comparison to normally nourished patients.

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Nutrición Hospitalaria

Trabajo Original

Nutrición en el anciano

Menus offered in long-term care homes: quality of meal service and nutritional analysis

Menús ofertados en residencias de mayores: calidad del servicio de las comidas y análisis nutricional

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Abstract

Background: Institutionalization is a risk factor for malnutrition. Low energy intake and/or nutrient deficiencies are considered to be the main causes.

Objective: To evaluate the quality of meals and meal service as well as the nutritional value of the main menus (regular menu, menu for diabetics, and pureed menu) offered in three long-term care (LTC) homes located in the metropolitan area of Granada (Spain).

Methods: Cross-sectional study. A validated "quality of meals and meal service" set of indicators was applied. The menus were assessed by weighed food records on 14 consecutive days. The results were compared with the dietary reference intakes (DRIs) and the recommended number of servings.

Results: Important deficiencies in the quality of meals and meal service have been reported. Average energy varies from 1,788 to 2,124 kcal/day in the regular menus, from 1,687 to 1,924 kcal/day in the menus for diabetics, and from 1,518 to 1,639 kcal/day in the pureed menus. Average protein varied from 71.4 to 75.4 g/day, from 72.6 to 76.1 g/day, and from 50.5 to 54.7 g/day, respectively. None of the menus complied with the recommendations for fiber, potassium, magnesium, iodine, vitamin D, vitamin E, folate, nor for vegetables, fruit, milk products, olive oil, legumes, or nuts.

Conclusions: It is necessary to ensure the implementation of regular routines for controlling the quality of meals and meal service as well as the nutritional value of the menus offered in LTC homes.

Key words:

Nursing homes. Elderly. Food services. Food quality. Menu planning. Serving size.

Resumen

Introducción: la institucionalización es un factor de riesgo de malnutrición. Se considera que las principales causas son una baja ingesta energética y/o deficiencias nutricionales.

Objetivo: evaluar la calidad de las comidas y el servicio de comidas así como el valor nutricional de los principales menús (menú basal, menú para diabéticos y menú triturado) ofrecidos en tres residencias de mayores de la provincia de Granada (España).

Método: estudio transversal. Se aplicó el set de indicadores denominado "calidad de las comidas y el servicio de comidas". Los menús se evaluaron por registro de pesada de alimentos durante 14 días consecutivos. Los resultados se compararon con las ingestas dietéticas de referencia (DRI) y el número de raciones recomendadas.

Resultados: se encontraron importantes deficiencias en la calidad de las comidas y el servicio de las mismas. La energía media varió de 1.788 a 2.124 kcal/día en los menús basales, de 1.687 a 1.924 kcal/día en los menús para diabéticos, y de 1.518 a 1.639 kcal/día en los menús triturados. La proteína media varió de 71,4 a 75,4 g/día, de 72,6 a 76,1 g/día, y de 50,5 a 54,7 g/día, respectivamente. Ninguno de los menús cumplió las recomendaciones de fibra, potasio, magnesio, yodo, vitaminas D y E y folato, ni de verduras, fruta, productos lácteos, aceite de oliva, legumbres o frutos secos.

Conclusiones: es necesario asegurar la implementación de protocolos de actuación que permitan controlar la calidad de las comidas y el servicio de las mismas, así como el valor nutricional de los menús ofertados en las residencias.

Palabras clave:

Residencias de mayores. Personas de edad avanzada. Servicios de comida. Calidad de la comida. Planificación de menús. Tamaño de ración.

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INTRODUCTION

Malnutrition is one of the principal geriatric syndromes in people over the age of 70. It is usually related to a low quality of life in the elderly as a result of an increased disability, the progress of chronic and acute diseases, immune system deterioration, longer hospital stays, more hospital readmissions, and, ultimately, a raised rate of morbidity and mortality associated with an increased use of sanitary, economic, and social resources (1-3).

The prevalence of malnutrition varies from 3-5% in the community-dwelling population to more than 60% in institutionalized older adults (4). Low-energy intake and/or nutrient deficiencies are considered to be the main causes of malnutrition in institutionalized people (5). A low-energy intake could be caused by multiple common age-related health problems, polypharmacy, anorexia, or disability (6,7). Moreover, other factors related to long-term care (LTC) homes should be considered to ensure an adequate food intake in institutionalized people. Some of them are the lack of tailoring meals to the needs and preferences of the residents, monotonous menus, mealtime atmosphere, lack of sufficient meal assistants, and the scarcity of records regarding dietary habits (8-13).

Although low dietary intake in LTC residents has been well documented, the quality of meal service and the nutritional value of the menus have not been sufficiently investigated. Therefore, the aim of this study was to evaluate the quality of meals and meal service as well as the nutritional value of the main menus (regular menu, menu for diabetics, and pureed menu) offered in three LTC homes located in the metropolitan area of Granada (southeastern of Spain).

MATERIALS AND METHODS

CHARACTERISTICS OF LTC HOMES

This is a cross-sectional study conducted at three LTC homes located in Granada. Home A, home B, and home C were recruited to participate in a larger study called the Granada Sarcopenia Study (GSS). The health professional team consists of a physician, nurses, physiotherapists, a psychologist, occupational therapists, and social workers. Data were collected by a registered dietitian.

The University of Granada Ethics Committee approved the study protocol, and the manager of each LTC home signed an agreement of participation. All participants were informed about the study procedures and provided written informed consent before participation, or, if unable, proxy-informed consent was obtained from their substitute decision maker.

MENUS SERVED AT THE LTC HOMES

The menus served at the LTC homes consisted of traditional Spanish food, which is based on the Mediterranean diet. Three main menus were cooked in the residence facilities: regular menu, menu for diabetics, and pureed menu. The menu for diabetics and the pureed menu were prepared from the regular menu, and all of them were prescribed by the physician. According to these menus, the residents are not allowed to choose their food. Only in one of them (home A), two options were offered for lunch, and in this study, we analyzed the choice made most frequently. The structure of the meals was quite similar in all of the LTC homes, with four or five meals being offered per day. For breakfast, milk and bread or biscuits were served. At each meal (lunch and dinner), two dishes, bread, and a dessert were served (with the exception of the pureed menu, in which only one dish was served). In the afternoon, milk and cookies were offered. At midday and before dinner, some liquids were served, such as juices, infusions, or water. After dinner, milk or yogurt was served in special cases (for example, for diabetic residents). The menus are not shown.

ASSESSMENT OF QUALITY OF MEALS AND MEAL SERVICE

A validated "quality of meals and meal service" set of indicators (14) was applied, which included 13 indicators: structural (from 1 to 6), process (from 7 to 10), and outcome (from 11 to 13) (Table I). The indicator set covers three domains related to meal satisfaction in the elderly: food, food service, and choice and assessment by a nutrition screening tool (Mini Nutritional Assessment short form [MNA-SF]).

NUTRITIONAL ANALYSIS

The menus were assessed by weighed food records on 14 consecutive days. The recipes' ingredients were weighed, and the medium portion was determined. Small quantities of food were weighed to the nearest 1 g, using a digital kitchen scale with 5 kg capacity (BC-275; Fagor, Guipúzcoa, Spain). Higher amounts of food were measured with a digital weight scale to the nearest 0.1 kg, with a 5 kg to 180 kg capacity (Mod. 494, Jata, Bizkaia, Spain).

DETERMINATION OF ENERGY AND NUTRIENTS

Energy and nutrient content of the menus were quantified using the computer program Nutrire®, a dietary assessment software that uses Spanish food composition tables developed by Jiménez-Cruz et al. (15). Missing values in the database were extrapolated from similar products or copied from other database (CESNID) (16). In other cases, some products (e.g., cream soups or desserts made from powder) were registered with only the nutritional content found on the product label. The results were compared with the dietary reference intakes (DRIs) for people 70 years of age or older (17,18). The estimated average requirement (EAR) or the adequate intake (AI) (if EAR was not available) were considered. These recommendations were selected because participants in the GSS presented an age range between 70 and 106 years.

Table I. Quality of meals and meal service set of indicators (13) applied to three long term care homes

	Home A	Home B	Home C
Structural indicators			
IND1: A procedure for screening and caring for malnourished residents is established	25%	25%	100%
Crit1a: Is a standardized weighing policy available?	No	No	Yes
Crit1b: Is a validated screening instrument available?	No	No	Yes
Crit1c: Is an action plan for malnourished residents available?	Yes	Yes	Yes
Crit1d: Is a staff member referred to as responsible for the screening and treatment policy?	No	No	Yes
IND2: A policy for tailoring meals to the preferences and needs of the residents is established	25%	25%	75%
Crit2a: Is a structural consultation established with kitchen staff and staff of at least two different care disciplines?	No	No	No
Crit2b: Is a procedure established to involve residents in compiling the menu?	No	No	Yes
Crit2c: Is a procedure established for systematically inquiring the residents about food, food service and choice?	No	No	Yes
Crit2d: Is it possible for residents to individually adjust the taste of their meals (e.g., presence of sauces, flavors, etc.)?	Yes	Yes	Yes
IND3: Recipes are tailored to the needs of the residents	0%	33%	33%
Crit3a: Are written recipes available for the staff preparing the meals?	No	Yes	Yes
Crit3b: Are specific recipes available for residents with chewing and swallowing difficulties?	No	No	No
Crit3c: Are the recipes systematically reviewed?	No	No	No
IND4: Staff involved in meal care has the right competences	66%	66%	66%
Crit4a: Has the chef de cuisine an appropriate diploma to execute his/her function in the kitchen?	Yes	Yes	Yes
Crit4b: Did the chef de cuisine follow a supplementary education in tailoring meals to the elderly?	No	No	No
Crit4c: Is training in meal care provided for each feeding assistant?	Yes	Yes	Yes
IND5: A vision on meal care is established	100%	100%	100%
Crit5a: Is a vision on meal care written?	Yes	Yes	Yes
Crit5b: Has the vision on meal care been communicated to the staff involved in meal care?	Yes	Yes	Yes
Crit5c: Has the vision on meal care been communicated to the residents?	Yes	Yes	Yes
IND6: The food being served is varied	100%	100%	100%
Crit6: Is a system that guarantees variation in food used?	Yes	Yes	Yes
Process indicators			
IND7: The proportion of residents whose weight change was documented (between last month and the month before)	0%	0%	0%
IND8: The proportion of residents with documented results of a malnutrition screening (during the last three months)	0%	0%	47%
IND9: The proportion of residents whose eating habits were documented (at least twice during the last year)	0%	0%	100%
IND10: The amount of residents per meal assistant, who need help with the principal meal.	6	8	8
Outcome indicators			
IND11: The prevalence of residents with risk of malnutrition	56%	50%	58%
IND12: The prevalence of malnourished residents	9%	25%	30%
IND13: The prevalence of residents expressing mealtime satisfaction	88%	66%	78%

ASSESSMENT OF FOOD GROUPS

The number of servings from the main food groups was estimated from the medium offered portion, taking into consideration the recommended portion size (19). The number of servings per day (grain foods, vegetables, fruit, olive oil, and milk and dairy products) or per week (legumes, lean meats and poultry, fish and shellfish, nuts, and eggs) was calculated. Fats, fatty meats and lunch meats, sugar, chocolate, and bakery were only occasionally recommended, but we calculated the servings offered per week, because they were served quite often. The results of this assessment were compared with the recommended number of servings (RNS) in the Spanish guide to healthy eating adapted to elderly people (19).

STATISTICAL ANALYSES

Descriptive statistics (mean ± standard deviation) were used to report the nutritional information of the menus offered for LTC homes. Differences among LTC homes were assessed using regular menus as a reference. The menu for diabetics and the pureed menu were compared with their pertinent regular menu for the LTC home. To run these analyses, Student's t-test or Mann-Whitney U test were used, checking for the normal distribution of variables. Statistical analysis was performed using Stata 14.0 (Stata Corp, College Station, TX, USA), and the significance level was set at $p < 0.05$.

RESULTS

Three types of menus were analyzed for 14 days in three LTC homes, resulting in more than 500 analyzed plates in 126 days. The quality of meals and meal service is shown in table I, illustrating the details and results of the 13 analyzed indicators. The structural indicators with the best results were indicators 5 and 6, which means that the vision on meal care was well established in every LTC home as well as an appropriate variety of food. Similarly, indicator 4 had good results, showing that the staff involved in meal care had the right competencies. Indicator 4 did not reach a 100%, because the chefs did not have specific education in tailoring meals to the elderly. On the other hand, the structural indicator with the worst results was indicator 3, because of the lack of specific recipes for dysphagia and the absence of a system for reviewing the recipes systematically. The two other indicators in this section had different results depending on the LTC home. A procedure for screening and caring for malnourished residents was completely established only in one LTC home, and a policy for tailoring meals to the preferences and needs of the residents was not 100% established in any of the LTC homes. Process indicators were also assessed, calculating the proportion of residents in four different items. Any of the three LTC homes recorded weight each month, and only in one of them weight was checked every six months. In the same manner, eating habits and malnutrition were not documented in two LTC homes.

Uniquely in home C malnutrition was assessed and eating habits were documented periodically. Indicator number 10 showed the amount of residents per meal assistant: six residents per meal assistant in home A, eight in home B, and eight in home C. Finally, outcome indicators showed the results of malnutrition after applying the MNA-SF tool in each group of residents. We found a similar prevalence of risk of malnutrition in all of the LTC homes studied (56% in home A, 50% in home B, and 58% in home C), a varied prevalence of malnourished residents (9%, 25%, and 30%, respectively), and a different prevalence of residents reporting being satisfied with the mealtime quality (88%, 66%, and 78%, respectively).

ENERGY AND NUTRIENT CONTENTS

The results of the nutritional analysis regarding energy and nutrients are shown in table II, according to each type of menu and LTC home. Average energy varies from 1,788 to 2,124 kcal/day in regular menus, from 1,687 to 1,924 kcal/day in menus for diabetics, and from 1,518 to 1,639 kcal/day in pureed menus ($p < 0.05$). Home A had the menus with the highest caloric content, whereas home C menus had the lowest. Regarding protein, if when comparing it with the recommended dietary allowance (RDA), protein content in regular menus and menus for diabetics is adequate, but pureed menus do not reach the recommendation. The amount of carbohydrates is above the minimum established, but fiber was insufficient. When comparing the menu for diabetics with its correspondent regular menu, from which it was prepared, we found a significant reduction of carbohydrates ($p < 0.05$), as well as a reduction of calories and an increase of fiber (only significant in home A). Even so, fiber was still insufficient. In the same way, the comparison of pureed menus with their corresponding regular menus resulted in a significant reduction of calories and all macronutrients, with the exception of carbohydrates in home C, where an increase was found. Regarding micronutrient content, the comparison between the menus offered and DRIs is presented in figure 1 for regular menus, figure 2 for menus for diabetics, and figure 3 for pureed menus. Six minerals had less than 100% of the EAR (or AI) in some or all of the menus (potassium, magnesium, zinc, iodine, calcium and selenium) as well as five vitamins (vitamins D, E, C, B_3 and folate). Pureed menus offered the lowest amount of micronutrients.

The results of the nutritional analysis by food groups are shown in table III. This table contains the food servings offered per day or week and their comparison with the number of servings recommended in the Spanish guide to healthy eating (19). None of the nine menus met recommendations for vegetables, fruit, milk products, olive oil, legumes, or nuts, and six of them did not meet the recommendation for fish and shellfish. Pureed menus were also below the recommendations for grain foods and lean meat. Moreover, pureed menus offered less than one serving of eggs per week, which is a very low amount. The food groups whose recommendation is defined as "occasionally" (other fats, fatty meats, and sweet products) could not be directly compared, but it seems evident that some of the averages were quite high, especially in regular menus.

Table II. Comparison of offered menus at three long-term care homes and the dietary reference intakes for calories, macronutrients and micronutrients

		Regular menu			Menu for diabetics			Pureed menu		
Nutrients	**EAR/AI**	**Home A**	**Home B**	**Home C**	**Home A**	**Home B**	**Home C**	**Home A**	**Home B**	**Home C**
Energy, kcal		2,124 ± 230	2,022 ± 203	1,788 ± 178	1,759 ± 223*	1,924 ± 217	1,687 ± 178	1,518 ± 82*	1,639 ± 109*	1,636 ± 75*
Protein, g	0.66 g/kg	71.4 ± 12.3	75.4 ± 11.0	71.6 ± 11.3	73.8 ± 12.2	76.1 ± 10.8	72.6 ± 11.3	50.5 ± 5*	54.7 ± 9.5*	52.8 ± 4.2*
Carbohydrates, g	100	261.0 ± 21.5	272.0 ± 30.2	226.1 ± 16.1	209.0 ± 22.2*	246.1 ± 29.8*	198.4 ± 15.5*	244.7 ± 14.1*	246.0 ± 20.6*	266.4 ± 8.0*
Fiber, g	30 M/21 F ǂ	18.7 ± 2.3	17.6 ± 4.6	15.7 ± 4.0	28.2 ± 2.3*	17.7 ± 4.6	18.3 ± 4.0	15.0 ± 1.5*	14.2 ± 2.2*	13.9 ± 1.7
Lipid, g		88.3 ± 17.2	70.3 ± 12.9	66.3 ± 15.0	69.8 ± 17.7*	70.6 ± 12.9	67.0 ± 15.0	37.5 ± 4.1*	48.5 ± 6.6*	39.9 ± 7.7*
SFA, g		28.7 ± 7.6	13.6 ± 3.2	14.4 ± 2.8	17.0 ± 7.6 *	13.7 ± 3.2	14.8 ± 2.8	17.4 ± 1.1*	9.8 ± 1.6*	10.4 ± 2.9*
MUFA, g		30.0 ± 9.3	30.2 ± 7.7	27.5 ± 11.4	24.3 ± 9.5	30.2 ± 7.7	27.7 ± 11.4	9.6 ± 2.0*	17.7 ± 4.8*	12.3 ± 3.6*
PUFA, g		11.9 ± 4.4	7.7 ± 4.2	6.7 ± 2.1	12.3 ± 5.1	7.7 ± 4.2	6.8 ± 2.1	2.0 ± 0.8*	5.8 ± 2.1	2.2 ± 1.0*
Cholesterol, mg		329.7 ± 179.2	308.2 ± 120.7	250.7 ± 143.7	244.3 ± 154.4	309.0 ± 120.7	252.2 ± 143.7	115.4 ± 25.0*	163.6 ± 64.3*	88.5 ± 28.6*
Potassium, mg	4,700 ǂ	2,277.9 ± 349.1	2,514.3 ± 546.3	2,162.4 ± 390.6	2,398.2 ± 347.9	2,521.5 ± 538.9	2,247.8 ± 390.6	1,707.9 ± 57.2*	2,097.1 ± 281.5*	1,435.6 ± 174.1*
Calcium, mg	1,000	1,125.6 ± 98.5	1,162.0 ± 164.6	1,033.8 ± 119.3	1,038.0 ± 103.0*	1,171.5 ± 155.2	1,046.1 ± 118.9	882.9 ± 53.6*	938.4 ± 57.6*	911.3 ± 31.2*
Phosphorus, mg	580	1,160.9 ± 174.4	1,285.2 ± 195.6	1,206.4 ± 203.7	1,326.2 ± 181.6*	1,298.9 ± 191.5	1,278.6 ± 203.7	945.5 ± 45.6*	980.0 ± 101.8*	885.4 ± 46.2*
Magnesium, mg	350 M/265 F	229.8 ± 29.3	247.4 ± 34.4	227.4 ± 40.0	289.2 ± 29.7*	244.8 ± 35.0	254.8 ± 39.8	221.9 ± 15.2	190.8 ± 22.1*	199.3 ± 15.4*
Iron, mg	6 M/5 F	10.7 ± 3.6	10.4 ± 1.8	8.5 ± 2.0	10.95 ± 3.7*	10.4 ± 1.7	9.1 ± 2.0	7.3 ± 0.7*	7.8 ± 1.8*	6.0 ± 0.5*
Zinc, mg	9.4 M/6.8 F	7.8 ± 1.3	8.2 ± 1.3	6.8 ± 1.2	11.0 ± 1.4	8.4 ± 1.4	8.4 ± 1.2	4.4 ± 0.6*	5.0 ± 0.5*	4.5 ± 0.7*
Selenium, µg	45	73.8 ± 25.1	70.8 ± 16.0	67.3 ± 21.4	94.1 ± 24.6	72.6 ± 15.6	76.1 ± 21.4	28.4 ± 14.0*	44.4 ± 14.1*	24.0 ± 5.4*
Iodine, µg	95	94.3 ± 15.6	33.3 ± 17.0	23.5 ± 12.4	23.5 ± 13.3*	33.1 ± 17.0	23.5 ± 12.4	71.8 ± 2.8*	48.5 ± 16.7*	10.6 ± 8.3*
Copper, µg	700	896.3 ± 176.0	1,029.0 ± 329.2	701.2 ± 200.4	1,068.1 ± 184.7*	1,037.0 ± 331.5	779.3 ± 200.4	914.5 ± 103.5	779.9 ± 158.4*	1,151.8 ± 427.5*
Vitamin A, µg eq	625 M/500 F	1,502.2 ± 527.1	2,344.3 ± 1,289.1	1,493.7 ± 846.2	1,270.7 ± 545.3	2,344.6 ± 1,292.0	1,500.4 ± 846.2	1,046.4 ± 229.5*	1,644.5 ± 692.2	1,202.0 ± 804.6
Vitamin D, µg	10 M/10 F	2.4 ± 1.4	2.1 ± 2.1	2.4 ± 3.3	1.3 ± 1.4*	2.1 ± 2.1	2.4 ± 3.3	0.9 ± 0.0*	0.5 ± 0.9*	0.1 ± 0.1*
Vitamin E, mg eq	12	6.4 ± 2.7	8.8 ± 2.1	7.1 ± 2.9	7.0 ± 2.6	8.8 ± 2.2	7.6 ± 2.9	2.0 ± 0.8*	6.5 ± 1.7*	4.1 ± 1.0*
Vitamin C, mg	75 M/60 F	155.4 ± 24.3	125.8 ± 51.2	63.4 ± 16.8	144.3 ± 24.9	125.5 ± 51.5	63.4 ± 16.8	57.3 ± 7.8*	85.3 ± 25.5*	65.0 ± 29.6
B_1, mg	1 M/0.9 F	1.3 ± 0.4	1.3 ± 0.3	1.1 ± 0.4	1.59 ± 0.4	1.3 ± 0.3	1.2 ± 0.4	0.9 ± 0.1*	0.9 ± 0.2*	0.7 ± 0.1*
B_2, mg	1.1 M/0.9 F	1.6 ± 0.2	1.6 ± 0.2	1.5 ± 0.3	1.7 ± 0.2	1.6 ± 0.2	1.6 ± 0.3	1.3 ± 0.9*	1.3 ± 0.1*	1.2 ± 0.6*
B_6, mg	1.4 M/1.3 F	1.4 ± 0.4	1.5 ± 0.3	1.4 ± 0.5	1.4 ± 0.3	1.5 ± 0.3	1.4 ± 0.5	1.5 ± 0.1	1.2 ± 0.3*	1.0 ± 0.1*
B_{12}, µg	2	4.1 ± 2.1	3.7 ± 0.9	3.7 ± 1.1	4.0 ± 2.1	3.8 ± 0.9	3.7 ± 1.1	2.1 ± 0.3*	3.6 ± 1.7	2.2 ± 0.4*
B_3, mg	12 M/11 F	10.4 ± 2.4	11.5 ± 3.3	13.0 ± 5.7	13.3 ± 2.4*	11.6 ± 3.3	14.3 ± 5.7	10.2 ± 1.7	8.5 ± 2.9*	7.6 ± 1.4*
Folate, µg	320	218.8 ± 44.1	190.0 ± 68.5	156.1 ± 35.8	230.1 ± 44.9	191.7 ± 68.5	162.9 ± 35.8	118.2 ± 9.2*	122.6 ± 27.4*	105.4 ± 18.3*

Note: Results are expressed as means ± SD. EAR: Estimated average requirement; AI: Adequate intake. EAR/AI is indicated for both male (M) and female (F) unless otherwise stated. ǂRepresents an AI rather than an EAR.
**Statistically significant difference ($p < 0.05$) using the regular menu as reference.*

[Nutr Hosp 2017;34(3):584-592]

Table III. Comparison of offered menus at three long term care homes with the recommended number of servings

		Regular menu			Menu for diabetics			Pureed menu		
Food groups	**RNS**	**Home A**	**Home B**	**Home C**	**Home A**	**Home B**	**Home C**	**Home A**	**Home B**	**Home C**
Servings per day										
Grain foods	4 to 6	4.0 ± 0.2	4.0 ± 0.3	3.8 ± 0.2	4.0 ± 0.2	4.0 ± 0.3	3.8 ± 0.2	3.9 ± 0.1	2.2 ± 0.1	5.1 ± 0.1
Vegetables	≥ 2	0.9 ± 0.1	1.6 ± 1.5	1.2 ± 0.2	0.9 ± 0.1	1.6 ± 1.5	1.2 ± 0.2	0.2 ±0.0	1.0 ± 0.1	0.6 ± 0.1
Fruit	≥ 3	2.2 ± 0.8	1.1 ± 0.6	1.1 ± 0.9	2.2 ± 0.8	1.1 ± 0.6	1.1 ± 0.9	2.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.1
Milk and dairy products	≥ 3	2.5 ± 0.8	2.8 ±1.3	2.6 ± 0.9	2.5 ± 0.8	2.8 ±1.3	2.6 ± 0.9	2.5 ± 0.0	2.9 ±0.0	2.5 ± 0.0
Olive oil	3 to 5	1.5 ± 1.7	1.0 ± 0.0	1.5 ± 0.2	1.5 ± 1.7	1.0 ± 0.0	1.5 ± 0.2	0.3 ± 0.1	1.0 ± 0.0	1.0 ± 0.2
Servings per week										
Legumes	2 to 3	1.3 ± 0.4	0.9 ± 0.5	0.5 ± 0.0	1.3 ± 0.4	0.9 ± 0.5	0.5 ± 0.0	0.6 ± 0.5	0.3 ± 0.4	0.3 ± 0.4
Lean meats and poultry	2 to 4	3.5 ± 1.1	3.3 ± 1.1	4 ± 1.4	3.5 ± 1.1	3.3 ± 1.1	4 ± 1.4	2.1 ± 0.2	1.9 ± 0.1	1.8 ± 0.0
Fish and shellfish	3 to 4	2.5 ± 1.4	4.3 ± 0.8	4.4 ± 0.1	2.5 ± 1.4	4.3 ± 0.8	4.4 ± 0.1	0.9 ± 0.5	2.0 ± 0.7	0.3 ± 0.0
Nuts	2 to 7	0.3 ± 0.4	0.0 ± 0.0	0.3 ± 0.4	0.3 ± 0.4	0.0 ± 0.0	0.3 ± 0.4	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.2
Eggs	≤ 3	4.0 ± 1.1	3.8 ± 1.1	2.3 ± 0.4	4.0 ± 1.1	3.8 ± 1.1	2.3 ± 0.4	0.0 ± 0.0	0.7 ± 0.2	0.2 ± 0.2
Occasionally										
Fats (others)	-	16.5 ± 13.4	14.1 ± 1.2	9.5 ± 2.1	16.5 ± 13.4	14.1 ± 1.2	9.5 ± 2.1	0.3 ± 0.4	7.8 ± 0.7	2.4 ± 2.3
Fatty meats and lunch meats	-	4.0 ± 2.5	1.8 ± 0.4	3 ± 0.7	4.0 ± 2.5	1.8 ± 0.4	3.0 ± 0.7	0.3 ± 0.4	1.2 ± 0.2	0.9 ± 1.4
Sugar, chocolate and bakery	-	15.3 ± 1.1	26.0 ± 0.0	10 ± 0.0	0.0 ± 0.0	7.0 ± 0.0	1.5 ± 0.7	14.0 ± 0.0	20.4 ± 6.9	7.0 ± 0.0

Note: Results are expressed as means ± SD. RNS: recommended number of servings from the Spanish Guide to Healthy Eating (19) adapted to elderly people.

Since only a few residents received oral fluid supplements, these were not included in the analysis. In the same manner, other kinds of supplementation were not taken into consideration, as it is quite uncommon to offer micronutrient tablets to LTC residents in Spain.

DISCUSSION

QUALITY OF MEALS AND MEAL SERVICE

As far as we know, this is the first study that applies the "quality of meals and meal service" set of indicators (14). Every LTC home should aspire to obtain 100% for each structural indicator. However, as previously mentioned, that only occurred in two of them (indicators 5 and 6) (Table I). These results helped to detect areas for improvement, such as establishing a procedure for screening malnutrition in all LTC homes, a policy for tailoring meals to the preferences and needs, and having and reviewing written recipes for the staff to prepare both regular and texture-modified menus. In the same manner, process indicators should tend to the best result. Moreover, it is important not only to carry out the activities of documenting the weight change, the results of malnutrition screening and eating habits, but also to do it as frequently as recommended (Table I). On the other hand, the prevalence of risk of malnutrition and already malnourished residents is notable, and this is a risk factor for other complications and for mortality (20). Finally, the prevalence of residents satisfied with mealtime could be considered as quite good, although it should aspire to reach 100% of the residents (Table I).

The "quality of meals and meal service" set of indicators suggests that a meal and meal service quality improvement process should be multidisciplinary (14). Other screening instruments were previously developed, but as far as we know, the checklist was not validated in one of them (21), or they were assessing only one of the meals in another one (22). Nevertheless, other researchers have analyzed the quality of meals in LTC homes using their own methodology (23-25).

ENERGY AND NUTRIENT CONTENTS

Regular menus are the most demanded menus in LTC homes, the best planned menus, and the most studied menus in research. However, regular menus are not meeting the dietary recommendations (Table II). Regarding macronutrients, the protein contribution of regular menus meets the RDA. However, it is remarkable that numerous researchers are suggesting that the RDA of protein for older adults is too low (26,27). Regarding micronutrients, the regular menus failed to meet the dietary recommendations (Fig. 1). The results are consistent with previous studies (28-31), but differ from others which indicated an appropriate nutritional value (24,32,33). Some of the discrepancies between studies may be caused by differences in the characteristics of the LTC homes, differences in the recommendations used as reference, or the study's methodology.

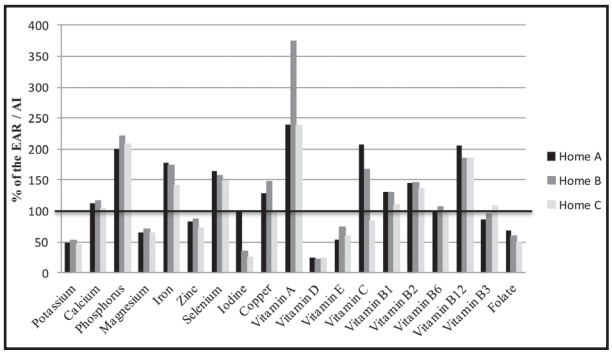

Figure 1.
Percentage of the EAR or AI covered by micronutrients in the regular menus.

The menus for diabetics are obtained by introducing small changes in the regular menus (adding sweeteners instead of sugar, offering brown bread instead of white bread, or serving skim milk instead of whole milk). Changes were notable in the energy and macronutrients, leading to a reduction of carbohydrates and energy as well as an increase of fiber (Table II). The differences in calories and fiber were only significant in home A. Micronutrients deficiencies in the menu for diabetics were similar to deficiencies in the regular menus (Fig. 2).

With respect to pureed menus, it is important to highlight that patients needing a texture-modified diet do not have a calorie or nutrient requirement different from people of the same age and sex, unless a condition or disease coexists (34). Therefore, pureed menus should differ from regular menus only in their modified texture. In contrast, the analyzed pureed menus were far less caloric and less nutritious, as observed in a previous study (35) (Table II, Fig. 3).

SERVINGS BY FOOD GROUPS

The assessment of menus served in LTC homes usually focuses on energy and nutrients, and only a few studies have analyzed

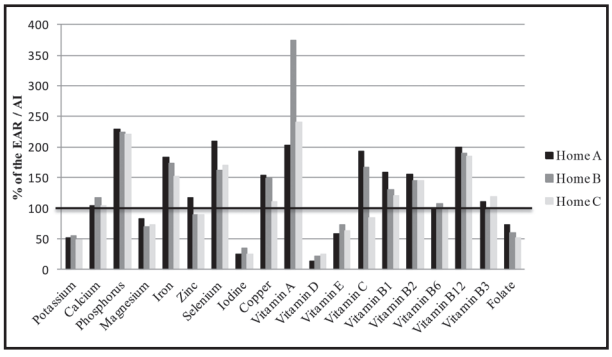

Figure 2.
Percentage of the EAR or AI covered by micronutrients in the menus for diabetics.

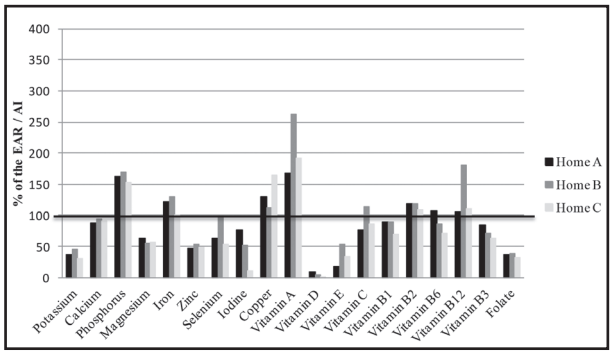

Figure 3.

Percentage of the EAR or AI covered by micronutrients in the pureed menus.

the number of food servings offered in these setting (28). In the present study, none of the analyzed menus met the minimum servings of vegetables, fruit, milk products, olive oil, legumes, or nuts (Table III). Olive oil was not the principal added fat in LTC kitchens, and others kind of oils were chosen. These food groups are important components of the Mediterranean diet, so menus were not correctly based on this diet, whose benefits in elderly people are well documented.

STRENGTHS AND LIMITATIONS

The principal strength of this study is that menus were assessed by weighed food records on 14 consecutive days, a method that is considered to be the gold standard (36). Therefore, results provided an accurate measurement of energy, macronutrients, and micronutrients. Moreover, apart from studying the nutritional quality of the menus, the quality of meals and meal services was assessed, offering an overall vision of the situation in LTC homes and how this situation could be improved. Nevertheless, the results cannot be generalized, and further studies are needed to confirm our findings.

CONCLUSIONS

The menus analyzed are not meeting the dietary recommendations, and the quality of their meal services can be improved. It would be necessary to ensure the implementation of regular routines in LTC homes for controlling the quality of meals and meal service, tailoring meals to the needs and preferences of the residents, and using a nutrition screening tool to evaluate their nutritional status. These actions could lead to a decrease of the high prevalence of malnutrition in these institutions.

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Trabajo Original

Obesidad y síndrome metabólico

Síndrome metabólico y riesgo cardiovascular en la población diabética de El Hierro, Islas Canarias

Metabolic syndrome and cardiovascular risk in diabetic population of El Hierro, Canary Islands

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Resumen

Introducción: en Canarias existe una elevada prevalencia de factores de riesgo vascular, superior a la del resto de España.

Objetivo: analizar las características clínicas de 300 adultos diabéticos tipo II de El Hierro, en el Archipiélago Canario.

Métodos: los pacientes fueron valorados en la Unidad de Medicina Interna del hospital entre 1982 a 2010, y seguidos hasta diciembre de 2014 o hasta su fallecimiento. La muestra se compone de 154 mujeres y 156 hombres (52%).

Resultados: la edad media fue de 66.40 ± 11,60 años, con un tiempo medio de seguimiento de 11,04 ± 4,93 años, y el 80,3% fue diagnosticados de síndrome metabólico, significativamente más frecuente entre las mujeres (86,43% *vs.* 74,67%; $\chi^2 = 5,62$, p = 0,018). Durante el periodo de seguimiento 51 pacientes murieron, y una proporción significativa desarrolló nuevas complicaciones cardiovasculares, como insuficiencia cardiaca (6,7%), cardiopatía isquémica (17,3%), fibrilación auricular (14,3%), ictus (4,7%), o enfermedad arterial periférica (6,9%). Mediante análisis de regresión de Cox observamos que, aunque la edad avanzada fue el factor principal implicado en el desarrollo de todas estas complicaciones y en la mortalidad, los niveles bajos de colesterol se relacionaron con el desarrollo de cardiopatía isquémica y de mortalidad, resultados que no eran dependientes del consumo de estatinas (como en otros ejemplos de epidemiología inversa). El consumo de etanol se relacionó con la incidencia de la enfermedad arterial periférica.

Conclusiones: la edad avanzada fue el factor principal implicado en el desarrollo de complicaciones y mortalidad. Además, los niveles bajos de colesterol se relacionaron con el desarrollo de cardiopatía isquémica y mortalidad.

Palabras clave:

Síndrome metabólico. Diabetes. Riesgo cardiovascular. Mortalidad. Epidemiología inversa.

Abstract

Introduction: In the Canary Islands there is a high prevalence of vascular risk factors.

Objective: To analyze the clinical characteristics of 300 patients with type 2 diabetes in El Hierro, in the Canary Islands.

Methods: Patients were assessed at the Internal Medicine Unit of the hospital from 1982 to 2010, and followed up until December 2014 or until death. The sample is composed of 154 women and 156 men (52%).

Results: mean age was 66.40 ± 11.60 years, with an average follow-up time of 11.04 ± 4.93 years, and 80.3% were diagnosed of metabolic syndrome, significantly more frequent among women (86.43% *vs* 74.67%, $\chi^2 = 5.62$, p = 0.018). During the follow-up period, 51 patients died and a significant proportion developed new cardiovascular complications, such as heart failure (6.7%), ischemic heart disease (17.3%), atrial fibrillation (14.3%), stroke 7%), or peripheral arterial disease (6.9%). Cox regression analysis showed that, although advanced age was the major factor involved in the development of all these complications and in mortality, low cholesterol levels were related to the development of ischemic heart disease and mortality, results that were not dependent on the consumption of statins (as in other examples of inverse epidemiology). Ethanol consumption was related to the incidence of peripheral arterial disease.

Conclusions: Old age was the main factor involved in the development of complications and mortality. In addition, low cholesterol levels were related to the development of ischemic heart disease and mortality.

Key words:

Metabolic syndrome. Diabetes. Cardiovascular risk. Mortality. Inverse epidemiology.

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INTRODUCCIÓN

El síndrome metabólico fue descrito en 1988 por Reaven como una entidad clínica definida por la asociación de varios factores de riesgo metabólicos, todos ellos relacionados con la resistencia a la insulina, que pueden aparecer de forma simultánea o secuencialmente en el mismo paciente (1). Su patogenia es compleja: la diabetes y/o resistencia a la insulina son características cardinales, y la asociación con la obesidad, la hipertensión, la esteatohepatitis y factores proinflamatorios y protrombóticos (2) le confieren relevancia clínica y explican su importancia como entidad asociada a alto riesgo vascular. Además, su prevalencia es muy elevada, y está aumentando incluso entre individuos jóvenes (3), por lo que se puede considerar una pandemia de nuestra época. En España, los estudios muestran valores de prevalencia que oscilan entre el 10,2 y el 61,7% (4). Proporciones aún mayores se han descrito en pacientes diagnosticados previamente de diabetes mellitus (5,6). Además de los criterios clásicos que definen el síndrome metabólico (7), otros factores de riesgo cardiovascular, como la hiperuricemia (6), la microalbuminuria (8) o la hipertrofia ventricular izquierda (9) se asocian a este síndrome y se han considerado en algunas series como características cardinales de esta enfermedad.

Los factores de riesgo cardiovascular son muy frecuentes en las Islas Canarias. En una encuesta reciente se demostró que la diabetes, la dislipemia y la hipertensión son más frecuentes en la población de las Islas Canarias que en la de la España continental (10). La isla de El Hierro, en el extremo suroccidental del Archipiélago (población total = 10.675 habitantes, 2.382 con más de 65 años) constituye un territorio relativamente aislado en el que el seguimiento médico de los pacientes se puede hacer fácilmente. Los datos preliminares han demostrado que la prevalencia de la diabetes es muy alta (en torno al 15% de la población adulta) (11), pero el riesgo cardiovascular asociado al estilo de vida y/o a las características clínicas y/o bioquímicas de estos pacientes es desconocido. El objetivo de este estudio es evaluar la prevalencia del síndrome metabólico en la población diabética de El Hierro, la incidencia a largo plazo de las enfermedades cardiovasculares en estos pacientes, y qué factores están relacionados con el desarrollo de estas complicaciones.

PACIENTES Y MÉTODOS

El Hierro es la isla más pequeña (268 km^2) y menos poblada (10.675 habitantes) del Archipiélago Canario. Según los datos de los centros de Atención Primaria en El Hierro, hay 988 pacientes diabéticos (10,8% de la población) y casi una cuarta parte de la población es mayor de 65 años (2.382 habitantes, 22,31% de la población). Para el cálculo de la prevalencia del síndrome metabólico en la población diabética adulta y el impacto de su presencia en la incidencia de enfermedades cardiovasculares y la mortalidad, se diseñó este estudio observacional. De 450 pacientes diabéticos que habían sido remitidos a la unidad de Medicina Interna desde 1982 hasta 2010, se excluyó inicialmente a 20 pacientes con enfermedades coexistentes que pudieran afectar el pronóstico en un corto periodo, y posteriormente se realizó una selección aleatoria de un total de 300 pacientes diabéticos adultos (mayores de 18 años), que fueron seguidos de forma ambulatoria al menos una vez al año. Dicha cifra representa la mayoría de pacientes de los que existe historia clínica y seguimiento estrecho por parte de Medicina Interna, remitidos por Atención Primaria para una evaluación y seguimiento clínico especializado (por riesgo de complicaciones metadiabéticas, por comorbilidad, etc.). El servicio de Medicina Interna ejerce un papel fundamental en el seguimiento de estos pacientes ya que centraliza la Atención Especializada de la isla por las características del sistema sanitario local (no hay consulta de Endocrinología a diario, solo una vez a la semana, y ocurre lo mismo con otras especialidades como Cardiología o Neurología), por lo que el especialista de referencia de estos pacientes en la isla es el internista. El seguimiento se continuó hasta diciembre de 2014 o hasta la muerte del paciente.

Evaluamos cuántos pacientes presentaban tres de los cinco criterios definitorios del síndrome metabólico según el NCP-ATP III (7): obesidad abdominal (definida por un perímetro abdominal mayor a igual a 102 cm en hombres y mayor o igual a 88 cm en mujeres, determinado mediante cinta métrica), triglicéridos séricos ≥ 150 mg/dl o que el paciente reciba medicación para la hipertrigliceridemia (fibratos), baja concentración de colesterol HDL (< 40 mg/dl en hombres y < 50 mg/dl en mujeres) o tratamiento con estatinas para hipercolesterolemia, presión arterial ≥ 130/≥ 85 mmHg o medicación para la hipertensión, y niveles de glucosa en ayunas ≥ 110 mg/dl o diabetes tratada.

Se incluyeron variables como la edad, el sexo, los antecedentes personales o familiares de interés, el tiempo desde el diagnóstico de la diabetes, el tiempo de seguimiento y el grado de cumplimiento de la medicación. Se valoró el estilo de vida, recogiendo hábitos como:

1. El consumo de alcohol y los gramos de alcohol consumidos por día, el tabaquismo y el índice de paquetes-año (número de cigarrillos fumados por día/20) × número de años fumando, el ejercicio y su intensidad, la siesta, el diagnóstico de ansiedad o tratamiento con benzodiazepinas. También se recogieron datos de la exploración física como la presión arterial, la frecuencia cardiaca, el peso (en kg), la altura (en metros) y el perímetro abdominal (en cm). Se calculó el índice de masa corporal (peso/talla 2) en cada paciente.
2. Variables de laboratorio: niveles de glucosa, hemoglobina glucosilada, colesterol total, colesterol LDL, colesterol HDL, triglicéridos, índice de Castelli (colesterol total/cHDL), ácido úrico, creatinina, y excreción de albúmina en orina de 24 horas.
3. Se registró la incidencia de nueva enfermedad cardiovascular a lo largo del estudio: hipertensión, dislipidemia, enfermedad arterial periférica, insuficiencia cardiaca, fibrilación auricular, enfermedad cerebrovascular, cardiopatía isquémica o la muerte.

El análisis estadístico se realizó con el programa SPSS, versión 19 (Springfield, Ill., Estados Unidos). Inicialmente se realizó una prueba de Kolmogorov-Smirnov para discernir si la distribución era paramétrica o no. Los resultados se presentan como medias y desviación estándar si la variable tiene una distribución paramé-

trica, y como porcentajes y frecuencias si la variable no tiene distribución paramétrica. Se compararon los datos mediante la prueba t de Student y ANOVA si hubiera tres grupos junto con una posterior prueba de Student-Newman-Keuls si la distribución fue normal, test de Mann-Whitney o prueba de Kruskall-Wallis si la distribución no fue normal, o χ^2 si las variables fueron cualitativas. Con el fin de estudiar las correlaciones se utilizó la correlación de Pearson para las variables cuantitativas con distribución normal o la correlación de Spearman para las variables cuya distribución no era normal. La mortalidad y la aparición de complicaciones durante el estudio se analizaron mediante curvas de Kaplan-Meier y se estudiaron las diferencias entre las curvas usando los test Log Rank y Breslow. También se realizaron análisis de regresión de Cox para determinar qué factores se relacionan de forma independiente con la supervivencia o con el desarrollo de cada una de las complicaciones cardiovasculares.

RESULTADOS

DESCRIPCIÓN DE LA MUESTRA

De los 300 pacientes diabéticos incluidos en el estudio, 156 eran hombres (52%). La edad media fue de 66,40 ± 11,60 años, con un tiempo medio de seguimiento de 11,04 ± 4,93 años, sin diferencias entre hombres y mujeres. El tiempo desde el diagnóstico de la diabetes también fue similar en hombres y mujeres (14,24 ± 7,33 años en los hombres y 14,92 ± 8,56 años en las mujeres). La diferencia entre el tiempo de diagnóstico y el tiempo de seguimiento se explica porque el diagnóstico de diabetes mellitus tipo 2, por lo general, se realizaba en Atención Primaria, no en la consulta de Medicina Interna. Además, muchos pacientes precisaban inicialmente solo tratamiento con dieta y ejercicio y eran manejados en Primaria, o bien se evaluaban en primer lugar por Endocrinología (hay una consulta de Endocrinología dos veces al mes en la isla) y luego eran remitidos a Medicina Interna.

La glucosa media en ayunas fue de 153.87 ± 40.01 mg/dl y la HbA1c media en el momento de la inclusión fue de 6,89 ± 1,74%. Sin embargo, el 20% de la muestra tenía niveles de HbA1c superiores a 7,82% y el 10% de ellos presentaban niveles por encima de 9,6%. Se recogieron los datos correspondientes a todos los componentes del síndrome metabólico en 290 pacientes. Las características basales de los pacientes se muestran en la tabla I. En el momento de inclusión en el estudio, el 80,3% de los pacientes cumplieron tres o más criterios de síndrome metabólico (ATP III). La prevalencia de cada componente fue: 87,2% para la hipertensión, 60,8% de obesidad abdominal, 42,7% de HDLc bajo, 45,2% de triglicéridos ≥ 150 mg/dl y, obviamente,

Tabla I. Características basales de los pacientes

	Hombres (n = 150)	Mujeres (n = 140)	p
Edad media (años)	66,47 ± 11,88	66,88 ± 11,07	t = 0,3, p = 0,76
Edad (terciles)			
Primer tercil (≤ 61 años)	61 (40,67%)	44 (31,43%)	
Segundo tercil (entre 61-72 años)	39 (26%)	49 (35%)	
Tercer tercil (≥ 72 años)	50 (33,33%)	47 (33,57%)	
Antecedentes personales			
Diabetes	78/98 (79,59%)	74/93 (79,57%)	χ^2 = 0,0,p = 1
Hipertensión	69/87 (79,31%)	75/90 (83,33%)	χ^2 = 0,24, p = 0,62
Dislipemia	45/69 (65,22%)	48/69 (69,56%)	χ^2 = 0,13, p = 0,72
Estilo de vida			
Tabaquismo activo	31/143 (21,68%)	15/137 (10,95%)	χ^2 = 5,11, p = 0,024
Consumo de alcohol	87/147 (59,18%)	17/135 (12,59%)	χ^2 = 63,64, p < 0,001
Sedentarismo	37/63 (58,73%)	51/68 (75%)	χ^2 = 3,22, p = 0,07
Siesta	42/66 (63,64%)	36/72 (50%)	χ^2 = 2,08, p = 0,15
Ansiedad/benzodiacepinas	22/70 (31,43%)	41/76 (53,95%)	χ^2 = 6,64, p = 0,01
Antropometría			
Índice de masa corporal (kg/m^2)	30,09 ± 3,79	31,93 ± 4,74	t = 3,37, p = 0,001
Perímetro abdominal	104,30 ± 8,61	105,00 ± 11,99	t = 0,32, p = 0,75
Síndrome metabólico			
Hipertensión	124/148	127/138	χ^2 = 3,78, p = 0,052
HDL < 40 mg/dl en hombres/ < 50 mg/dl en mujeres	84/132	59/118	χ^2 = 4,19, p = 0,041
Triglicéridos (< 150 mg/dl).	68/144	57/131	χ^2 = 0,25, p = 0,62
Obesidad abdominal	59/127	93/123	χ^2 = 21,07, p < 0,001
Diabetes Mellitus type 2	150 (100%)	140 (100%)	

100% para la diabetes. La prevalencia del síndrome metabólico fue mucho mayor en las mujeres (86,43% frente a 74,67%; χ^2 = 5,62, p = 0,018). Entre las mujeres había también una mayor prevalencia de hipertensión (92,09% frente a 82,67%; χ^2 = 4,92, p = 0,017), de obesidad (75,61% frente a 46,46%; χ^2 = 21,07, p < 0,001) y peor control de los niveles de colesterol HDL (49,59% *vs.* 36,36%; χ^2 = 3,99, p = 0,046).

La muestra se dividió en terciles según la edad (menor tercil: ≤ 61 años; tercil medio: 61-72 años; tercil superior: > 72 años). Se encontró que en el tercil inferior la prevalencia del síndrome metabólico fue de 74,3%. Después de la diabetes, el segundo componente más frecuente del síndrome metabólico en este grupo fue la hipertensión (que apareció en el 88% de los pacientes). En el tercil medio, el 80,7% cumplía los criterios para el síndrome metabólico y el 97% de los pacientes tenían hipertensión. En el tercil superior, la prevalencia del síndrome metabólico fue del 86,6% y el 94% de los pacientes tenían hipertensión.

No se encontró una relación entre hábito de dormir siesta, tratamiento con benzodiacepinas, consumo de alcohol o tabaco y la existencia de síndrome metabólico. Por otra parte, cuando se consideró solo a los pacientes con síndrome metabólico y se comparó por sexos, se encontró que los hombres bebían más alcohol (χ^2 = 63,64, p < 0,001) y fumaban más (χ^2 = 5,11, p = 0,024). Sin embargo, las mujeres consumían benzodiacepinas con más frecuencia que los hombres (χ^2 = 6,64, p = 0,01) (Tabla I).

Cuando se compararon los parámetros de laboratorio utilizando la t de Student, se encontró que la presión arterial sistólica, la presión arterial diastólica, los triglicéridos y el colesterol HDL fueron mayores en pacientes con síndrome metabólico (p < 0,05 en todos los casos). También encontramos más alta la glucemia basal y los niveles de hemoglobina glicosilada en pacientes sin síndrome metabólico, sin diferencias estadísticamente significativas entre los grupos. Se encontró un mayor perímetro abdominal e IMC en pacientes con síndrome metabólico (p < 0,05 en ambos casos) (Tabla II).

INCIDENCIA DE COMPLICACIONES Y MORTALIDAD

La incidencia de complicaciones y mortalidad se muestra en la tabla III. No se observaron diferencias con respecto a estas variables entre pacientes con o sin síndrome metabólico. Los pacientes que cumplían los criterios de síndrome metabólico no mostraron mayor mortalidad que los diabéticos restantes (Fig. 1).

Se analizaron los factores que se asociaron con la incidencia de complicaciones o de mortalidad a lo largo del periodo de estudio. Los factores analizados incluyen edad (en terciles), sexo, presión arterial sistólica y diastólica, obesidad, mediana de colesterol, glucosa, hemoglobina glicosilada, triglicéridos, colesterol HDL, colesterol LDL, índice de Castelli y ácido úrico, ingesta de alcohol, consumo de tabaco y sedentarismo (todos estos datos se registraron a su inclusión en el estudio). Como vemos en la tabla IV, la edad es el principal factor relacionado con la incidencia de nuevos casos de fibrilación auricular, insuficiencia cardiaca y accidente isquémico transitorio entre los pacientes con o sin síndrome metabólico. Las mujeres desarrollaron significativamente más casos nuevos de insuficiencia cardiaca que los hombres, mientras que los hombres desarrollan más enfermedad arterial periférica e hipertensión. La obesidad y la hipertensión sistólica estaban relacionadas con el desarrollo de insuficiencia cardiaca. Sorprendentemente, los niveles bajos de colesterol total, de

Tabla II. Datos clínicos y analíticos

	Síndrome metabólico (n = 233)	Sin síndrome metabólico (n = 57)	t, p
Tensión arterial sistólica (mmHg)	146,48 ± 22,30	133,94 ± 24,67	3,61, p < 0,001
Tensión arterial diastólica (mmHg)	81,55 ± 12,60	77,21 ± 9,25	2,36, p = 0,019
Triglicéridos (mg/dl)	176,22 ± 116,02	111,42 ± 48,74	6,29, p < 0,001
Colesterol total (mg/dl)	202,51 ± 42,54	195,56 ± 39,51	1,09, p = 0,27
Colesterol HDL (mg/dl)	46,12 ± 12,04	53,10 ± 14,55	3,24, p = 0,001
Índice Castelli	4,62 ± 1,45	3,84 ± 1,13	3,20, p = 0,002
Colesterol LDL (mg/dl)	125,10 ± 69,29	123,97 ± 33,46	0,10, p = 0,92
Glucosa basal alterada (mg/dl)	150,95 ± 43,55	164,54 ± 57,16	1,66, p=0,10
Creatinina (mg/dl)	0,82 ± 0,20	0,83 ± 0,25	0,54, p = 0,59
HbA1c (%)	6,79 ± 1,64	7,38 ± 2,15	1,44, p = 0,16
Ácido úrico (mg/dl)	5,31 ± 1,36	5,39 ± 1,78	0,37, p = 0,71
Albuminuria en 24 horas (mg/24 h)	29,96 ± 69,74	46,88 ± 124,52	0,76, p = 0,45
Frecuencia cardiaca (latidos por minuto)	69,69 ± 11,18	70,74 ± 11,49	0,55, p = 0,58
Perímetro abdominal (cm)	105,30 ± 9,98	94,83 ± 9,13	2,50, p = 0,014
IMC (kg/m^2)	31,36 ± 4,26	29,07 ± 4,54	3,04, p = 0,003

Tabla III. Incidencia de complicaciones y mortalidad

	Total	χ^2, p	Pacientes con síndrome metabólico	χ^2, p
Insuficiencia cardiaca Hombres Mujeres	20 (6,7%) 3 (1,9%) 17 (11,8%)	$\chi^2 = 10,22$; p = 0,001	18 (7,7%) 3 (2,7%) 15 (12,4%)	$\chi^2 = 6,40$; p = 0,011
Cardiopatía isquémica Hombres Mujeres	37 (17,3%) 23 (14,7%) 14 (9,8%)	$\chi^2 = 1,26$; NS	31 (18,1%) 19 (17%) 12 (10%)	$\chi^2 = 1,86$; NS
Enfermedad arterial periférica Hombres Mujeres	16 (6,9%) 12 (7,9%) 4 (2,9%)	$\chi^2 = 2,57$; NS	15 (8,5%) 11 (10,2%) 4 (3,4%)	$\chi^2 = 3,06$; p = 0,08
Enfermedad cerebrovascular Hombres Mujeres	14 (4,7%) 3 (1,9%) 14 (7,6%)	$\chi^2 = 4,29$; p = 0,038	10 (4,3%) 1 (0,9%) 9 (7,4%)	$\chi^2 = 4,58$; p = 0,032
Fibrilación auricular Hombres Mujeres	43 (14,3%) 17 (10,9%) 26 (18,1%)	$\chi^2 = 2,57$; NS	33 (14,2%) 11 (10%) 22 (18,2%)	$\chi^2 = 2,69$; NS
Mortalidad Insuficiencia cardiaca Enfermedad cerebrovascular Infarto de miocardio/muerte súbita Cáncer Otras Desconocido	51 (17%) 3 (6%) 4 (8%) 10 (20%) 9 (18%) 11 (22%) 14 (26%)		36 (15,5%) 3 (8,3%) 3 (8,3%) 5 (13,9%) 7 (19,4%) 8 (22,2%) 10 (27,9%)	

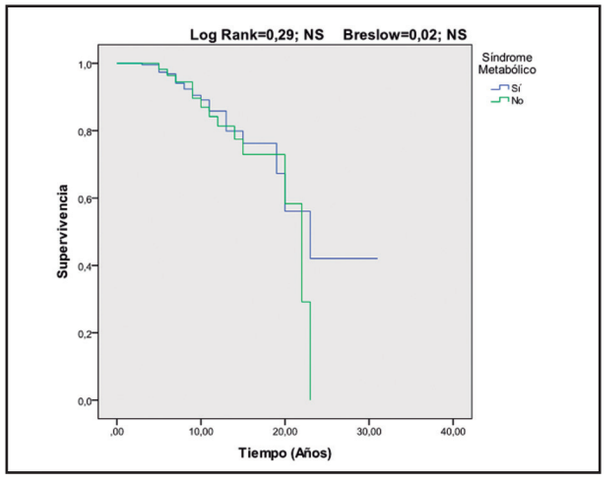

Figura 1.

No existen diferencias en la mortalidad entre los pacientes diabéticos que cumplen criterios de síndrome metabólico y los que no.

colesterol LDL y el índice de Castelli estaban relacionados con el desarrollo de la enfermedad isquémica del corazón (Figs. 2A y B). Este hallazgo es independiente del uso de las estatinas (Tabla V).

También se realizó el análisis de Cox incluyendo los factores de riesgo para el desarrollo de las complicaciones cardiovasculares y la mortalidad, con el fin de comprobar cuáles se relacionaron de forma independiente con la mortalidad y las complicaciones cardiovasculares. Como se muestra en la tabla V, la edad fue el factor independiente relacionado con el desarrollo de fibrilación auricular, insuficiencia cardiaca y ataque isquémico transitorio; el sexo masculino fue el único factor relacionado con el desarrollo de hipertensión; la obesidad se asoció de forma independiente con el desarrollo de insuficiencia cardiaca, en pacientes con o sin síndrome metabólico, pero jerárquicamente, después de la variable edad. Como sucedió con el análisis de Kaplan-Meyer, el colesterol total por debajo de la mediana fue el único factor relacionado con el desarrollo de cardiopatía isquémica, en pacientes con o sin síndrome metabólico, y el colesterol LDL por encima de la mediana se asoció independientemente con menor mortalidad (aunque después de la variable edad) en la muestra total. El consumo de alcohol (más de 40 g/día) desplaza el sexo masculino en la relación con el desarrollo de enfermedad arterial periférica.

DISCUSIÓN

Este estudio se realizó con dos objetivos principales: en primer lugar, para establecer la prevalencia del síndrome metabólico y, en general, de los factores de riesgo cardiovascular en la población diabética de la isla de El Hierro; y en segundo lugar, para evaluar cuál de estos factores de riesgo estuvo involucrado en

Tabla IV. Factores relacionados con la incidencia de complicaciones y mortalidad

Factores de riesgo	HTA		Fibrilación auricular		Insuficiencia cardiaca		Cardiopatía isquémica		Ictus		AIT		Arteriopatía periférica		Mortalidad	
	Total n = 48 (17%)	SM n = 31 (14,2%)	Total n = 43 (14,3%)	SM n = 33 (14,2%)	Total n = 20 (6,7%)	SM n = 18 (7,7%)	Total n = 35 (11,7%)	SM n = 28 (12,1%)	Total n = 8 (2,7%)	SM n = 6 (2,6%)	Total n = 6 (2%)	SM n = 4 (1,7%)	Total n = 16 (5,5%)	SM n = 15 (6,4%)	Total n = 51 (17%)	SM n = 36 (15,5%)
Edad (terciles)	LR = 4,7 p = 0,09 B = 1,14; NS	LR = 0,87; NS B = 0,35; NS	LR = 21,88; p < 0,001 B = 14,54 p = 0,001	LR = 21,7 p < 0,001 B = 13,09; p = 0,001	LR = 25,3 p < 0,001 B = 23,0; p < 0,001	LR = 21,0 p < 0,001 B = 18,49; p < 0,001	LR = 0,39; NS B = 0,52; NS	LR = 1,86; NS B = 1,10; NS	LR = 5,16; p = 0,08 B = 4,24; NS	LR = 1,01; NS B = 2,02; NS	LR = 17,22; p < 0,001 B = 14,5 p = 0,001	LR = 14,08; p = 0,001 B = 12,03; p = 0,002	LR = 1,00; NS B = 0,00; NS	LR = 1,15; NS B = 0,10; NS	LR = 40,2 p < 0,001 B = 35,73; p < 0,001	LR = 26,22; p < 0,001 B = 22,94 p < 0,001
Sexo	LR = 3,8 p = 0,05 B = 4,71; p = 0,03	LR = 5,45 p = 0,02 B = 7,2 p = 0,007	LR = 1,51; NS B = 0,47; NS	LR = 1,45; NS B = 0,88; NS	LR = 9,27 p = 0,002 B = 22,16; NS	LR = 5,32 p = 0,021 B = 0,95; NS	LR = 2,30; NS B = 2,21; NS	LR = 3,5; p = 0,059 B = 2,65; NS	LR = 6,9 p = 0,01 B = 5,44; p = 0,02	LR = 4,1 p = 0,04 B = 3,57 p = 0,06	LR = 0,00; NS B = 0,00; NS	LR = 0,68; NS B = 0,56; NS	LR = 4,4 p = 0,04 B = 2,03; NS	LR = 6,5 p = 0,01 B = 2,42; NS	LR = 1,16; NS B = 2,31; NS	LR = 0,90; NS B = 1,43; NS
TAS (mmHg)	LR = 1,3 NS B = 0,16; NS	LR = 0,78; NS B = 0,38; NS	LR = 4,1; p = 0,043 B = 1,83; NS	LR = 1,95; NS B = 1,34; NS	LR = 14,2 p < 0,001 B = 4,38; p = 0,036	LR = 6,21 p = 0,013 B = 2,04; NS	LR = 2,59; NS B = 1,16; NS	LR = 1,41; NS B = 0,32; NS	LR = 0,02; NS Br = 0,52; NS	LR = 0,03; NS B = 1,00; NS	LR = 1,09; NS B = 0,73; NS	LR = 1,01; NS B = 0,56; NS	LR = 0,23; NS B = 0,56; NS	LR = 0,10; NS B = 0,14; NS	LR = 1,10; NS B = 0,07; NS	LR = 1,10; NS B = 0,21; NS
TAD (mmHg)	LR = 3,06; p = 0,08 B = 0,22; NS	LR = 1,62; NS B = 0,12; NS	LR = 0,04; NS B = 0,29; NS	LR = 0,44; NS B = 0,59; NS	LR = 3,41 p = 0,065 B = 0,45; NS	LR = 1,77; NS B = 0,85; NS	LR = 1,34; NS B = 0,02; NS	LR = 0,65; NS B = 0,01; NS	LR = 0,18; NS B = 0,67; NS	LR = 0,06; NS B = 0,75; NS	LR = 1,02; NS B = 0,99; NS	LR = 0,96; NS B = 0,90; NS	LR = 0,58; NS B = 0,21; NS	LR = 0,54; NS B = 0,12; NS	LR = 0,15; NS B = 0,58; NS	LR = 0,26; NS B = 1,01; NS
Obesidad	LR = 0,81; NS B = 0,06; NS	LR = 0,67; NS B = 0,03; NS	LR = 0,04; NS B = 0,14; NS	LR = 0,12; NS B = 0,007; NS	LR = 6,61 p = 0,010 B = 4,44; p = 0,035	LR = 5,56 p = 0,018 B = 3,23; p = 0,07	LR = 0,12; NS B = 0,01; NS	LR = 0,21; NS B = 0,02; NS	LR = 0,49; NS B = 1,71; NS	LR = 1,38; NS B = 2,62; NS	LR = 1,25; NS B = 0,76; NS	LR = 2,23; NS B = 1,71; NS	LR = 0,002; NS B = 0,49; NS	LR = 0,25; NS B = 0,15; NS	LR = 1,08; NS B = 1,22; NS	LR = 2,13; NS B = 2,98; p = 0,08
Colesterol total (mediana)	LR = 0,06; NS B = 0,38; NS	LR = 0,11; NS B = 0,70; NS	LR = 0,003; NS B = 0,19; NS	LR = 0,03; NS B = 0,25; NS	LR = 0,002; NS B = 0,40; NS	LR = 0,021; NS B = 0,40; NS	LR = 11,43 p = 0,001 B = 10,19 p = 0,001	LR = 6,59 p = 0,010 B = 7,01; p = 0,008	LR = 0,17; NS B = 1,09; NS	LR = 0,55; NS B = 0,49; NS	LR = 3,04; p = 0,08 B = 2,37; NS	LR = 0,73; NS B = 0,54; NS	LR = 0,17; NS B = 0,41; NS	LR = 0,17; NS B = 0,52; NS	LR = 4,6 p = 0,03 B = 5,2; p = 0,023	LR = 1,24; NS B = 2,61; NS
Glucosa (mediana)	LR = 0,02; NS B = 0,07; NS	LR = 0,03; NS B = 0,007; NS	LR = 0,23; NS B = 0,03; NS	LR = 0,002; NS B = 0,48; NS	LR = 2,22; NS B = 0,23; NS	LR = 2,58; NS B = 0,22; NS	LR = 0,58; NS B = 0,001; NS	LR = 0,10; NS B = 0,15; NS	LR = 0,77; NS B = 1,36; NS	LR = 0,001; NS B = 0,58; NS	LR = 2,53; NS B = 1,92; NS	LR = 0,49; NS B = 0,33; NS	LR = 0,64; NS B = 3,40; p = 0,06	LR = 0,90; NS B = 3,54; p = 0,06	LR = 0,01; NS B = 0,00; NS	LR = 0,005; NS B = 0,11; NS

(Continúa en la página siguiente)

Tabla IV (Cont.). Factores relacionados con la incidencia de complicaciones y mortalidad

Factores de riesgo	HTA		Fibrilación auricular		Insuficiencia cardiaca		Cardiopatía isquémica		Ictus		AIT		Arteriopatía periférica		Mortalidad	
	Total n = 48 (17%)	SM n = 31 (14,2%)	Total n = 43 (14,3%)	SM n = 33 (14,2%)	Total n = 20 (6,7%)	SM n = 18 (7,7%)	Total n = 35 (11,7%)	SM n = 28 (12,1%)	Total n = 8 (2,7%)	SM n = 6 (2,6%)	Total n = 6 (2%)	SM n = 4 (1,7%)	Total n = 16 (5,5%)	SM n = 15 (6,4%)	Total n = 51 (17%)	SM n = 36 (15,5%)
HbA1c (mediana)	LR = 0,06; NS B = 0,26; NS	LR = 0,42; NS B = 0,57; NS	LR = 0,00; NS B = 0,43; NS	LR = 0,06; NS B = 0,60; NS	LR = 1,08; NS B = 0,001; NS	LR = 1,42; NS B = 0,006; NS	LR = 0,62; NS B = 2,44; NS	LR = 1,37; NS B = 2,59; NS	LR = 0,0; NS B = 0,28; NS	LR = 0,01; NS B = 0,24; NS	LR = 0,13; NS B = 0,07; NS	LR = 0,30; NS B = 0,12; NS	LR = 0,012; NS B = 0,001; NS	LR = 0,01; NS B = 0,014; NS	LR = 1,91; NS B = 0,40; NS	LR = 0,77; NS B = 0,19; NS
TGD (mediana)	LR = 0,99; NS B = 0,60; NS	LR = 1,04; NS B = 0,37; NS	LR = 1,99; NS B = 0,20; NS	LR = 1,40 NS Bw = 0,44; NS	LR = 1,52; NS B = 0,50; NS	LR = 1,97; NS B = 1,47; NS	LR = 0,28; NS B = 1,24; NS	LR = 1,22; NS B = 3,58; p = 0,058	LR = 3,5 p = 0,06 B = 1,29; NS	LR = 0,84; NS B = 0,02; NS	LR = 1,58; NS B = 1,50; NS	LR = 0,78; NS B = 0,88; NS	LR = 1,6 p = 0,20 B = 0,85; NS	LR = 0,20; NS B = 0,04; NS	LR = 0,03; NS B = 0,18; NS	LR = 0,03; NS B = 0,23; NS
HDL (mediana)	LR = 0,12; NS B = 0,44; NS	LR = 0,04; NS B = 0,02; NS	LR = 0,27; NS B = 0,11; NS	LR = 1,45; NS B = 0,96; NS	LR = 0,54; NS B = 0,65; NS	LR = 1,76; NS B = 1,37; NS	LR = 1,03; NS B = 1,29; NS	LR = 0,10; NS B = 0,28; NS	LR = 0,18; NS B = 0,05; NS	LR = 0,10; NS B = 0,53; NS	LR = 0,13; NS B = 0,01; NS	LR = 0,11; NS B = 0,04; NS	LR = 1,35; NS B = 0,08; NS	LR = 0,62; NS B = 0,001; NS	LR = 0,003; NS B = 0,56; NS	LR = 0,21; NS B = 1,64; NS
LDL (mediana)	LR = 0,003; NS B = 0,42; NS	LR = 0,002; NS B = 0,15; NS	LR = 0,42; NS B = 0,03; NS	LR = 0,51; NS B = 0,00; NS	LR = 1,99; NS B = 1,88; NS	LR = 1,95; NS B = 1,91; NS	LR = 5,05; p = 0,025 B = 3,75; p = 0,053	LR = 3,92; p = 0,048 B = 3,11; p = 0,078	LR = 3,00; p = 0,08 B = 2,81p = 0,09	LR = 2,06; NS B = 1,90; NS	LR = 3,36; p = 0,067 B = 2,39; NS	LR = 0,76; NS B = 0,53; NS	LR = 0,40; NS B = 0,02; NS	LR = 0,32; NS B = 0,04; NS	LR = 9,05; p = 0,003 B = 8,56 p = 0,003	LR = 3,97; p = 0,046 B = 4,68; p = 0,030
Índice Castelli	LR = 0,13; NS B = 0,09; NS	LR = 0,10; NS B = 0,03; NS	LR = 0,01; NS B = 0,18; NS	LR = 0,22; NS B = 0,14; NS	LR = 2,98 p = 0,084 B = 1,41; NS	LR = 5,73 p = 0,017 B = 2,17; NS	LR = 3,9 p = 0,048 B = 6,39; p = 0,012	LR = 8,21; p = 0,004 B = 9,47; p = 0,002	LR = 0,76; NS B = 0,28; NS	LR = 0,03; NS B = 0,15; NS	LR = 3,0 p = 0,08 B = 2,07; NS	LR = 0,85; NS B = 0,59; NS	LR = 0,03; NS B = 0,58; NS	LR = 0,36; NS B = 1,04; NS	LR = 2,70; NS B = 3,77; p = 0,05	LR = 3,27; p = 0,07 B = 5,12; p = 0,02

SM: síndrome metabólico; HTA: hipertensión arterial; AIT: accidente isquémico transitorio; LR: log rank; B: Breslow; TAS: tensión arterial sistólica; TAD: tensión arterial diastólica; TGD: triglicéridos.

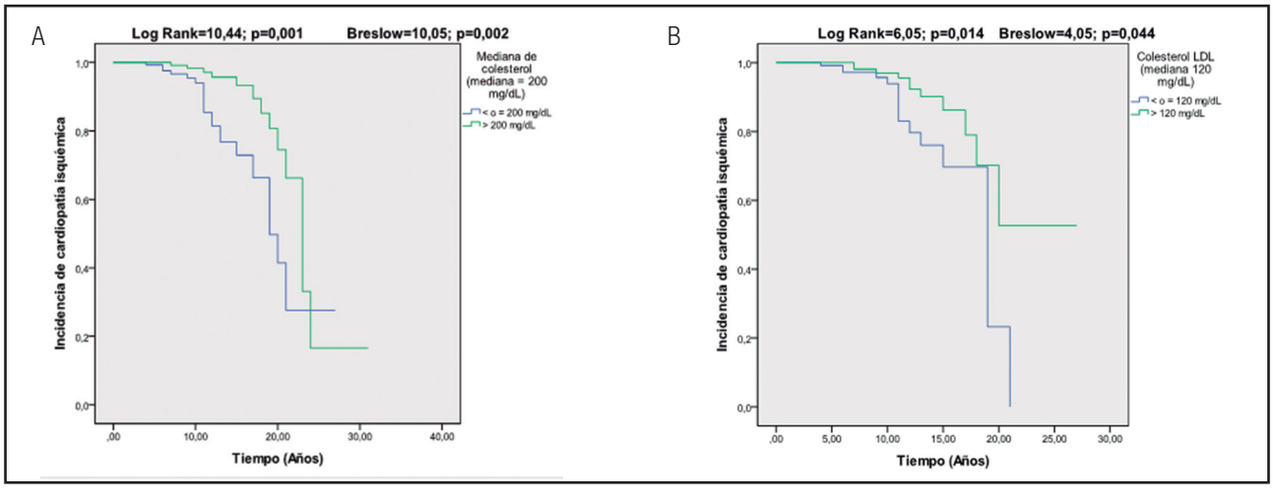

Figura 2A y B.

Los pacientes con niveles bajos de colesterol total y de colesterol LDL muestran una mayor incidencia de cardiopatía isquémica.

la incidencia de las principales enfermedades cardiovasculares durante el largo periodo de seguimiento de la población analizada.

La importancia clínica del síndrome metabólico radica en que confiere una elevada mortalidad y morbilidad. Este estudio descriptivo ilustra esta afirmación en un colectivo de pacientes que representa aproximadamente el 4% de la población adulta de la isla El Hierro y alrededor del 35% del número total de los diabéticos adultos de la isla. Utilizando los criterios de la NCP-ATP III, se encontró que el 80,3% de los pacientes tenía síndrome metabólico. Esta proporción es en general superior a la encontrada en otros estudios. En este sentido, Hathur y cols. (2015), en una población de Mysore, encontraron una prevalencia del 33,7% en 249 diabéticos (12), pero, por otro lado, Ipadeola y Adeleye (2015) hallaron una prevalencia del 66% en una población de 340 diabéticos (13). Sin embargo, otros autores encuentran una prevalencia de síndrome metabólico en pacientes diabéticos similar (14) o superior a la descrita en nuestra población, de un 83% (15) o de un 77% en un estudio cubano (16). En España, la prevalencia es elevada, aunque ligeramente inferior a la encontrada en nuestro estudio. Así, un trabajo que incluyó 1.259 diabéticos tipo 2 encuentra una prevalencia de síndrome metabólico del 78,2% según los criterios de la NCP-ATP III (17), aunque en otros estudios nacionales se describen prevalencias más bajas, entre un 63% y un 68,3%, (18-20). Finalmente, en el estudio realizado por Cabrera de León (2008) en Canarias, en un subgrupo de pacientes diabéticos derivado de la cohorte "CDC de Canarias" se objetivó una prevalencia de síndrome metabólico del 69% (21).

La alta prevalencia de síndrome metabólico y de obesidad puede explicar el considerable porcentaje de pacientes diabéticos con niveles elevados de hemoglobina glicosilada: más del 7,82% en el 20% de la muestra y más del 9,6% en el 10% de los pacientes. La HbA1c es un excelente marcador del grado de daño causado por la hiperglucemia crónica, relacionada a su vez con el daño vascular. En nuestro estudio se registró la incidencia de nuevos episodios de enfermedades cardiovasculares más importantes y analizamos qué factores habían contribuido a su desarrollo. Como era de esperar, la edad es el principal factor relacionado con la mayoría de los eventos cardiovasculares, pero llama la atención que los pacientes con niveles bajos de colesterol mostraron una mayor incidencia de cardiopatía isquémica y mortalidad. Este hallazgo es independiente del uso de las estatinas, y debe ser analizado en el contexto de la llamada epidemiología inversa (22). En las dos últimas décadas hay varios estudios que encuentran resultados similares en varios colectivos, como los pacientes con insuficiencia cardiaca (23), los pacientes en hemodiálisis (24), los pacientes con sida (25), o simplemente los pacientes hospitalizados mayores de 60 años (26). Las razones de esta paradoja epidemiológica no se conocen completamente, pero están posiblemente relacionadas con una alteración en el estado nutricional (27), o un mayor estado inflamatorio subyacente en pacientes con niveles bajos de colesterol (28). Manteníamos la hipótesis de que quizá solo aquellos pacientes con niveles más bajos de colesterol tenían este perfil bioquímico debido a que recibieron estatinas previamente para tratar la dislipemia, pero en el análisis multivariante la relación entre los niveles bajos de colesterol y la mortalidad fue independiente del uso de estatinas.

La única variable independiente relacionada con la enfermedad arterial periférica es la ingesta de etanol, una asociación que es independiente del consumo de tabaco (Tabla IV). A pesar de algunos datos contrarios (29), el consumo de etanol es un factor bien conocido relacionado con el riesgo vascular y con la mortalidad (30), lo que concuerda con nuestros hallazgos, aunque la incidencia es baja.

CONCLUSIÓN

Los pacientes diabéticos en la isla de El Hierro tienen una prevalencia de síndrome metabólico muy alta. Durante el periodo de seguimiento se registró la incidencia de varias enfermedades

Tabla V. Análisis de Cox

Fibrilación auricular			**B**	**ET**	**Wald**	**gl**	**Sig.**	**Exp (B)**
Total	Paso 1	Edad	0,597	0,242	6,079	1	0,014	1,817
Síndrome metabólico	Paso 1	Edad	0,853	0,299	8,107	1	0,004	2,346
Insuficiencia cardiaca			**B**	**ET**	**Wald**	**gl**	**Sig.**	**Exp (B)**
Total	Paso 1	Edad	1,454	0,611	5,664	1	0,017	4,280
	Paso 2	Edad	1,435	0,593	5,855	1	0,016	4,199
		Obesidad	-12,078	175,707	,005	1	0,945	0,000
Síndrome metabólico	Paso 1	Edad	1,364	0,606	5,067	1	0,024	3,913
	Paso 2	Edad	1,374	0,589	5,435	1	0,020	3,950
		Obesidad	-11,926	184,336	0,004	1	0,948	0,000
Accidente isquémico transitorio			**B**	**ET**	**Wald**	**gl**	**Sig.**	**Exp (B)**
Total	Paso 1	Edad	0,597	0,242	6,079	1	0,014	1,817
Síndrome metabólico	Paso 1	Edad	3,447	3,071	1,260	1	0,262	31,399
Hipertensión			**B**	**ET**	**Wald**	**gl**	**Sig.**	**Exp (B)**
Total Síndrome metabólico	Paso 1	Sexo	-0,891	0,432	4,256	1	0,039	0,410
Síndrome metabólico	Paso 1	Sexo	-1,038	0,456	5,185	1	0,023	0,354
Cardiopatía isquémica			**B**	**ET**	**Wald**	**gl**	**Sig.**	**Exp (B)**
Total	Paso 1	Colesterol (mediana)	-1,679	0,567	8,783	1	0,003	0,187
	Paso 2	Colesterol (mediana)	-1,203	0,358	11,269	1	0,001	0,300
		Uso de estatinas	-1,021	0,396	6,648	1	0,010	0,360
Síndrome metabólico	Paso 1	Colesterol (mediana)	-1,548	0,576	7,231	1	0,007	0,213
	Paso 2	Colesterol (mediana)	-1,072	0,376	8,122	1	0,004	0,342
		Uso de estatinas	-0,977	0,435	5,050	1	0,025	0,376
Enfermedad arterial periférica			**B**	**ET**	**Wald**	**gl**	**Sig.**	**Exp (B)**
Total	Paso 1	Alcohol (> 40 g/día)	-1,515	0,706	4,606	1	0,032	0,220
Síndrome metabólico	Paso 1	Alcohol (> 40 g/día)	-1,461	0,702	4,335	1	0,037	0,232
Mortalidad			**B**	**ET**	**Wald**	**gl**	**Sig.**	**Exp (B)**
Total	Paso 1	Edad	1,083	0,292	13,728	1	0,000	2,953
	Paso 2	Edad	1,046	0,293	12,734	1	0,000	2,846
Síndrome metabólico		LDL Colesterol (mediana)	0,896	0,454	3,904	1	0,048	2,451
Síndrome metabólico	Paso 1	Edad	1,309	0,372	12,419	1	0,000	3,704

Los pacientes con niveles bajos de colesterol mostraron una mayor incidencia de cardiopatía isquémica y los pacientes con bajos niveles de colesterol LDL mostraron una mayor mortalidad. Estos hallazgos son independientes del tratamiento con estatinas. La ingesta de alcohol es la única variable independiente relacionada con la enfermedad arterial periférica, una asociación que era independiente del consumo de tabaco.

relacionadas con el riesgo cardiovascular, tales como insuficiencia cardiaca (6,7% de los pacientes), cardiopatía isquémica (17,3%), fibrilación auricular (14,3%), ictus (4,7%), o enfermedad arterial periférica (6,9%). Murieron 51 pacientes. Aunque la edad avanzada fue el factor principal implicado en el desarrollo de todas estas complicaciones y de la mortalidad, es un hallazgo relevante que los niveles bajos de colesterol se relacionaron con el desarrollo de cardiopatía isquémica y con la mortalidad general. Además, el consumo de etanol se relacionó con la incidencia de la enfermedad arterial periférica.

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Nutrición Hospitalaria

Trabajo Original

Obesidad y síndrome metabólico

Comparison of gene expression profile between blood cells and white adipose tissue of patients with obesity

Comparación del perfil de expresión génica entre células de la sangre y el tejido adiposo blanco de pacientes con obesidad

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Abstract

Introduction: Gene expression analyses from peripheral blood mononuclear cells (PBMC) and white adipose tissue are conflicting. It seems that results from single tissue are not enough to explain how changes affect humans as a complex biological system.

Objective: The aim of this study was to compare, from obesity subjects, PBMC and white adipose tissue gene expression that regulates adipogenesis (perilipin 1 [PLIN1], adrenoreceptor beta 3 [ADRB3] and peroxisome proliferator-activated receptor [PPARG2]) and the energy metabolism (uncoupling protein UCP1, UCP2 and UCP3) process.

Methods: This study enrolled 35 obese patients, with a body mass index (BMI) > 40 kg/m^2 (obesity group [OG]), and ten eutrophic health subjects, 18 > BMI > 24.9 kg/m^2 (control group [CG]). Anthropometric and body composition data were assessed at recruitment using standardized protocols. Samples of peripheral blood and subcutaneous adipose tissue (biopsy) were collected to analyze gene expression by RT-qPCR technique. For statistical analysis, we used the Shapiro-Wilk test and Wilcoxon tests by the SPSS software version 20.0; a $p < 0.05$ significance level was adopted.

Results: There were significant differences of PLIN1, ADRB3, PPARG2 and UCP3 expression between blood against adipose tissue samples, showing that these genes are upregulated in adipose tissue. UCP2 expression was upregulated in PBMC.

Conclusion: The PLIN1, ADRB3, PPARG2 and UCP3 genes were preferentially expressed in adipose tissue. However, UCP2 was upregulated in PBMC, suggesting that this gene may be assessed in a peripheral blood cell, which is easily accessible, safe and practical.

Key words:

Gene expression.
Adipose tissue.
Blood cells. Obesity.
Real-time polymerase chain reaction.

Resumen

Introducción: la expresión de genes de células mononucleares de sangre periférica y de tejido adiposo blanco es contradictoria. Los resultados del tejido no son suficientes para explicar cómo afectan los cambios al ser humano como un sistema biológico complejo.

Objetivo: el objetivo de este estudio fue comparar, en individuos con obesidad, la expresión de genes que regulan los procesos de adipogénesis (PLIN1, ADRB3 y PPARg2) y el metabolismo energético (UCP1, UCP2 y UCP3) en sangre y tejido adiposo blanco.

Métodos: este estudio incluyó a 35 pacientes con obesidad e índice de masa corporal (IMC) > 40 kg/m^2 en el grupo obesidad (GO) y a diez personas sanas con peso normal (18 > IMC > 24,9 kg/m^2) en el grupo control (GC). Los datos antropométricos y de composición corporal fueron obtenidos por protocolos estandarizados. Se recogieron muestras de sangre periférica y tejido adiposo subcutáneo (biopsia) para analizar la expresión génica por la técnica de RT-qPCR. Para el análisis estadístico se utilizaron el test de Shapiro-Wilk y pruebas de Wilcoxon mediante el programa SPSS versión 20.0 ($p < 0,05$).

Resultados: no se encontraron diferencias significativas en la expresión de genes PLIN1, ADRB3, PPARg2 y UCP3 entre la sangre y las muestras de tejido adiposo, mostrando que estos genes son regulados positivamente en el tejido adiposo. La expresión del gen *UCP2* fue regulada positivamente en sangre.

Conclusión: los genes PLIN1, ADRB3, PPARg2 y UCP3 se expresaron de forma preferente en el tejido adiposo. Sin embargo, el gen UCP2 se reguló positivamente en sangre, lo que sugiere que puede ser evaluado en sangre periférica, que es fácilmente accesible, de forma segura y práctica.

Palabras clave:

Expresión génica.
Tejido adiposo.
Células de la sangre.
Obesidad. Tiempo real de reacción en cadena de polimerasa.

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INTRODUCTION

High-throughput genomic technologies have provided opportunities for increased understanding of nutritional modulation of gene and proteins expression (1,2). However, this approach has limitations, such as evaluating slight changes and limited access to specific tissues, especially in patient samples composed of healthy volunteers.

According to the literature, some genes are expressed in tissue-specific manner (2,3), consequently, it is necessary to access to the biological material. In cases of patients who will undergo surgery or biopsy, collecting tissue is considered as feasible. Otherwise, without this procedure, collection of internal organ samples such as visceral and adipose tissue is less probable, especially for ethical reasons (4,5).

A minimally invasive method for the study of health-illness transitions is the collection of blood obtained by using the standard venipuncture technique. Peripheral blood mononuclear cells (PBMC) are exposed to all physiological changes, including the change of nutrient concentrations according to their ingestion and absorption (1,6-8).

The evaluation of PBMC for transcriptome analysis has been successfully used to discriminate potential diseases to healthy populations (7-10). Despite PBMC is easily obtainable compared to adipose tissue, liver and muscle, literature has shown conflicting results, and assessing a single tissue could not be enough to fully understand changes in the body (1-3). In this study, we aimed to determine whether targets gene expression in the PBMC is able to reflect the same expression profile in the subcutaneous white adipose tissue in patients with severe obesity.

MATERIALS AND METHODS

This transversal study enrolled patients from a mixed population (11), 35 obese grade III individuals (OG) with a BMI > 40 kg/m^2 and ten eutrophic individuals (BMI ranging from 18.5 kg/m^2 to 24.9 kg/m^2) as a CG. The sample size was defined by convenience, according to the number of patients treated at the hospital where they were selected. The control individuals underwent surgery of an umbilical hernia (incisional or epigastric) or gallstones without acute cholecystitis, both from the Clinical Hospital of Ribeirão Preto Medical School, of the University of São Paulo. After a thorough introduction to the study, all participants gave their written informed consent to participate. This study was approved by the Ethical Committee of the institution (Certificate of Presentation for Ethical Consideration - CAAE: 18973913.0.0000.5440).

Anthropometric and body composition data, blood and adipose tissue were collected from both groups. Weight (kg), height (m) and BMI (kg/m^2) were determined at recruitment using standardized protocols. Body composition was assessed by bioelectrical impedance through Quantum BIA 101 q-RJL Systems analyzer (Clinton Township, MI, USA). Adipose tissue was collected during the surgery procedure or by biopsy in the right upper quadrant region above umbilicus cicatrix.

GENE EXPRESSION

RNA was extracted from PBMC and white adipose tissue for gene expression analysis of gene involved in adipogenesis and energy metabolism (PLIN1, *ADRB3* and PPARG2, UCP1, UCP2 and UCP3).

RNA was extracted from samples of subcutaneous white adipose tissue and PBMC using the phenol-chloroform extraction method modified by Chomczynski & Sacchi (1987) (12). The real-time quantitative polymerase chain reaction (RT-qPCR) method was prepared as described above. RNA was reverse transcribed using a high capacity cDNA reverse transcription with a RNase inhibitor kit (Applied Biosystems-Life Technologies, Carlsbad, CA). Quantitative PCR was performed in triplicate on the ABI 7500 Fast Plate (Applied Biosystems). The RT-qPCR reactions were assembled based on the TaqMan Universal PCR Master Mix protocol (Applied Biosystems), using the following genes: UCP1 (Hs00222453_m1), UCP2 (Hs01075227_m1), UCP3 (Hs01106052_m1), ADRB3 (Hs00609046_m1), PLIN1 (Hs00160173_m1) and PPARG2 (Hs01115513_m1). GAPDH (Hs02758991_m1) and ACTB (Hs99999903_m1) were used as the calibrator genes. Quantitative real-time PCR was performed essentially as described and followed the MIQE guidelines (13). The fold change in gene expression in PBMCs and white adipose tissue is quantified relative to the use of the control group as calibrator in this study.

STATISTICAL ANALYSIS

Descriptive statistics consisted of mean values and standard deviation. The normality of data was verified by the Shapiro-Wilk test. The Mann-Whitney test was used to compare gene expression between tissues. Statistical significance was set at $p < 0.05$,

Table I. Anthropometric and body composition data of obese patients and normal weight individuals

Variables	Obese subjects (OG)	Eutrophic subjects (CG)
Number of individuals	35	10
Age (years)	34 ± 8	34 ± 11
Weight (kg)	130 ± 27	57 ± 7[a]
Height (cm)	163 ± 1	161 ± 7
BMI (kg/m^2)	49 ± 10	22 ± 2[a]
AC (cm)	133 ± 18	79 ± 9[a]
LBM (kg)	62 ± 8	40 ± 6[a]
% LBM	48 ± 6	69 ± 4[a]
FM (kg)	69 ± 21	17 ± 3[a]
% FM	52 ± 2	31 ± 4[a]

Unpaired t test. BMI: Body mass index; AC: Abdominal circumference; LBM: Lean body mass; FM: Fat masss. [a]p < 0.05 compared to OG.

and all analyses were performed in the Statistical Package software for Social Sciences (SPSS version 20.0 Inc. Chicago. IL).

RESULTS

Anthropometric and body composition data are described in table I. We found, as expected, that weight, BMI, waist circumference (WC), lean mass (LM, kg), fat mass (FM, kg) and fat proportion (%) were increased in patients with obesity grade III compared with eutrophic ($p < 0.05$).

Figure 1 shows the relative gene expression in blood and adipose tissue of target genes. The present study indicates that the UCP1 gene was slightly expressed in evaluated tissues, and PLIN1, ADRB3, PPARG2 and UCP3 were upregulated only in samples of subcutaneous adipose tissue in patients with severe

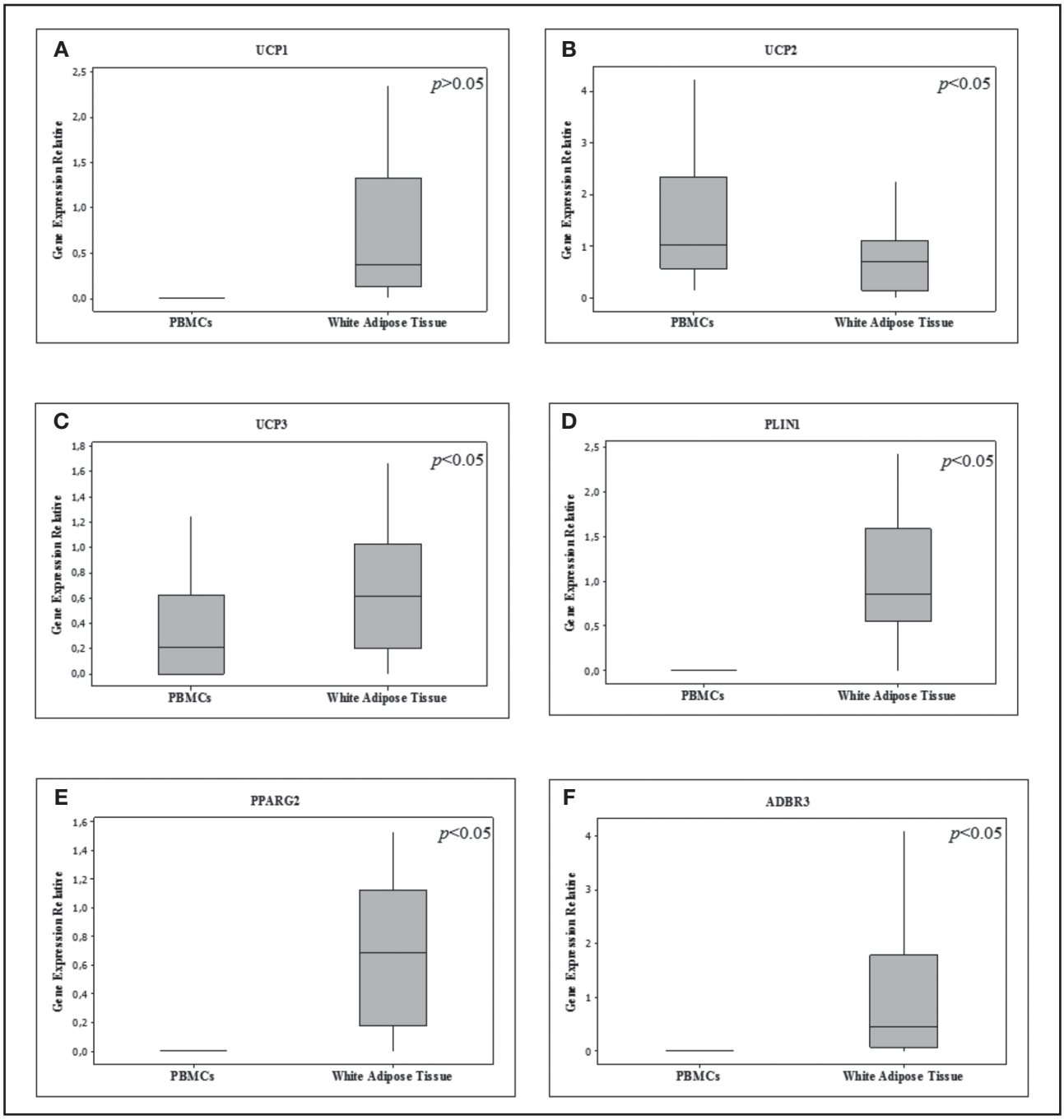

Figure 1.

Gene expression in mononuclear cells from peripheral blood (PBMC) and white adipose tissue of obese patients. A. UCP1. B. UCP2. C. UCP3. D. PLIN1. E. PPARG2. F. ADRB3.

obesity. On the other hand, UCP2 expression was upregulated in blood cells in the same patients (Fig. 1A). Statistical analysis showed some outliers, therefore, a new analysis was performed by removing possible confounding factors, but results remained the same. In order to avoid reducing the number of samples, original values, which are featured by asterisk in the graphs, are maintained (Figs. 1A-F).

DISCUSSION

In the current study, we demonstrated that the expression of genes involved in energy and lipid metabolism is different in white subcutaneous adipose tissue when compared to mononuclear cells from peripheral blood of patients with severe obesity. We observed that expression of UCP2 was upregulated in blood samples, whereas UCP3, PLIN1, PPARG2 and ADRB3 were upregulated in white adipose tissue.

The main purpose of this study was to identify similarities between gene expression in PBMCs and white adipose tissue, and validate the use of peripheral blood considering easy access, availability and handling. However, all genes evaluated behaved differently among tissues, suggesting that it is not possible to obtain a reflection of all changes in specific tissues from this biological material.

Dietary interventions for weight loss have shown an impact of several genes on subcutaneous adipose tissue (14-16), although intra- and inter-individual variation has not been fully studied, especially in blood samples. Brattbakk et al. (2013) (3) showed that the correlation between gene expression in peripheral blood and adipose tissue varies according to gene function, suggesting that more studies about this relation are needed for better understanding the impact of diet on the body. In the same way, a recent study showed that the expression of some genes in white adipose tissue and blood can be used for nutritional studies as predictive markers expansion of white adipose tissue (17). Likewise, a study by Diaz-Rua et al. (2015) (18) argues that the analysis of gene expression in PBMCs allows the detection of physiological deviations induced by diet.

Nutrigenomic studies in humans involving the regulation of gene transcription in different tissues are still scarce, first, because this is a relatively new scientific field, and also, because it is not being fully integrated into clinical practice. Moreover, costs for the implementation of this technology are still significant, especially in numerous approaches involving populations (1).

Additionally, most studies in this area aim to identify whether changes in gene transcription can be detected after changes in food intake, suggesting that food and nutrients can cause a significant impact on the ability of adaptive cellular response to changes in the gene expression pattern (1,19). Nevertheless, for this analysis, specific tissue fragments, which are often difficult to access, are needed to evaluate the best response induced by intervention.

The present study found that some genes are more significantly expressed in white adipose tissue; however, the UCP2 gene, an important regulator of energy metabolism, is more expressed in blood cells. Alternatively, Mello et al. (2012) (2) emphasize that gene expression of PBMC after a dietary intervention can be used to examine the gene response related to the PPAR path and cholesterol metabolism, suggesting that PBMCs appear to be promising for their use in nutritional genomics.

Other studies suggest that gene expression in peripheral blood may be more variable when compared to other tissues (3,20). However, literature has also shown that gene expression of the same individual at the right time is stable in blood cells (7,8,21,22). These factors suggest that peripheral blood could be used in transcriptome analysis studies to verify responses to dietary interventions derived from the same individual over time (3).

The main limitations of this study relate to the sample size and the reduced number of genes evaluated. However, our research group has achieved positive results for the analysis of gene expression in small numbers of patients (16,23), although it would be important to assess the whole transcriptome comparing PBMCs and specific tissue to detect biomarkers for disorders or physiological changes related to the pathogenesis of diseases. Thus, having a gene signature from a biological material easily accessible, such as blood cells, would be important so that this approach could identify specific nutritional problems and chances for disease.

In conclusion, the current study demonstrated that the expression of genes involved in energy expenditure (UCP3) and lipid metabolism (PLIN1, PPARG2 and ADRB3) are downregulated in peripheral blood of patients with severe obesity. Moreover, UCP2 is upregulated in PBMCs, suggesting that the expression of this gene in peripheral blood could be used as a marker present in the material easily accessed and handled.

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ETHICAL APPROVAL

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki of 1964 and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of the institution (Certificate of Presentation for Ethical Consideration - CAAE: 18973913.0.0000.5440).

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Obesidad y síndrome metabólico

Exercise improved semen quality and reproductive hormone levels in sedentary obese adults

Mejora de calidad seminal y perfil hormonal en adultos obesos sedentarios mediante ejercicio

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Abstract

Introduction: From the previously published literature on the relationship between obesity and infertility, it is clear that male obesity negatively impacts semen quality. Accordingly, this study was conducted to determine whether regular exercise may improve semen quality in sedentary obese adults.

Material and methods: Ninety obese adults were randomly allocated to the intervention (n = 45) or control group (n = 45). Participants in the intervention group performed a 16-week aerobic training program in a treadmill, three sessions per week, consisting of a warm-up (10-15 minutes), 35-50 minutes treadmill exercise (increasing five minutes per four weeks) at a work intensity of 50-65% of peak heart rate (increasing a 5% per four weeks) and cooling-down (5-10 minutes). Semen quality assessment included semen volume, sperm concentration and the percentages of progressive motility and normal morphology. Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone and estradiol were determined by ELISA. Body composition and physical fitness were also assessed.

Results: After the completion of the training program, sperm count, motility and normal morphology were significantly increased. A second key finding was that exercise improved reproductive hormone levels by increasing serum testosterone. Lastly, significant correlations were found between seminal outcomes and abdominal obesity.

Conclusion: A short-term intervention program based on aerobic training improved semen quality in sedentary obese adults. This finding may be explained, at least in part, by an improvement of the reproductive hormone profile.

Key words:

Obesity. Aerobic training. Semen. Testosterone.

Resumen

Introducción: cada vez existe un mayor nivel de evidencia sobre el impacto negativo de la obesidad en la calidad seminal. Sin embargo, la utilidad del ejercicio en este grupo de pacientes ha recibido escasa atención. El presente estudio pretende determinar la influencia de un programa de entrenamiento aeróbico en la calidad seminal de adultos obesos.

Material y métodos: noventa adultos varones se asignaron aleatoriamente al grupo experimental (n = 45) o control (n = 45). El grupo experimental desarrolló un programa de entrenamiento aeróbico en tapiz rodante de 16 semanas con tres sesiones/semana. Cada sesión se estructuró en calentamiento (10-15 minutos), 35-50 minutos en tapiz rodante (incrementando cinco minutos/cuatro semanas) a una intensidad del 50-65% de su frecuencia cardiaca máxima (incrementando 5%/cuatro semanas) y vuelta a la calma (5-10 minutos). La calidad seminal se evaluó mediante determinación de volumen seminal, concentración espermática, así como porcentajes de motilidad y morfología normal según criterios de la Organización Mundial de la Salud (OMS). Los niveles séricos de las hormonas folículo estimulante (FSH), luteinizante (LH) y testosterona se determinaron mediante ELISA. También se evaluó la composición corporal y condición física de los participantes.

Resultados: tras finalizar el entrenamiento, la concentración, la motilidad y la normal morfología se incrementaron significativamente. Asimismo, se observó una mejoría de los niveles de testosterona. Finalmente, se observaron correlaciones estadísticamente significativas entre parámetros seminales y marcadores de masa grasa abdominal.

Conclusión: el ejercicio aeróbico mejoró la calidad seminal de adultos obesos sedentarios. Estos resultados podrían explicarse, al menos en parte, por la mejora del perfil hormonal de los participantes.

Palabras clave:

Obesidad. Entrenamiento aeróbico. Semen. Testosterona.

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INTRODUCTION

There is emerging evidence that male obesity negatively impacts fertility (1,2). In this respect, in a multivariate analysis conducted by Bener et al. (3), patients having a body mass index (BMI) > 30 were found to have a three-fold increased risk of infertility. In a more detailed way, Hammiche et al. (2) found sperm concentration and total motile sperm count in men of subfertile couples were detrimentally affected by a high central adiposity. Lastly, a systematic review of the literature also concluded overweight and obesity were associated with an increased prevalence of azoospermia or oligozoospermia (4).

Several hypotheses have been proposed to explain the pathological mechanisms underlying this association. Recent studies have found that excess adipose tissue has a negative impact on reproductive hormone levels such as testosterone (5). Furthermore, given that human spermatogenesis is highly sensitive to heat (6), raised gonadal heat resulting from increased scrotal adiposity might be associated with reduced sperm function and subfertility. Lastly, a relationship between obesity and increased sperm oxidative stress was also reported by Fariello et al. (7).

Fortunately, a recent animal study has found that simple diet and exercise interventions can be used to reverse the damaging effects of obesity on sperm function (8).

However, to date, no intervention studies have been focused on reversing these deleterious effects by regular exercise, despite recent observational studies showed that physically active subjects seemed to have a more anabolic hormonal environment and a healthier semen production (9). The lack of information in the literature may be explained, at least in part, given that previous studies suggested a negative impact of some types of exercise on semen quality (10,11). Fortunately, a recent study concluded that physical activity was not deleterious to testicular function in young healthy adults (12).

For the reasons already mentioned, it was hypothesized that aerobic training could improve semen quality. Accordingly, the main objective was to determine the effect of a short-term aerobic training program on semen quality and reproductive hormone profile in sedentary obese adults.

MATERIALS AND METHODS

PARTICIPANTS

Ninety adults with obesity volunteered for this longitudinal study from the community. Characteristics of participants at baseline are summarized in table I. All subjects met the following inclusion criteria: a) young adults (25-40 years); b) obese, defined as a BMI ≥ 30 kg/m^2 as was suggested for reproductive endocrinology research (13); and c) medical approval after completing a pre-participation physical examination.

On the other hand, exclusion criteria were: a) participation in a training program in the six months prior to their participation in the trial; b) testicular varicocele and/or genital infection, leukocytospermia, chronic illness and serious systemic diseases; c) previous surgery (e.g., vasectomy reversal, varicocele removal, etc.); d) receiving medication and/or antioxidant consumption that may interfere with the redox homeostasis; and e) toxic habits (smoking and/or alcohol).

Table I. Characteristics of sedentary obese adults enrolled in the intervention (n = 45) and control (n = 45) groups

	Intervention	Control	p value
Age (years)	36.3 (3.2)	35.6 (3.5)	0.664
Fat mass (%)	34.6 (3.6)	33.8 (3.8)	0.479
BMI (kg/m^2)	31.2 (1.1)	30.9 (0.8)	0.341
WC (cm)	107.6 (5.3)	106.8 (5.7)	0.265
c-HDL (mg/dl)	177.9 (14.6)	174.2 (15.2)	0.383
c-HDL (mg/dl)	38.3 (1.9)	40.0 (2.3)	0.206
Triglycerides (mg/dl)	168.4 (13.6)	165.8 (14.1)	0.410
Glycaemia (mg/dl)	109.4 (5.8)	106.1 (6.2)	0.242
Daily energy intake (kcal)	2394 (172)	2308 (185)	0.568
Fitness (ml/kg/min)	27.8 (1.7)	28.4 (1.9)	0.211

Results expressed as mean (SD). BMI: Body mass index; WC: Waist circumference; c-HDL: High density lipoprotein cholesterol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Participants were randomly allocated to the intervention (n = 45) or control group (n = 45) using a concealed method.

This research has been conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (version 2002). Participants gave their written informed consent prior to study participation. Furthermore, this protocol was approved by an Institutional Ethics Committee.

INTERVENTION PROGRAM

Participants in the intervention group performed a 16-week aerobic training program in a treadmill, three sessions per week, consisting of a warm-up (10-15 minutes), 35-50 minutes treadmill exercise (increasing five minutes each four weeks) at a work intensity of 50-65% of peak heart rate (increasing a 5% each four weeks) measured during a maximal treadmill test, and cooling-down (5-10 minutes). In order to ensure that the training workload was appropriate, all participants from the intervention group wore a wireless wearable heart rate monitor (Sport Tester PE3000, Polar Electro, Kempele, Finland).

SEMEN ANALYSIS

Semen was collected after three days of ejaculation abstinence (verified by self-report on the day of sample collection) by manual masturbation into a sterile container on site and examined within

30 minutes of ejaculation. It should be pointed out that within this time it has been shown that sperm motility is stable (14). Semen quality assessment included semen volume (ml), sperm concentration (%), sperm motility (%) and normal morphologic features (%). All parameters were examined out according to the World Health Organization (WHO) guidelines (15) by trained laboratory technicians. A 1-ml sample was diluted (1:20) with formaldehyde to examine the sperm concentration by hemocytometer (Hauser Scientific Inc., Horsham, PA). The progressive sperm motility percentage was measured using the known volume of the specimen, which was placed onto a clean glass slide and covered by a coverslip, and examined under positive phase-contrast microscopy at a magnification of ×400 with the help of an ocular grid. For morphological classification, 100 spermatozoa were counted using a high-quality phase-contrast microscope (magnification ×600). Thin, well-spread smears were air-dried, fixed, and stained according to the Papanicolaou method. The classification, including head shape/size defects, neck and midpiece defects, tail defects, and cytoplasmic droplets, was based on the manual published by the WHO.

SERUM REPRODUCTIVE HORMONES

Blood samples (5 ml) were collected from the antecubital vein after a 12-h fast (08.00-09.00 a.m.). The whole blood was centrifuged at 3,000 rpm for ten minutes. The plasma was separated and stored at -80 °C until further analysis. Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol and testosterone were determined by ELISA (Diagnostics Systems Laboratories Inc., Texas, USA).

BODY COMPOSITION AND PHYSICAL FITNESS

Regarding anthropometric assessment, fat free mass percentage was assessed by bioelectrical impedance analysis (MC-180, Tanita Ltd., UK). Participants were requested to not perform moderate or vigorous exercise for 24 hours prior to testing as well as to abstain from eating or drinking for two hours before testing. Moreover, they were asked to urinate immediately prior to data collection. The following equation was used to calculate the body mass index (BMI = weight [kg]/height $[m]^2$) being expressed as kg/m^2. Height was determined with an accuracy of 0.1 cm by precision stadiometer. Body weight was assessed with an accuracy of 0.1 kg using an electronic balance. Lastly, waist circumference (WC) was measured as halfway between the costal edge and the crista.

In order to determine physical fitness, all participants (n = 90) performed a continuous maximal incremental test, using the standard Bruce treadmill protocol, until exhaustion. Gas exchange data were collected throughout the test using a breath by breath metabolic system. The electrocardiograms (ECGs) were continuously recorded using a 12 lead stress analysis system. In this respect, the criteria used to determine the maximal oxygen consumption (VO_2 max) was the maximal O_2 value at plateau despite increasing workload (< 2 ml/kg/min increase in VO_2 between progressive stages). Furthermore, it should be pointed out that all participants, including the control group, underwent a pre-training period to be familiarized with the correct use of the treadmill.

NUTRITIONAL INTAKE RECORD

To control the potential confounding effect of diet, participants included in intervention and control groups recorded their nutritional intake for seven days. Participants were instructed about completion of the nutritional protocol.

STATISTICAL ANALYSIS

The results of biochemical and anthropometric assessments were expressed as mean (SD). Given the limited sample size, the Shapiro-Wilk test was used to assess whether data were normally distributed. To compare the mean values, repeated one-way analysis of variance (ANOVA), with post hoc Bonferroni correction to account for multiple tests, were used. Regarding semen quality and reproductive hormone assessments, results were expressed as median (5-95th percentiles). The Mann-Whitney U test was used to compare differences between the intervention and control groups. Spearman's coefficient was used to identify correlations among tested parameters. The significance of the changes observed was ascertained to be $p < 0.05$.

RESULTS

Physical fitness, expressed as VO_2 max, was significantly improved (27.8 ± 1.7 *vs* 30.6 ± 1.4 ml/kg/min; p = 0.0371) in the intervention group. Body composition was improved as fat mass percentage was significantly reduced (34.6 ± 3.2 *vs* 32.1 ± 3.0%; p = 0.0322). Similarly, WC was significantly decreased after being exercised (107.6 ± 5.3 *vs* 104.1 ± 4.7; p = 0.0438).

When compared to pre-test, sperm concentration (p = 0.032), progressive sperm motility (p = 0.021) and normal morphology percentages (p = 0.026) were significantly improved after the completion of the training program. On the other hand, no significant changes were observed in semen volume in the intervention group.

Regarding reproductive hormone profile, the ratio testosterone/estradiol was significantly improved (p = 0.002). In addition, it was found testosterone level was significantly increased (p = 0.037) after being exercised. These results are summarized in table II. Furthermore, negative significant correlations were found between WC and both sperm concentration (r = -0.32; p = 0.028) and progressive sperm motility (r = -0.29; p = 0.036) in the intervention group. Similar results were found between WC and testosterone levels (r = -0.38; p = 0.017) after being exercised.

Lastly, no significant differences were found between the intervention and control groups when assessing energy intake (2,394 ± 172 *vs* 2,306 ± 188 kcal; p = 0.316) and mean daily vitamin

Table II. Semen quality and serum reproductive hormone profile in sedentary obese adults enrolled in the intervention (n = 45) group

	Pre-test	Post-test	p value
Volume	2.81 (0.89-6.2)	2.92 (1.12-6.5)	0.182
Concentration	45.0 (4.7-296.4)	48.8 (5.3-312.8)	0.040
Progressive motility	42.6 (9.0-56.8)	46.2 (10.2-60.0)	0.015
Morphology	21.0 (2.7-61.8)	23.3 (3.9-64.6)	0.028
LH	4.46 (0.76-10.3)	4.58 (0.81-9.9)	0.094
FSH	5.33 (1.52-21.8)	5.57 (1.47-20.6)	0.166
Testosterone	4.36 (2.88-24.6)	4.78 (3.62-25.1)	0.036
Estradiol	56.3 (41.6-69.8)	54.9 (40.1-68.7)	0.220

Results expressed as median (5-95th percentiles). Volume: semen volume expressed as ml. Sperm concentration expressed as 10^6/ml. Progressive sperm motility and normal morphology expressed as percentages (%). FSH and LH expressed mIU/ml. Testosterone expressed as ng/ml. Estradiol expressed as pg/ml.

Table III. Seminal outcomes and serum reproductive hormone profile in sedentary obese adults enrolled in the control group (n = 45)

	Baseline	Final	p value
Volume	2.71 (0.94-6.11)	2.64 (0.88-5.98)	0.12
Concentration	43.2 (4.1- 306.8)	42.8 (3.8-301.4)	0.36
Progressive motility	41.2 (8.4-50.6)	40.4 (8.2-52.8)	0.44
Morphology	20.3 (2.4-61.2)	19.4 (2.1-60.5)	0.08
LH	4.60 (0.98-10.7)	4.72 (1.12-11.1)	0.31
FSH	5.82 (1.76-22.3)	6.02 (1.90-24.1)	0.26
Testosterone	4.34 (2.46-23.7)	4.18 (2.39-23.0)	0.54
Estradiol	57.9 (42.8-70.6)	58.4 (43.3-72.1)	0.18

Results expressed as median (5-95th percentiles). Volume: semen volume expressed as ml. Sperm concentration expressed as 10^6/ml. Progressive sperm motility and normal morphology expressed as percentages (%). FSH and LH expressed mIU/ml. Testosterone expressed as ng/ml. Estradiol expressed as pg/ml.

intake (9.2 ± 1.8 *vs* 9.6 ± 2.1 mg/d vitamin E, p = 0.512; 79.7 ± 18.2 *vs* 81.4 ± 20.6 mg/d vitamin C, p = 0.431).

No significant changes in any of the tested parameters were found in the control group (Table III). Finally, it should be also pointed out that neither sports-related injuries nor withdrawals from the program were reported during the entire study period.

DISCUSSION

The most striking finding was that aerobic training improved semen quality in sedentary obese adults. Similarly, Gaskins et al. (16) demonstrated that higher physical activity and less TV watching were significantly associated with higher total sperm count and sperm concentration in young healthy men. However, it should be pointed out when designing a training protocol that, depending on sport modality and/or intensity, physical activity may impact in a positive or negative way on semen quality. In this respect, bicycling ≥ 5 h/week was associated with lower sperm concentration and motility (17). Likewise, long-term strenuous treadmill exercises (80% VO_2 max) have a deleterious effect on reproduction (11). Lastly, physical exercise at high altitude was associated with a testicular dysfunction leading to a reduced sperm concentration in non-obese mountaineers (10).

Despite neither antioxidants nor markers of oxidative damage in seminal plasma were assessed in the present study, it may be hypothesized that the reduction of oxidative damage induced by aerobic training may explain, at least in part, the improvement of semen quality, mainly if we take into consideration a similar intervention program based on aerobic training increased antioxidant system and reduced oxidative damage in adults with type 2 diabetes mellitus (18). Similarly, Tartibian and Maleki (19) found that spermatozoa from recreationally active men may be less susceptible to oxidative stress-induced DNA damage and hence infertility.

Previous studies have concluded that the reduction in semen quality found in men with BMI > 25 kg/m^2 could be explained, at least in part, by an increased serum estradiol level (20). The current study also showed reproductive hormone profile was improved after the completion of the training program. The significant reduction of fat mass after the completion of the training program may play a key role supporting this finding (21). Consistent with these results, aerobic training at moderate intensity for 24-weeks significantly increased testosterone level in abdominally obese adults (22). It should be emphasized that our intervention program lasted just 16 weeks so that it may be considered to be more feasible and practical for participants. Lastly, it should be noted that participants remained overweight or obese after the completion of the training program. This could explain why we did not observe a larger improvement in the reproductive hormonal profile, as was previously reported by Hakonsen et al. (21).

Another challenge of the present study was to identify significant associations between semen characteristics and anthropometric parameters in order to provide an easier, quicker, cheaper assessment of the seminal outcomes. In this line, negative significant correlations were found between WC and both sperm count and progressive motility, thus confirming that abdominal fat impairs semen quality (2,23). Conversely, it should be pointed out that Eskandar et al. (24) did not find any significant correlation between BMI and semen quality parameters in men seeking fertility treatment. However, they did not assess any indices of central fat distribution, such as WC and/or hip circumference, to confirm their results. Similarly, a systematic review with meta-analysis revealed little evidence for a relationship with semen parameters and increased BMI (25). The latter authors also concluded the main limitation of this review was that data from most studies could not be aggregated for meta-analysis (25).

This study had some limitations and strengths. The major weakness was the relatively short duration of the exercise intervention, so that there was no follow-up to determine whether these positive effects induced by aerobic training were maintained. In addition, the short sample size may also limit the generalization of the results.

Strengths of the present study included the excellent adherence, rate suggesting the training program was effective and easy to follow up. Secondly, the majority of studies previously reported were originated from fertility clinics, where patient cohorts are frequently biased toward, sub-fertile men, which may also confound findings. Thirdly, some studies rely on self-reporting of parameters such as lifestyle factors and BMI, which can lead to under reporting (8). Lastly, given that spermatogenesis takes approximately 64 days (26), the follow-up period in the present study (112 days) should be able to detect any change induced by the intervention program.

Finally, it was concluded that: a) aerobic training improved semen quality in obese sedentary adults; and b) this finding could be explained, at least in part, by an improvement of the reproductive hormone profile after the completion of the intervention program.

There is a clear need for long-term, well-conducted studies to determine whether correction of semen quality induced by exercise improves the outcomes of live birth and pregnancy rate in obese adults.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Dietary antioxidant quality score (DAQs) is associated with bone mass assessed by calcaneal quantitative ultrasound in young women

El índice de calidad antioxidante de la dieta (DAQS) está asociado con la masa ósea evaluada mediante ultrasonido cuantitativo en el calcáneo en mujeres jóvenes

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Abstract

Introduction: Evidence suggests that intake of antioxidants could positively influence bone mass by preventing bone metabolism against oxidative stress.

Objective: We aimed to investigate the possible influence of single antioxidant intakes and dietary antioxidant quality score (DAQs) on calcaneal quantitative ultrasound (QUS) in a population of young adults.

Methods: A total of 605 young Spanish adults participated in this study (median age 20.38 ± 2.67). Bone mass was measured by calcaneal QUS to determine broadband ultrasound attenuation (BUA, dB/MHz) parameter. Body composition was assessed by bioelectrical impedance analysis and dietary intakes were determined using a 72-hour diet recall interview. DAQs was applied to calculate antioxidant nutrients intake. Linear regression analyses were performed to investigate the possible influence of DAQs on calcaneal QUS.

Results: Most of young adults showed a low-quality antioxidant intake (only 17.6% of women and 20.3% of men had a score of 4 or 5 in DAQs). A positive correlation between DAQs and BUA was observed in women ($r = 0.117$; $p = 0.024$). Linear regression analysis revealed that DAQs was significantly associated with BUA parameter in women after adjusting by body weight, height, calcium intake and physical activity (PA) ($p = 0.035$). No significant associations between single antioxidant and calcaneus QUS measurement were found.

Conclusion: Our findings suggest that high-quality antioxidant intakes could influence bone health in young women. Future studies should further investigate the protective role of antioxidant nutrients against osteoporosis.

Key words:

Antioxidants. Calcaneus quantitative ultrasound. Nutrition. Young adults.

Resumen

Introducción: la evidencia sugiere que la ingesta de antioxidantes podría influir positivamente en la masa ósea mediante la prevención contra el estrés oxidativo del metabolismo óseo.

Objetivo: el objetivo fue investigar la posible influencia del consumo de antioxidantes y del índice de calidad antioxidante de la dieta (DAQs) en la masa ósea, evaluada mediante ultrasonido cuantitativo (QUS) en el calcáneo en una población de adultos jóvenes.

Métodos: un total de 605 adultos jóvenes españoles participaron en este estudio (mediana 20,38 ± 2,67 años). La masa ósea se evaluó mediante QUS en el calcáneo para determinar el parámetro de atenuación de ultrasonido de banda ancha (BUA, dB/MHz). La composición corporal se determinó mediante bioimpedancia eléctrica y la ingesta dietética se determinó a través del recordatorio de 72 horas. El DAQs se aplicó para calcular la ingesta total de nutrientes antioxidantes. Se realizaron análisis de regresión lineal para investigar la posible influencia del DAQs en QUS en el calcáneo.

Resultados: la mayoría de los adultos jóvenes mostraron una ingesta de antioxidantes de baja calidad (solo el 17,6% de las mujeres y el 20,3% de los hombres presentaron una puntuación de 4 o 5 en DAQs). Se observó una correlación positiva entre el DAQs y el BUA en las mujeres ($r = 0,117$; $p = 0,024$). El análisis de regresión lineal reveló que el DAQs se asociaba significativamente con el parámetro BUA en las mujeres después de ajustar por peso corporal, altura, ingesta de calcio y actividad física ($p = 0,035$). No se encontraron asociaciones significativas entre la ingesta de antioxidantes individuales y QUS en el calcáneo.

Conclusión: nuestros resultados sugieren que una ingesta de antioxidantes de alta calidad podría influir en la salud ósea en mujeres jóvenes. Futuros estudios deben profundizar en el papel protector de los nutrientes antioxidantes contra la osteoporosis.

Palabras clave:

Antioxidantes. Ultrasonido cuantitativo de calcáneo. Nutrición. Adultos jóvenes.

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INTRODUCTION

Osteoporosis is considered to be a public health problem characterized by low bone density and reduced bone quality through the deterioration of bone microarchitecture (1). As a consequence, sufferers have an increased susceptibility to osteoporotic fractures (2). Osteoporosis is a multifactorial and complex disease determined by both genetic and environmental factors (3).

Oxidative stress and low serum levels of antioxidants have been proposed to be contributors to osteoporosis. *In vitro* and animal studies have shown that oxidative stress could induce bone loss by modulating osteoclast activation and osteoblast suppression (4-7). In this line, a number of epidemiologic studies have reported positive associations between oxidative stress and bone mineral density (BMD) (8,9).

Evidence suggests that intake of antioxidants could positively influence bone mass by preventing bone metabolism against oxidative stress. Previous studies have investigated a relationship between antioxidants intake and BMD, fracture risk and osteoporosis reporting contradictory results (10-14). Most studies generally analyzed the association between single antioxidant intake and bone status. Little is yet known regarding diet quality indexes of antioxidant intakes and their potential relation with bone status. However, people consume foods with complex combinations of antioxidant nutrients (15) and therefore, this traditional approach misses information regarding interactions between different antioxidant contained in food.

Quantitative ultrasound (QUS) has been proposed as an alternative method to assess bone mass and provides parameters of bone structure (microstructure, elasticity and connectivity) (16). The QUS has been valued for its high correlation with BMD measured by DXA (17). Its portability, non-invasiveness, radiation-free and low cost nature make it a useful method for assessing bone status (18). Until now, no studies have examined the relationship between antioxidant intakes and bone mass assessed by QUS. Therefore, the aim of the current study was to investigate the influence of single antioxidant intakes and dietary antioxidant quality score (DAQs) on calcaneal QUS in young adults. We hypothesized that a high-quality antioxidant intake would be associated with a greater calcaneal QUS parameter.

METHODS

SUBJECTS

Six hundred and five individuals aged 18 to 25 (69.3% females and 30.7% males) agreed to participate in this study and were recruited from different academic centers of Granada (Spain). All participants were evaluated by means of a detailed medical history. Subjects with any of the following criteria were excluded from the study: history of bone disease, metabolic or endocrine diseases, hormone-replacement therapy or current treatments that could affect bone mass. Written informed consent was obtained from each participant and the study was approved by local ethics committees and conducted in accordance with the Declaration of Helsinki.

ANTHROPOMETRIC MEASUREMENTS

Body weight (kg) and fat mass (%) were measured twice (without shoes and in light clothes) to the nearest 0.11 kg by bioelectrical impedance analysis (TANITA BC-418MA®). A Harpenden stadiometer (Holtain 602VR®) was used for height measurements. Height was measured twice without shoes to the nearest 0.5 cm. The averages of the two values for each measurement were used in the analysis. Anthropometric measurements were performed in the morning after a 12-h fast and 24-h abstention from exercise. BMI was calculated as weight over height squared (kg/m^2).

CALCANEAL QUS

Bone mass status was measured by ultrasonography at the right calcaneus (BUA, dB/MHz) using the CUBA clinical ultrasound bone densitometer (McCue Ultrasonics Limited, Compton, Winchester, UK). The calcaneus is used for QUS assessment because it contains a high percentage of trabecular bone and it is easily accessible (19). Daily calibrations were made with physical phantom to control the long-term stability of the apparatus.

DAILY NUTRIENT INTAKE

Daily nutrient intake was assessed by a 72-hour diet recall interview considering intakes on Thursday, Friday and Saturday to capture weekly variations in weekdays and weekend. In a face-to-face interview with well-trained investigators, individuals were asked to recall all food consumed in the preceding 72 hours, including foods eaten outside the home, nutrition supplements and beverages. In order to improve the accuracy of the descriptions of meals, pictorial food models were employed. A computerized food analysis program (Nutriber 1.1.5) was used to assess completed food records (20). The food composition table reported by Mataix et al. was used for conversion of food into nutrients (21).

PHYSICAL ACTIVITY

Physical activity was assessed using a self-administered questionnaire (International Physical Activity Questionnaire-IPAQ*).* The questionnaire has proven to be a valid instrument for measuring PA in the European adult population (22). It was used to calculate the total hours of vigorous PA, moderate PA and walking over the last seven days. A MET-h was derived by multiplying the respective total hours by the metabolic equivalent of task (MET) value for vigorous PA (MET = 8.0), moderate PA (4.0) and walking (3.3), and then adding all three (22).

ANTIOXIDANT NUTRIENT INTAKE

A DAQs was used to calculate antioxidant nutrients (23). The test score assessed the consumption of vitamin C, vitamin E, vitamin A, selenium and zinc. Daily nutrient intake was compared to that of the daily recommended intake for the Spanish population (RDI) (24). When the nutrient intake was below 2/3 of the RDI, a value of 0 was obtained, and when the intake was above 2/3 of the RDI, a value of 1 was obtained. DAQs is scored with a final score range from 0 (very poor quality) to 5 (high quality).

STATISTICAL ANALYSIS

SPSS Statistic version 21.0 (SPSS, Chicago, IL, USA) was used for all the analyses. Mean and standard deviation (SD) where normally distributed and as median (interquartile range) where skewed are given as descriptive statistics. Sex-specific differences were assessed by independent t-test. Sperman's correlation coefficient (r) was used to test the correlation between antioxidant nutrients, DAQs and calcaneus QUS adjusted by age, body weight, height, calcium intake and physical activity. To analyze the associations between single antioxidants intake, DAQs and calcaneus QUS, multiple regression analysis was performed after adjusting by age, body weight, height, calcium intake and physical activity. Results are reported as standardized β-coefficient, R, R^2, adjusted R^2, t and p value. p-values < 0.05 were considered to be statistically significant.

RESULTS

The basic characteristics were summarized separately for men and women in table I. The mean age for the study population was 20.4 ± 2.7, and the mean BMI was 22.6 ± 3.7 kg/m^2. Significant differences between men and women were observed in height, weight, BMI, fat mass, physical activity and BUA values. Men had a significantly higher body height, weight, and BMI than women ($p < 0.001$), whereas women had a significantly higher fat mass than men ($p < 0.001$). The reported energy intake was higher in men than in women, but there was no evidence of any significant differences. Average calcium intake was below the recommended intake level (RDA) in both genders. The mean calcaneus BUA for the sample was 86.7 ± 17.6 (dB/MHz) and males had a significantly higher BUA than females ($p < 0.001$). Regarding the intake of antioxidant nutrients, the average intakes of vitamin E, vitamin A and zinc were lower than the recommended in both sexes. By contrast, the intake of vitamin C and selenium reached the dietary goals. Considering gender, a significant difference has been observed concerning the intake of vitamin C ($p = 0.036$).

The percentages of young adults that are below 2/3 of the RDI for antioxidant nutrients are shown in table II. Regarding vitamin E, a higher percentage of women and men had inadequate antioxidant intake (defined as intakes below 2/3 of the DRI). As can be observed, most women were low antioxidant consumers (only 17.6% of women had a score of 4 or 5 in DAQs). In this line, only 20.3% of men showed a high-quality antioxidant intake (DAQs 4 or 5).

Sperman's correlation revealed a positive relationship between DAQs and calcaneus BUA in women ($r = 0.117$; $p = 0.024$) (Table III). In order to analyze the influence of DAQs and each antioxidants intake on calcaneal QUS, multiple regression models were applied after adjusting by body weight, height, calcium intake and physical activity (Table IV). Interestingly, the multiple regression analysis revealed that DAQs was significantly associated with BUA parameter in women ($p = 0.035$). No significant

Table I. Basic characteristics of the study population (n = 605)

	Females	Males
N (%)	419 (69.3)	186 (30.7)
Age	20.4 ± 2.7	20.5 ± 2.6
Height (m)	1.6 ± 0.1**	1.7 ± 0.1
Weight (kg)	59.4 ± 10.1**	73.1 ± 13.0
BMI (kg/mg^2)	22.1 ± 3.6**	23.6 ± 3.7
Fat mass (%)	24.4 ± 7.3**	15.1 ± 5.4
Intake		
Daily energy intake (kcal/day)	1,990 ± 1,275**	2,139 ± 716
Calcium intake (mg/day)	799.7 ± 346.4	855.2 ± 377.1
Vitamin C (mg/day)	79.6 ± 65.5*	93.2 ± 76.9
Vitamin E (mg/day)	5.4 ± 3.4	5.9 ± 3.9
Vitamin A (ug/day)	595.2 ± 489.8	627.7 ± 447.8
Zn (mg/day)	8.9 ± 3.9	9.9 ± 4.3
Se (ug/day)	132.8 ± 89.0	143.9 ± 79.3
Total physical activity (MET-hrs)[a]	38.7 (0-246.2)**	61.7 (0- 243.5)
BUA (dB/MHz)	83.3 ± 15.8**	96.31 ± 16.8

*Data are shown as mean ± SD. *p < 0.05 between females and males; **p < 0.001 between females and males. All the nutrients were adjusted for energy intake. BMI: Body mass index mineral; MET: Metabolic equivalent of a task, representing energy expenditure per day. [a]MET-hrs are expressed as mean and range.*

Table II. Daily intake of the antioxidant nutrients in the study population

	Females	Males
	% sample 2/3 RDI	% sample 2/3 RDI
Vitamin C (mg/day)	34.2	32.3
Vitamin E (mg/day)	84.8	78.9
Vitamin A (ug/day)	57.7	66.7
Zn (mg/day)	67.1	61.3
Se (ug/day)	12.5	6.4

Table III. Spearman correlation coefficients (r) between antioxidant nutrients, DAQs and calcaneal QUS

	Calcaneal BUA			
	Females		Males	
	r	p-value	r	p-value
Vitamin C (mg/day)	0.083	0.107	0.089	0.251
Vitamin E (mg/day)	0.047	0.343	0.047	0.547
Vitamin A (ug/day)	0.036	0.487	0.036	0.487
Zn (mg/day)	0.041	0.431	0.111	0.151
Se (ug/day)	0.079	0.128	-0.048	0.533
DAQs	0.117	0.024	0.049	0.531

DAQs: Dietary antioxidant quality score. Adjusted by age, weight, height, calcium intake and physical activity.

associations between single antioxidant nutrient and calcaneus QUS measurement were found.

DISCUSSION

The present study explores the associations between DAQs and single antioxidant intakes on calcaneal QUS measurement in a sample of 605 young adults. Our findings provide evidence for the influence of DAQs on calcaneal BUA parameter in young women, supporting the hypothesis that a high-quality antioxidant intake could positively influence bone mass in young women. To our knowledge, there has been no previous study investigating the association of DAQs on bone mass assessed by calcaneal QUS measurement.

To date, only two studies have investigated the association between DAQs and bone status (11,12). In agreement with our findings, Rivas et al. reported a significant positive association between DAQs and BMD among 280 healthy women aged 18 to > 45 (p = 0.021) (12). On the other hand, in the study of De França et al., 150 postmenopausal women over 45 years old with osteoporosis were included (11). In contrast to Rivas et al. and with our findings, any relationship was found between DAQs and BMD in any skeletal sites. One possible reason for this discrepancy may be attributed to the limited sample size or to the sample consisting of osteoporotic women. DAQs could not be suitable for assessing the association of antioxidant dietary intakes and bone mass in osteoporotic subjects since the antioxidant considered in this score could have a minimum effect on low BMD values. In addition, in this study they applied an adaption of the original DAQs since they used estimated averages requirements (EAR) instead of RDI. It should be noted that both previous studies used DXA for measurements of bone mass, none of them used calcaneal ultrasound, and hence, we could not compare our effect sizes for BUA.

This study is the first one to explore the association of DAQs with bone mass in a population of men. Although our study report-

Table IV. Association between antioxidant nutrients and DAQs on calcaneal QUS measurement (dB/MHz)

	Females						Males					
Variables	r	r^2	Adjusted r^2	SE	Coefficient	t	p	r	r^2	Adjusted r^2	SE	Coefficient	t	p
Vitamin C (mg)	0.335	0.112	0.100	14.988	0.080	1.618	0.106	0.259	0.067	0.040	16.485	0.090	1.194	0.234
Vitamin E (mg)	0.329	0.108	0.096	15.003	0.045	0.912	0.362	0.240	0.058	0.029	16.630	0.057	0.743	0.458
Vitamin A (ug)	0.327	0.107	0.095	15.011	0.033	0.683	0.495	0.251	0.063	0.035	16.648	0.064	0.838	0.403
Zn (mg)	0.328	0.107	0.095	15.009	0.036	0.733	0.464	0.276	0.076	0.049	16.525	0.136	1.813	0.072
Se (ug)	0.334	0.112	0.100	14.973	0.075	1.531	0.127	0.246	0.060	0.033	16.626	-0.040	-0.535	0.593
DAQs	0.341	0.117	0.105	14.951	0.104	2.114	0.035	0.248	0.062	0.033	16.556	0.087	1.123	0.263

DAQs: Dietary antioxidant quality score. Adjusted by age, weight, height, calcium intake and physical activity.

ed a lack of association, we cannot completely discard an association of DAQs with bone mass in men due to the relatively small sample size compared to that of women. Further studies including larger samples are required to assess the relationship between DAQs and bone mass in men.

In this study, when antioxidant nutrient intakes were analyzed separately, any association between single antioxidants and calcaneus QUS was observed. Previous studies have assessed the association between select dietary antioxidants, vitamin C (10,14,25-28), vitamin E (14,29), vitamin A (14,30-32), zinc (33) and selenium (14,29,34) and bone mass, revealing inconsistent findings. One possible cause of inconclusive results could be differences in sample sizes and characteristics, study designs and dietary assessments among studies. It must be highlighted that these studies have focused on the effects of single antioxidants on bone health. By using this approach, potential interactions among different antioxidant dietary intakes have been ignored because people consume food with a complex combination of antioxidants, rather than single antioxidants. Consequently, in order to analyze the effect of overall diet and detect possible interactions, recent studies are using diet quality indexes as an alternative method (10,35,36).

The current study has a larger sample size than previous studies exploring the association of DAQs and bone mass. Moreover, this study provides the first investigation of DAQs and bone health in both men and women. Furthermore, all analyses were adjusted for relevant covariates known to affect bone mass. One limitation of our study was its cross-sectional design, from which causality could not be inferred. Another limitation is inherent to the assessment of dietary intake using a self-administered questionnaire. The literature supports the use of 72-hour recall as a pertinent method for assessing nutrient intake since it collects better data on the typical or average diet (37). However, evidence of underreporting of food intake in self-administered questionnaires has been reported previously (37,38). In our study the 72-hour recall was interviewer-driven. Additionally, well-trained investigators asked study subjects to recall all food intakes and, in order to improve the accuracy of the descriptions of meals, pictorial food models were employed. Another potential limitation is the lack of data regarding the culinary treatments that might influence on the reported intake of antioxidants. Finally, the effect of other antioxidants such as flavonoids was not considered.

In summary, our findings of significant associations between DAQs and calcaneal ultrasound in young women reflect the protective role of high-quality antioxidant intakes as an environmental factor contributing to bone health. Future studies should further explore the potential influence of antioxidant nutrients against osteoporosis.

HUMAN AND ANIMAL RIGHTS AND INFORMED CONSENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki of 1964 and its later amendments or comparable ethical standards. Written informed consent was obtained for all participants.

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Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Triceps skinfold compressibility in hospitalized patients

Compresibilidad del pliegue cutáneo del tríceps entre los pacientes hospitalizados

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Abstract

Objective: To explore triceps skinfold (TSF) compressibility and its associated factors among hospitalized patients.

Methods: A cross-sectional study was conducted among hospitalized adult patients. Evolution of tissue compressibility during two seconds was registered and 120 TSF values were obtained using a digital calliper. Compressibility was determined according to the difference between the initial value and the final value (TSF difference) and according to time (τ). Multivariable linear regression models were performed in order to identify factors associated with TSF compressibility.

Results: One hundred and six patients (30.2% aged ≥ 65 years) composed the study sample. Compressibility based on TSF difference was independently associated with TSF thickness (regression coefficient, 95% confidence interval [CI] = 0.38, 0.01-0.05, p = 0.002) and nutritional risk (regression coefficient, 95% CI = 0.23, 0.12-1.23, p = 0.018), but time of compressibility (τ) was not significantly associated with any of the studied variables.

Conclusions: Among a sample of hospitalized patients, undernutrition risk and higher TSF thickness were factors independently associated with higher compressibility assessed by the difference between the initial and final TSF value. Time of compressibility (τ) was not affected by any of the studied factors.

Key words:

Anthropometry. Body composition. Nutritional assessment. Skinfold thickness.

Resumen

Objetivo: explorar la compresibilidad del pliegue cutáneo del tríceps (PCT) y sus factores asociados entre los pacientes hospitalizados.

Métodos: se realizó un estudio transversal en pacientes adultos hospitalizados. Se registró la evolución de la compresibilidad del tejido durante dos segundos y se obtuvieron 120 valores del PCT utilizando un calibrador digital. La compresibilidad se determinó según la diferencia entre el valor inicial y el valor final (diferencia PCT) y según el tiempo (τ). Se realizaron modelos de regresión lineal múltiple con el fin de identificar los factores asociados con la compresibilidad del PCT.

Resultados: ciento seis pacientes (30,2% ≥ 65 años) compusieron la muestra del estudio. La compresibilidad basada en la diferencia de PCT se asoció independientemente con el espesor del PCT (coeficiente de regresión, intervalo de confianza 95% [IC] = 0,38, 0,01-0,05, p = 0,002) y el riesgo nutricional (coeficiente de regresión, IC del 95% = 0,23, 0,12-1,23, p = 0,018), pero el tiempo de compresibilidad (τ) no se asoció significativamente con ninguna de las variables estudiadas.

Conclusiones: entre una muestra de pacientes hospitalizados, el riesgo de desnutrición y el mayor espesor del PCT fueron factores asociados independientemente con una mayor compresibilidad evaluada por la diferencia entre el valor inicial y final del PCT. El tiempo de compresibilidad (τ) no se vio afectado por ninguno de los factores estudiados.

Palabras clave:

Antropometría. Composición corporal. Evaluación nutricional. Espesor del pliegue cutáneo.

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INTRODUCTION

Skinfold thickness is often used for body composition assessment and widely used in the clinical practice due to its accessibility, non-invasive features and the ability to measure subcutaneous adiposity (1,2). In skinfold thickness measurement with a skinfold calliper, constant pressure is applied for a defined period of time (3,4). The tissue's dynamic response to this pressure is defined as compressibility (1,5). This characteristic has been studied by comparing skinfold calliper measurements and subcutaneous fat thickness assessed by coarse methods such as imaging methods, cadaver studies and empiric comparisons (1,5).

There are underlying suppositions on the estimation from skinfold measurement: skin thickness is negligible, adipose tissue has constant characteristics, and also that proportion of subcutaneous to visceral fat is equivalent in all subjects (1). Notwithstanding this, it has been previously shown that compressibility varies according to the sites of measurement and between individuals, influencing the relation between the measurement and the actual adipose tissue thickness, introducing error in the estimation of body fatness (1,5).

Gender (5), age (6), hydration status (6), skin thickness (7), subcutaneous tissue pressure (7) and site of measurement (8) have been previously described as factors associated with compressibility. Nevertheless, over the past few years, knowledge in regards to compressibility has not increased significantly.

An integrated system, Lipotool®, was recently developed. This equipment consists of a digital skinfold calliper and a software application. This system registers 60 measurements per second (9). Thus, this novel methodology firstly permits the study of dynamic tissue's response evolution during the measurement (9).

From all skinfold thickness sites, triceps skinfold (TSF) is the most widely used in clinical practice, as, along with mid-arm circumference, it integrates mid-arm muscle circumference formula, a simple method that allows for the estimation of muscle mass (10).

Regarding the wide use of TSF, the minimization of error is of utmost importance in order to provide an adequate use and interpretation for clinical practice. Nonetheless, as far as we are concerned, skinfolds compressibility has not been explored yet in a clinical setting. Therefore, the present study aims to explore, through an innovative technique, TSF compressibility and its associated factors among a sample of hospitalized patients.

MATERIALS AND METHODS

STUDY SAMPLE AND DESIGN

A cross-sectional study was conducted in a general university hospital among a convenience sample of 106 participants, during a six months period. Patients were eligible to participate in the study if they were aged 18 years and over, Caucasian, conscious, cooperative and able to provide written informed consent.

Critically ill patients, i.e., with a life-threatening medical or surgical condition requiring Intensive Care Unit level care, presenting severe organ system dysfunction and requiring active therapeutic support were excluded (11). Pregnancy and patient ward isolation were also defined as exclusion criteria.

ETHICS

This research was carried out according to the recommendations established by the Declaration of Helsinki and approved by institutional ethics and review boards. All study participants provided a written informed consent.

DATA COLLECTION

Demographical data were obtained by a trained registered nutritionist through a structured questionnaire within 72 hours of admission to hospital.

Education was evaluated by the number of completed school years and the following categories were created: 0-4, 5-12 and over 12 years. Marital status was categorized as single, married or in a civil partnership, divorced and widowed. Independence in activities of daily living was assessed with the Katz index (12).

Patients' nutritional status was evaluated with Nutritional Risk Screening (NRS) 2002 (13). Standing height (cm) was measured with a metal tape (Rosscraft, Innovations Incorporated, Surrey, Canada) with a 0.1 cm resolution and with a headboard. Body weight (kg) was assessed with a calibrated portable beam scale with 0.5 kg resolution.

Triceps skinfold thickness (mm) was obtained with the Lipotool® digital calliper after performing the measurement during two seconds, as established by the International Society for the Advancement of Kinanthropometry (ISAK) protocol (3).

All measurements were performed by the same trained registered nutritionist. Intra-observer error ranged from 0.2% to 1.8%. These values are considered as acceptable for a trained anthropometrist (14,15).

Body mass index (BMI) was determined through the standard formula (weight [kg]/height^2 [m]) (16), and BMI categories were created according to the World Health Organization cutoffs (17).

STATISTICS

Results were described as mean and standard deviation (SD) or as median and interquartile range (IQR) according to normality of distribution, assessed with the Kolmogorov-Smirnov test.

Data on TSF measurements were provided by LipoTool® software and the evolution of tissue compressibility during two seconds was registered, as this method registers 60 values per second. Thus, at the end of the measurement, 120 values were obtained.

Compressibility was determined according to a method based on the difference computed between the initial value and the final value, from the 120 TSF measurements acquired by the digital

caliper (18). Thus, high difference between the initial and final TSF value corresponds to high compressibility (18).

Another method was used to define compressibility. This method was based on τ, *tau*, a measurement of time expressed in seconds, that reflects adipose tissue dynamic response to compression, being an individual characteristic (19). Thus, lower τ values mean that the skinfold compresses faster, and, therefore, presents higher compressibility. τ value was obtained after computing the inverse of the exponent of a regression equation displayed for the 120 measurement sets of each patient (19,20).

Data set was divided into tertiles of TSF, tertiles of τ and tertiles of difference between the TSF initial and final values (TSF difference). In order to select variables associated to compressibility, patients' baseline characteristics were compared across τ tertiles and TSF difference tertiles. Patients' baseline characteristics were also compared across TSF tertiles.

All the comparisons were computed by the one-way ANOVA test if distribution was normal, or by the Kruskal-Wallis test in case of non-normal distribution. Categorical variables were reported as frequencies. Differences between proportions were assessed with the Pearson's χ^2 test or Fisher's exact test.

Furthermore, multivariable linear regression models were built in order to identify the independent variables associated with compressibility, assessed by τ or as TSF difference. The following variables were included in the models: TSF value (continuous), age (continuous), nutritional status (categorical; normal nutritional status used as reference) and gender (categorical; women used as reference), as these variables were considered to be potential confounders or covariates.

Table I. Patients' characteristics for the entire sample and according to triceps skinfold tertiles (mm)

Characteristics	Entire sample (n = 106)	1st ≤ 11.5 (n = 35)	2nd 11.8-21.2 (n = 34)	3rd ≥ 21.3 (n = 37)	p
Age (years), mean (SD)	53.1 (15.8)	55.5 (15.7)	53.5 (13.8)	47.0 (16.9)	0.066*
Age categories (years), n (%)					
< 65	74 (69.8)	23 (65.7)	23 (67.6)	28 (75.7)	0.258†
≥ 65	32 (30.2)	12 (34.3)	11 (32.4)	9 (24.3)	
Gender, n (%)					
Women	49 (46.2)	1 (2.9)	19 (55.9)	29 (78.4)	< 0.001†
Men	57 (53.8)	34 (97.1)	15 (44.1)	8 (21.6)	
Education (years), n (%)					
0-4	41 (38.7)	9 (25.7)	17 (50.0)	15 (40.5)	0.188†
5-12	54 (50.9)	20 (57.1)	14 (41.2)	20 (54.1)	
> 12	11 (10.4)	6 (17.1)	3 (8.8)	2 (5.4)	
Marital status, n (%)					
Single	15 (14.2)	6 (17.1)	3 (8.8)	6 (16.2)	0.310†
Married	72 (67.9)	23 (65.7)	25 (73.5)	24 (64.9)	
Widowed	12(11.3)	5 (14.3)	5 (14.7)	2 (5.4)	
Divorced	7 (6.6)	1 (2.9)	1 (2.9)	5 (13.5)	
Katz index, n (%)					
Independent	103 (97.2)	33 (94.3)	34 (100)	36 (97.3)	0.359†
Moderate and severe dependence	3 (2.8)	2 (5.7)	0 (0)	1 (2.7)	
Nutritional status (NRS-2002), n (%)					
Normal	94 (88.7)	28 (80.0)	30 (88.2)	36 (97.3)	0.068†
Risk	12 (11.3)	7 (20.0)	4 (11.8)	1 (2.7)	
BMI (kg/m^2), mean (SD)	26.2 (6.0)	22.6 (5.4)	26.1 (3.5)	29.7 (6.3)	< 0.001*
BMI categories (kg/m^2), n (%)					
Underweight or normal weight	46 (43.4)	25 (71.4)	12 (35.3)	9 (24.3)	< 0.001‡
Overweight or obesity	60 (56.6)	10 (28.6)	22 (64.7)	28 (75.7)	
TSF (mm), mean (SD)	19.1 (12.1)	8.6 (2.0)	16.9 (2.9)	31.7 (11.1)	< 0.001*
τ (s), median (IQR)	0.16 (0.16)	0.15 (0.13)	0.23 (0.14)	0.16 (0.11)	0.015‡
TSF difference (mm)¶, median (IQR)	0.87 (1.02)	0.60 (0.98)	0.72 (0.94)	1.2 (1.3)	0.007‡

*TSF: Triceps skinfold; SD: Standard deviation; IQR: Interquartile range; BMI: Body mass index; NRS-2002: Nutritional Risk Screening-2002. *One-way ANOVA. †Pearson Chi-square test or Fisher's exact test. ‡Kruskal-Wallis test. ¶Triceps skinfold difference: Initial value - Final value, across a set of 120 measurements.*

Statistical significance was set at $p < 0.05$. All analyses were conducted with MATLAB (MathWorks, Inc., Natick, MA) and the Software Package for Social Sciences (SPSS) for Windows (version 20.0; SPSS, Inc., Chicago, IL).

RESULTS

The characteristics of the 106 patients enrolled in the present study are displayed in table I, for the entire sample and stratified by TSF tertiles. Mean age (SD) was 53.1 (15.8), and 30.2% patients were aged ≥ 65 years. There were 56.6% overweight or obese patients and 11.3% patients were at undernutrition risk (Table I). The highest and the lowest time of compressibility (τ) were observed for patients in the 2nd TSF tertile and in the 1st TSF tertile, respectively. The highest TSF difference was observed for patients in the 3rd TSF tertile (Table I).

As shown in table II, BMI, TSF thickness and τ value increased from the 1st to the 3rd TSF difference tertiles. Otherwise, patients' characteristics did not differ across τ tertiles, with the exception of the TSF difference, which was higher in the 2nd and 3rd τ tertiles than in the 1st τ tertile (Table III).

Results from the multivariable linear regression models are presented in table IV. As shown in model 1, compressibility based on the TSF difference was associated with TSF magnitude (regression coefficient = 0.38 [0.01-0.05], p = 0.002) and nutritional status (regression coefficient = 0.23 (0.12-1.23), p = 0.018), after adjusting for age and gender. Thus, presenting a higher TSF

Table II. Patients' characteristics according to triceps skinfold difference *tertiles of sample distribution (mm)

Characteristics	1st ≤ 0.53 (n = 34)	2nd 0.54-1.27 (n = 36)	3rd ≥ 1.28 (n = 36)	p
Age (years), mean (SD)	56.1 (14.3)	52.9 (17.2)	50.4 (15.7)	0.418†
Age categories (years), n (%)				
< 65	23 (67.6)	24 (66.7)	27 (75.0)	0.703‡
≥ 65	11 (32.4)	12 (33.3)	9 (25.0)	
Gender, n (%)				
Women	10 (29.4)	19 (52.8)	20 (55.6)	0.056‡
Men	24 (70.6)	17 (47.2)	16 (44.4)	
Education (years), n (%)				
0-4	10 (29.4)	14 (38.9)	17 (47.2)	0.434‡
5-12	19 (55.9)	20 (55.6)	15 (41.7)	
> 12	5 (14.7)	2 (5.6)	4 (11.1)	
Marital status, n (%)				
Single	1 (2.9)	6 (16.7)	8 (22.2)	0.169‡
Married	24 (70.6)	23 (63.9)	25 (69.4)	
Widowed	6 (17.6)	5 (13.9)	1 (2.8)	
Divorced	3 (8.8)	2 (5.6)	2 (5.6)	
Katz index, n (%)				
Independent	33 (97.1)	35 (97.2)	35 (97.2)	0.999‡
Moderate and severe dependence	1 (2.9)	1 (2.8)	1 (2.8)	
Nutritional status (NRS-2002), n (%)				
Normal	31 (91.2)	33 (91.7)	30 (83.3)	0.459‡
Risk	3 (8.8)	3 (8.3)	6 (16.7)	
BMI (kg/m^2), mean (SD)	24.9 (4.1)	26.6 (7.0)	26.9 (6.3)	< 0.001†
BMI categories (kg/m^2), n (%)				
Underweight or normal weight	19 (55.9)	13 (36.1)	14 (38.9)	0.199‡
Overweight or obesity	15 (44.1)	23 (63.9)	22 (61.1)	
TSF (mm), mean (SD)	14.2 (7.1)	20.6 (12.4)	22.8 (14.0)	< 0.001†
τ (s), median (IQR)	0.13 (0.08)	0.20 (0.24)	0.21 (0.20)	0.002¶
TSF difference (mm), median (IQR)	0.30 (0.18)	0.83 (0.44)	1.92 (1.6)	< 0.001¶

*TSF: Triceps skinfold; SD: Standard deviaton; IQR: Interquartile range; BMI: Body mass index; NRS-2002: Nutritional Risk Screening-2002. *Triceps skinfold difference: Initial value - Final value, across a set of 120 measurements. †One-way ANOVA. ‡Pearson Chi-square test or Fisher's exact test. ¶Kruskall-Walis test.*

Table III. Patients' characteristics according to time of compressibility (τ) tertiles of sample distribution (second)

Characteristics	1st ≤ 0.13 (n = 35)	2nd 0.14-0.23 (n = 35)	3rd ≥ 0.23 (n = 36)	p
Age (years), mean (SD)	54.4 (14.6)	54.0 (15.6)	50.9 (17.4)	0.591*
Age categories (years), n (%)				
< 65	23 (65.7)	24 (68.6)	27 (75.0)	0.682†
≥ 65	12 (34.3)	11 (31.4)	9 (25.0)	
Gender, n (%)				
Women	13 (37.1)	17 (48.6)	19 (52.8)	0.394†
Men	22 (62.9)	18 (51.4)	17 (47.2)	
Education (years), n (%)				
0-4	11 (31.4)	15 (42.9)	15 (41.7)	0.669†
5-12	19 (54.3)	16 (45.7)	19 (52.8)	
> 12	5 (14.3)	4 (11.4)	2 (5.6)	
Marital status, n (%)				
Single	6 (17.1)	4 (11.4)	5 (13.9)	0.472†
Married	23 (65.7)	22 (62.9)	27 (75.0)	
Widowed	5 (14.3)	6 (17.1)	1 (2.8)	
Divorced	1 (2.9)	3 (8.6)	3 (8.3)	
Katz index, n (%)				
Independent	34 (97.1)	34 (97.1)	35 (97.2)	0.984†
Moderate and severe dependence	1 (2.9)	1 (2.9)	1 (2.8)	
Nutritional status (NRS-2002), n (%)				
Normal	28 (80.0)	34 (97.1)	32 (88.9)	0.077†
Risk	7 (20.0)	1 (2.9)	4 (11.1)	
BMI (kg/m^2), mean (SD)	25.9 (6.0)	26.3 (4.0)	26.3 (7.5)	0.952a
BMI categories (kg/m^2), n (%)				
Underweight or normal weight	16 (45.7)	15 (42.9)	15 (41.7)	0.940†
Overweight or obesity	19 (54.3)	20 (57.1)	21 (58.3)	
TSF (mm), mean (SD)	18.9 (13.6)	18.0 (9.2)	21.1 (13.0)	0.542*
τ (s), median (IQR)	0.09 (0.04)	0.16 (0.05)	0.33 (0.14)	<0.001‡
TSF difference (mm)¶, median (IQR)	0.61 (1.0)	0.75 (1.1)	1.19 (1.2)	0.026‡

*TSF: Triceps skinfold; SD: Standard deviation; IQR: Interquartile range; BMI: Body mass index; NRS-2002: Nutritional Risk Screening-2002. *One-way ANOVA. †Pearson Chi-square test or Fisher's exact test. ‡Kruskall-Walis test. ¶Triceps skinfold difference: Initial value - Final value, across a set of 120 measurements.*

Table IV. Multivariable linear regression models for prediction of triceps skinfold (TSF) compressibility

Models	Regression coefficient (95% CI)	p
*Model 1**		
TSF	0.38 (0.01-0.05)	0.002
Nutritional Status (NRS-2002; reference: normal)	0.23 (0.12-1.23)	0.018
Model 2†		
TSF	0.03 (-0.01-0.01)	0.824
Gender (reference: women)	-0.06 (-0.37-0.21)	0.599
Age	-0.04 (-0.01-0.01)	0.695
Nutritional Status (NRS-2002; reference: normal)	-0.16 (-0.71-0.08)	0.112

*CI: Confidence interval; TSF: Triceps skinfold thickness (mm); NRS-2002: Nutrition Risk Screening 2002. Variables included: Age (years; continuous), nutrition status according to NRS-2002 (normal used as reference), gender (women used as reference) and TSF value (mm; continuous). *Dependent variable: TSF compressibility computed as TSF initial value - TSF final value, across a set 120 measurements. †Dependent variable: TSF compressibility defined as time (τ).*

value, i.e., a thicker TSF, and being at risk of undernutrition are factors apparently related to an increase in the difference between TSF initial and final values, meaning that the skinfold was more compressed and, therefore, presents higher compressibility.

In contrast, as displayed in model 2, time of compressibility (τ) was not significantly associated with any of the included variables.

DISCUSSION

The present study results show that quantification of compressibility and its associated factors is dependent on the method used to analyze this adipose tissue feature.

When compressibility was defined as the difference between initial and final TSF values obtained by the digital calliper, only BMI and time of compressibility differed between the tertiles of this variable. Nevertheless, after adjustment for potential confounders, such as gender and age, results from the multivariable linear regression model showed that undernutrition risk and higher TSF thickness were factors associated with higher compressibility.

In contrast, when compressibility was defined as time, i.e., the time taken by the adipose tissue to respond to the pressure exerted by the calliper, differences were observed between TSF thickness tertiles, which could indicate that the skinfold magnitude was associated with compressibility. In addition, it is worth noting that patients in the 2nd TSF tertile presented higher τ than patients in the 3rd TSF tertile. However, after performing a multivariable linear regression model, no independent association was found for any of the included variables, showing that, apparently, time of compressibility was not influenced by any of the studied factors.

Explanations for these associations can be formulated, although only in a theoretical perspective as, with the present data, it is not possible to confirm them. Therefore, a thicker TSF presents a larger area of adipose tissue, and this increases the potential of being compressed. Otherwise, an individual classified as being at risk of undernutrition is potentially likely to present more laxity in skin and adipose tissue, which can influence skinfolds compressibility towards higher values.

Transposing the present results for clinical practice, TSF thickness and undernutrition risk are characteristics susceptible of affecting the association between the actual value and the calliper reading, potentially introducing error by an increase in adipose tissue compressibility. Thus, by causing more compression in the skinfold, this error can lead to an underestimation of TSF thickness, i.e., to a lower value reading and, therefore, to a misinterpretation of the measurement.

Moreover, once τ indicates skinfolds compressibility, as time of response to a constant pressure, a higher time of response is expected to be associated to lower compressibility, as the tissues compress slowly. In contrast, a higher difference between the initial and final TSF values means that the tissue went through more compression, and is, therefore, associated with higher compressibility. Notwithstanding this, our results show that τ and TSF difference vary in the same direction, as τ values are higher in TSF difference 2nd and 3rd tertiles and TSF difference values are higher in the 2nd and 3rd tertiles of τ.

Considering the aforementioned methods for evaluating compressibility and the results actually obtained, there is an apparent counterintuitive observation. Nevertheless, it is worth noting that these two methods are related with two different aspects of compressibility, time of response and the skinfold dimension. Thus, a skinfold that takes more time to be compressed is, therefore, less compressible according to this definition. It may also simultaneously present a higher difference between the value at the beginning of the measurement and the value attained when the process is complete.

Although this novel methodology has been previously used in other settings (21), as far as we are concerned, this is the first report on the exploration of TSF compressibility as a quantifiable variable and its associated factors in a clinical setting. Consequently, there are no previous results to which our findings can be compared. Even though one approach detected consistent associations and the other one did not, they cannot be compared in terms of accuracy as these two methods assess different features.

The absence of association with other factors found for compressibility defined as time is not sufficient to conclude that there are no differences or even that compressibility did not affect measurements performed in the present sample. We can further hypothesize that, in the two seconds the measurement is performed, τ may be related to an earlier moment of the process than the TSF difference. Thus, it is not known if in a larger period of measurement these results could be different.

Present results concern TSF only. As it has been already documented through results from studies (5,8,22) using different methodologies, adipose tissue compressibility varies according to the site of measurement. Thus, it is not known whether these results would be different if other skinfolds were evaluated.

In order to comply with the inclusion criteria, no critically ill or functionally impaired patients were enrolled. Moreover, the majority of the participants were independent in activities of daily living and there was a small proportion of patients at nutritional risk. Thus, the present sample can be considered as homogenous and this feature may have influenced the results obtained. Therefore, it is not known if present results would be different in a wider sample of hospitalized patients or, even, among critically ill or bedridden patients.

In the future, it would be important to further explore compressibility through the present methodologies in other settings, such as in community-dwelling adults and older adults and different ethnic groups. The application of the present methods in different settings could allow for both testing their reproducibility and improving the techniques used.

In conclusion, among a sample of hospitalized patients, undernutrition risk and higher TSF thickness were factors independently associated with higher compressibility assessed by the difference between the initial and final TSF values. Time of compressibility (τ) was not affected by any of the studied factors. Although the present study is merely an exploratory attempt to describe compressibility and its effects, our results emphasize the need for

further research in order to determine the most accurate method to quantify compressibility, to infer on the associated factors and to control its effect.

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Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Hand span influences optimal grip span in adolescents with Down syndrome

La envergadura de la mano determina la longitud del agarre óptimo en adolescentes con síndrome de Down

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Abstract

Introduction: The hand grip strength test provides useful and reliable information about overall health. Different studies have investigated the optimal grip span for determining maximal hand grip strength in different populations such as adults, adolescents and children without disabilities.

Objective: To ascertain whether there is an optimal grip span for determining maximal hand grip strength in adolescents with Down syndrome (DS).

Methods: Twenty-seven right-handed youths with DS (seven females) aged 15.5 ± 3.6 years were evaluated in this methodological study. Each hand was randomly tested on ten times using five different grip spans, allowing one-minute rest between attempts. The hand span was measured from the tip of the thumb to the tip of the small finger with the hand widely opened. To confirm the usefulness of the optimal grip span, a new group of 15 adolescents with DS were recruited.

Results: An optimal grip span was identified for the dominant hand in adolescents with DS. The equation relating grip span as a function of dominant hand span in this group is formulated as follows: $y = 0.342x - 1.161$ cm ($r = 0.63$, $p < 0.05$). In the case of non-dominant hand, a tendency towards a linear association ($p = 0.058$) was found; the equation is formulated as follows: $y = 0{,}210x + 1.324$ cm.

Conclusion: It is important to standardize the procedure and increase reliability when measuring hand grip strength in DS population. The values stated in this study are recommended to assess hand grip strength in adolescents with Down syndrome.

Key words:

Intellectual disability. Dynamometry. Reliability. Standardization.

Resumen

Introducción: la fuerza isométrica máxima de antebrazo está relacionada con diferentes componentes de salud. Investigaciones previas han determinado la longitud de agarre óptima para el test de dinamometría manual tanto en adultos como en adolescentes y niños sin discapacidad.

Objetivo: determinar si existe una longitud de agarre óptima para el cálculo de la fuerza máxima de antebrazo mediante dinamometría manual en adolescentes con síndrome de Down (SD).

Métodos: en este estudio participaron 27 jóvenes con SD, diestros de mano y con una edad media de 15,5 ± 3,6 años. Ambas manos fueron evaluadas aleatoriamente diez veces usando cinco amplitudes de agarre diferentes y permitiendo un descanso de un minuto entre intentos. La envergadura de mano se midió desde la punta del primer al quinto dedo de la mano con la mano en su máxima amplitud. Para confirmar la utilidad del agarre óptimo establecido fueron reclutados otros 15 adolescentes con SD.

Resultados: se identificó una longitud de agarre óptima para la mano dominante de los adolescentes con SD. La ecuación que determina la longitud de agarre en función de la envergadura de la mano quedó definida como: $y = 0{,}342x - 1{,}161$ cm ($r = 0{,}63$, $p < 0{,}05$). En la mano no dominante se observó una tendencia ($p = 0.058$), siendo la fórmula $y = 0{,}210x + 1{,}324$ cm.

Conclusión: es importante estandarizar el procedimiento para aumentar la reproductibilidad del test de dinamometría manual cuando se mide la fuerza isométrica máxima del antebrazo en adolescentes con SD. Se recomienda usar los valores descritos en este artículo para el ajuste del dinamómetro cuando se realiza el test en adolescentes con SD.

Palabras clave:

Discapacidad intelectual. Dinamometría manual. Fiabilidad. Estandarización.

Ethical approval: The study was performed in accordance with the Declaration of Helsinki of 1975 (revised in Fortaleza, 2013) and was approved by the Research Ethics Committee (C.I. PI10/026). An informed consent was obtained from the parents of each participant as well as verbal assent from all participants.
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INTRODUCTION

Muscular strength, one of the five components of health-related physical fitness, is associated with the ability to perform activities that require muscular force. The most commonly performed strength test for assessing this component is the measurement of grip strength with a hand grip dynamometer. The hand grip strength test provides useful and reliable information about overall health (1).

Several external factors are affecting results of the tests such as the angle of the shoulder, elbow, forearm, and wrist (2); the posture of the subject (3), and the grip span (4,5). The grip span is concretely the most influential among the previous factors because hand and palm lengths (6), and palm width (7) are highly related to the strength performed during the dynamometry.

Different studies have investigated the optimal grip span for determining maximal hand grip strength in different populations such as adults (8), adolescents (4) and children (5). Firstly, Ruiz et al. (4) found that there was an optimal grip span to measure hand grip strength in teenagers. Similar results were found in children some years later by España-Romero et al. (5). However, to our knowledge, no studies on this regard have focused on persons with Down syndrome (DS), despite the relevance that this might have. Muscle hypotonicity and low muscular strength (9) are clinical characteristics among persons with DS. Concerning their hands, individuals with DS have a smaller hand size compared with their counterparts without the condition (10). For these reasons, it would be expected that individuals with DS would have a unique optimal grip span, different from the ones described for non-disabled adolescents. Thus, the aims of the present study were: a) to ascertain whether there is an optimal grip span for determining the maximal hand grip strength in adolescents with DS; and b) to define the specific span values for optimal grip span in this particular population.

MATERIAL AND METHODS

This study has been performed following the methodological considerations published elsewhere (4,5,8).

PARTICIPANTS

Two different groups of adolescents with DS were involved in this research. The optimal grip span was determined from the first group (27 adolescents with DS). Then, the usefulness and the reliability of the calculated optimal grip span were confirmed in a new group of 15 adolescents with DS.

PROCEDURES

Measurement of hand span

Right and left hand spans, corresponding to the dominant and non-dominant hands, were measured with the hand widely opened, taking as reference from the tip of the thumb to the tip of the little finger. The precision of the measure was 0.1 cm, but the results of the hand span measurement were rounded to the nearest centimeter.

Measurement of handgrip strength

Hand grip strength was measured using a digital dynamometer (T.K.K. 5401 Grip-D; Takey, Tokyo, Japan), and the scores were recorded in kilograms (precision 0.1 kg). When performing the test, participants were instructed to maintain the standard bipedal position during the entire test with the shoulder in slight abduction, the elbow in complete extension, the forearm in pronation and the wrist in neutral position without touching any part of their body (11). Each subject performed (alternately with both hands) the test twice using different grip spans in random order, allowing a one-minute rest between the measurements (12). Latin square approach was used to avoid an ordering effect in the randomization of the testing. The used grip spans ranged from 3.5 to 7.0 cm. If the hand span was less than 20 cm, the broadest grip span was deleted; if the hand span was more than 20 cm, the thinnest grip span was deleted. For each hand, the best strength result for each grip span was selected.

Determination of optimal grip span

The kind of association relating grip span to hand grip strength was determined to establish the individual optimal grip span for each hand of each individual. The type of association could be linear, logarithmic, potential, quadratic, exponential, or polynomial. All functions were considered in the statistical analyses, and the most relevant was retained. The mathematical function was individually determined through the least-squares fit and graphically represented (Fig. 1).

Once the equation was defined, the optimal grip span was calculated as xIf´(x) = 0, where x corresponds to the optimal grip span (cm), and f´(x) is the handgrip strength (kg). In graphic terms, this corresponds with the maximum of the curves, as seen in figure 1. Only in six cases the association was quadratic (corresponding to a second-degree polynomial equation). For linear associations (n = 11), the optimal grip span was graphically determined. For those adolescents in whom there was no statistically significant association (n = 21 for the dominant hand and n = 17 for the non-dominant hand), the average strength of the chosen grip spans was retained.

Determination of the optimal grip span for a given hand span

The least-squares approach was used to establish the optimal grip span for a given hand span.

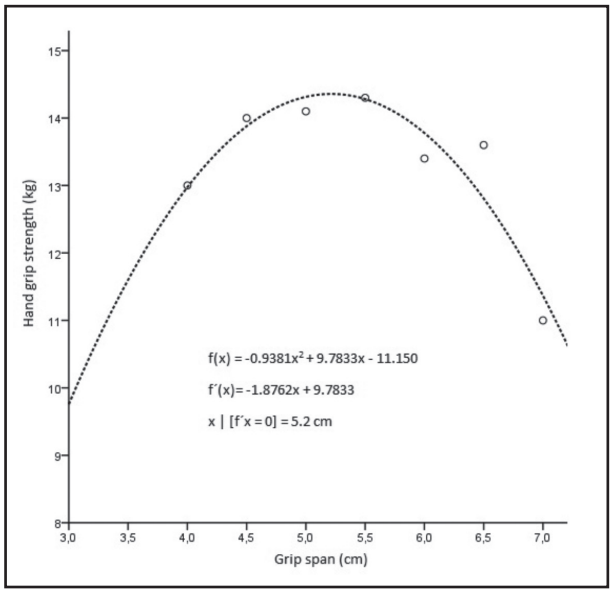

Figure 1.

Association relating grip span and hand grip strength for the dominant hand of an adolescent with DS. The maximum of the second-degree polynomial regression equation relating hand grip strength and grip span, f´(x), was the optimal grip span for each hand of each individual.

Usefulness and reliability of the optimal grip span

To confirm the usefulness of the optimal grip span when measuring hand grip strength in adolescents with DS, a new group of 15 adolescents with DS (ten boys, five girls) were recruited. The new group of adolescents performed the hand grip strength test at three grip spans using the Latin square design: 1 cm below the optimal grip span, optimal calculated grip span, and 1 cm above the optimal grip span. Each participant performed the test following the same protocol described above. For each hand, the best result at each grip span was retained. To confirm the reliability of measurements of hand grip strength at the optimal grip span, the same participants performed the test at the optimal grip span one hour later. All participants were watching a movie during this time.

STATISTICAL ANALYSES

The hand span, hand grip strength, and the optimal grip span obtained for each hand span by gender was compared with 1-way analysis of variances (ANOVA). Bivariate correlation was performed to evaluate the relationship between optimal grip span and hand span for each hand by gender. In the case of an association, the mathematical function defining the association was calculated through the least-squares fit. ANOVA for repeated measures was used to confirm the usefulness of measuring hand grip strength in three different conditions (optimal grip span, 1 cm below and above). The reliability coefficient of hand grip strength measured at the optimal grip span on two different occasions was compared through 1-way ANOVA for repeated measures, and correlated through parametric bivariate correlation analysis. The SPSS version 19.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Mean and standard deviations (SD) are given; otherwise, they are stated. The α error was fixed at 0.05.

RESULTS

The average hand span was 17.6 ± 1.4 cm for the dominant hand and 17.8 ± 1.5 cm for the non-dominant hand (n = 27). The optimal grip span was not significantly different between dominant and non-dominant hands (all $p > 0.05$) (Table I). Although no differences were found between hands, the optimal grip span and the span showed higher correlation with the dominant hand ($r = 0.660$, $p < 0.05$) than with the non-dominant hand ($r = 0.408$, $p < 0.05$), and the subsequent analyses were individually performed for each hand.

Table I. Optimal grip span determined in adolescents with Down syndrome (n = 27) for each hand span*

Hand span (cm)	Optimal grip span for sight hand (cm)	Optimal grip span for left hand (cm)	Optimal grip span† (cm)	p value‡
15	3.7 (0.4)	4.6 (1.0)	4.1	0.264
16	4.1 (0.2)	4.4 (0.7)	4.2	0.623
17	4.8 (0.7)	4.7 (0.8)	4.7	0.840
18	5.0 (0.5)	5.0 (0.5)	5.0	0.822
19	5.8 (0.2)	6.4 (0.2)	6.1	0.053
20	5.4 (0.9)	5.1 (1.0)	5.2	0.645

*Values are given in mean and standard deviation (SD). *The precision of the hand span measure was 0.5 cm and the value was rounded to the nearest centimetre. †Optimal grip span obtained from the mean of right- and left-hand optimal grip span. ‡Comparison between optimal grip span obtained with right hand* versus *optimal grip span obtained with left hand for each hand span.*

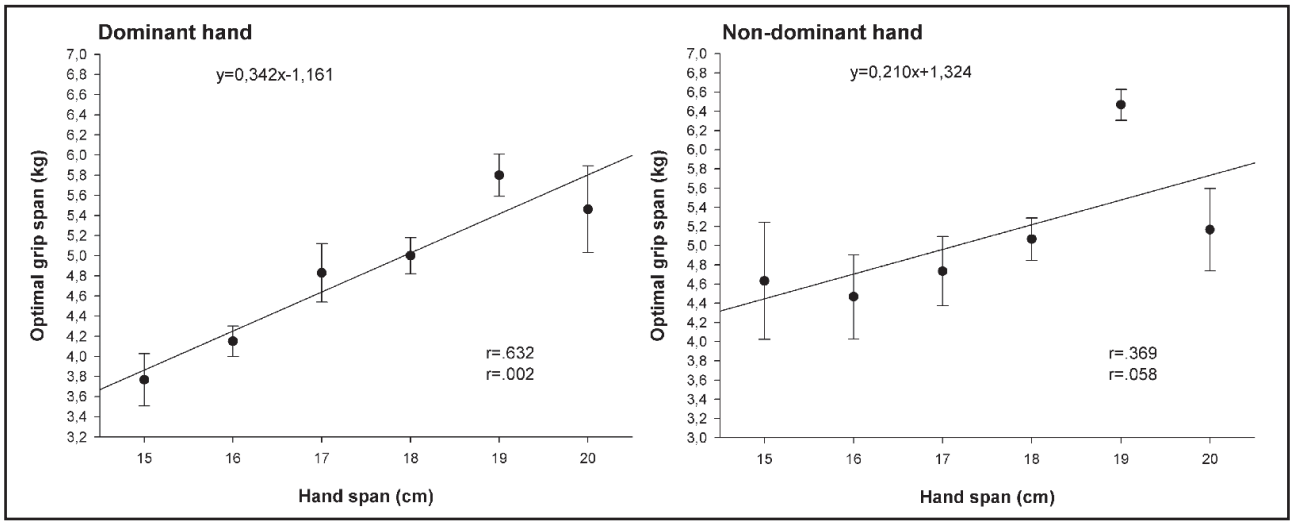

Figure 2.

Association between optimal grip span and hand span in adolescents with DS (n = 27). Values are means ± standard error of the mean.

Table II. Optimal grip span for each hand span calculated from the equations provided*

Hand size (cm)	Optimal grip span for the right hand (cm)	Optimal grip Span for the left hand (cm)	Optimal grip span† (cm)
13	3.3	4.1	3.7
13.5	3.5	4.2	3.9
14	3.6	4.3	4.0
14.5	3.8	4.4	4.1
15	4.0	4.5	4.3
15.5	4.1	4.6	4.4
16	4.3	4.7	4.5
16.5	4.5	4.8	4.7
17	4.7	4.9	4.8
17.5	4.8	5.0	4.9
18	5.0	5.1	5.1
18.5	5.2	5.2	5.2
19	5.3	5.3	5.3
19.5	5.5	5.4	5.5
20	5.7	5.5	5.6
20.5	5.9	5.6	5.8
21	6.0	5.7	5.9
21.5	6.2	5.8	6.0
22	6.4	5.9	6.2

**For the right hand y = 0.342x - 1.161 cm (r = 0.63, p < 0.05); for the left hand y = 0,210x + 1.324 cm (r = 0.369, p < 0.05); where x is the hand span (maximal width between thumb and little finger, with 0.5-cm precision), and y is the optimal grip span in centimetres. †Optimal grip span obtained from the mean of right- and left-hand optimal grip span.*

Hand span and optimal grip span showed a significant linear association in the studied adolescents with DS ($y = 0.273x + 0.141$; $r = 0.48$, $p < 0.05$), where *x* is the hand span (maximal width between first and fifth fingers), and *y* is the optimal grip span at which the dynamometer should be adjusted before testing. The equation relating grip span as a function of dominant hand span in this group is formulated as $y = 0.342x - 1.161$ cm ($r = 0.63$, $p < 0.05$). In the case of non-dominant hand, the equation is formulated as $y = 0,210x + 1.324$ cm ($r = 0.369$, $p > 0.05$), as seen in figure 2. The optimal grip spans for each hand span calculated from the equations provided are presented in table II. The hand grip strength obtained at the optimal grip span was significantly higher than the strength obtained when the grip was set 1 cm below the optimal grip span for the dominant hand ($p < 0.05$) (Fig. 3).

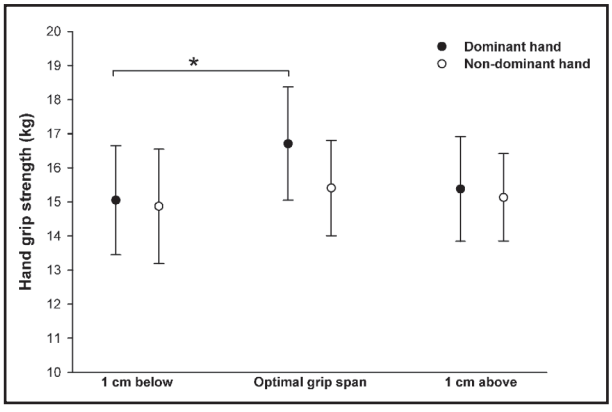

Figure 3.

Hand grip strength measured in dominant and non-dominant hands at optimal grip span, 1 cm below, and 1 cm above in adolescents with DS (n = 15). Values are means ± standard error of the mean. *p < 0.05 compared to 1 cm below.

The reliability coefficients for the optimal grip were 0.93 and 0.98 for dominant and non-dominant hands respectively. However, the one-way ANOVA for repeated measures showed statistical differences between test and retest ($p < 0.05$) for non-dominant hand and no differences for dominant hand ($p = 0.460$). A significant correlation between test and re-test for dominant ($r = 0.871$, $p < 0.01$) and non-dominant ($r = 0.967$, $p < 0.01$) hands was obtained at the optimal grip span.

DISCUSSION

The main finding of the present study is that there is an optimal grip span for the assessment of maximal strength in the dominant hand of adolescents with DS.

As previously recommended by Oppewal et al. (13), for adults with intellectual disabilities, both hands were tested in order to get a valid result of maximal strength.

The results of our study showed that the optimal grip span is more influenced by hand span in the dominant hand in comparison with the non-dominant one, which implies the need of adjusting the grip span of the dynamometer for each hand. For that reason, specific equations for each hand have been developed herein. The level of awareness, attention and their ability to cooperate are factors that make more difficult to measure hand grip strength in adolescents with intellectual disabilities than in those without. At the same time, they may be affecting our results and could explain the discrepancies between both hands. Nonetheless, our findings are in concordance with previous researches in which the optimal grip was influenced by hand span in non-disabled children (5), teenagers (4) and adults (8). Each population has some different physical characteristics; children have smaller hands than teenagers, who in their turn have smaller hands and lower hand grip strength compared with adults. For these reasons, it is possible to think that each specific group may need a specific optimal grip span to assess hand grip strength. This argument can be extrapolated to disabled-population such as adolescents with DS because they have some determined clinical characteristics as smaller hand spans or lower strength levels than those without (14).

The hand grip test has been shown to be a valid tool for measuring muscle strength in persons with some diseases and disabilities (15). This relatively cheap device is associated with many health-related parameters that are especially relevant in a population at risk such as adolescents with DS. On this regard, maximal muscular strength in the dominant arm has been demonstrated to be a good predictor to determine the risk of fracture in adolescents with DS (16). A recent study performed by Izquierdo-Gómez et al. (17) reported information about hand grip strength in adolescents with DS, showing lower hand grip strength compared to those without DS (14.9 *vs* 26.2 kg). It might be possible that their results were influenced for the use of the ALPHA health-related fitness test battery, which has been established for youth people without disabilities (18). In other populations with intellectual disabilities, similar results were reported by Kern et al. (19), finding that children with an autism spectrum disorder had significantly poorer hand grip strength than control children.

Muscle strength and tone in DS population may play an important role in activities of daily living. Positive improvements in grip strength can be found even after a single exercise session (20). As individuals with premature ageing, sarcopenia appears earlier in life and this is an issue for reduced functional abilities and quality of life for these persons. Several test can be used to measure specific strength, but none of them have been specifically designed for disabled adolescents, neither for those with DS. This study provides key information for therapists or sport scientist on how to better use the hand grip strength test in adolescents with intellectual disabilities.

This study is not exempt of limitations, being the main one the analysis of the sample as a whole, and not by gender. Our limited sample size, due to the intrinsic difficulty on getting a bigger number of participants in this limited age range and with the DS condition made it extremely hard to achieve a larger sample. On the other hand, the rigorous methodology and statistical analyses, together with the validation performed in a sample of 15 participants, ensure the feasibility of the obtained results.

To conclude, the specific grip values stated in this study for dominant hand span are recommended for assessing maximal hand grip strength in adolescents with DS.

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Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Cambios de la composición corporal tras un periodo de desentrenamiento deportivo

Body composition changes after sport detraining period

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Resumen

Introducción: la influencia del ejercicio físico en sujetos entrenados tiene efectos beneficiosos en la condición física y la composición corporal. Sin embargo, el desentrenamiento tiene un efecto desfavorable en todas ellas.

Objetivo: el propósito del estudio fue analizar los cambios de la composición corporal después de un periodo de desentrenamiento de seis semanas de duración en dos grupos: uno de 43 jóvenes varones jugadores de fútbol (grupo experimental [GE], n = 43), y un grupo control de escolares no activos de la misma edad (grupo control [GC], n = 10).

Métodos: las variables de composición corporal fueron evaluadas mediante antropometría, para estimar la masa grasa (MG) y la masa muscular esquelética (MME), y mediciones de bioimpedancia eléctrica, para estimar agua corporal total (ACT), agua extra (AEC) e intracelular (AIC). Las mediciones se realizaron tanto en situación de entrenamiento como de desentrenamiento.

Resultados: tras el desentrenamiento, se encontraron diferencias significativas en el ACT (35,5 ± 5,2 *vs.* 36,7 ± 4,9 kg), el AIC (14,2 ± 1,8 *vs.* 14,8 ± 1,6 kg) y el AEC (21,5 ± 3,6 *vs.* 22,0 ± 3,4 kg, $p < 0,001$ para todas las variables), sin existir diferencias en los ratios AEC/ACT (0,4 ± 0,02 *vs.* 0,4 ± 0,02) y AIC/ACT (0,6 ± 0,02 *vs.* 0,597 ± 0,02, ambos $p > 0,05$). La MG aumentó significativamente (8,6 ± 3,2 *vs.* 8.95 ± 3,1 kg, $p < 0,01$); sin embargo, la MME no sufrió modificaciones (21,2 ± 2,5 *vs.* 22,22 ± 2,8 kg, $p > 0,05$)

Conclusiones: el principal resultado de este estudio fue que en un periodo de desentrenamiento de seis semanas se observaron aumentos del ACT y de su distribución en el grupo de jóvenes futbolistas. La importancia fisiológica de esta desadaptación en el rendimiento deportivo tiene que ser analizada en futuros estudios.

Palabras clave:

Composición corporal.
Antropometría.
Bioimpedancia eléctrica.
Desentrenamiento.

Abstract

Introduction: The influence of exercise in trained subjects has beneficial effects in the physical fitness and body composition; however, detraining has an unfavorable effect in all of them.

Objective: The current study was designed to ascertain the influence of a six week-detraining period on body composition in both well-trained young soccer players (GE, n = 43) and sedentary male adolescents (GC, n = 10).

Methods: Forty-three well-trained soccer players and ten sedentary adolescents accepted to participate in the study. Body composition measurements included fat mass and skeletal muscle mass (SMM), which were estimated by anthropometry. In addition, total body water (TBW), intracellular water (ICW) and extracellular water (ECW) were assessed by bioelectrical impedance analysis (BIA) at the end of training and after detraining periods.

Results: After the six-week-detraining period, significant increments were found in TBW (35.5 ± 5.2 *vs.* 36.7 ± 4.9 kg; $p < 0.001$), ICW (14.2 ± 1.8 *vs.* 14.8 ± 1.6 kg; $p < 0.001$) and ECW (21.5 ± 3.6 *vs.* 22.0 ± 3.4 kg; $p < 0.001$) in soccer players. Conversely, no changes were observed in ECW/TBW (0.4 ± 0.02 *vs.* 0.4 ± 0.02; $p > 0.05$) and ICW/TBW (0.6 ± 0.02 *vs.* 0.597 ± 0.02; $p > 0.05$) ratios. Finally, fat mass was significantly increased (8.6 ± 3.2 *vs.* 8.95 ± 3.1 kg; $p < 0.01$) in the detrained group. No significant changes were found in SMM (21.2 ± 2.5 *vs.* 22.22 ± 2.8 kg, $p > 0.05$).

Conclusions: After a six-week detraining period, body composition changed significantly in well-trained adolescents. The main finding of this study was that increments of TBW and water distribution were observed in the soccer group, which reflects an increase of fat free mass compartment. The physiological importance of this miss-adaptation needs to be elucidated in future research. Further studies on this topic are still required to assess its impact on physical performance.

Key words:

Body composition.
Anthropometry.
Bioelectrical impedance analysis.
Detraining.

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INTRODUCCIÓN

La influencia del ejercicio físico en sujetos sometidos a entrenamiento tiene efectos beneficiosos en la condición física, la composición corporal (CC) y el perfil lipídico; sin embargo, el desentrenamiento (DT) tiene un efecto desfavorable en todos ellos (1,2). Las consecuencias del DT son complejas y caracterizadas por diferentes ritmos de desadaptación, como son la disminución de la fuerza, la potencia y el equilibrio (2), y, en general, por sus efectos sobre la disminución de la función neuromuscular (3).

Está bien demostrado que la CC y la morfología corporal se asocian a los diferentes patrones de juego y a la competencia en jóvenes futbolistas (4), y por ello el DT también debe de interferir y representar un mecanismo fisiológico que explique la pérdida de rendimiento físico. Estas modificaciones pueden circunscribirse solamente a ciertos marcadores de adiposidad regional central como el perímetro abdominal o el índice cintura-cadera, sin afectar al índice de masa corporal (IMC) (5). Por todo ello es importante el control de la CC, pues tras cinco semanas de desentrenamiento se ha observado un aumento de la masa grasa y del perímetro de la cintura y estos cambios estuvieron asociados a disminuciones del consumo máximo de oxígeno y la tasa metabólica de reposo en jóvenes nadadores (6). Otro componente también afectado es la estructura ósea, ya que en gimnastas que cesaron su actividad deportiva se pudo observar un descenso de la mineralización y de la densidad ósea (7).

Otro aspecto que influye en las consecuencias producidas por el DT es el entrenamiento previo. En un estudio aleatorio y controlado con jóvenes se confirmó que los sujetos que realizaron entrenamiento aeróbico experimentaron una pérdida más rápida de la masa magra después de 24 semanas de DT que aquellos que lo realizaron de fuerza (8). Por otro lado, estas adaptaciones del entrenamiento son menores si ocurren anteriormente al máximo pico de crecimiento (MPC) y las desadaptaciones son más rápidas y viceversa una vez culminado el MPC, sobre todo en cualidades como la fuerza, la potencia y la velocidad.

Aunque está bien definido que a partir de seis semanas el DT es considerado como un periodo de larga duración (9), no todas las adaptaciones conseguidas desaparecen a la misma velocidad. Son sobre todo las capacidades anaeróbicas las que más rápidamente se ven afectadas, entre ellas, la fuerza muscular explosiva y los componentes asociados al metabolismo anaeróbico (10). Estas capacidades anaeróbicas parecen estar afectadas por la hidratación (11) e incluso por el grado de adiposidad. Entre los métodos de campo para la evaluación de la CC, figuran las técnicas antropométricas y el análisis de bioimpedancia eléctrica multifrecuencia (BIA) (12). La utilización de ambos métodos nos permitirá una evaluación más funcional de la CC y de sus modificaciones con el ejercicio y con los estados clínicos y nutricionales relacionados con los periodos de entrenamiento o de desentrenamiento (13).

Un periodo de DT puede producir cambios de la masa grasa (MG) y de la masa libre de grasa (MLG); sin embargo, los cambios de la MLG son difíciles de evaluar con el método clásico de dos componentes (14). Por ejemplo, el análisis individual de algunos componentes de la MLG puede ayudar a explicar cambios asociados al proceso de entrenamiento. Entre estos componentes, uno de los más importantes es el agua corporal total (ACT), que representa el componente más abundante del cuerpo humano y cuyas alteraciones modifican el rendimiento y las estimaciones de otros componentes (11,15).

Por otro lado, el ACT se distribuye en agua intracelular (AIC) y agua extracelular (AEC), que no puede considerarse fija puesto que puede estar influida por el nivel de adiposidad, la maduración y el nivel de entrenamiento (16). Utilizando modelos de CC multicompartimental para evaluar los componentes de la MLG después de un periodo de desentrenamiento, LaForgia detectó pequeñas alteraciones hídricas que en ocasiones pueden ser significativas (14). Por el contrario, en otro estudio no fue posible detectar la pérdida de fluidos corporales tras un entrenamiento, tanto con el control de las variaciones del peso corporal como por medio de medidas de ACT, AEC y AIC mediante BIA (17).

La controversia de estos estudios puede ser debida a diversos motivos, entre ellos, los más importantes son los referentes al ámbito metodológico, destacando el tipo de modelo y método de CC utilizado, así como el tiempo necesario para provocar las modificaciones de la CC y la propia magnitud de estas. Con respecto a la BIA, el análisis de los vectores de impedancia es una herramienta que permite estudiar los cambios de la hidratación corporal y de la masa celular, sin la influencia del modelo matemático utilizado para estimar la composición corporal (18). Utilizando los vectores estimados a partir de las medidas físicas de la BIA, como la resistencia y la reactancia, normalizadas para la altura (19), se ha demostrado en jugadores de fútbol de élite que el acortamiento de estos vectores indica una desviación hacia elipses de mayor hidratación y masa celular (20). El desentrenamiento asociado a la ausencia de cargas de competición es una razón suficiente para provocar alteraciones de la CC susceptibles de ser evaluadas con precisión, por ejemplo, con la BIA; sin embargo, estas han sido poco estudiadas rigurosamente en jóvenes deportistas.

El objetivo del presente estudio fue evaluar los cambios de la CC referentes a la masa grasa y la masa muscular esquelética (MME) por técnicas antropométricas, así como los cambios del agua corporal total, del agua intracelular y del agua extracelular, por medio de BIA, tras un periodo de desentrenamiento de seis semanas de duración.

MATERIAL Y MÉTODOS

SUJETOS

La población de estudio estuvo compuesta por 43 jóvenes varones, sanos, de las categorías infantil y cadete (edad: 14,11 ± 1,07 años) de la ciudad de Málaga (España), así como diez escolares adolescentes (14,5 ± 1,08 años) que sirvieron como grupo control (GC) y caracterizados por no realizar ningún tipo de actividad física de entrenamiento deportivo extraescolar, los cuales fueron evaluados en nuestro laboratorio a finales del mes de junio (grupo control - primera determinación [CON1]) y

en la primera semana de septiembre (grupo control - segunda determinación [CON2]).

El grupo experimental (GE) estaba compuesto por jóvenes futbolistas que entrenaron durante once meses, cuatro sesiones semanales de 90 minutos (360 minutos por semana). Adicionalmente, en el fin de semana se jugaba un partido de competición oficial de 90 min. El periodo de desentrenamiento establecido por el cuerpo técnico fue de seis semanas completas, desde la segunda mitad de junio de 2009 hasta final de julio de 2009.

PROCEDIMIENTO

Todas las evaluaciones se realizaron al final de la fase (temporada) de entrenamiento (GE-ENT), en la primera quincena de junio y durante la primera semana de inicio del entrenamiento de la siguiente temporada (grupo experimental fase desentrenamiento [GE-DT]), en la última semana de julio e inicio de agosto. Se explicaron los procedimientos y objetivos de las exploraciones a los padres y/o tutores y entrenadores, procediendo a la firma del consentimiento informado para poder participar en el estudio. Todos los protocolos se ajustaron a la Declaración de Helsinki para estudios biomédicos en humanos y el Comité de Ética de la Facultad de Medicina de la Universidad de Málaga aprobó los procedimientos del estudio. A todos los sujetos se les realizó una batería de exploraciones médicas y fisiológicas consistentes en una historia médica-deportiva, antecedentes familiares, bioimpedancia eléctrica de cuerpo entero, antropometría, auscultación, espirometría forzada, electrocardiograma de reposo y esfuerzo y prueba de esfuerzo incremental máxima, con análisis de gases respiración a respiración. Todos los sujetos estuvieron exentos de enfermedades agudas o crónicas y en el momento de las exploraciones no estaban tomando ninguna medicación.

MÉTODOS

Estimación de la composición corporal

Evaluación antropométrica

Se midió el peso (en kg) utilizando una balanza digital Seca 770 (Hamburgo, Alemania), con una precisión de 0,1 kg, y la estatura (H, en cm) mediante un tallímetro de pared Seca 208 (Hamburgo, Alemania), con una precisión de 1 mm. Se obtuvieron los pliegues tricipital, muslo anterior y medial de la pierna con un calibre de pliegues cutáneos Holtain (Holtain, Crymych, Reino Unido), con una precisión de 0,2 mm. El porcentaje de MG fue calculado con la ecuación de Slaughter (21). La masa muscular esquelética (MME) se estimó a partir de la ecuación de Poortmans (22), basada en perímetros musculares corregidos de brazo, muslo medio y pierna. Todas las medidas antropométricas fueron tomadas por el mismo antropometrista, con un error técnico de medida menor de un 2% para pliegues de grasa y menor de un 1% para el resto de medidas, según los criterios internacionales estandarizados por la International Society for Advancement in Kinanthropometry (23).

Análisis de bioimpedancia eléctrica

Se utilizó un equipo multifrecuencia MediSystem (Sanocare Human System, Madrid). La evaluación fue realizada en la primera hora de la mañana, en condiciones de ayuno y sin haber realizado ejercicio físico moderado o intenso en las últimas 24 horas. Antes de efectuar la evaluación, todos los sujetos realizaron una micción, se ordenó retirar todos los elementos metálicos de su cuerpo y permanecieron en posición de decúbito supino sobre una camilla no conductora entre ocho y diez minutos (24). Los valores de impedancia (Z), resistencia (R) y reactancia (Xc) se obtuvieron habiendo dispuesto cuatro electrodos de contacto (PKR 170, Sanocare Human System, Madrid) en el dorso de la mano y del pie derechos, haciendo pasar una corriente alterna de 800 mA por los mismos (8). Los cálculos del AEC fueron obtenidos con la aplicación de las ecuaciones de Deurenberg (25) y el AIC, por sustracción (AIC = ACT-AEC). Adicionalmente, se obtuvo el vector de impedancia a partir de las relaciones índice reactancia-altura (Xc/H) (ordenadas) e índice resistencia-altura (R/H) (abscisas), conformando el gráfico resistencia-reactancia (gráfico RXc) con el objetivo de monitorizar los cambios de fluidos con independencia de la propia composición corporal (19,26).

Nivel de actividad física

La cuantificación de la actividad física del grupo control se realizó para confirmar que presentaban un patrón diario de movimiento relativamente sedentario. Para este efecto, se utilizó el cuestionario *Physical Activity Questionnaire-Adolescents* (PAQ-A), con aplicación para adolescentes de 14 a 20 años. Este cuestionario ha demostrado una buena precisión y una razonable validez en un estudio en adolescentes españoles (27). Igualmente, el PAQ-A presenta una sensibilidad y especificidad altas para la valoración de actividades moderadas-vigorosas de 60 min (sensibilidad de 87% y especificidad de 93%) y para actividades vigorosas de 30 min (sensibilidad de 87% y especificidad de 77%) (28).

Análisis estadístico

El procesamiento de datos se realizó utilizando el programa estadístico MedCalc para Windows, versión 12.7.5.0 (Mariakerke, Bélgica). Todas las variables cuantitativas se expresaron con el valor medio y la desviación estándar (DE), después de confirmar su distribución normal mediante el test de Shapiro-Wilk. La comparación de valores medios entre el grupo experimental y el grupo control se realizó mediante el test no paramétrico de Mann-Withney, para muestras independientes. Las comparaciones entre las evaluaciones del grupo control se realizaron mediante una prueba t de Student para datos apareados En todas las pruebas estadísticas, se aceptó como significativo un valor de $p < 0,05$.

RESULTADOS

Grupo ENT y CON1: se observan diferencias significativas en la talla y en el porcentaje de ACT, así como mayores valores de AEC y AIC entre el grupo ENT y el grupo CON1 ($p < 0,05$). Así mismo, el ratio AEC/ACT es mayor también en el grupo CON1 ($p < 0,001$) (Tabla I).

Tabla I. Características antropométricas básicas y de composición corporal entre el grupo experimental (GE) en fase de entrenamiento (ENT) con el grupo control (CON1)

Variables		ENT		CON 1		
		Media	DT	Media	DT	p
Edad	años	14,11	1,07	13,3	± 0,58	ns
Peso	(kg)	55,99	± 8,65	60,69	± 5,73	ns
Talla	(kg)	166,5	± 6,3	171,3	± 4,82	*
ACT	(kg)	35,52	± 5,2	38,63	± 5,55	ns
ACT	(%)	62,25	± 3,31	60,24	± 4,19	*
AEC	(kg)	14,19	± 1,76	15,75	± 1,86	*
AIC	(kg)	21,47	± 3,65	22,88	± 3,71	*
AEC/ACT		0,4	± 0,02	0,41	± 0,01	**
AIC/ACT		0,6	± 0,02	0,59	± 0,01	ns

*$p < 0,05$; **$p < 0,001$; ns: no significativo.*

Grupo ENT y DT: se observan cambios significativos en la talla, en el ACT, tanto en el valor porcentual como en el absoluto, y en el AEC y el AIC ($p < 0,05$) (Tabla II).

Grupo control: no se observan diferencias significativas de ninguna de las variables ($p > 0,05$) desde la primera (CON1) a la segunda evaluación (CON2) (Tabla II).

Hay que destacar que el GC no presentó cambios en la puntuación del cuestionario PAQ-A del mes de junio a septiembre (2,75 ± 0,5 *vs.* 2,8 ± 0,8; $p > 0,05$), confirmándose que su nivel de actividad física no se modificó; por tanto, fueron clasificadas como personas muy poco activas durante este periodo. En el GE, después del periodo de DT, se encontraron diferencias significativas entre los dos momentos de estudio (ENT *vs.* DT) en las variables de Z y R, así como aumentos significativos de la MG por métodos antropométricos (8,63 ± 3,2 *vs.* 9,95 ± 3,2 kg; $p < 0,05$) (Tabla II). Los valores de la MME no experimentaron cambios significativos tras el periodo de DT ($p > 0,05$) (Tabla III).

En la figura 1 se representa el gráfico de los vectores de impedancia (ENT y DT), mostrando un desplazamiento, en un doble sentido, hacia la izquierda, lo que denota un aumento de los tejidos, y hacia abajo, por un aumento del componente hídrico.

DISCUSIÓN

Los hallazgos más importantes del presente estudio radican principalmente en que diversas variables de la CC, estimadas por BIA o por técnicas antropométricas, cambian de forma significativa después del periodo de DT, fundamentalmente en lo

Tabla II. Características antropométricas básicas y de composición corporal del grupo experimental (GE) en fase de entrenamiento (ENT) *vs.* desentrenamiento (DT) y del grupo control (GC)

Variables		GE (n = 43)					GC (n = 10)				
		ENT		DT			CON1		CON2		
		Media	DT	Media	DT	p	Media	DT	Media	DT	p
Edad	años	14,11	± 1,1	14,12	± 1,07	ns	14,05	± 1,08	14,05	± 1,08	ns
Peso	(kg)	55,99	± 8,7	56,56	± 8,42	ns	60,69	± 5,7	59,5	± 6,72	ns
Talla	(kg)	166,5	± 6,3	167,6	± 5,89	*	171,3	± 4,8	171	± 5,03	ns
Antropometría											
MG	(kg)	8,63	± 3,26	8,95	± 3,16	*					
MME	(kg)	21,2	± 2,49	21,22	± 2,83	ns					
ACT	(kg)	35,52	± 5,2	36,75	± 4,89	*	38,63	± 5,6	36,3	± 4,78	ns
ACT	(%)	62,25	± 3,3	65,31	± 3,38	*	60,24	± 4,2	60,9	± 3,45	ns
AEC	(kg)	14,19	± 1,8	14,76	± 1,63	*	15,75	± 1,9	15	± 1,76	ns
AIC	(kg)	21,47	± 3,7	21,99	± 3,39	*	22,88	± 3,7	19,4	± 3,88	ns
AEC/ACT		0,4	± 0,02	0,4	± 0,02	ns	0,41	± 0,01	0,42	± 0,01	ns
AIC/ACT		0,6	± 0,02	0,6	± 0,02	ns	0,59	± 0,01	0,53	± 0,07	ns

$p < 0,05$ para el t-test de muestras emparejadas para las diferencias entre ENT y DT. MG: masa grasa; MME: masa muscular esquelética; ACT: agua corporal total; AEC: agua extracelular; AIC: agua intracelular; ns: no significativo.

Tabla III. Modificaciones de la composición corporal por BIA y antropometría en el grupo experimental

Variables		ENT		DT		p
		Media	DE	Media	DE	
Bioimpedancia						
Impedancia	Ω	545,51	± 57	514,98	± 51	**
Resistencia	Ω	532,94	± 61,4	502,19	± 52,7	**
Reactancia	Ω	117,45	± 20,7	112,66	± 21,6	ns
Angulo de Fase		12,61	± 2,81	12,76	± 2,9	ns
Antropometría						
Masa grasa	kg	8,63	± 3,26	8,95	± 3,16	*
Masa musc. Esquelética	kg	21,2	± 2,49	21,22	± 2,83	ns

**p < 0,01; **p < 0,001 para el t-test de muestras emparejadas para las diferencias entre ENT y DT; ns: no significativo.*

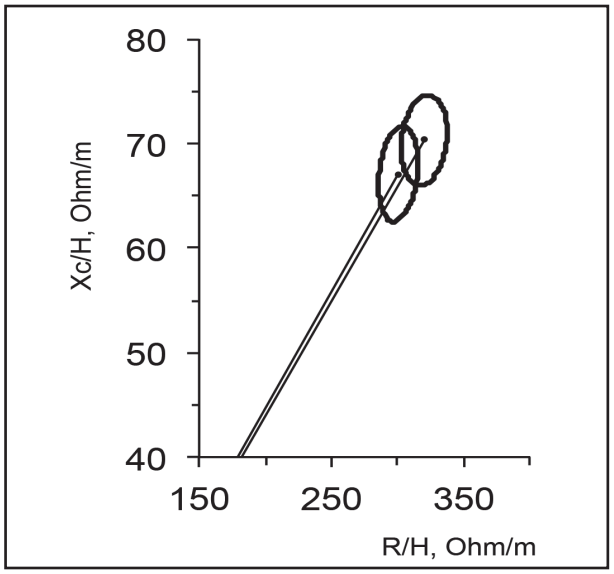

Figura 1.

Gráfico RXc de la migración del vector de impedancia tras el desentrenamiento en el grupo Experimental. Vector derecho: ENT; Vector izquierdo: DT. Elipses corresponden al 95% IC.

que respecta al compartimento de la hidratación. Una fortaleza a destacar de este estudio es que los resultados han sido obtenidos en el momento en el cual los sujetos del GE se sometieron al descanso natural de la temporada competitiva, en el llamado periodo de transición y/o de descanso de seis semanas, considerado como el periodo clásico de desentrenamiento y no un protocolo artificial, por lo que constituyen datos descriptivos poco comunes en jóvenes futbolistas adolescentes (29,30) y, como tales, datos que probablemente se repitan cada temporada.

Datos complementarios de este estudio confirman que el GE, tras el periodo de DT, ha sufrido una serie de cambios a nivel de diversas variables fisiológicas consideradas importantes para el rendimiento aeróbico-anaeróbico, como son el consumo de oxígeno, que descendió entre el 21 y el 26%, en los puntos correspondientes al umbral aeróbico, en el punto de compensación respiratoria (PCR) y en el máximo consumo de oxígeno, así como disminuciones de las velocidades, del 7% tanto en el umbral aeróbico como en el PCR, entre otras desadaptaciones del ámbito cardiorrespiratorio (31). Se confirma de esta manera que durante esas seis semanas ha existido un deterioro del rendimiento físico debido al periodo de DT.

En este trabajo se destaca que el periodo de DT produce una recuperación de todos los compartimentos acuosos, tanto en los términos absolutos del ACT como de los compartimentos intra y extracelular. Con respecto a los cambios en los compartimentos hídricos, la literatura sugiere que estos pueden estar afectados por la adiposidad corporal total (16). Al verificarse la existencia de cambios significativos de la MG tras el DT, se exploró la posible relación con correlaciones parciales. Sin embargo, los cambios de la MG no se correlacionaron con los cambios del ACT ($r = 0,18$; $p = 0,32$; IC 95%: -0,17 a 0,49), por lo cual, se podría afirmar que los cambios del ACT con el periodo de desentrenamiento no estuvieron influenciados por los cambios de la MG.

Con respecto a los diferentes ratios de los compartimentos hídricos intra y extracelular, no se han encontrado trabajos en la literatura que comprueben dichos cambios tras un periodo de desentrenamiento. Sin embargo, nuestros datos confirman evidencias de la literatura que sugieren que los sujetos más hidratados intracelularmente muestran rendimientos en el salto y la velocidad mayores que aquellos que presentan una menor fracción o ratio de AIC (11). En nuestro GE durante el momento ENT (0,6 ± 0,02) se observó una diferencia significativa con respecto al GC (0,59 ± 0,01) (Tabla I); por otro lado, aunque la reducción del ratio de AIC no fue significativa entre los momentos ENT (0,6 ± 0,02) *vs.* DT (0,597 ± 0,02) (Tabla II), la diferencia con el GC en el momento DT dejó de ser significativa y los valores se aproximaron 0,597.

En jóvenes atletas adolescentes de diversas modalidades, se ha confirmado que existe una relación entre las horas de entrenamiento y las modificaciones moleculares (ACT) y celulares (masa libre de grasa y masa ósea) en el grupo que practicaba más de nueve horas de entrenamiento en relación a los practicantes de menos de nueve horas, y, por tanto, parece ser que las personas que entrenan más desarrollan un estatus celular y molecular de composición corporal más favorable (32).

Los cambios significativos del porcentaje de grasa corporal total tras el DT están en concordancia con los datos aportados por otros autores en diversas modalidades deportivas y tras periodos de DT (3,4,6,9,14). El ligerísimo aumento no significativo de la MME podría ser debido a la asociación del ACT con la masa muscular y sus componentes tanto extra como intracelular que se observa tras el DT, habiéndose descrito modelos de regresión múltiple de los cambios del peso corporal a través de cambios del AEC que explicarían un 55% de la varianza en el cambio del peso corporal (13). La migración del vector de impedancia eléctrica (19,26) indica una doble dirección: hacia abajo y hacia la izquierda, lo cual denota un aumento del líquido corporal o rehidratación y un aumento de la masa grasa, que está en consonancia con los resultados encontrados en nuestras pruebas antropométricas y con la literatura (5). El análisis del vector de impedancia es considerado una buena herramienta para detectar cambios en la hidratación ya que no depende del peso del sujeto y permite la visualización gráfica de cambios tanto de la hidratación como de la masa celular activa (19,26,33,34).

En los estudios longitudinales de CC, los métodos utilizados no siempre poseen una buena sensibilidad para detectar cambios, pues pueden realizar estimaciones cuantitativas de la MG y la MLG diferentes y que dependen fundamentalmente de la ecuación utilizada y la validez de las mismas en relación a la población de estudio (22), afectando sobre todo a las mediciones longitudinales. La determinación de la MG y la MLG y la distribución de los fluidos corporales son importantes para observar los efectos funcionales, tanto de periodos de entrenamiento como de desentrenamiento (9,12). Nuestros resultados confirman este paradigma, pues se constataron resultados diferentes. Así pues, los cambios más significativos tras el DT parecen encontrarse con las variables que se obtienen de la BIA, siendo los de la antropometría menos sensibles. Esto puede indicar que la antropometría no es un método tan bueno para controlar los cambios de la densidad de la masa libre de grasa como lo es para estimar la densidad corporal total.

Con respecto al control de los cambios hídricos, la BIA sí parece ser un método más sensible a los cambios en los fluidos corporales. Además, es el único método de campo disponible para este efecto; sin embargo, los cambios agudos asociados a las sesiones de entrenamiento reportados en la literatura (29,30) no han sido siempre confirmados con los resultados de impedancia y/o resistencia corporal, así como las fracciones del ACT tras sesiones de entrenamiento (17). No obstante, en otro estudio, en el cual se analizó el efecto sobre los fluidos corporales de una sesión de entrenamiento de remo de resistencia de larga duración de más de dos horas y a una intensidad del 75% del umbral anaeróbico, sí se encontraron disminuciones significativas del agua corporal total y del agua extracelular a los 30, 60 y 120 minutos tras el ejercicio y con respecto al momento previo y posterior al ejercicio (35). Esto parece indicar que es necesario un periodo más amplio de entrenamiento y recuperación para poder comprobar cambios significativos en este compartimento. Los cambios detectados mediante la BIA (aumento del ACT) parecen ser válidos a juzgar por lo ocurrido en el periodo entre ENT y DT.

Un estudio de LaForgia no detectó cambios en la CC tras solo tres semanas de DT, lo cual está en contraposición con nuestros resultados, tanto con el método antropométrico como con el de BIA, que sí detectó cambios significativos con el desentrenamiento (14). El origen de esta diferencia de resultados puede radicar en el hecho de que nuestro periodo de DT fue el doble que el de este estudio, lo cual puede sugerir un efecto de dosis-respuesta (entendiendo dosis como el tiempo de DT), más que un efecto inmediato que actúe en horas o días.

Cabría destacar finalmente que la limitación principal de este estudio es que ha sido realizado con un número limitado de sujetos y en jóvenes en fase de crecimiento y maduración, y los datos deberían ser corroborados en sujetos con diferentes edades y estadios de maduración. Además, las evaluaciones repetidas en diferentes momentos del DT podrían ayudar a encontrar tiempos medios de desadaptación al entrenamiento.

CONCLUSIONES

Se confirmaría que tras el periodo de DT existen cambios de componentes moleculares, tanto del ACT como de sus compartimentos extra e intracelular, y que estos son recuperados tras el periodo de inactividad o desentrenamiento de seis semanas, sin modificación de las proporciones de agua extracelular e intracelular con el agua corporal total y sin verse afectados por los cambios en la grasa corporal. No todos los métodos de campo utilizados en la estimación de la CC son sensibles de igual manera a los cambios tras periodos de entrenamiento o desentrenamiento.

AGRADECIMIENTOS

El análisis de los vectores de impedancia ha sido posible por las orientaciones y la utilización del BIVA software (2002) del profesor Piccoli, de la Universidad de Padova (Padova, Italia), disponible en apiccoli@unipd.it.

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Nutrición Hospitalaria

Trabajo Original

Epidemiología y dietética

Grado de malnutrición y su relación con los principales factores estructurales y alimentarios de la población preescolar hondureña. Prevalencia de la lactancia materna en los mismos

Degree of malnutrition and its relationship with major structural and eating factors in Honduran preschool population. Prevalence of breastfeeding

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Resumen

Introducción: la desnutrición infantil sigue siendo un grave problema de salud pública en Honduras, con una prevalencia nacional según valores de referencia de la Organización Mundial de la Salud (OMS) del 29% en niños menores de cinco años. Además, el promedio de desnutrición crónica en la región asciende hasta el 80% en comunidades pobres e indígenas, convirtiendo a Honduras en el segundo país en la región centroamericana con mayor incidencia de desnutrición crónica. Otro de los problemas que presenta la región resulta del abandono precoz de la lactancia materna exclusiva: solo el 29,7% de los menores fue alimentado exclusivamente con leche materna hasta los seis meses. Por ello, el estudio busca conocer, identificar y cuantificar la situación con factores determinantes y brindar información para el diseño de políticas públicas.

Material y método: el estudio consistió en una evaluación antropométrica descriptiva transversal en la que se analizó el estado nutricional y la prevalencia de malnutrición en 141 niños con edades comprendidas entre los seis meses y los cinco años, pertenecientes a regiones urbanas y rurales del país, así como la valoración de la prevalencia de la lactancia materna en cinco departamentos hondureños (Intibucá, Lempira, Atlántida, Olancho y Francisco Morazán).

Resultados y conclusión: al analizar por departamentos observamos diferencias en el estado nutricional y de lactancia según fuese un área urbana o rural, siendo esta última el doble en el caso de la desnutrición crónica y la desnutrición global, con porcentajes del 14,6% en áreas urbanas frente a 28,8% áreas rurales, y el 4,6% en áreas urbanas frente al 9% en áreas rurales, respectivamente. Sin embargo, en cuanto a la desnutrición aguda y el sobrepeso en ambas regiones se observaron valores afines, por encima del 1,1% para la desnutrición aguda y del 14% para el sobrepeso. En relación con la lactancia materna exclusiva durante seis meses, los departamentos de Lempira y Olancho mostraron una duración de la misma hasta los dos años, con una distribución porcentual del 80% y el 48%, respectivamente. Es importante destacar que un 36% de las madres no proporcionaron lactancia, destacando como la tasa más elevada un 15% en el departamento de Francisco Morazán.

Palabras clave:

Honduras.
Desnutrición infantil.
Lactancia maternal.

Abstract

Introduction: Child malnutrition remains a serious public health problem in Honduras, with a national prevalence according to the World Health Organization (WHO) reference values of 29% in children under five. In addition, the average chronic malnutrition in the region amounts to 80% in poor and indigenous communities, making Honduras the second country in Central America with the highest incidence of chronic malnutrition. Another problem of the region is the early cessation of exclusive breastfeeding: only 29.7% of children were exclusively breastfed until they were six months. Therefore, the study seeks to understand, identify and quantify the situation determinants and provide information for the design of public policies.

Material and method: The study consisted of a cross-sectional descriptive anthropometric assessment in which the nutritional status and the prevalence of undernourishment, malnutrition and malnutrition in 141 children aged between six months and five years, belonging to urban and rural regions of the country, were analyzed, as well as assessing the prevalence of breastfeeding in five Honduran departments (Intibucá, Lempira, Atlántida, Olancho and Francisco Morazán).

Results and conclusion: When making the analysis by departments, differences regarding nutritional status and breastfeeding were observed between urban and rural areas, the latter being doubled in the case of chronic malnutrition and underweight, with percentages of 14.6% in urban areas *versus* 28.8% in rural areas, and 4.6% in urban areas compared to 9% in rural areas, respectively. However, with respect to acute malnutrition and overweight in both regions, similar values were observed, above 1.1% for acute and 14% for overweight malnutrition. In relation to exclusive breastfeeding for six months, the departments of Olancho and Lempira maintained it for two years, with a percentage distribution of 80% and 48%, respectively. It must be noted that 36% of mothers did not provide breastfeeding, with the highest rate (15%) in the department of Francisco Morazán.

Key words:

Honduras. Child malnutrition. Breastfeeding.

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INTRODUCCIÓN

Centroamérica presenta un porcentaje de personas desnutridas de un 6% por encima de la media de América Latina y el Caribe (14,2% frente al 9%) y constituye una de las zonas más vulnerables en cuanto a insuficiencia permanente de alimentos en cantidad y calidad adecuada para satisfacer las necesidades energéticas de la población, es decir, en cuanto a subnutrición dentro del continente americano (1).

En concreto, Honduras presenta una tasa de desnutrición en la infancia más elevada que otros países de la misma región y grupo de ingresos (2). Concretamente, la prevalencia de desnutrición crónica, es decir, el retraso en el desarrollo pondoestatural, entre los niños hondureños menores de cinco años es del 23% (3). Además, se aprecian disparidades regionales y socioeconómicas en el estado nutricional de la infancia: así, en un tercio de las regiones de Honduras, el 50% de los niños padece retardo en el crecimiento, siendo los niños pertenecientes a las zonas rurales los que presentan mayor riesgo de crecimiento deficitario, con una incidencia superior en un 3% sobre el valor anterior, frente a aquellos que viven en el entorno urbano (4). Asimismo, se observa que el retraso en el crecimiento se ve incrementado en un 48% en aquellos hogares sin formación académica y en un 42% en los hogares más pobres (3). En la actualidad, se evidencia un proceso de déficit alimentario crónico en niños menores de cinco años derivado de una sucesión de deterioros, tales como la desnutrición proteico energética, y un déficit de micronutrientes como las vitaminas A y B_9 y los minerales hierro (Fe) y zinc (Zn), que continúan siendo persistentes y que son un problema de salud pública, al que hay que añadir, paradójicamente, nuevas enfermedades asociadas a la malnutrición como la obesidad (5).

De acuerdo con los nuevos estándares de medición aprobados por la OMS en 2006, el concepto de desnutrición se divide fundamentalmente en tres tipos basados en la relación de las variables talla (T), edad (E), altura (A) y peso (P), siendo la desnutrición crónica la relación entre talla y edad (T/E); la desnutrición aguda, entre peso y talla (P/T); y la desnutrición global, entre peso y edad (P/E). Al aplicar estos criterios en la población infantil hondureña menor de cinco años se observó un retardo de altura para la edad, es decir, una tasa de desnutrición crónica del 11,7% en niños menores de 12 meses, y que se ve aumentada entre los 24 y 35 meses de edad, alcanzando el 29,7% (6). La situación más acusada se localiza entre las áreas rurales (Intibucá, Lempira, Copan, Ocotepeque y Santa Bárbara, predominantemente indígenas del suroeste) y en el corredor seco en el sur de Choluteca, Valle, La Paz y el sur de Francisco Morazán (7). Este retraso se asocia normalmente a situaciones de pobreza, a dificultades de aprendizaje y a menores ingresos económicos (8).

A diferencia de la desnutrición crónica, el porcentaje de desnutrición aguda, al que hace referencia la deficiencia de peso por altura, tiende a aumentar con la edad (9). Entre los niños hondureños menores de cinco años, el 1% sufre de desnutrición aguda y son demasiado delgados para su estatura (3). Ciertos estudios relacionan este tipo de desnutrición con pérdidas de peso asociadas a periodos recientes de hambruna o enfermedad que se desarrollan muy rápidamente y son limitados en el tiempo (10).

Finalmente, la desnutrición global, que se refiere a la deficiencia de peso por edad, o la también llamada insuficiencia ponderal (11), es el índice utilizado para seguir la evolución nutricional de niños y niñas y el indicador utilizado para el seguimiento de los Objetivos de Desarrollo de Milenio (ODM). En Honduras, las cifras más recientes (2012-2013) indican valores medios de desnutrición global (DG) del 7,9% y, como en los casos anteriores, los valores difieren según sea una zona urbana, en la que la DG alcanza el 4,6%, o rural, con un 9%, donde, además, el 5% de los niños presenta sobrepeso (3).

La subnutrición de esta población, sobre todo en la primera etapa de la vida, puede ser paliada por la lactancia materna, que juega un papel fundamental en la salud del lactante. La lactancia fue propuesta como recomendable en mayo de 2001 en la Asamblea Mundial de la Salud (OMS Ginebra), en la que se exhortó a promover la lactancia materna exclusiva durante los seis primeros meses del lactante como una recomendación mundial de salud pública (12). Sin embargo, en la actualidad en Honduras solo el 31% de los niños menores de seis meses recibe lactancia materna exclusiva, y el 71% pasa a recibir una alimentación complementaria entre los seis y los nueve meses (3).

Con todo lo expuesto hasta ahora, en el presente trabajo se planteó como objetivo conocer el estado actual de los distintos tipos de nutrición (crónica, aguda y global), determinar y correlacionar los principales factores estructurales que condicionan el estado nutricional de niños y niñas menores de cinco años, así como identificar las principales pautas en materia de lactancia materna y alimentación complementaria en niños menores de 24 meses residentes en áreas urbanas frente a las zonas rurales en los departamentos hondureños de Intibucá, Lempira, Olancho, Francisco Morazán y Atlántida.

MATERIAL Y MÉTODOS

TIPO DE ESTUDIO NUTRICIONAL

La investigación fue de tipo no experimental descriptivo transversal y correlacional, debido a que buscábamos la prevalencia de una exposición y/o resultado en una población definida en un punto específico de tiempo. El estudio fue aprobado por un comité de expertos de la Universidad de Murcia. Se seleccionó una muestra de conveniencia de 141 individuos de edades comprendidas entre seis meses y cinco años como edad límite de inclusión en el estudio. El trabajo se realizó en cinco de los 18 departamentos más representativos por región de la población hondureña (Francisco Morazán, Atlántida, Olancho, Intibucá y Lempira) previo consentimiento informado de las madres. Se empleó para el estudio un cuestionario que incluía edad en meses, sexo, lugar de residencia y duración del periodo lácteo, y un cuestionario sobre la alimentación complementaria (cereales, frutas, verduras, legumbres y hortalizas, carnes y pescados, huevo, leche de fórmula). Las encuestas y los cuestionarios los realizaron docen-

tes y alumnos de la Universidad Pedagógica Nacional Francisco Morazán (UPNFM) de Tegucigalpa (Honduras) a las madres o los responsables de los menores. La técnica de muestreo fue estratificada y bietápica, ya que la población seleccionada se dividió en conglomerados por localización como unidades primarias, y cada una de estas unidades primarias fue dividida en nuevas unidades llamadas secundarias (rural o urbano). El elemento seleccionado en cada estrato fue aleatorio en centros de salud y hospitales.

CONSIDERACIONES ÉTICAS

El estudio se llevó a cabo siguiendo las normas deontológicas reconocidas por la Declaración de Helsinki (revisión de Corea, octubre 2008) y las recomendaciones de Buena Práctica Clínica de la CEE (documento 111/3976/88 de julio de 1991). Antes del comienzo del estudio, se explicó detalladamente el mismo y se solicitó conformidad previa por escrito por parte de cada padre/madre o tutor legal del preescolar. Se obtuvo el visto bueno del comité de ética de los diferentes centros de salud y hospitales.

EVALUACIÓN DEL ESTADO NUTRICIONAL Y DE LA COMPOSICIÓN CORPORAL MEDIANTE CUMPLIMENTACIÓN DE CUESTIONARIOS Y TOMA DE MEDICIONES ANTROPOMÉTRICAS

Siguiendo los nuevos estándares de crecimiento de la OMS (2006) (13) para niños menores de cinco años, los puntajes Z de peso para la edad (P/E), talla para la edad (T/E) y peso para la talla (P/T) se calcularon con el software WHO Anthro 2005 (14). La talla del niño fue tomada en posición de decúbito supino usando un tallímetro de madera con soporte en la cabeza y una base móvil que se frena con el contacto de los pies. La medición fue realizada por uno de los investigadores y por dos auxiliares de enfermería previamente entrenadas. Se tomaron tres medidas en la totalidad de los niños, y se utilizó su promedio para el cálculo de los puntajes Z (14). El pesado del niño se realizó con una balanza pediátrica de plato hasta los dos años (16 kg/500 g), y con una digital de los dos hasta los cinco años. Las mismas balanzas fueron utilizadas en todos los niños y calibradas antes de cada toma. Los niños fueron pesados completamente desnudos en tres ocasiones (15). El promedio de las tres medidas se utilizó para los análisis. La talla y el peso fueron transformados a puntajes Z según la población de referencia del año 1978 de la OMS (14). El estado nutricional se clasificó como la relación entre los diferentes índices peso/talla (P/T) y talla/edad (T/E), y los valores se clasificaron según percentiles y/o puntuación Z. Además, para clasificar la sobrenutrición y obesidad se empleó el índice de masa muscular para la edad (IMC) y el índice de peso para la longitud/talla (PL/T) mediante percentiles y puntuación Z, según las categorías indicadas a continuación:

- Bajo peso < P15 y > P3 (Z P/E menor o igual a -2 desviaciones estándar [DE]).
- Bajo peso severo (Z P/E menor o igual a -3 DE).
- Emaciación (Z P/T o Z IMC/E menor o igual a -2 DE).
- Emaciación severa (P/T menor o igual a -3 Z).
- Talla alta (Z T/E mayor o igual a +2 DE).
- Talla baja (Z T/E mayor o igual a -2 DE).
- Talla baja severa (Z T/E, cuando la talla para la edad es menor o igual a -3 Z).
- Posible riesgo sobrepeso (un punto por encima de +1 muestra un posible riesgo. Una tendencia hacia la línea de puntuación Z 2 muestra un riesgo definitivo).
- Sobrepeso > P85 y < P97 (Z P/T o Z IMC/E mayor o igual a +1 DE).
- Obesidad > P97 (Z P/T o Z IMC/ mayor o igual a +2 DE).

La normalidad fue considerada entre P15-P85 (Z-1,99 y +0,99 DE) para todos los indicadores excepto para la talla (normalidad T/E entre -1,99 DE y +1,99 DE). Las medianas fueron comparadas con la mediana del estándar OMS 2006 (15).

ENTREVISTA DE LAS MADRES

Se llevó a cabo una entrevista personalizada, previo consentimiento informado, a 141 madres reclutadas en hospitales y centros de salud de cinco departamentos hondureños: Hospital de Área en Gracias (Lempira), Centro de Salud Luis Alonso Suazo, Hospital Regional Atlántida, Hospital Dr. Enrique Aguilar Cerrato de la Esperanza (Intibucá) y Hospital Regional San Francisco (Olancho). El cuestionario fue elaborado a partir de distintos modelos de encuestas dietéticas, como cuestionarios de frecuencia de consumo de alimentos (CFCA), que se apoyaron con fotografías de raciones de los alimentos para calcular el tamaño de la ración ingerida, y cuestionarios generales con respecto a actitudes sobre la dieta, actividad física, datos sociodemográficos y antecedentes personales de enfermedad y de salud percibida. El cuestionario era pre-codificado y compuesto por preguntas abiertas y cerradas que incluían variables de tipo demográfico, socioeconómico, ambiental, epidemiológico, clínico, patrones alimentarios para niños menores de cinco años y prevalencia de lactancia materna (16). El cuestionario fue confeccionado para obtener una visión más amplia sobre las condiciones de vida de los niños menores de cinco años y sus madres con el principal objetivo de completar la información obtenida y excluir de la muestra a quienes se encontraran en alguna situación particular que pudiera influir directamente sobre los resultados en las pruebas. Teniendo en cuenta la uniformidad de los procedimientos de campo por parte de los entrevistadores, fue creado un manual (17) con normas y conceptos para el cumplimiento del cuestionario.

ANÁLISIS ESTADÍSTICO

Se tomó una muestra probabilística por conglomerados de distancia re-escalados y estratificada, constituida por 141 niños de seis meses a cinco años residentes en el área urbana y rural de Honduras, para analizar el estado nutricional y la prevalencia de subnutrición, malnutrición y desnutrición de esta población.

La muestra se calculó con un error de estimación del 6% y una pérdida del 10%. El marco de muestreo se conformó a partir de los registros de los niños que asisten a los diferentes centros de salud y hospitales oficiales comunitarios de la zona urbana y rural de cada municipio. Los datos fueron tratados mediante un análisis de componentes principales para las diferentes variables. La medida de adecuación muestral basada en el Kaiser, Meyer y Olkin (KMO) fue de 0,674 y el nivel de significación para la prueba de esfericidad de Bartlett fue inferior a 0,05, es decir, es significativo. El porcentaje de la varianza explicada fue del 72,9%. Todos los análisis estadísticos fueron analizados con el paquete estadístico SPSS versión 15.0 (SPSS Inc., Chicago, IL, Estados Unidos).

RESULTADOS

De los 141 preescolares de ambos sexos de entre seis meses y cinco años reclutados, los grupos de edad referentes a la población infantil total del estudio se repartieron de una forma proporcional de acuerdo con su edad. El 37% (52 niños) se ubicó en el grupo de edad de 0-12 meses, seguido de las edades de 13-35 meses, con el 35% (49 niños), y de tres a cinco años, con el 28% (40 niños). En todos los departamentos la proporción de población infantil reclutada de ambos sexos fue equilibrada, salvo en el departamento de Francisco Morazán, con una mayor prevalencia de niños (63%) en el grupo de 0-12 meses. De media por grupo de departamento el número de niños estudiado fue de 29.

DESNUTRICIÓN CRÓNICA

La tabla I muestra el promedio de las variables antropométricas analizadas para el índice de longitud/talla en la detección de la prevalencia de la desnutrición crónica. En los grupos de edad de entre uno y cinco años, el cálculo de Z se efectuó con el software de la OMS Anthro. La puntuación Z indica la distancia que hay entre una medición y la media de la población de referencia. De acuerdo con los resultados obtenidos en los niños menores de cinco años, un 80% de la muestra se ubicaba dentro del criterio normal, con valores de normalidad entre -1,99 DE y +1,99 DE. Estos límites definen el 95% central de la distribución de referencia como intervalo de los valores de normalidad tanto en la zona urbana como en la zona rural. Se presenta un 12% de baja talla para la edad (Z T/E por debajo de -2 DE) en la zona urbana y un 13% de baja talla severa (Z T/E menor de -3 Z) en niños de procedencia rural, especialmente en los departamentos de Intibucá y Lempira, lo que permite identificar en esta zona del país una mayor prevalencia de niños con retardo en el crecimiento debido a un aporte insuficiente de nutrientes prolongado en el tiempo o a una mayor incidencia de enfermedades recurrentes. En los criterios para el procesamiento y el análisis de la información en todos los casos, la edad de los niños se marcó como semanas cumplidas desde el nacimiento hasta los tres meses de edad, como meses cumplidos de tres a 12 meses, y posteriormente como años y meses cumplidos.

DESNUTRICIÓN GLOBAL

Los resultados obtenidos en la tabla II están relacionados con el P/E de los niños menores de cinco años. En ella se muestra que un 98% los niños de procedencia urbana y un 89% de procedencia rural se encuentran dentro del criterio normal con valores Z y de percentiles iguales a P15-P85 (Z-1,99 y +0,99 DE). La prevalencia de bajo peso fue de un 6% (Z P/E por debajo de -2 DE) y la prevalencia de bajo peso severo fue de un 5% (Z

Tabla I. Distribución porcentual de la longitud/talla para edades en niños menores de cinco años en cinco departamentos. Los datos analizados son expresados como la media (n = 3)

Área	Departamento	Normal	Baja talla	Baja talla severa
Urbana	Olancho	81%	13%	6%
	Intibucá	92%	0%	8%
	Lempira	73%	27%	0%
	Atlántida	80%	13%	7%
	Fco. Morazán	77%	8%	15%
	Promedio	80%	12%	7%
Rural	Olancho	89%	0%	11%
	Intibucá	69%	6%	25%
	Lempira	68%	11%	21%
	Atlántida	94%	0%	6%
	Fco. Morazán	93%	7%	0%
	Promedio	83%	5%	13%

Tabla II. Distribución porcentual de la peso para la edad en niños menores de cinco años en cinco departamentos. Los datos analizados son expresados como la media (n = 3)

Área	Departamento	Normal	Baja peso	Baja peso severa
Urbana	Olancho	100%	0%	0%
	Intibucá	92%	8%	0%
	Lempira	100%	0%	0%
	Atlántida	100%	0%	0%
	Fco. Morazán	100%	0%	0%
	Promedio	98%	2%	0%
Rural	Olancho	89%	11%	0%
	Intibucá	81%	6%	13%
	Lempira	79%	11%	11%
	Atlántida	99%	0%	0%
	Fco. Morazán	99%	0%	0%
	Promedio	89%	6%	5%

P/E por debajo de -3 DE) para los niños de procedencia rural, especialmente en los departamentos de Intibucá y Lempira. De esta forma, la región occidental del país se muestra como la que mayores diferencias significativas en prevalencia de desnutrición presenta con respecto al resto de departamentos y como la región más afectada en materia de desnutrición, ya que las evaluaciones transversales del estado nutricional que incluyeron más índices determinaron una mayor incidencia de desnutrición crónica especialmente en estos departamentos del país.

En la figura 1 se muestra el análisis de conglomerados o clúster que utiliza una vinculación media con respecto a la información reclutada mediante el instrumento elaborado a partir de distintos modelos de encuestas nutricionales, pre-codificado, de acuerdo a las variables, índices e indicadores reclutados durante el estudio se midió la similitud entre ellas; al tipo grado de formación de los padres, departamento al que pertenecen los niños, época de nacimiento del niño lluviosa o seca, acceso a alimentos de los padres, patologías de los niños, región en la que residen urbana o rural y grado de desnutrición global. Los resultados evidencian dos subcategorías: una en la que se relaciona el estado de desnutrición global del niño hondureño con la época de nacimiento del lactante, apreciándose una mayor incidencia de desnutrición global y patologías de índole respiratorias entre aquellos niños nacidos en la época lluviosa frente a la seca, y otra subcategoría en la cual la interacción entre las variables mostró un menor efecto asociado con la desnutrición global en relación a la formación de los padres, el área urbana o rural, la región de origen del niño y el acceso a alimentos, ya que en prácticamente todo el país la disponibilidad de alimentos para lactantes era la misma.

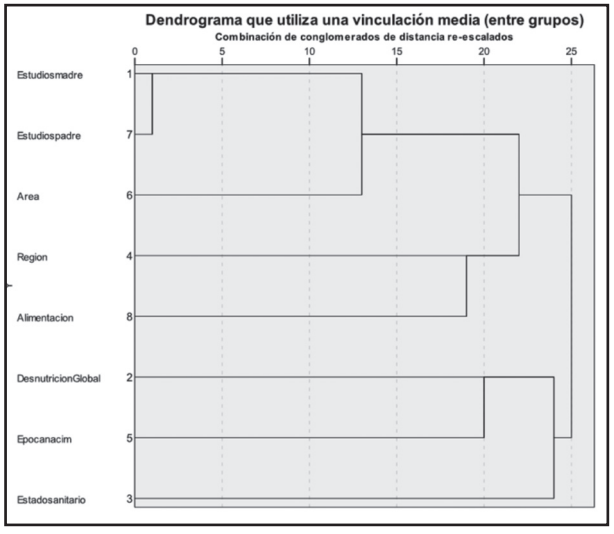

Figura 1.

Análisis de conglomerado o clúster que utiliza una vinculación media con respecto a la información reclutada mediante el instrumento elaborado a partir de distintos modelos de encuestas nutricionales, pre-codificado.

En general, los valores obtenidos para determinar la desnutrición aguda (peso en relación con longitud/talla) se encuentran dentro de la normalidad en más de un 50% de la población estudiada. Sin embargo, en los criterios de sobrepeso y posible riesgo de sobrepeso, en ambas regiones se observan valores superiores al 14%. Se interpreta que un 9% de los niños de las muestras corresponde al criterio de obeso (18% en Lempira y 15% en Francisco Morazán). De acuerdo con los resultados expuestos en la tabla III, la prevalencia de sobrepeso y de emaciación se ve reflejada en el estado nutricional actual de los niños hondureños mediante el peso en relación a la longitud/talla, un índice que posibilita la detección de la emaciación o el sobrepeso**.** Los criterios de emaciado se observan solo en la región rural de Lempira e Intibucá (Tabla III).

Los valores obtenidos para determinar el índice de masa corporal para la edad (Tabla III) en las muestras analizadas se encontraban dentro de los considerados normales (normalidad T/E entre -1,99 DE y +1,99 DE) en más de un 50% de los niños.

Tabla III. Distribución porcentual de la peso para la longitud/talla en niños menores de cinco años en cinco departamentos

Área	Departamento	Normal	Sobrepeso	Posible riesgo sobrepeso	Obeso	Emaciado	Sev. emaciado
Urbana	Olancho	75%	13%	6%	0%	0%	0%
	Intibucá	42%	17%	33%	0%	8%	0%
	Lempira	55%	18%	9%	18%	0%	0%
	Atlántida	53%	7%	20%	13%	7%	0%
	Fco. Morazán	54%	15%	15%	15%	0%	0%
	Promedio	56%	14%	17%	9%	3%	0%
Rural	Olancho	67%	11%	22%	0%	0%	0%
	Intibucá	50%	19%	19%	6%	0%	6%
	Lempira	74%	5%	11%	5%	0%	5%
	Atlántida	69%	31%	0%	0%	0%	0%
	Fco. Morazán	71%	7%	21%	0%	0%	0%
	Promedio	66%	15%	14%	2%	0%	2%

Sin embargo, en los criterios de sobrepeso (Z P/T o Z IMC/E por encima de +1 DE) y posible riesgo de sobrepeso (1 punto por encima de +1 muestra un posible riesgo. DE. una tendencia hacia la línea de puntuación Z 2 muestra un riesgo definitivo.) En las regiones urbana y rural se observaron valores similares, siendo estos superiores al 14%. En base a lo anterior, se observa que un 9% de los niños en la región urbana de la muestra se ajustan al criterio de obeso (Z P/T o Z IMC/E por encima de +2 DE), destacando dos departamentos frente al resto (18% en Lempira y 15% en Francisco Morazán), mientras que en la zona rural el promedio alcanzó apenas un 2%. Los criterios de emaciado (Z P/T o Z IMC/E por debajo de -2 DE) estudiados en ambas regiones, urbana y rural, determinaron que un 3% de los casos analizados la sufrían especialmente en los departamentos de Intibucá, Lempira y Atlántida. Finalmente, se observaron algunos casos concordantes con el criterio de severamente emaciado (P/T está por debajo de -3 Z) principalmente localizados en la región rural de Lempira e Intibucá.

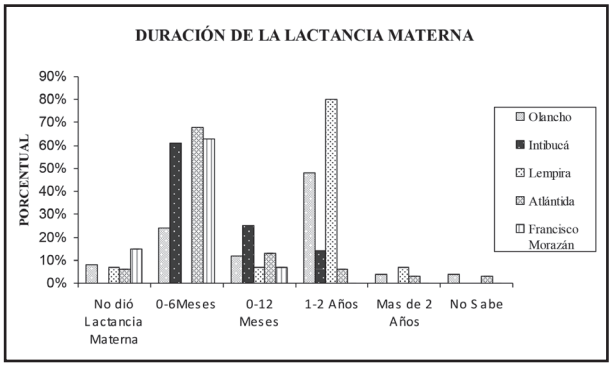

Figura 2.

Distribución porcentual de la duración de la lactancia materna en cinco departamentos.

PAUTAS DE LACTANCIA MATERNA

El promedio de las madres que participaron en el estudio y estaban dando lactancia, o bien habían dado lactancia en algún momento durante el periodo lácteo, era del 94%, con el porcentaje más bajo en el departamento de Francisco Morazán. Respecto a la distribución porcentual de la lactancia materna, en los cinco departamentos se observa que los distritos con mayores porcentajes en la prevalencia de lactancia materna durante los primeros seis meses de vida son Atlántida, Francisco Morazán e Intibucá, con un 68%, 63% y 61% respectivamente (Fig. 2). En el departamento de Lempira se observa que se extiende la lactancia materna, en el 80% de los casos, durante un periodo de tiempo mayor (1-2 años). La lactancia materna como único alimento durante los seis primeros meses en Honduras alcanza a un 43% de los niños.

DISCUSIÓN

En Honduras, la población infantil actual de entre 0 y 5 años representa el 28,3% de la población infantil total. Los resultados más destacados de este estudio muestran una disminución en la prevalencia de la desnutrición infantil en los niños menores de cinco años hondureños desde 2005, a la vez que pone de manifiesto un incremento de las tasas de sobrepeso y obesidad en este grupo de población. En relación a los valores promedio de los diferentes índices empleados en la evaluación del estado nutricional de los niños menores de cinco años en los departamentos de Olancho, Intibucá, Lempira, Francisco Morazán y Atlántida,

encontramos que el promedio de niños que padecen desnutrición crónica (DC) también ha manifestado una tendencia a la baja en la última década en América Latina y el Caribe con respecto a otras regiones. No obstante, sigue afectando al 24,7% de los preescolares hondureños (18). Estos valores ponen de manifiesto una desnutrición de carácter mayoritariamente crónico que indica que, aunque posiblemente estén consumiendo una ingesta adecuada de calorías, pueden presentar carencias en lípidos o micronutrientes como Fe, Zn o vitaminas A o B_9.

Al igual que en diversos estudios realizados por la Observatorio de Derechos de la Niñez - Instituto Hondureño de la Niñez y la Familia (ODN-IHNFA) (19) en materia de desnutrición crónica, encontramos una situación más acusada en las áreas rurales frente a las urbanas, siendo los departamentos predominantemente indígenas del suroeste del país (Intibucá y Lempira) y corredor seco en el sur del departamento de Francisco Morazán los que duplican los porcentajes de bajo peso en los preescolares hondureños, con valores del 28,8% frente al 14,6% del área urbana (8). La prevalencia de la DC puede verse incrementada significativamente por el periodo en el que se inicia la alimentación complementaria, puesto que la elevada preponderancia de la desnutrición crónica en los 24 primeros meses de vida de los niños hondureños se inicia al principio del periodo de la alimentación complementaria, llegando a alcanzar su valor medio más elevado (aproximadamente el 30%) al finalizar el segundo año de vida del niño (20). Así mismo, este estudio corrobora lo obtenido por otros estudios de la Encuesta Nacional de Demografía y Salud (ENDESA 2011-2012) que muestran unos índices de desnutrición crónica del 23%. Por lo anteriormente descrito, se recomienda el desarrollo de nuevos instrumentos, prácticas y políticas de seguridad alimentarias entre estos grupos de edad en el país.

Con respecto a los índices de desnutrición aguda (DA) y desnutrición global (DG), observamos que la población infantil hondureña no presenta variaciones significativas desde 2005, y mantiene en ambos tipos de desnutrición valores medios estables, con una incidencia de desnutrición del 1% y el 7%, respectivamente, en la última década (3). Estos valores están muy próximos a los obtenidos en nuestro estudio (inferiores al 1,5%) en el caso de la desnutrición aguda y menores al 6% en la desnutrición global, lo que permite inferir según nuestros resultados una concordancia en el caso de la deficiencia de peso en relación a la altura entre los niños menores de cinco años con los altos índices de infecciones respiratorias agudas (IRA) (13%), diarrea severa (18%), anemia leve (29%), mala praxis nutricional y condiciones sanitarias insuficientes obtenidos. Se determina así una probable relación entre estas condiciones en los niños menores de cinco años hondureños estudiados y estados carenciales agudos (21).

La DG es un indicador empleado para la fijación de metas (ODM 2015), así como también en los distintos programas diseñados para reducir el hambre en el mundo. Paradójicamente, en nuestro estudio este índice detectó otros problemas de salud infantil asociados a la nutrición, como el sobrepeso y la obesidad infantil, como consecuencia de los cambios en los patrones alimentarios debidos fundamentalmente a la dieta basada en alimentos procesados con alto contenido en azúcares, grasas y sal, así como una merma en el consumo de alimentos tan importantes como los cereales integrales, las frutas y la verdura (22). Estudios llevados a cabo recientemente ponen de manifiesto resultados similares a los nuestros, con una prevalencia del sobrepeso en la región que se ha mantenido durante los últimos 25 años (23). En nuestro caso, los resultados mostraron valores muy superiores de obesidad en la zona urbana, con porcentajes del 13%, 15% y 18% de los niños menores de cinco años en los departamentos de la Atlántida, Francisco Morazán y Lempira, respectivamente. Este hecho pone de manifiesto la necesidad de una intervención y mejora de las políticas de seguridad y prácticas alimentarias en estos grupos de edad para el tratamiento de la malnutrición en el país.

La baja prevalencia de la lactancia materna exclusiva (LME) en los primeros seis meses de vida del lactante en Honduras, así como el abandono precoz de la lactancia materna (LM) antes de los dos primeros años de vida del niño que se muestran en nuestro estudio presentan similitudes con otros análisis recientes en el país (3). El problema del abandono de la LME no ha variado sustancialmente. Ello puede ser debido, probablemente, a las costumbres o a la tendencia adquirida por la práctica en el entorno materno, a creencias populares, y a la falta de formación de las madres, que en ocasiones, y paradójicamente, como ocurre en los departamentos rurales debido al su aislamiento de la sociedad de consumo, permite que las madres recurran más a la lactancia materna exclusiva y que la prolonguen hasta los dos años. Es el caso del departamento de Lempira, donde existe una prevalencia de la lactancia hasta los 24 meses en un 80% de las madres estudiadas. Como resultado de estas prácticas más saludables de las madres, en las regiones rurales se observa una prevalencia de desnutrición crónica inferior al 4% en niños menores de seis meses (3). Otro de los factores con influencia en la baja tasa de lactancia materna exclusiva es la escasa oportunidad que tienen las madres que trabajan fuera de casa (24). Aunque la mayoría de niños son amamantados, hay que destacar que el 44% recibió alimentos durante el periodo recomendado de lactancia exclusiva (4).

CONCLUSIÓN

La primera infancia comprende el ciclo de vida de las niñas y niños desde el nacimiento hasta los cinco años de edad. Analizar esta etapa es fundamental, dada su importancia en el desarrollo de sus capacidades cognitivas, sensoriales, afectivas, motrices y sociales. Las conclusiones más importantes de este estudio se derivan en términos de reducción de la desnutrición global en menores de cinco años hondureños, con una disminución en un 7% desde el periodo 1990-96 hasta el momento del estudio. Además, en este proceso coexisten la desnutrición y un progresivo aumento en el sobrepeso u obesidad como consecuencia del aumento de la oferta de alimentos procesados y la reducción de la actividad física. Cabe consignar, sin embargo, que la malnutrición por déficit ocasiona casi el doble de los costos sociales que el

sobrepeso, a pesar de que durante las dos últimas décadas la primera ha disminuido mientras que la prevalencia de sobrepeso y obesidad se ha duplicado (22). En cuanto a la lactancia materna, no resulta ser exclusiva debido a que en el país no se protege esta práctica de manera articulada. La única norma aprobada para la protección de la lactancia materna por acuerdo ministerial (2005) no ha sido operativizada. Además, el país no ha implementado el código internacional de comercialización de los productos sucedáneos de la leche materna, y la población resulta confundida con mensajes que le hacen valorar más en muchas ocasiones los productos artificiales en pro de la leche materna. Por lo tanto, se recomienda una transición en los patrones alimentarios y en la divulgación de guías alimentarias y orientación en el programa de crecimiento y desarrollo para una lactancia adecuada, así como una correcta introducción de la alimentación complementaria como estrategia para disminuir la malnutrición en Honduras.

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Nutrición Hospitalaria

Trabajo Original

Epidemiología y dietética

Infrapeso materno y resultados perinatales: estudio de cohortes retrospectivo

Maternal underweight and perinatal outcomes: a restrospective cohort study

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Resumen

Introducción: algunos estudios han asociado el infrapeso materno con resultados perinatales adversos tales como aborto espontáneo, desprendimiento placentario, feto pequeño para edad gestacional, crecimiento intrauterino retardado y parto pretérmino.

Objetivos: determinar si el infrapeso materno al inicio de la gestación influye sobre la forma de inicio y vía del parto, peso al nacer, índice de Apgar al minuto 5 y edad gestacional en el momento del parto.

Métodos: estudio de cohortes retrospectivo en gestantes adscritas al Hospital Universitario de Puerto Real. Periodo de estudio: 2002-2011. Grupo de estudio: infrapeso al inicio de la gestación (índice de masa corporal [IMC] < 18,5); grupo control: IMC normal al inicio de la gestación (18,5-24,9). Analizamos el riesgo (OR) de inducción de parto, cesárea, bajo peso al nacer, macrosomía, Apgar a los 5' < 7 y parto pretérmino.

Resultados: la prevalencia de infrapeso fue del 2,5% frente al 58,9% de gestantes que presentaron un IMC normal. No encontramos diferencias significativas en la tasa de inducción de parto, macrosomía fetal, Apgar a los 5' < 7 ni parto pretérmino. El infrapeso materno se asoció a una disminución en el riesgo de cesárea (OR ajustada 0,45; IC 95% 0,22-0,89) y a un riesgo aumentado de presentar recién nacido pequeño para su edad gestacional (OR ajustada 1,74; IC 95% 1,05-2,90).

Conclusiones: el infrapeso materno al inicio de la gestación se asocia a una menor probabilidad de que el parto finalice mediante la realización de una cesárea y a un mayor riesgo de que el recién nacido presente un peso al nacer por debajo del percentil 10.

Palabras clave:

Infrapeso. Índice de masa corporal. Inducción de parto. Cesárea. Peso al nacer. Parto pretérmino.

Abstract

Introduction: Some studies have linked maternal underweight with adverse perinatal outcomes such as spontaneous abortion, *abruptio placentae,* small for gestational age newborn, intrauterine growth retardation and preterm birth.

Objective: To determine the influence of maternal underweight in the onset of labor, route of delivery, birth weight, Apgar score and preterm birth.

Methods: Retrospective cohort study. We included pregnant women from the Hospital Universitario de Puerto Real. Period of study: 2002-2011. Study group: underweight at the beginning of gestation (BMI < 18.5 kg/m^2). Control group: pregnant women with normal body mass index (BMI) at the beginning of gestation (18.5-24.9 kg/m^2). The risk (OR) of induction of labor, cesarean section, small for gestational age newborn, macrosomia, 5' Apgar score < 7, and preterm birth was calculated.

Results: The prevalence of underweight was 2.5% *versus* 58.9% of pregnant women who had a normal BMI. We found no significant differences in the rate of induction of labor, fetal macrosomia, Apgar at 5' < 7 or preterm delivery. Maternal underweight was associated with a decreased risk of caesarean section (adjusted OR 0.45, 95% CI 0.22 to 0.89) and an increased risk of small for gestational age newborn (adjusted OR 1.74; 95% CI 1.05 to 2.90).

Conclusions: Maternal underweight at the start of pregnancy is associated with a lower risk of caesarean section and a greater risk of small for gestational age newborns (birth weight < P10).

Key words:

Underweight. Body mass index. Induced labor. Cesarean section. Birth weight. Premature labor.

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INTRODUCCIÓN

La delgadez puede definirse como una reducción de la grasa corporal que conduce a un peso subóptimo. En la edad adulta, la Organización Mundial de la Salud (OMS) define el infrapeso como la presencia de un índice de masa corporal (IMC) inferior a 18,5 kg/m^2. El infrapeso, a su vez, puede subclasificarse en leve (17-18,49 kg/m^2), moderado (16-16,99 kg/m^2) y severo (< 16 kg/m^2) (1).

Aunque en la mayoría de los países desarrollados la prevalencia de obesidad supera a la de infrapeso (2), el número de mujeres que comienza el embarazo con un peso subóptimo está aumentando (3,4). De hecho, en muchos países desarrollados, el IMC se está polarizando hacia los extremos de la escala, de manera que, por un lado, están aumentando las tasas de sobrepeso y obesidad y, por el otro, las de infrapeso, tal vez en relación con la creciente insatisfacción frente a la propia imagen corporal. En este sentido, algunos estudios ponen de manifiesto que aproximadamente el 50% de la población adolescente femenina en Europa, Canadá y Estados Unidos presenta insatisfacción con su imagen corporal (5). En España, donde se estima una prevalencia de infrapeso del 1,8%, disponemos de escasa información al respecto, si bien un reciente estudio comunica que la tasa de insatisfacción corporal en mujeres jóvenes españolas con IMC normal alcanza el 16,50% (6).

Aunque existe un número importante de trabajos centrados en la influencia que el sobrepeso y la obesidad ejercen sobre los resultados perinatales, la posible relación del infrapeso sobre la gestación ha sido menos estudiada. Algunos estudios asocian el infrapeso a resultados perinatales adversos tales como aborto espontáneo, desprendimiento placentario, feto pequeño para edad gestacional (FPEG), crecimiento intrauterino retardado o restringido (CIR) o parto pretérmino (PP) (7). Recientemente, además, se ha asociado a un mayor riesgo de paladar hendido, con o sin labio leporino (8).

El aumento progresivo en la tasa de infrapeso de nuestra población gestante, junto a los posibles efectos negativos que dicho infrapeso podría ejercer sobre determinados resultados perinatales, nos ha llevado a plantearnos la realización del presente estudio, en el que pretendemos determinar el impacto que el infrapeso pregestacional ejerce sobre los resultados perinatales en nuestro medio.

MÉTODO

Se trata de un estudio retrospectivo de cohortes. La población estudiada se encuentra situada al sur de España, dentro de la Comunidad Autónoma de Andalucía y, en concreto, en el Área de Salud adscrita al Hospital Universitario de Puerto Real (Cádiz) entre los años 2002 y 2011.

Los criterios de inclusión comprenden: gestantes cuyo embarazo y parto ha sido atendido en la Unidad de Gestión Clínica de Obstetricia y Ginecología del Hospital Universitario de Puerto Real (Cádiz) durante el periodo estudiado.

Los criterios de exclusión fueron feto muerto intraútero, malformaciones mayores, gestantes cuyo embarazo fue seguido en nuestro hospital pero el parto fue atendido en otro centro, y aquellas gestantes cuyo IMC al inicio de la gestación fue mayor o igual a 25 kg/m^2 (sobrepeso u obesidad).

Siguiendo los criterios establecidos por la Organización Mundial de la Salud (OMS), el infrapeso fue definido como la presencia de un IMC al inicio de la gestación inferior a 18,5 kg/m^2. El IMC normal fue definido como el comprendido entre 18,5 y 24,9 kg/m^2.

El peso y la talla materna se obtuvieron en el primer control prenatal, realizado a las embarazadas en su Centro de Atención Primaria de Salud, y fueron medidos y registrados por la correspondiente matrona de Atención Primaria. Solo se tomaron en consideración aquellos registros en los que la primera visita prenatal se realizó antes de la octava semana de gestación cumplida. En la cohorte considerada como expuesta al factor de riesgo se incluyeron las gestantes con infrapeso y en la cohorte control (no expuesta al factor de riesgo) se incluyeron aquellas que presentaban un IMC normal, siendo excluidas del análisis tanto las gestantes con sobrepeso como las obesas.

En todos los casos se registraron las siguientes variables: forma de inicio del parto (espontáneo *vs.* inducido); vía del parto (vaginal *vs.* cesárea); parto instrumentado (ventosa obstétrica o fórceps); presencia de un feto pequeño para la edad gestacional (FPEG), definido como aquel recién nacido cuyo peso al nacer se encontraba por debajo del percentil 10 para la edad gestacional y sexo; presencia de macrosomía (peso al nacer > 4.000 gramos) y presencia de un índice de Apgar a los cinco minutos inferior a 7.

La posible asociación del infrapeso materno con estas variables fue estudiada determinando, en primer lugar, la *odds ratio* (OR) no ajustada, considerando significativos aquellos resultados cuyo intervalo de confianza para el 95% no incluyera la unidad. A continuación, realizamos un análisis de regresión logística multivariante por pasos para determinar si el infrapeso se asocia de manera independiente a la aparición de un FPEG o a la finalización del parto mediante cesárea. En el caso del FPEG, el modelo se construyó tomando como variable dependiente la presencia o no de FPEG. La covariable principal fue la presencia o ausencia de infrapeso, y se introdujo como variable de control la presencia o ausencia de hipertensión arterial por su frecuente asociación con el bajo peso al nacer.

Para el análisis de la asociación entre el infrapeso materno y la vía del parto, tomamos como variable independiente la vía del parto (vaginal o cesárea). La covariable independiente principal fue la presencia o ausencia de infrapeso y las variables de control incluidas en el análisis fueron la nuliparidad, la presencia de una cesárea anterior, la edad materna mayor a 35 años, edad materna < 20 años, inicio inducido del parto, hipertensión arterial, CIR, diabetes gestacional y macrosomía, todas ellas circunstancias relacionadas con la vía del parto.

Los datos fueron obtenidos retrospectivamente de la base de datos de informes de alta clínica de la Unidad.

El análisis estadístico se llevó a cabo con el programa SPSS v 19.0 para Windows®.

RESULTADOS

Analizamos un total de 18.244 registros (informes de alta clínica de partos). De ellos, el IMC al inicio de la gestación se encontraba registrado en 4.711 casos (25,82%). De estos, el 2,5% presentó infrapeso y el 58,9% presentó un IMC normal al inicio de la gestación.

Entre las gestantes con infrapeso la tasa de inducciones de parto en nuestro servicio fue del 13,6%, frente al 16,6% registrado en el grupo de gestantes con IMC normal. Esta diferencia no resultó estadísticamente significativa (OR 0,79; IC 95% 0,46-1,34). En las gestantes con infrapeso la tasa de cesáreas fue del 12,7%, frente al 20,8% registrado en gestantes con IMC normal. Esta diferencia sí resultó estadísticamente significativa ($p < 0,05$). El infrapeso se asoció a una menor probabilidad de que el parto finalizara mediante la realización de una cesárea con una OR de 0,56 (IC para el 95% 0,32 a 0,96; estadísticamente significativo).

Al objeto de descartar la posible influencia en este resultado de determinadas variables de confusión y determinar la influencia que el infrapeso ejerce sobre la vía del parto de manera independiente, realizamos un análisis de regresión logística multivariante. El resultado de dicho análisis se muestra en la tabla I. Las gestantes que comenzaron la gestación con infrapeso presentaron una menor probabilidad de que su parto finalizara mediante cesárea, incluso cuando se tomaron en consideración todas las variables de control incluidas en el análisis. La OR ajustada resultó ser de 0,45, con un IC para el 95% de 0,22 a 0,89 (estadísticamente significativo).

Por lo que se refiere a la tasa de parto instrumentado (*vacuum* o fórceps), entre las gestantes con infrapeso fue del 6,8%, aunque si excluimos las cesáreas del total de los partos, la tasa de instrumentación obstétrica fue del 7,8%. En las gestantes con normopeso, las tasas son del 6,9% y del 8,7% respectivamente. Sin embargo, esta diferencia no resultó significativa (OR 0,88; IC 95% 0,42-1,84).

Cuando analizamos si el infrapeso representa un factor de riesgo para que el recién nacido sea pequeño para su edad gestacional (PEG), en nuestro estudio encontramos que la tasa global de PEG hallada en toda la población de referencia fue del 8,8%. En las gestantes con infrapeso la tasa fue del 16,1% frente al 10,1% hallado en las madres con IMC normal pregestacional, diferencia que sí se mostró estadísticamente significativa (OR 1,70; IC 95% 1,02-2,81).

Cuando realizamos el análisis de regresión logística (Tabla II), el infrapeso mantuvo su comportamiento como factor de riesgo,

Tabla I. Análisis de regresión logística multivariante realizado para analizar el riesgo ajustado de que el parto finalice en cesárea en gestantes con infrapeso

	Coeficiente	ET	Wald	GI	Sig.	OR	IC 95% de OR	
							Inferior	Superior
Infrapeso	-0,807	0,351	50,276	1	0,022	0,45	0,22	0,89
Nuliparidad	1,389	0,152	83,613	1	0,000	4,01	2,98	5,40
Cesárea anterior	1,773	0,195	82,455	1	0,000	5,89	4,02	8,64
Edad mat. > 35 años	0,929	0,144	41,887	1	0,000	2,53	1,91	3,36
Edad mat. < 20 años	-0,294	0,277	10,127	1	0,288	0,745	0,43	1,28
Parto inducido	0,122	0,146	0,704	1	0,401	1,13	0,85	1,50
Hipertensión	1,162	0,317	13,447	1	0,000	3,19	1,72	5,94
CIR	0,027	0,185	0,022	1	0,882	1,03	0,71	1,48
Diabetes gestacional	0,165	0,251	0,434	1	0,510	1,18	0,72	1,93
Macrosomía	0,503	0,226	40,961	1	0,026	1,65	1,06	2,57
Constante	-2,144	0,683	90,857	1	0,002	0,12		

ET: error típico; GI: grados de libertad; Sig: nivel de significación estadística; OR: odds ratio; IC: intervalo de confianza.

Tabla II. Análisis de regresión logística multivariante realizado para analizar el riesgo ajustado de presentar FPEG en gestantes con infrapeso

	Coeficiente	ET	Wald	GI	Sig.	OR	IC 95%	
							Inferior	Superior
Infrapeso	0,556	0,259	4,616	1	0,032	1,744	1,050	2,895
Hipertensión	1,092	0,287	14,515	1	0,000	2,981	1,699	5,228
Constante	0,571	0,378	2,286	1	0,131	1,770		

ET: error típico; GI: grados de libertad; IC: intervalo de confianza.

incluso incluyendo como variable de control la hipertensión arterial (OR 1,74; IC 95% 1,05-2,90), principal factor de riesgo asociado al bajo peso al nacer.

Cuando estudiamos el infrapeso como factor de riesgo de macrosomía fetal, encontramos una tasa de macrosomía entre las gestantes con infrapeso del 2,5% frente al 5,6% hallado en gestantes con normopeso. Sin embargo, esta diferencia no resultó significativa (OR 0,44; IC 95% 0,14-1,39).

También analizamos la presencia de un índice de Apgar a los cinco minutos del nacimiento menor de 7 como indicador de un mal resultado perinatal. El 1,8% de los recién nacidos de gestantes con infrapeso presentaron un Apgar a los cinco minutos < 7, frente al 2,2% hallado en gestantes con normopeso. Esta diferencia tampoco resultó significativa (OR 0,82; IC 95%: 0,20-3,39).

La tasa de parto pretérmino (menos de 37 semanas de gestación) fue mayor entre las gestantes con infrapeso (8,2% frente al 6,6% hallado en las gestantes con normopeso).

La OR del infrapeso pregestacional como factor de riesgo para que se produjera un parto pretérmino fue de 1,26, con un IC 95% (0,63-2,54), no resultando estadísticamente significativo.

En la tabla III se muestran, a modo de resumen, los resultados anteriormente enumerados.

DISCUSIÓN

En nuestra muestra hemos encontrado una prevalencia de infrapeso al inicio de la gestación del 2,5%.

El infrapeso al inicio de la gestación se asoció a una menor probabilidad de que el parto finalizara mediante la realización de una cesárea y a una mayor probabilidad de que el peso del recién nacido fuera inferior al percentil 10 ajustado por edad gestacional y sexo (recién nacido pequeño para su edad gestacional).

Por otra parte, las gestantes con infrapeso al inicio de la gestación no presentaron diferencias estadísticamente significativas en lo que se refiere a la forma de inicio del parto (espontáneo *vs.* inducido), la tasa de instrumentación obstétrica, la macrosomía fetal, la tasa de índice de Apgar a los cinco minutos inferior a 7 ni la tasa de partos pretérmino.

La tabla IV muestra la prevalencia de infrapeso en gestantes reflejada en la bibliografía revisada. Como se puede apreciar, la

Tabla III. Estudio comparativo de los resultados perinatales en gestantes con infrapeso pregestacional frente a gestantes con IMC normal

	Infrapeso		Normopeso		OR no ajustada (IC 95%)	OR ajustada (IC 95%)
	n	%	n	%		
Inducción de parto	16	13,6	461	16,6	0,79 (0,46-1,34)	
Cesárea	15	12,7	557	20,8	0,56* (0,32-0,96)	0,45* (0,22-0,89)
Parto instrumental	8	7,8	192	8,7	0,88 (0,42-1,84)	
FPEG	19	16,1	282	10,1	1,70* (1,02-2,81)	1,74* (1,05-2,90)
Macrosomía (> 4.000 g)	3	2,5	156	5,6	0,44 (0,14-1,39)	
Apgar 5´< 7	2	1,8	59	2,2	0,82 (0,2-3,39)	
Parto pretérmino	9	8,2	176	6,6	1,26 (0,63-2,54)	

**Estadísticamente significativo. FPEG: feto pequeño para edad gestacional.*

Tabla IV. Prevalencia de infrapeso en gestantes

Autor	Año	n	Periodo de reclutamiento	Prevalencia infrapeso	Población estudiada
Fujiwara (10)	2014	8.011	Ene 2001-Dic 2012	13,2%	Japón
Lynch (14)	2014	13.683	Oct 2005-Oct 2010	5%	Colorado
Scott-Pillai (13)	2013	30.298	2004-2011	2,8%	Reino Unido
Jeric (16)	2013	4.678	-	7,6%	Croacia
Watson (11)	2013	37.912	2008	4,2%	Queensland
Harita (9)	2012	1.391	Nov 2006-Abr 2008	15,09%	Japón
Ralph (15)	2011	23.893	Ene 2005-Dic 2007	9,3%	Liverpool
Tennant (12)	2011	29.856	2003-2005	3,5%	Reino Unido
Salihu (17)	2008	437.403	1989-1997	13,3%	Missouri
Manzanares (18)	2011	3.016	2007-2009	5,5%	España
Nosotros	2016	4.711	2002-2011	2,5%	España

prevalencia de infrapeso en embarazadas oscila entre el 2,8% y el 15,9% (9-18).

De todos los estudios revisados, las tasas más altas de infrapeso en gestantes son las publicadas en Japón por Harita (15,09%) (9) y Fujiwara y cols. (13,2%) (10). En países con estilo de vida occidental, la prevalencia más alta de infrapeso en embarazadas la encontramos en el estudio de Salihu y cols. (17), que, incluyendo gestantes estadounidenses de Missouri, registra una tasa de infrapeso materno del 13,3%.

Nuestra prevalencia del 2,5%, notablemente inferior, resulta muy similar a la publicada en Reino Unido tanto por Scott-Pillai y cols. (2,8%) (13) como por Tennant y cols. (3,5%) (12), y resulta algo inferior al 5,5% hallado por Manzanares y cols. en España (18).

Como anteriormente se ha reseñado, la tasa de inducción de parto en las gestantes con infrapeso incluidas en nuestro estudio fue discretamente inferior a la de las gestantes con normopeso (13,5% *vs.* 16,6%), aunque esta diferencia no resultó estadísticamente significativa. Este dato concuerda con la mayoría de trabajos publicados que utilizan la misma definición de infrapeso que nosotros (13,18,19). Solo Dodd y cols. (20) encuentran una menor probabilidad de que el embarazo finalice mediante una inducción del parto en las gestantes con infrapeso (OR: 0,80; IC 95%: 0,65-0,98).

Por lo que se refiere a la vía del parto (vaginal *vs.* cesárea), nuestros resultados son similares a los encontrados en la bibliografía (13,18-24), que se exponen en la tabla V. En todos los estudios revisados el infrapeso materno se asoció a una menor probabilidad de que el parto finalizara mediante la realización de una cesárea. La causa por la que las gestantes con infrapeso presentan una menor probabilidad de que su parto precise la realización de una cesárea no ha sido totalmente aclarada, aunque entre los posibles motivos que pueden justificar la disminución del riesgo de cesárea en estas gestantes podrían incluirse los siguientes:

1. El peso medio de los recién nacidos de madres con infrapeso es significativamente menor al de las madres con IMC normal. Por ello, parece razonable pensar que la tasa de cesáreas por desproporción cefalopélvica debe ser menor.
2. Las gestantes con sobrepeso u obesidad presentan mayores tasas de cesárea que las gestantes con un IMC normal. Entre las causas que motivan este aumento del riesgo se ha incluido el aumento del espesor de los tejidos blandos, que podría dificultar el paso del feto a través del canal del parto, dando lugar a distocias que acabarían en cesárea. Siguiendo el razonamiento inverso, parece razonable pensar que en las gestantes con infrapeso el espesor de los tejidos blandos ha de ser inferior, hasta el punto de que el principal obstáculo para la progresión del parto va a consistir fundamentalmente en la resistencia que ofrezca el canal óseo del parto. Por ello, parece lógico pensar que las cesáreas por no progresión de parto serían menos frecuentes en las gestantes con infrapeso.
3. Las gestantes con infrapeso presentan, además, menores tasas de diabetes gestacional e hipertensión arterial. Por ello, es razonable pensar que presenten menos cesáreas secundarias a las complicaciones asociadas a dichas patologías.

En lo referente a la relación entre el infrapeso materno y la necesidad de instrumentar el parto (aplicar una ventosa obstétrica o fórceps), nuestros resultados también son coherentes con los encontrados por los diversos autores revisados, que al igual que nosotros no encuentran una asociación entre el infrapeso al inicio de la gestación y la necesidad de instrumentar el parto (13,18,20,24).

Todos los autores revisados que estudiaron la asociación entre el peso al nacer y el infrapeso materno encontraron mayores tasas de FPEG en las gestantes con infrapeso cuando se las comparó con aquellas que presentaban un IMC normal al inicio de la gestación (9,18,22,26-28). De ellos, además, la asociación de infrapeso y FPEG resultó significativa en todos menos en el estudio de Manzanares. Centrándonos en este aspecto, resulta de especial interés el metaanálisis publicado por Han y cols. en 2011 (29) en el que se incluyen 52 estudios de cohortes y 25 estudios de casos y controles. Los autores encuentran que el infrapeso materno se asocia a un mayor riesgo de presentar bajo peso al nacer, con un riesgo relativo ajustado de 1,64 (IC 95%: 1,38-1,94), resultado

Tabla V. Riesgo de que el parto finalice mediante cesárea en gestantes con infrapeso

Autor	Criterio infrapeso (kg/m²)	Cesáreas global		Cesáreas electivas		Cesáreas urgentes	
		Tasa (%)	OR; IC 95%	Tasa (%)	OR; IC 95%	Tasa (%)	OR; IC 95%
Sebire (21)	IMC < 20			3,5	0,85; IC 99% (0,79-0,93)	6,45	0,71; IC 99% (0,67-0,75)
Ehrenberg (22)	IMC ≤ 19,8	12,6	0,8; (0,71-0,91)				
Bhattacharya (23)	IMC < 20	11,3		2,6	0,8; (0,6-1,0)	8,7	0,9; (0,8-1,1)
Abenhaim (24)	IMC < 20		0,89; (0,81-0,97)				
Dodd (20)	IMC < 18,5				0,83; (0,57-1,21)		0,70; (0,51-0,96)
Doherty (19)	IMC < 18,5		0,81; (0,58-1,14)				0,64; (0,22-1,81)
Manzanares (18)	IMC < 18,5				0,87 (0,37-2,06)	5,4	0,32 (0,11-0,88)
Scott-Pillai (13)	IMC < 18,5		0,8; IC 99% (0,7-1,0)		0,9; IC 99% (0,7-1,3)		0,8; (0,6-1,0)

Tabla VI. Infrapeso al inicio de la gestación y macrosomía fetal

Autor	Punto de corte de infrapeso (kg/m²)	> Percentil 90		> 4.000 g		> 4.500 g	
		Tasa (%)	OR; IC 95%	Tasa (%)	OR; IC 95%	Tasa (%)	OR; IC 95%
Sebire (21)	IMC < 20	4,55	0,50; IC 99% (0,45-0,56)				
Kanadys (27)	IMC < 19,8			4,7	0,51 (0,30-0,88)	0,6	0,33 (0,08-1,47)
Bhattacharya (23)	IMC < 20			3,5	0,5 (0,4-0,6)		
Abenhaim (24)	IMC < 20						0,43 (0,28-0,68)
Dodd (20)	IMC < 19,8				0,38 (0,22-0,67)		
Manzanares (18)	IMC < 18,5				1,09 (0,38-3,11)		
Jeric (16)	IMC < 18,5			8,3			
Yu (26)	IMC < 20		0,51 (0,46-0,56)		0,51 (0,43-0,61)		0,51 (0,42-0,61)
Scott-Pillai (13)	IMC < 18,5				0,5; IC 99% (0,3-0,7)		

muy similar al hallado en el presente estudio. La asociación con el bajo peso al nacer nos parece especialmente relevante por su posible relación no ya con un mal resultado perinatal, sino también con una mayor probabilidad de desarrollar en la edad adulta hipertensión arterial, alteraciones en el metabolismo de los hidratos de carbono o insuficiencia renal (30).

Con respecto a la macrosomía fetal, en la tabla VI exponemos los resultados encontrados por los diversos autores revisados (13,16,18,20,21,23,24,26,27). Como se puede apreciar, en general, los estudios publicados encuentran que las tasas de macrosomía son inferiores en los recién nacidos de madres con infrapeso frente a las gestantes con IMC normal. En nuestro estudio, la tasa de macrosomía en gestantes con infrapeso fue prácticamente la mitad de la hallada en las gestantes con IMC normal al inicio de la gestación (2,5% frente al 5,6%). Sin embargo, esta diferencia no resultó estadísticamente significativa, muy probablemente por el escaso número de gestantes con macrosomía hallados en el grupo de estudio.

En los estudios de Dodd y cols. (20) y Sebire y cols. (21) se analizó la posible asociación del infrapeso con la presencia de un índice de Apgar a los cinco minutos inferior a 7, parámetro que se asocia a un mal pronóstico neonatal. Ninguno de los dos encontró una asociación estadísticamente significativa entre el infrapeso materno y un índice de Apgar a los cinco minutos inferior a 7. En nuestro estudio encontramos resultados similares, con una tasa de índice de Apgar inferior a los 7' del 1,8% en las gestantes con infrapeso, frente al 2,2% en las gestantes con IMC normal (estadísticamente no significativo).

Por último, por lo que se refiere a la asociación entre el infrapeso materno y el parto pretérmino, los datos hallados en la bibliografía son controvertidos. Si bien la tendencia hallada es a encontrar una mayor tasa de partos pretérmino en gestantes con infrapeso, esta diferencia no resultó estadísticamente significativa para muchos autores (13,18,23,25,26).

Otros, en cambio, sí encontraron un aumento del riesgo de que el parto finalizara antes de las 37 semanas de manera estadísticamente significativa (17,20,21,28,31). En nuestro estudio, la tasa de parto pretérmino fue discretamente superior en las gestantes con infrapeso (8,2% frente al 6,6%), aunque esta diferencia no se mostró estadísticamente significativa.

CONCLUSIONES

El infrapeso materno al inicio de la gestación se asocia a una menor probabilidad de que el parto finalice mediante la realización de una cesárea y a un mayor riesgo de que el recién nacido presente un peso al nacer por debajo del percentil 10 (PEG).

En nuestra opinión, el consejo nutricional debería formar parte fundamental de la consulta preconcepcional. Las mujeres con deseo reproductivo que presentan infrapeso deberían recibir una adecuada orientación encaminada a conseguir un peso óptimo en el momento de la gestación. Esto podría contribuir a la mejora de los resultados perinatales y disminuir el impacto negativo que el bajo peso al nacer ejerce tanto en la infancia como en la edad adulta.

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Trabajo Original

Epidemiología y dietética

Association between meal intake behavior and blood pressure in Spanish adults

Asociación entre conductas relacionadas con la ingesta de alimentos y tensión arterial en adultos españoles

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Abstract

Introduction and objectives: Eating frequency has been suggested to modify blood pressure. Yet, the results are inconclusive, possibly because eating frequency, particularly meal intake behavior (MIB), does not differentiate between meals and snacks. Hence, the aim of this study was to examine the association between more specific MIBs, like the consumption of the three main meals, the intake of forenoon and afternoon meals and snacking between the regular meals, and systolic/diastolic blood pressure (SBP/DBP).

Methods: This cross-sectional study includes 1,314 Spanish adults aged 20-79 years. Data collection occurred during cardiovascular health day events organized in four Spanish cities (Madrid, Las Palmas, Seville and Valencia) in 2008. Linear regression analysis was performed to assess the independent association between the mentioned MIBs and SBP/DBP, controlling for several confounders in multiples models.

Results: After adjusting for sex, age and individual risk factors, having an afternoon meal was associated with lower SBP (ß -3.91, 95% CI [-6.33, -1.49]) and DBP (ß -2.35, 95% CI [-3.76, -0.94]). This association was attenuated when introducing dietary intake and waist circumference in the predictive models (SBP: ß -2.83, 95% CI [-5.25, -0.40]; DBP: ß -1.67, 95% CI [-3.04, -0.31]), although it still remained significant. None of the other investigated MIBs showed any associations with SBP/DBP.

Conclusions: This study suggests that SBP/DBP might be reduced by the intake of an afternoon meal. However, population-based prospective studies are needed in order to confirm the consequences of the investigated associations on health.

Key words:

Systolic and diastolic blood pressure. Waist circumference. Forenoon meal. Afternoon meal. Snacking.

Resumen

Introducción y objetivos: evidencias sugieren que el número de ingestas alimentarias modifican la presión arterial. Sin embargo, los resultados encontrados no son concluyentes, probablemente debido a que esta conducta relacionada con la ingesta de alimentos (CRIA) no diferencia entre comidas y *snacks.* Este estudio examina la asociación entre CRIA más específicas como la realización de las tres comidas principales, de la media mañana, de la merienda y picar entre las comidas regulares, y la tensión arterial sistólica y diastólica (TAS y TAD).

Métodos: es un estudio transversal, en el cual fueron incluidos 1.314 españoles (20-79 años). Los datos fueron recogidos en las Jornadas de Salud Cardiovascular en Madrid, Las Palmas, Sevilla y Valencia, durante el año 2008. Se aplicaron análisis de regresión lineal, controlando el efecto de diversos factores de confusión en múltiples modelos.

Resultados: después de ajustar por sexo, edad y factores de riesgo individual, tomar la merienda se asoció directamente a menor TAS (ß -3,91, 95% CI [-6,33, -1,49]) y TAD (ß -2,35, 95% CI [-3,76, -0,94]). La introducción del consumo alimentario y la circunferencia de cintura en los modelos predictivos atenuó esta asociación (TAS: ß -2,83, 95% CI [-5,25, -0,40]; TAD: ß -1,67, 95% CI [-3,04, -0,31]). Ninguna de las otras CRIA investigadas mostró asociaciones con TAS y TAD.

Conclusiones: el estudio sugiere que tanto la TAS como la TAD podrían verse reducidas mediante la ingesta de la merienda, aunque se requieren estudios adicionales para confirmar y profundizar en las consecuencias sobre la salud de las asociaciones investigadas.

Palabras clave:

Tensión arterial sistólica y diastólica. Circunferencia de cintura. Media mañana. Merienda. Picar.

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INTRODUCTION

Hypertension is a known risk factor for cardiovascular diseases. Therefore, its high prevalence worldwide is a concern. Prevention is reached through lifestyle modifications (1,2). Hence, decreasing sodium chloride and cholesterol intake and increasing fruit and vegetable consumption are recommended by the European Society of Cardiology (3), alongside with weight reduction, regular physical activity, restricted alcohol consumption and smoking cessation. However, the intake of nutrients and specific food groups is only one aspect of dietary behavior. Another aspect are meal intake behaviors (MIBs) like eating frequency (EF), irregular eating, snacking or skipping meals. These are related to specific lifestyles and dietary patterns and, therefore, might contribute to the development of cardiovascular risk factors (4-8). However, only a few studies have explored the associations between MIB and blood pressure (BP) (9-17).

In the case of EF, a systematic review of weight-loss and maintenance intervention studies carried out by Palmer et al. (15) suggested no associations between EF and BP. Moreover, different cross-sectional studies did not find any associations (16,17) with EF. By contrast, Edelstein et al. (9) showed that systolic blood pressure (SBP) was lower in those subjects who ate more frequently. This was confirmed by Kim et al. (12), who observed an inverse association between EF and BP. Furthermore, a longitudinal study (10) evaluating 115 non-diabetic men and women found that a high eating frequency was associated with decreased systolic (SBP) and diastolic BP (DBP).

Altogether, the results are inconclusive, suggesting either no associations or negative associations between EF and SBP/DBP. This might be due to different methodological limitations: a) EF does not differentiate between meals and snacks; and b) the definition of meals, snacks or even eating occasions is inconsistent across the literature (18,19). For example, most studies consider only breakfast, lunch and dinner to be meals, coding the rest of the eating occasions as snacks (4,6). However, most traditional meal patterns consist of more than three meals per day (18,20). In Spain, for example, in addition to the three main meals, two smaller eating occasions occur, and they are perceived as meals rather than snacks (20). They occur between breakfast and lunch (a forenoon meal, *"media mañana"*) and between lunch and dinner (an afternoon meal, *"merienda"*).

Based on the above mentioned, the present study aims to determine the associations of several MIBs, such as the intake of the three main meals, a forenoon meal, an afternoon meal and snacking between regular meals, with SBP and DBP in a sample of Spanish adults.

MATERIALS AND METHODS

PARTICIPANTS

Data from 1,314 adults (63.2% women and 36.8% men) aged 20-79 years (mean age 57.8 ± 14.9 years) were examined in a cross-sectional study. The survey was carried out in 2008 in four Spanish cities (Madrid, Las Palmas, Seville and Valencia) during a cardiovascular health event organized by the Fundación Española del Corazón and the Sociedad Española de Cardiología. A random sampling of participants was not carried out since the main purpose of these events was to promote the prevention of cardiovascular diseases and to screen for cardiovascular risk factors. Hence, all the volunteers were accepted. Participants were included in the study after completing a guided questionnaire, as well as measurements of waist circumference (WC) and BP. Technicians used standardized anthropometric instruments during measurements, following the recommendations of the International Biological Program (21). The study was approved by the Ethics Committee of the Fundación Española del Corazón, and conducted according to the guidelines in the Declaration of Helsinki (22). Signed consent forms were obtained from all participants.

MEASUREMENTS

A digital tensiometer (Visomat® Comfort 20/40) was used to assess SBP (mmHg) and DBP (mmHg). Participants were measured while sitting and after having completed the questionnaire, the intention of which was to achieve a calm state. These measurements were repeated when values were beyond the normal range: from < 90/60 mmHg or > 140/90 mmHg for SBP/DBP (23). WC (cm) was measured midway between the last rib and the upper edge of the iliac crest, using a non-stretchable tape.

MEAL INTAKE BEHAVIORS

The four MIBs investigated (the intake of all three main meals, having a forenoon meal, having an afternoon meal and snacking) were assessed by means of short self-reported questions. Participants were asked about the meals consumed during the day, given the following meals to choose from: breakfast, forenoon meal, lunch, afternoon meal and dinner (1 = yes/0 = no). The intake of all three main meals was confirmed when the three questions on breakfast, lunch and dinner were answered positively. The habit of snacking between their regular meals was estimated by the question "Do you snack between meals?" (1 = yes/0 = no), immediately after asking about their meal intake.

CONFOUNDERS

Known risk factors for hypertension, such as sex, age, individual risk factors and dietary intake, were considered as potential confounders of the MIB-BP association. Individual risk factors were assessed using self-report questions. Participants were asked whether they currently drank alcohol (1 = yes/0 = no) or smoked (1 = yes/0 = no). Additionally, they had to indicate their level of physical activity during spare time. They could select from the following options: sedentary (reading, watching television), light

exercise (minimum effort: yoga, walking, fishing), moderate exercise (minimum four hours a week: hiking, cycling, gardening) and intensive exercise (high heart rate: running, football, swimming). For the analysis, moderate and intensive exercises were grouped into one category.

Furthermore, the data from a short food habits questionnaire was used to create two scores that reflect dietary intake. First, the Achievement of the Dietary Guideline Score (ADGS) was based on five short questions about the usual daily intake of: a) meat, fish and eggs (responsive options: zero to five or more servings); b) milk and dairy products (zero to three servings); c) fruit (zero to five or more servings); d) vegetables (zero to three servings); and e) bread, pasta, rice and cereals (zero to five or more servings). One point was obtained for each food group when the serving recommendations of the Spanish dietary guidelines, as presented by Salvador et al. (24), were reached: a) meat, fish and eggs (less than three servings); b) milk and dairy products (more than one serving); c) fruit (more than one serving); d) vegetables (more than one serving); and e) bread, pasta, rice and cereals (more than three servings). By adding up the points obtained, the score ranges from 0 to 5 points, and it is categorized into 1 = very low (0-1 points), 2 = low (2 points), 3 = middle (3 points), and 4 = high (4-5 points). The second score (Unhealthy Habit Score [UHS]) was based on the regular consumption of: a) fatty foods; b) ready-made meals; c) salty foods; d) adding salt to already prepared meals; and e) intake of sugary drinks during a meal. It was assessed by the results of a short question about whether or not each habit was performed regularly (1 = yes/0 = no). The UHS was determined by totaling the points obtained for each question answered with yes (the range is 0 to 5 points), and then recoding them into 1 = very low (0 points), 2 = low (1 point), 3 = medium (2 points) and 4 = high (3-5 points).

STATISTICAL ANALYSIS

Continuous variables were tested for normality and described using means and standard deviation, whereas categorical variables were represented by frequencies. First, the association between the confounders and the dependent variables (SBP and DBP) was assessed by means of linear regression, and adjusted for the investigated MIB. Second, multiple linear regression models were used to examine the associations between the MIBs (the intake of the three main meals, having a forenoon meal, having an afternoon meal and snacking) and SBP/DBP. Model 1 described the analysis adjusted by sex, age, smoking, alcohol consumption, and physical activity during leisure time. Additionally, this model included the MIBs not considered as the main independent variable in each regression, controlling for the mutual effect between them. To examine whether the associations were mediated by dietary intake, represented by ADGS and UHS, or WC, they were introduced in the second (Model 2) and third (Model 3) model, respectively. Finally, Model 4 included all the confounders in the regression. Statistical analysis was conducted using the software package SPSS 17, considering p-value < 0.05 as statistically significant.

RESULTS

Table I presents the sample characteristics according to the investigated MIBs: the intake of all three main meals, having a forenoon meal, having an afternoon meal and snacking. The majority of the sample consumed all three main meals. More than one third of the participants took a forenoon meal and nearly half of them an afternoon meal, whereas only a fourth of the individuals snacked between their regular meals. SBP was significantly lower among the participants who usually had a forenoon meal, an afternoon meal and those who snacked between the regular meals. In contrast, subjects who had all three main meals showed a significantly higher SBP. Additionally, those who had a forenoon meal and an afternoon meal also presented lower DBP.

Table II shows the associations between SBP/DBP and the confounders (sex, age, smoking, drinking alcohol, physical activity during spare time, the ADGS and UHS). Subjects with an increased WC had significantly higher BP. SBP was lower among men and individuals with moderate to intense physical activity, whereas SBP increased with age. In contrast, DBP did not show any associations with the confounders.

Finally, table III shows the associations between the MIBs and SBP/DBP. After adjusting for the confounders, MIB not being considered to be the main independent variable, having an afternoon meal was directly associated with SBP and DBP. The participants who had an afternoon meal had significantly lower SBP and DBP. Those associations were attenuated when the ADGS, UHS and WC were included in the regression models, yet, the association remained significant. In contrast, making all three main meals, the intake of a forenoon meal and snacking did not show associations with SBP and DBP.

DISCUSSION

In this study, we used linear regression models to assess associations between the MIBs (intake of the three main meals, forenoon meal, afternoon meal and snacking between the regular meals) and SBP/DBP. Our findings showed that subjects who consumed an afternoon meal seemed to have lower BP independently of other variables such as sex, age and individual risk factors. However, the association was attenuated through dietary intake, represented by ADGS and UHS, and WC. On the other hand, the rest of the investigated MIBs were not related to SBP/DBP.

To the best of our knowledge, the negative direct association between the afternoon meal and SBP/DBP is a unique result, as meals in addition to breakfast, lunch and dinner are underexplored for several reasons. First, in previous studies extra meals or small meals are usually examined as snacks, and therefore are considered the same as snacking in general (4,6). For example, Kim et al. (12) found snack frequency, but not meal frequency, to be inversely associated with BP. However, the used meal definition included only breakfast, lunch and dinner, whereas other eating occasions were considered as snacks. Second, an afternoon and a forenoon meal are meals traditionally taken in Spain.

Table I. Study sample characteristics according to meal intake behaviors: intake of all three main meals, having a forenoon meal, having an afternoon meal and snacking

	Intake of all three main meals					Having a forenoon meal					Having an afternoon meal					Snacking					Total	
	Yes		No		p-value	Yes		No		p-value	Yes		No		p-value	Yes		No		p-value		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD
SBP	132.3	21.5	127.1	20.9	< 0.05	129.2	20.9	133.6	21.6	< 0.001	128.9	20.1	134.6	22.2	< 0.001	129.7	22.4	132.7	21.1	< 0.01	132.0	21.5
DBP	77.5	11.9	76.5	11.3	0.765	75.8	11.3	78.3	12.0	< 0.001	75.7	10.8	78.9	12.4	< 0.001	77.4	12.1	77.4	11.7	0.917	77.4	11.8
WC (cm)	93	12.0	91.3	11.1	0.206	91.9	11.3	93.5	12.3	< 0.05	91.1	11.2	94.4	12.4	0.641	93.2	12.4	92.8	11.8	0.641	92.9	12.0
	n	%	n	%		n	%	n	%		n	%	n	%		n	%	n	%		n	%
Men	448	36.6	35	44.3	0.151	158	32.6	325	39.2	< 0.05	166	27.8	317	44.3	< 0.001	109	33.1	374	39.0	0.115	483	36.8
Women	787	63.7	44	55.7		326	67.4	505	60.8		432	72.2	399	55.7		220	66.9	611	62.0		831	63.2
Age (years)																						
20-44 years	239	90.5	25	9.5	< 0.05	103	39.0	161	61.0	0.057	117	44.3	147	55.7	0.633	92	34.8	172	65.2	< 0.001	264	20.1
45-64 years	491	94.1	31	5.9		207	39.7	315	60.3		246	47.1	276	52.9		131	25.1	391	74.9		522	39.7
> 64 years	505	95.6	23	4.4		174	33.0	354	67.0		235	44.5	293	40.9		106	20.1	422	79.9		528	40.2
Smoking (yes)	165	13.4	25	3.6	< 0.001	69	14.3	121	14.6	0.873	77	12.9	113	15.8	0.136	60	18.2	130	13.2	< 0.05	190	14.5
Drinking alcohol (yes)	592	47.9	42	53.2	0.367	223	46.1	411	49.5	0.228	257	43.0	377	52.7	< 0.001	155	47.1	479	48.6	0.634	634	48.2
Physical activity during spare time																						
Sedentary	249	20,2	32	40.5	< 0.001	96	19.8	185	22.3	0.463	128	21.4	153	21.4	0.363	97	29.5	184	18.7	< 0.001	281	21.4
Light	419	33,9	20	25.3		170	35.1	269	32.4		211	35.3	228	31.8		101	30.7	338	34.3		439	33.4
Moderate + intensive	567	45.9	27	34.2		218	45.0	376	45.3		259	43.3	335	46.8		131	39.8	463	47.0		594	45.2
Achievement Dietary Guideline Score																						
Very low (0-1)	123	10.0	26	32.9	< 0.001	33	22.1	116	14.0	< 0.001	30	5.0	119	16.6	< 0.001	38	11.6	111	11.3	0.625	149	11.3
Low (2)	323	26.2	26	32.9		112	23.1	237	28.6		137	22.9	212	29.6		96	29.2	253	25.7		349	26.6
Middle (3)	539	43.6	18	22.8		199	41.1	358	43.1		284	47.5	273	38.1		132	40.1	425	43.1		557	42.4
High (4-5)	250	20.2	9	11.4		140	28.9	119	14.3		147	24.6	112	15.6		63	19.1	196	19.9		259	19.7
Unhealthy Habit Score																						
Very low (0)	534	43.2	17	21.5	< 0.001	199	41.1	352	42.4	0.577	269	45.0	282	39.4	0.065	77	23.4	474	48.1	< 0.001	551	41.9
Low (1)	353	28.6	24	30.4		132	27.3	245	29.5		157	26.3	220	30.7		99	30.1	278	28.2		377	28.7
Middle (2)	204	16.5	17	21.5		87	18.0	134	16.1		91	15.2	130	18.2		73	22.2	148	15.0		221	16.8
High (3-5)	144	11.7	21	26.6		66	13.6	99	11.9		81	13.5	84	11.7		801	24.3	85	8.6		165	12.6
Meal intake behaviors (yes)																						
Having three main meals						448	92.6	787	94.8	0.097	558	93.3	677	94.6	0.346	304	92.5	931	94.5	0.162	1,235	94.0
Having																						
Breakfast	1235	100.0	30	38.0	< 0.001	461	95.2	804	96.9	0.135	579	96.8	686	95.8	0.335	312	94.8	953	96.8	0.112	1,265	96.3
Forenoon meal	448	36.6	36	45.6	0.097						345	57.7	139	19.4	< 0.001	138	41.9	346	35.1	< 0.05	484	36,8
Lunch	1235	100.0	68	86.1	< 0.001	477	98.6	826	99.5	0.064	591	98.8	712	99.4	0.225	325	98.8	978	99.3	0.384	1,303	99.2
Afternoon meal	558	45.2	40	50.6	0.346	345	71.3	253	30.5	< 0.001						168	51.1	430	43.7	< 0.05	598	45.5
Dinner	1235	100.0	51	64.6	< 0.001	473	97.7	813	98.0	0.786	579	96.8	707	98.7	< 0.05	320	97.3	966	98.1	0.380	1,286	97.9
Snacking	304	24.6	25	31.6	0.162	138	28.5	191	23.0	< 0.05	168	28.1	161	22.5	< 0.05						329	25.0

n: Number; SD: Standard derivation; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; WC: Waist circumference.

Table II. Unstandardized regression coefficients (ß) and 95% CI for linear regression of SBP, and DBP with WC, sex, age, smoking, drinking alcohol, physical activity during spare time, the Achievement of the Dietary Guideline Score and Unhealthy Habit Score adjusted for the investigated meal intake behavior

	SBP		DBP	
	Coef.	**95% CI**	**Coef.**	**95% CI**
WC	0.398	0.290, 0.505[b]	0.253	0.197, 0.318[b]
Sex (women)[a]	-3.396	-5.879, -0.914[b]	-0.297	-1.733, 1.140
Age (years)	0.339	0.255, 0.423[b]	-0.004	-0.053, 0.045
Smoking (yes)[a]	-2.808	-6.050, 0.434	-1.024	-2.900, 0.852
Drinking alcohol (yes)[a]	0.298	-1.926, 2.522	-0.058	-1.345, 1.229
Physical activity during spare time[a]				
Light	-2.621	-5.374, 2.334	-1.075	-2.905, 0.755
Moderate + intensive	-0.654	-3.690, - 2.382[b]	0.191	-1.556, 1.948
Achievement of the Dietary Guideline Score[a]				
Low (2)	-1.034	-4.930, 2.862	-1.526	-3.781, 0.728
Middle (3)	-1.520	-5.374, 2,334	-1.231	-3.461, 0.999
High (4-5)	-2.529	-6.832, 1.774	-1.679	-4.169, 0.811
Unhealthy Diet Score[a]				
0	2. 393	-1.485, 6.271	2.041	-0.203, 4.285
Low (1)	1.552	-2.300, 5.405	1.937	-0.292, 4.285
Middle (2)	1.385	-2.747, 5.517	0.511	-1.880, 2.902

DBP: Diastolic blood pressure; SBP: Systolic blood pressure; WC: Waist circumference; [a]Reference categories: Sex (men), smoking (no), alcohol consumption (no), physical activity during spare time (sedentary), Achievement of the Dietary Guideline Score (very low), Unhealthy Diet Score (very low). [b]Significant association p ≤ 0.05.

Table III. Unstandardized regression coefficients (ß) and 95% CI for the associations between meal intake behaviors and SBP/DBP

	SBP							
	Model 1[a]		**Model 2[b]**		**Model 3[c]**		**Model 4[d]**	
	Coef.	**95% CI**	**Coef.**	**95% CI**	**Coef.**	**95% CI**	**Coef.**	**95% CI**
Intake of all three main meals[e]	2.47	-2.16, 7.10	2.96	-1.75, 7.66	1.98	-2.55, 6.50	2.14	-2.46, 6.74
Having a forenoon meal[e]	-1.62	-4.10, 0,85	-1.32	-3.83, 1.19	-1.65	-4.06, 0.77	-1.43	-3.88, 1.02
Having an afternoon meal[e]	-3.91	-6.33, -1.49[f]	-3.60	-6.07, -1.13[f]	-2.99	-5.37, -0.62[f]	-2.83	-5.25, -0.41[f]
Snacking[e]	-0.38	-2.93, 2.17	-0.08	-2.71, 2.55	-1.10	-3.60, 1.40	-0.72	-3.29, 1.86
	DBP							
	Model 1[a]		**Model 2[b]**		**Model 3[c]**		**Model 4[d]**	
	Coef.	**95% CI**	**Coef.**	**95% CI**	**Coef.**	**95% CI**	**Coef.**	**95% CI**
Intake of all three main meals[e]	0.42	-2.28, 3.11	0.68	-2.05, 3.41	0.10	-2.52, 2.72	0,16	-2.50, 2.83
Having a forenoon meal[e]	1.37	-2.81, 0.08	1.18	-2.64, 0.28	-1.38	-2.78, 0.20	-1.25	-2.67, 0.17
Having an afternoon meal[e]	-2.35	-3.76, -0.94[f]	-2.16	-3.60, -0.73[f]	-1.77	-3.15, -0.39[f]	-1.67	-3.07, -0.27[f]
Snacking[e]	0.66	-0.83, 2.14	0.99	-0.54, 2.51	0.20	-1.25, 1.65	0.58	-0.91, 2.07

[a]Model 1: Adjusted for sex, age, individual risk factors (smoking, alcohol consumption, physical activity in leisure time); MIB not considered to be the main independent variable. [b]Model 2: Model 1 and Achievement of the Dietary Guideline Score, Unhealthy Habit Score. [c]Model 3: Model 1 and WC. [d]Model 4: Model 1 and Achievement of the Dietary Guideline Score, Unhealthy Habit Score and WC. DBP: Diastolic blood pressure; SBP: Systolic blood pressure; WC: Waist circumference. [e]Reference category: no. [f]Significant association p ≤ 0.05.

However, they are much less common in other populations. For instance, Barba et al. (25) studied the association between EF and BP in children from southern Italy. When defining EF, they included, in addition to the three main meals, a forenoon meal, an afternoon meal and milk before bed.

The possible mechanisms by which the intake of an afternoon meal might reduce SBP and DBP are unclear, especially, as there was no observed association with the forenoon meal. However, we believe that the afternoon meal might somehow affect the intake of the subsequent meal. In the case of the forenoon meal this is lunch, whereas for the afternoon meal it is dinner. The amount of energy consumed during dinner might be one of the highest of the day, as observed by several studies from different countries. Additionally, previous investigations showed a decline in insulin sensitivity throughout the day, reaching its lowest point in the evening (27). Hence, the intake of an afternoon meal may result in a decreased energy intake during dinner and thus, perhaps, it improves insulin metabolism. Yet, given the observational nature of the study, we were not able to test this assumption. However, an intervention study carried out by Chapelot et al. (18) showed a lower dinner intake in those participants who usually had a traditional French mid-afternoon eating occasion. This occurred even though the participants who never make such a small meal in the afternoon ate a snack out of the same food items as provided for this afternoon meal. However, after a five-year follow-up, Karatzi et al. (10) found a direct link between high EF and a lower rate of SBP and DBP, independently of the homeostatic model assessment-insulin resistance (HOMA-IR). Nevertheless, they suggest that over the long term a reduced insulin concentration might benefit cardiovascular health. As the afternoon meal is part of a traditional Spanish meal pattern, the long-term effect postulated might have acted over metabolism. Additionally, it is important to mention that in the study by Karatzi et al. (8) participants were screened to have no conditions, such as diabetes mellitus, liver or endocrine diseases, that may impact blood pressure. In our study, participants were enrolled regardless of the diseases they had.

In addition, with the use of regression models we could assess the role of dietary intake, represented by ADGS and UHS, as well as WC on the associations between MIBs and SBP/DBP. In the first place, we observed that the association between the intake of the afternoon meal and BP was unconnected to these two confounders. This is in line with the study carried out by Karatzi et al. (10), who also found that the association of EF with BP after a five-year follow-up remained significant after the adjustment of BMI and energy intake. In contrast, Barba et al. (25) found an association between EF and BP in children from southern Italy that was not independent from BMI, which is also confirmed by Kim et al. (12) in an adult population. Secondly, although the association was still significant, attenuation could be observed when WC and dietary intake were included in the regression models, which may also indicate an indirect pathway of the MIB-BP association. Both confounders are known risk factors of high BP, although the metabolic pathways underlying the mechanism are still under discussion. The mechanisms are possibly multifactorial, such as endothelial dysfunction, alteration of the nervous system and kidney function, and the modification of the balance of specific hormones like insulin and leptin (28,29).

This study had several limitations. First, the sample was neither randomly selected nor representative of the Spanish population. The data were collected during events whose objectives were targeting cardiovascular risk factors among the participants and providing information about current lifestyle. Therefore, the study was biased towards certain risk groups that might be more sensitive to their own health, as observed by the higher participation of women and older people. Second, causal relationships could not be established because of the cross-sectional design of the study, even though the analysis was carefully adjusted. However, residual confounding cannot be ruled out. For example, our results might be biased for not having considered the use of antihypertensive medication. This might have led to underestimation of the MIBs-BP association and the presence of disease with an impact on cardiovascular health, such as diabetes mellitus or kidney diseases. Third, the questionnaire used to assess dietary intake was not previously validated.

In contrast, the study had various strengths. First, the use of linear regression models allowed us to deepen into the nature of the associations. Second, WC was measured directly rather than self- reportedly, thus avoiding response errors and underestimations. Finally, a trained person guided the participants through the questionnaire, guarding against wrong interpretations of questions, as well as memory gaps and inexactness.

In conclusion, we found that the intake of an afternoon meal was directly associated with lower BP. This represents a novel result as MIBs, which had rarely been studied before, were investigated. The results might easily be included in dietary advisories. However, in order to confirm the findings, further population-based studies by means of validated measurements of dietary pattern and confounders are needed.

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ARÁN

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Trabajo Original

Epidemiología y dietética

Iodine levels are associated with oxidative stress and antioxidant status in pregnant women with hypertensive disease

Los niveles de yodo están asociados con estrés oxidativo y estado antioxidante en mujeres embarazadas con enfermedad hipertensiva

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Abstract

Background: The antioxidant function of iodine and iodine deficiency as a risk factor of preeclampsia have been previously reported.

Aim: To analyze the association between iodine deficiency, oxidative stress and antioxidant status with hypertensive disease of pregnancy (HPD).

Method: Fifty-seven pregnant women were recruited in the last trimester of pregnancy; 20 were diagnosed with hypertensive disease (HPD) of pregnancy and 37 were normotensive pregnant women. Urinary iodine concentration (UIC), TSH, free T4 (fT4), total antioxidant status (FRP), superoxide dismutase (SOD), catalase (CAT), and oxidative stress (TBARS) were evaluated by colorimetric methods.

Results: UIC median for all pregnant women was 151.9 µg/l. The UIC for pregnant women with HPD was 50-149 µg/l, compared to 150-249 µg/l in normotensive women. No significant differences in levels of TSH and fT4 in normotensive pregnant compared with HPD women were found. Pregnant women with HPD had significant high levels of TBARS, and significant low levels of FRP, SOD, CAT and UIC compared to normotensive pregnant. In addition, pregnant women with optimal levels of UIC had a higher SOD activity ($r = 0.354$, $p = 0.011$), while iodine deficiency was associated with HPD ($r = -0,281$, $p = 0.039$). Similarly, pregnant women with HPD had a significant negative association with SOD activity ($r = -0.702$, $p = 0.005$), CAT ($r = -0.409$, $p = 0.002$), and FRP ($r = -0.624$, $p = 0.003$), and a positive association with TBARS ($r = 0.744$, $p = 0.001$).

Conclusion: Iodine contributes to redox balance during pregnancy; its deficiency is associated with HPD. This study shows the importance of iodine during pregnancy.

Key words:

Iodine deficiency.
Pregnancy-induced hypertension.
Oxidative stress.
Antioxidant status.

Resumen

Antecedentes: previamente se han reportado la función antioxidante del yodo y su deficiencia como un factor de riesgo de preeclampsia.

Objetivo: analizar la asociación entre la deficiencia de yodo, el estrés oxidativo y el estado antioxidante con la enfermedad hipertensiva del embarazo (HPD).

Métodos: cincuenta y siete mujeres embarazadas se reclutaron en el último trimestre del embarazo, 20 diagnosticadas de enfermedad hipertensiva del embarazo y 37 gestantes normotensas. La concentración urinaria de yodo (UIC), TSH, T4 libre (hT4), estado antioxidante total (FRP), superóxido dismutasa (SOD), catalasa (CAT), y estrés oxidativo (TBARS) se evaluaron por métodos colorimétricos.

Resultados: la mediana de UIC para todas las mujeres embarazadas fue de 151,9 µg/l. La UIC para las mujeres embarazadas con HPD fue de entre 50 y 149 µg/l, comparada con 150-249 µg/l de las gestantes normotensas. No se encontraron diferencias significativas entre los niveles de TSH y fT4 en embarazadas normotensas y en mujeres con HPD. Las mujeres embarazadas con HPD tuvieron niveles altos de TBARS y niveles bajos de FRP, SOD, CAT y UIC comparadas con las gestantes normotensas. Además, las mujeres gestantes con niveles óptimos de UIC tuvieron la actividad SOD más alta ($r = 0,354$, $p = 0,011$), mientras que la deficiencia de yodo se asoció con HPD ($r = -0,281$, $p = 0,039$). De manera similar, las gestantes con HPD tuvieron una asociación negativa con la actividad de SOD ($r = -0,702$, $p = 0,005$), CAT ($r = -0,409$, $p = 0,002$) y FRP ($r = -0,624$, $p = 0,003$), y una asociación positiva con TBARS ($r = 0,744$, $p = 0,001$).

Conclusión: el yodo coadyuva en el balance redox durante la gestación; su deficiencia está asociada con HPD. Este estudio muestra la importancia del yodo durante la gestación.

Palabras clave:

Deficiencia de yodo.
Hipertensión inducida por el embarazo.
Estrés oxidativo.
Estado antioxidante.

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INTRODUCTION

Hypertensive disorders of pregnancy are a major cause of maternal morbidity and mortality worldwide; within this group of diseases preeclampsia is very interesting because it causes about 50,000 deaths per year worldwide (1). In Mexico, hypertensive disorders of pregnancy represent about 34% of all maternal deaths, so it is considered as one of the main causes of death (2). Although there have been great advances in medicine, the frequency of this disease has not been successfully modified significantly (3). Currently, the etiology of this disease remains unknown, therefore, in order to explain its origin various theories have been raised, and within each of them the genetic origin, immune factor, endothelial dysfunction, increased oxidative stress, micronutrients deficiency, among others, can be mentioned (3-8). During pregnancy, there is a normal increase in the production of reactive oxygen species (ROS); likewise, the antioxidant capacity is increased. However, in women with hypertensive disorders an imbalance that causes increased oxidative stress has been found (9,10). It has been suggested that lipid peroxides, from altered oxidative stress, are likely promoters of maternal vascular malfunction, vasoconstriction and imbalance between thromboxane and prostacyclin, inducing endothelial cell dysfunction (8,11). Deficiency of several trace element is reported in pregnant women with preeclampsia (12). One of the most important micronutrients during pregnancy is iodine, which must be consumed through daily intake (250-300 µg/l). One of its main functions is the synthesis of thyroid hormones involved in the proper development of the fetus as well as in the regulation of various metabolic processes in adulthood. During gestation, iodine deficiency is a risk factor of preeclampsia (13-17). Iodine *per se* has several functions: bactericidal, apoptosis inducer, antioxidant, and it has been recently involved in migration, invasion and trophoblast differentiation (18-22). Regarding the role of iodine as an antioxidant, it has been proposed that it can act directly as an electron donor and compete for binding sites with free radicals (23). While in an indirect way iodine can be iodinated fatty acids derived from arachidonic acid and join a superfamily of known nuclear receptors as receptors activators peroxisomal proliferation (PPAR), which have the function of acting as transcription factors that regulate antioxidant genes activation (24-26). Iodine deficiency may be involved in the alteration of the antioxidant balance, and thus increase levels of oxidative stress, causing the development of complications during pregnancy and hypertensive disorders (5). This study aimed to establish the association between iodine levels in urine, antioxidant status and oxidative stress and women diagnosed with hypertensive disorder of pregnancy.

MATERIALS AND METHODS

PATIENTS

A case-control study in pregnant women from Xalapa, Veracruz (Mexico), who received antenatal care in the Hospital Regional Luis F. Nachón was carried out. The hospital Ethics Committee and the Bioethical Committee of the health institute of the University of Veracruz approved the study, which complies with the Declaration of Helsinki of 1964 and its later amendments or comparable ethical standards. In this study, we incorporated 57 pregnant women in the third trimester between 18 and 35 years old, 20 pregnant women with hypertensive pregnant disease (HPD) as cases, and 37 normotensive pregnant as controls. Each pregnant woman signed an informed consent letter and questionnaires in order to known their sociodemographic and clinical characteristics, and food consumers were applied. The subjects with diabetes mellitus, severe anemia, and thyroid disease were excluded from this study. The blood collection and urinary sampling were carried out from January 2015 to April 2015 in the Gynecology and Obstetrics area of the Hospital Luis F. Nachón (Xalapa, Veracruz). Five milliliters of fasting venous blood were collected in BD Vacutainer® and preserved using packs of ice blocks; later, they were transported to the laboratory for the assessment of TBARS level, an indicator of oxidative stress. SOD, catalase, and total antioxidant status (TAS) were measured as indicators of antioxidant status as previously reported (5). The blood samples were centrifuged at 5,000 rpm for five minutes to separate plasma. The layers of white blood cells above the packed erythrocytes were discarded. Erythrocyte pellet was washed three times with 0.15 HCL, diluted in 33% of phosphate buffer saline (mM; NaCl, 136.9; KCl, 2.68; KH_2PO_4, 1.47; $Na_2 HPO_4$, 6.62; and pH 7.4), and kept at 4 °C until use. Similarly, the urine samples were collected and 10 ml were preserved in frozen-capped plastic tubes and 20% of formalin (two drops) were added in order to minimize iodine volatilization; then, they were frozen and analyzed. All blood samples were preserved in the refrigerator and the prooxidants and antioxidant parameters were estimated using a spectrophotometer within 48 hours of collection of the blood samples.

URINARY IODINE CONCENTRATION, TSH AND FREE T4 DETERMINATIONS

Urinary iodine concentration (UIC) was measured using a fast colorimetric method, appropriate for population studies (5,15). Briefly, 0.2 ml of serum or iodine calibrator (50-300 µg/l) and 1.0 ml of ammonium persulfate solution were heated for one hour at 100 °C. After adding arsenious acid solution (10 g of As_2C_3, 50 g of NaCl, 400 ml of 2.5 mol/l H_2SO_4) to each tube, it was mixed in a vortex mixer. Then, fresh ferroine-arsenic acid solution (10.8 mol/l H_2SO_4, arsenious acid, 200 g/l sodium chloride, and 2 ml ferroine) was added. Finally, ceric ammonium sulfate solution was added with the multipipetter, and the content of each glass tube (150 µl) was then transferred to a sterile polystyrene microtiter plate. Iodine was determined by the rate of color disappearance at 504 nm of each well in a microplate reader (Spectramax Plus; Molecular Devices, Sunnyvale, CA). The UIC was determined by subtracting the OD of the blanks, and is expressed as µg/l against a standard iodine concentration (50-300 µg/l). The adequate values according to the UNICEF/WHO/ICCID (1) criteria were: exces-

sive UIC, > 250 µg/l; optimal iodine concentration, 150-200 µg/L; mild deficiency, 50-99 µg/l; moderate deficiency, 20-49 µg/l; and severe deficiency, < 20 µg/l. Serum TSH was measured using the Monobind Thryotropin Test System kit, and serum free T4 was measured with kit; both determinations were done with IMMULITE® 1000. The normal range of TSH and fT4 were considered as 0.39-6.16 UiO/ ml and 0.8-2.0 ng/dl, respectively.

ANTIOXIDANT STATUS

Catalase enzymatic activity was measured colorimetrically by the method of Sinha (27). The activity of SOD in erythrocytes was determined by the method described by Madesh and Balasubramanian (28). The total antioxidant status (TAS) was measured colorimetrically as reported (5), and hemoglobin, by the method previously described (29).

DETERMINATION OF OXIDATIVE STRESS BY TBARS

TBARS were measured in 90 µl of sample, which was mixed with 70 µl of TRIS (150 mM pH 7.5), 300 µl of mix with 0.4% of tiobarbituric acid, 20% acetic acid pH 3.0, and then, 90 µl of each sample were added. All samples were warmed to 100 °C during 45 minutes in a thermoblot. The samples were cooled in ice, and 1.2% of KCl was added. After centrifugation, 180 µl of overnadant were read and measured at 532 nm in a microplate reader (Spectramax Plus; Molecular Devices, Sunnyvale, CA). The results were expressed in absorbance units per 0.1 ml of sample nanomoles/gram hemoglobin.

STATISTICAL ANALYSIS

Data obtained were analyzed statistically using SPSS 17 for Windows (SPSS Inc., Chicago, IL, USA). The Student's t test and the ANOVA test were used to compare the continuous variables with normal distribution in two or more independent groups, whereas the Mann-Whitney U and Kruskal Wallis test were used for continuous variables with non-Gaussian distribution. Normally distributed data (CAT, FRP, TBARS, fT4 and creatinine) were expressed as means ± SD; non-normally distributed variables (SOD, THS and UIC) were expressed as medians (interval 5-95%). Differences with $p < 0.05$ were considered as significant. Spearman correlation tests were done with SPSS, and $p < 0.05$ were considered as significant.

RESULTS

A total of 57 eligible women consented to participate in the study. Table I presents data concerning sociodemographic and lifestyle variables. Mean age was 24.35 years (SD = 5.83; range = 15-40); 13.5% of controls and 20% of pregnant women had a history of preeclampsia and arterial hypertension. Maternal median UIC in the spot urine sample was 155.85 µg/l, with a range of 54.85-332.84 µg/l, and when was corrected for median urinary creatinine (168.9 µg/g creatinine). Seventy per cent (n = 14) of pregnant women with HPD had UIC between 50-149 µg/l, while 30% (n = 6) had the adequate level of 150-249 µg/l. As for control normotensive pregnant women, 24.32% (n = 9) had 50-149 µg/l, 48.64% had 150-249 µg/l (n = 18), and 27.02% (n = 10) had > 250 µg/l. Median values of the serum TSH in normotensive and HPD women were 1.7 ± 1.11 mIU/l, and 1.86 ± 1.58 mIU/l, respectively. While free T4 were 1.16 ± 0.17 ng/dl, and 1.07 ± 0.18 ng/dl, for normotensive and HPD women, respectively. The sub-clinical hypothyroidism (SCH), defined as elevated serum TSH with normal fT4 level, was seen among 14% (n = 8) of pregnant women, and none of them were found to be overt hypothyroid, although five pregnant women had iodine deficiency (50-149 µg/l) and four had HPD.

Table I. Sociodemographic characteristics from pregnant normotensive and HPD women

Characteristics	Cases (n = 20)	Control (n = 37)
Years (mean ± SD)	24.5 ± 6.06	24.21 ± 5.61
Education (years) (mean ± SD)	10.20 ± 2.04	10.22 ± 2.72
History of gestational hypertension and preeclampsia (%)	20	13.5
History of abortion (%)	20	10.8
History of stillbirth (%)	0	0
Primiparous (%)	50	54.1

The values of TBARS (oxidative stress), FRP, SOD, CAT activity (antioxidant status), TSH, fT4 and UIC are included in table II. We compared values between the normotensive and HPD groups, and significant higher levels of TBARS were found in the HPD group, 10.68 ± 2.9 *vs* 4.82 ± 1.13 µmol/l in normotensive pregnant women. Also, significant lower levels of SOD (2.29 ± 0.54 units mg/Hb), CAT (46.16 ± 8.8 units mg/Hb) and FRP (451.2 ± 29.2 µmol Fe2/l) enzymatic activities were found in the HPD group, compared to upper levels of SOD (3.5 ± 0.26 units mg/Hb), CAT (55.5 ± 9.53 units mg/Hb) and FRP (538.4 ± 29.3 µmol Fe2/l) in the normotensive pregnant control group. Likewise, significant lower levels of UIC were found in HPD (142.15 ± 84.8 µg/l) *vs* (185.7 ± 77.16 µg/l) in normotensive pregnant women ($p = 0.0174$). In table III, groups were separated in normotensive and HPD pregnant women with sufficiency, deficiency iodine levels, and differences in the biochemical parameters compared by the two-way ANOVA test. We found a significant statistical difference between UIC from HPD women with iodine deficiency *vs* HPD women with iodine deficiency ($p < 0.001$). In SOD activity low levels were found in HPD women vs normotensive pregnant women ($p < 0.05$). In normotensive pregnant women with sufficiency

Table II. Biochemical and hormonal parameters in normotensive and HPD pregnant women

Parameters	media ± DE	Median	Range	95% IC	p value
SOD (units mg/Hb)[a]					
Normotensive	3.6 ± 0.26	3.6	3.07-4.00	3.4-3.6	= 0.001*
HPD	2.29 ± 0.54	2.4	1.1-2.83	2.03-2.55	
CAT (units mg/Hb)					
Normotensive	55.5 ± 9.53	55.83	19.33-81.23	53.3-59.85	= 0.0317**
HPD	46.16 ± 8.8	46.83	37.36-57.03	40.04-48.28	
FRP (µmol Fe2/l)					
Normotensive	538.4 ± 29.3	537.3	485.83-603.61	528.5-548.4	= 0.001**
HPD	451.2 ± 29.2	460.8	401.56-488.40	437.6-464.9	
TBARS (µmol/l)					
Normotensive	4.82 ± 1.13	4.9	3.20-7.52	4.4-5.2	= 0.001**
HPD	10.68 ± 2.9	10.60	4.97-14.63	9.32-12.04	
TSH (µmlU/ml)[a]					
Normotensive	1.7 ± 1.11	1.3	0.31-5.66	1.3-2.0	= 0.9115
HPD	1.86 ± 1.58	1.37	0.51-6.07	1.1-2.6	
T4L (ng/dl)					
Normotensive	1.16 ± 0.17	1.18	0.83-1.60	1.10-1.22	= 0.0905
HPD	1.07 ± 0.18	1.03	0.69-1.29	0.98-1.15	
UIC (µg/l)[a]					
Normotensive	185.7 ± 77.16	176.4	54.39-291.97	159.6-211.8	= 0.0175*
HPD	142.15 ± 84.8	98.8	57.72-332.85	102-181	

*[a]There was not normal (Gaussian) distribution of the values, and the assessment was done on the basis of the median value. *Significance between normotensive and HPD women, Mann-Whitney test. **Significance between normotensive and HPD women-independent samples t test (paired t test).*

Table III. Biochemical parameters in normotensive and HPD pregnant women with sufficiency and deficiency iodine levels

Pregnant women	No.	SOD (units mg/Hb)	CAT (units mg/Hb)	FRP (µmol Fe2/l)	TBARS (µmol/)	TSH (µIU/ml)	hT4L (ng/dl)
Normotensive							
Iodine defficiency (< 149 µg/l)	11	3.5 ± 0.2[a]	59.8 ± 7.9[a]	532.9 ± 20.7[b]	4.8 ± 0.9[b]	1.4 ± 0.6	1.12 ± 0.1
Iodine sufficiency (> 150 µg/l)	25	3.6 ± 0.2[b]	55.1 ± 10.1[b]	540.9 ± 32.5[c]	4.8 ± 1.2[c]	1.8 ± 1.2	1.18 ± 0.1
Total	36	3.6 ± 0.2	55.1 ± 10.1	540.9 ± 32.5	4.8 ± 1.2	1.8 ± 1.2	1.18 ± 0.1
HPD							
Iodine deficiency (< 149 µg/l)	16	2.1 ± 0.5	43.3 ± 9.2	450.5 ± 30.7	10.3 ± 2.9	1.6 ± 1.3	1.0 ± 0.1
Iodine sufficiency (> 150 µg/l)	4	2.6 ± 0.2	47.4 ± 6.3	454.0 ± 26.0	11.8 ± 2.7	2.9 ± 2.1	0.9 ± 0.1
Total	20	2.6 ± 0.2	47.4 ± 6.3	454.0 ± 26.0	11.8 ± 2.7	2.9 ± 2.1	1.0 ± 0.1

Significant differences between media ± DE of normotensive and hypertensive pregnant women with two-way ANOVA test. [a]$p < 0.05$ between media ± DE of normotensive women with iodine deficiency vs HPD women with iodine deficiency. [b]$p < 0.001$ between media ± DE of normotensive women with iodine sufficiency vs HPD women with iodine sufficiency. [c]$p < 0.001$ between media ± DE of normotensive women with iodine deficiency vs HPD women with iodine deficiency.

and deficiency iodine levels, FRP (antioxidant status) was higher in comparison with HPD pregnant women ($p < 0.001$). Higher TBARS levels were found in HPD women with iodine sufficiency and deficiency compared with normotensive pregnant women ($p < 0.05$).

Table IV shows a significant positive correlation between normal UIC with SOD activity increase ($r = 0.354$, $p = 0.011$), although low UIC negatively correlated with HPD ($r = -0.281$, $p = 0.039$), suggesting that iodine deficiency and HPD are associated. In addi-

Table IV. Correlation between biochemical and hormonal parameters with iodine levels in normotensive and HPD pregnant women

Pregnant women	UIC		SOD		CAT		FRP		TBARS		TSH		T4L	
Normotensive	**R**	**P**	**R**	**P**	**R**	**P**	**R**	**P**	**R**	**P**	**R**	**P**	**R**	**P**
Iodine defficiency	0.193	0.343	-0.508	0.110	-0.266	0.429	0.451	0.164	-0.221	0.514	-0.302	0.366	0.066	0.847
Iodine sufficiency	-0.062	0.638	0.398	0.011	0.080	0.768	-0.214	0.426	-0.111	0.683	0.078	0.774	0.273	0.306
HPD														
Iodine deficiency	-0.281	0.038	-0.975	0.025	-0.409	0.030	0.641	0.059	-0.562	0.078	-0.196	0.468	0.255	0.341
Iodine sufficiency	-0.362	0.113	-0.016	0.953	0.771	0.229	0.018	0.946	0.047	0.863	0.168	0.332	-0.340	0.660

tion, SOD ($r = 0.975$, $p = 0.025$) and CAT ($r = -0.409$, $p = 0.027$) activities correlate with HPD women with iodine deficiency.

DISCUSSION

This study shows that iodine deficiency is associated with hypertensive disease of pregnancy, as 70% of women with hypertensive disease of pregnancy had iodine deficiency with a median iodine level of 99.9 µg/l, as compared with 24.32% of normotensive women who had iodine deficiency with a median of 138.9 µg/l urinary iodine. This is consistent with previous studies that report a 45 mg/l UIC in pregnant women with preeclampsia (15,17). This data confirming that iodine deficiency is associated with hypertensive disease. In Mexico, the lack of nutritional information, as well as water contamination with heavy metals and consumption of foods rich in goitrous substances or junk foods, may be contributing to iodine deficiency in vulnerable groups such as children and pregnant women (30-32). However, further studies are required to determine the source of iodine deficiency in vulnerable groups, pregnant women and children specifically.

Oxidative stress is characterized by the presence of an excess of reactive oxygen species, outstripping the available capacity of antioxidants. This increase has been associated with various diseases such as cancer, atherosclerosis and preeclampsia (PE), among others (33-35). Imbalance between antioxidant defenses and lipid peroxidation leads to endothelial dysfunction and cell damage mediated by free radicals, altering trophoblast differentiation processes and migration to the uterine spiral arteries, and causing poor placentation and, consequently, pregnancy hypertensive disease (5,36,37). In pregnant women with preeclampsia, high levels of oxidative stress and low antioxidant status were found (38). It has been suggested to free radicals, superoxide anions primarily as promoters of maternal vascular malfunction, causing endothelial dysfunction (11), which leads to PE. About this study in pregnant women with hypertensive disease of pregnancy, they showed high levels of oxidative stress and low levels of antioxidant enzymes such as SOD, CAT and total antioxidant status compared with normotensive pregnant women. In this regard, our results clearly show high levels of markers of oxidative stress in pregnant women with HPD and low antioxidant levels, as reported by other authors (39-41); however, they are accented in pregnant women with iodine deficiency.

Micronutrient deficiency has been associated with increased oxidative stress during pregnancy. In this regard, this study shows for the first time that pregnant women with normal levels of iodine have significantly increased activity of SOD enzyme, compared with pregnant women with HPD, where it is decreased, indicating that normal iodine levels contribute to redox balance during pregnancy. In this respect, previous studies with iodine deficient rats showed that supplementation with potassium iodide increases the antioxidant activity in retina, an effect that is mediated by an increase of glutathione peroxidase (42). Similarly, patients with type II diabetes mellitus who received iodine brine drinking cure had increased antioxidant levels due to increased GSH-Px activity (43), indicating an antioxidant effect of iodine. In this study, pregnant women with HPD had low levels of SOD and CAT enzymes, decreased total antioxidant status and increased oxidative stress compared to normotensive pregnant women. On the other hand, normotensive pregnant women with normal levels of iodine had high levels of SOD and CAT enzymes and antioxidant status, as well as low oxidative stress compared to pregnant women with HPD, indicating that adequate levels of iodine contribute to redox maintenance during pregnancy. In addition, it has been shown that iodine deficiency alters trophoblast differentiation and induced an aberrant migration mediated by ROS increase, suggesting that iodine deficiency contributes to a dysfunctional endothelium and thus pregnancy complications (22). Besides iodine deficiency, other trace elements such as magnesium, selenium, copper, and iron were associated with PE (12). In conclusion, pregnant women with HPD had higher levels of oxidative stress and low antioxidant status, values accentuated in pregnant women with iodine deficiency, indicating that normal levels of iodine during pregnancy contribute to maintaining redox balance. In addition, these facts confirm that iodine deficiency is associated with HPD.

It is important to develop nutritional education programs aimed at women of reproductive age and pregnant women from the first trimester in order to avoid complications of pregnancy associated with micronutrient deficiency.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Epidemiología y dietética

A low fermentable oligo-di-mono-saccharides and polyols (FODMAP) diet is a balanced therapy for fibromyalgia with nutritional and symptomatic benefits

Una dieta baja en oligo-, di- y monosacáridos (FODMAPs) es un tratamiento adecuado para pacientes con fibromialgia, con beneficios clínicos y nutricionales

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Abstract

Introduction: Fibromyalgia is a chronic rheumatic disease producing widespread pain, associated to a major comorbidity -irritable bowel syndrome. Low FODMAPS diet (low fermentable oligo-di-mono-saccharides and polyols diet) has been effective in controlling irritable bowel syndrome symptoms. Overweight is an aggravating factor for fibromyalgia. We studied effects of low fermentable oligo-di-mono-saccharides and polyols diets on fibromyalgia symptoms and weight status.

Methods: A longitudinal study was performed on 38 fibromyalgia patients using a four-week, repeated assessment as follow: M1 = first assessments/presentation of individual low fermentable oligo-di-mono-saccharides and polyols diet; M2 = second assessments/reintroduction of FODMAPs; M3 = final assessments/nutritional counselling. The assessment instruments applied were: Fibromyalgia Survey Questionnaire (FSQ); Severity Score System (IBS-SSS); visual analogic scale (VAS). Body mass-index/composition and waist circumference (WC) were also measured. Daily macro-micronutrients and FODMAP intake were quantified at each moment of the study.

Results: The studied cohort was 37% overweight, 34% obese (average body mass-index 27.4 ± 4.6; excess fat mass 39.4 ± 7%). Weight, body mass-index and waist circumference decreased significantly ($p < 0.01$) with low fermentable oligo-di-mono-saccharides and polyols diet, but no significant effect on body composition was observed. All fibromyalgia symptoms, including somatic pain, declined significantly post-LFD ($p < 0.01$); as well for severity of fibromyalgia [Fibromyalgia survey questionnaire: M1 = 21.8; M2 = 16.9; M3 = 17.0 ($p < 0.01$)]. The intake of essential nutrients (fiber, calcium, magnesium and vitamin D) showed no significant difference. The significant reduction in FODMAP intake (M1 = 24.4 g; M2 = 2.6g; $p < 0.01$) reflected the "Diet adherence" (85%). "Satisfaction with improvement of symptoms" (76%), showed correlating with "diet adherence" ($r = 0.65$; $p < 0.01$).

Conclusions: Results are highly encouraging, showing low fermentable oligo-di-mono-saccharides and polyols diets as a nutritionally balanced approach, contributing to weight loss and reducing the severity of FM fibromyalgia symptoms.

Key words:

FODMAP. Fibromyalgia. Irritable bowel syndrome. Pain. Diet. Short-chain. Carbohydrates.

Resumen

Introducción: la fibromialgia es una enfermedad reumática crónica, que tiene unas importantes comorbilidades -síndrome del intestino irritable (SII). La dieta baja en FODMAPs (*low fermentable oligo-di-mono-saccharides and polyols diet*) ha sido eficaz en el tratamiento del síndrome del intestino irritable. El sobrepeso es un factor agravante. Se estudiaron los efectos nutricionales del FODMAPs en la fibromialgia.

Métodos: estudio longitudinal en 38 pacientes con fibromialgia en el que se utilizó una evaluación repetida, durante cuatro semanas, de lo siguiente: Moment 1 (M1) = primeras evaluaciones/presentación de FODMAPs; M2 = segundas evaluaciones/reintroducción de FODMAPs; M3 = evaluaciones finales/asesoramiento nutricional. Instrumentos de evaluación: *Fibromialgia Survey Questionnaire;* síndrome del intestino irritable (IBS-SSS), escala visual analógica (EVA) y parámetros antropométricos. Cuantificación en todo momento de las ingestas diarias de macro/micro nutrientes y FODMAPs.

Resultados: el estudio de cohorte mostró 37% de sobrepeso y 34% obesidad; índice de masa corporal = 27,4 ± 4,6; masa grasa = 39,4 ± 7%. El peso y la circunferencia de la cintura disminuyeron significativamente con FODMAPs, pero no cambió la composición corporal. Los síntomas y la severidad de la fibromialgia (FSQ: M1 = 21,8; M2 = 16,9; M3 = 17,0) se redujeron significativamente después de FODMPAs ($p < 0,01$). No fueron observadas diferencias significativas en el consumo de nutrientes esenciales, especialmente la fibra, calcio, magnesio y vitamina D. El "seguimiento de la dieta" fue del 85% con reducción significativa de la ingesta de FODMAPs ($p < 0,01$: M1 = 24,4 g; M2 = 2,6 g). "La satisfacción con la mejora de los síntomas" (76%) se correlacionó con el "seguimiento de la dieta" ($r = 0,65$; $p < 0,01$).

Conclusiones: los resultados son muy alentadores, mostrando FODMAPs como un enfoque equilibrado nutricionalmente, que contribuyó a la pérdida de peso y redujo significativamente la severidad de la FM.

Palabras clave:

FODMAP. Fibromialgia. Síndrome del intestino irritable. Dolor. Dieta. Hidratos de carbono de cadena corta.

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INTRODUCTION

Fibromyalgia (FM) is a functional, diffuse, widespread pain-syndrome classified and recognized by the World Health Organization as a rheumatic pathology with unknown aetiology and currently with no specific effective pharmacotherapy (1). Globally, FM is the third most frequent rheumatic disease, presenting a prevalence of 3.7%, in Portugal (2) and an average age of affliction of 59 years old (3).

FM is a chronic disease having strong impact on the quality of life and, similarly to the majority of chronic diseases, there is a substantial relationship between nutrition, health and well-being (4). Current guidelines consistently recommend a multidisciplinary approach for treating FM (5), wherein nutrition could play a key role.

In addition, obesity is a common factor in patients presenting FM (6). However, it is difficult to determine if obesity associated with FM is a consequence of inactivity imposed by pain, mental state, medication or other factors, or inversely, if obesity directly contributes to FM as an physiopathological aspect. Several studies found that being overweight can affect symptoms of FM (6). Arranz et al. showed a specific body composition in FM patients (high fat mass and low fat free mass) and found that BMI and body composition were correlated with quality of life and symptoms in FM patients (7).

Fava et al. described an increased metabolic risk, with insulin resistance, in FM patients probably due to a relationship between BMI and C-reactive protein, reflecting a micro-inflammation environment, especially in obese FM patients (8). In another study, Alcocer-Gómez et al. showed, *in vitro,* that restricting caloric content to patients fibroblasts, resulted in improved AMP phosphorylation, mitochondrial function and stress response, suggesting diet might have an *in vivo* role in FM treatment (9).

Food sensitivities are also frequently reported by FM patients, indicating a potential dietary link to central sensitization (10). A food awareness survey showed that 30% of FM patients attempted to control symptoms by restricting particular foods (11). Slim et al. proposed dietary interventions for FM treatment using a restricted gluten, lactose or FODMAPs diet; recently, published the results of the pilot trial comparing a gluten free diet (GFD) with a hypocaloric diet (HCD) in FM patients with gluten sensitivity symptoms (NCGS) (12,13); showed no significant difference between the two interventions but with similar benefits in the outcomes. Despite its specificity, GFD wasn't superior to HCD, including the effects in NCGS (14).This study is in accordance with the opinion of other authors as Biesiekiersk: gluten restriction has no effect in patients with non-celiac gluten sensitivity (NCGS), and suggested that "wheat FODMAP" could be the trigger of FM symptoms, instead of gluten (15).

As a whole, the above results suggest that diet can have a potential therapeutic role in the balance of FM syndrome. One possible dietary approach could be to restrict FODMAPs (Fermentable Oligo-Di-Mono-saccharides And Polyols) as part of a multidisciplinary treatment of FM (16). FODMAPs are composed by, poorly absorbed, short-chain carbohydrates, including excess free fructose, lactose, polyols, fructo-oligosaccharides, and galacto-oligosaccharides (17). A low FODMAP diet (LFD) was already found to alleviate GI disorders and symptoms of IBS (16,18) and by comparison, as about 70% of FM patients report IBS symptoms (19), we hypothesized that LFDs may have some therapeutic benefit on FM symptoms.

It's based in the evidence that, patients with IBS could present extraintestinal symptoms (2/3 prevalence of rheumatic disease). Symptoms of IBS usually overlap in 70% of FM patients and 60% inversely. Clinically FM does not differ whether or not it has associated IBS symptoms (19,20,22).

Literature suggests a possible common cause, responsible by both conditions. Common characteristics between IBS and FM: both are characterized by functional pain, not explained by biochemical or structural abnormalities, with predominance in females, associating with life-stressing and complain of sleep disturbances and fatigue. Therapeutic response to the same pharmacotherapy and psychotherapy is described.

Some authors consider contradictory the association between IBS and FM relating it with anti-inflammatory drugs or possible diagnosis of celiac disease in a history of FM.

To date weren't found studies showing the impact of results of LFDs on FM symptoms. This study was a pilot clinical trial on LFDs impact on FM symptoms and nutritional status of participants. Also, was included the objective of demonstrate the nutritional balance of the LFDs.

MATERIALS AND METHODS

PARTICIPANTS

A longitudinal study, involving introduction of LFDs to participants suffering from FM. All participants were referred from a qualified rheumatologist having a confirmed diagnosis of FM, according to American College of Rheumatology criteria, 2011 (22). The trial was conducted between January and May 2015, based on a four-week, repeated assessment model.

All patients signed an Informed consent agreement (2013 Declaration of Helsinki) to participate in the trial. The research project was approved by the Ethics Committee, Medical Academic Centre of Lisbon.

Inclusion criteria for participants were: 18-70 years old; diagnosed with FM at least one year; having received FM therapy for at least 3 months prior to the study enrollment; and having already excluded referrals on a restricted FODMAP diet, or having comorbidities requiring specific nutritional therapy. Exclusion criteria included the co-morbidities requiring specific nutritional approaches such as renal insufficiency, diabetes, celiac disease. Participants with intercurrences as Influenza and respiratory infections were excluded.

STUDY PROTOCOL

The study consisted in three different assessments "Moments" of four weeks each, at repeated intervals, completing eight weeks

of intervention. A physician and a registered dietician were present at all assessments and available throughout the trial.

At the beginning (Moment 0) participants were introduced to the purpose and protocol of the trial. They signed informed consent agreements and received a booklet containing instructions and recipes for preparing food, as well as tables with the food rich in FODMAPs and a record-keeping section for cataloguing foods and food amounts consumed over a 72 h period.

The recommended diet in Moment 1 (M1) was elaborated reducing lactose, replacing it by lactose free products and dairy alternative drinks; reducing excess of fructose replacing apple, mango, peaches, pear, watermelon, honey, sweeteners as fructose, HFCS, by banana, blueberry, grape, melon, orange, strawberry; reducing fructans rich foods as wheat, rye, onion, garlic replacing them by corn, spelt, rice, oat, gluten free products and garlic-infused oil; reducing galactans rich foods as cabbage, chickpeas, beans, lentils replacing them by vegetables as carrot, celery, green beans, lettuce, pumpkin, potato, tomato; reducing polyols rich foods as apricots, cherries, nectarine, plums, cauliflower, sorbitol xilitol replacing them by fruits as grapefruit, kiwifruit, lemon, lime, passionfruit.

Total FODMAP intake [collective amounts of lactose, fructans, galactans, free fructose and polyols (g/day)], energy (kcal/day), and macronutrients/micronutrients consumed by the participants were quantified for each monitoring period (Moment). Participants reported individual food intake based on standardized dish, cup, and spoon measurements. The estimated dietary intake was calculated from these measurements. Quantities were based upon published amounts of FODMAPs and respective food composition tables (23,24).

At Moment 1 (M1), a clinical/dietary anamnesis was performed to obtain biographic and demographic data, comorbidities, medication requirements, food allergies or intolerances. Anthropometric assessments [weight, body mass index (BMI) and waist circumference (WC)] were performed. OMRON equipment (HBF-511B-E/HBF-511T-E) was used to evaluate fat mass and fat free mass.

All participants completed the questionnaires, which included:

- *Fibromyalgia Severity Questionnaire (FSQ),* validated according to the new ACR criteria, using a "widespread pain index" (19 points) and a "severity score index" (12 points), wherein combined scores ≥ 13 (0-31) indicate positive criteria of FM (22).
- *Irritable Bowel Syndrome-Symptom Severity Scale (IBS-SSS)*- uses a five visual analogue scale to quantify abdominal pain, abdominal distension, intestinal transit and the interference of IBS in daily life (0-500), score-ranked as "mild disease" (75-175), "moderate disease" (175-300) and "serious illness" (> 300) (25).
- *Clinical Outcomes in Routine Evaluation-Outcome Measure (Core-OM)* assessed the mental state and is scored 0-4 (26).
- *Visual Analogic System (VAS)* was applied for calibrating individual symptoms.

All assessment tolls are validated in English language; FSQ, Core-OM and VAS in Portuguese language. Each participant received a personal dietary plan (DP) for restricting foods rich in accordance to FODMAPs. The delivery of the DP was accompanied with accurate instructions and a request for utmost cooperation and compliance. Investigators and participants were totally available to communicate by phone or email in a regular basis.

At Moment 2 (M2) clinical/nutritional data were collected and all questionnaires were filled in, as at Moment 1. In addition, participants completed a questionnaire concerning their satisfaction and adherence to their diet. This questionnaire included questions about overall satisfaction with the study and specific satisfaction with symptoms improvement. Instructions were then given for gradual reintroduction of FODMAPs into their assigned dietary plan (DP). Was chosen a food, representing each FODMAP group, to be reintroduce, increasing the doses along 3 days with a three-day washout period.

Moment 3 (M3) was dedicated to determine any effects resulting from reintroduction of FODMAPs. Clinical and nutritional evaluations were made and assessment questionnaires applied in Moments 1 and 2 were filled in. Lastly, final dietary advice was provided to participants, encouraging them to maintain a balanced diet adjusted to body weight, and to exclude FODMAPs individually identified as being triggers of any negative symptoms.

STATISTICAL ANALYSIS

The Kolmogorov-Smirnov normality test, with Lillifors correction, was initially used to assess data normality. Changes in values between Moments were tested using analyses of variance (ANOVA) for repeated measures or the non-parametric Friedman test, if data were evaluated as not normally distributed. For the correlations analyses Pearson test or Spearman test were used. All analyses were performed using SPSS (version 22.0; SPSS, Inc., Chicago, IL, USA), and the significance level was set at $p \leq 0.01$ for all tests.

RESULTS

NUTRITIONAL STATUS OF PARTICIPANTS

The cohort consisted of 38 female participants with an average age of 51 years old, and 10 years of diagnosed FM. Thirty-one participants (82%) completed all trial phases. Four types of comorbidities were identified among participants, including gastrointestinal (GI) disorders as diarrhoea, constipation, gastritis, being most common (n = 33; 88%), osteoarthritic disorders (n = 28; 74%), immuno-allergies (n = 23; 60%) and endocrine disorders, such as thyroid dysfunction (n = 7; 18%). 60% of participants (n = 23) reported some form of food intolerance and 11% (n = 4) were allergic to certain foods (documented).

At the outset of the trial, the cohort presented a mean weight of 69 ± 12 kg, BMI of 27.4 ± 4.6 kg/m^2, body composition with excess fat mass (39.4 ± 7%) and a fat free mass in the lower limit (25.5 ± 3%), with an average WC of 84 ± 9 cm. Accordingly, a total of 27/38 (71%) of participants had excess of weight, 14

(37%) of them classified as obese. Only 11/38 (29%) were normal weight (Table I).

There was a significant decline in certain anthropomorphic indices among participants between M1 and M2 (restricting FODMAPs). There were significant reductions in mean Weight (> -1 kg; $p < 0.01$), BMI (-0.4 kg/m^2; $p < 0.01$) and WC (-2.5 cm; $p < 0.01$). However, no significant changes occurred with body composition (fat mass and fat free mass). The assessment made after reintroduction of FODMAPs, showed no significant changes (between M2 and M3) in all the parameters studied (Table II). Reduction in WC occurred simultaneously with a large reduction in abdominal distension with significant decline (VAS bloating score: M1 = 6.9, M2 = 2.8; M3 = 3.8; $p < 0.01$) (Table III).

DIETS

During all assessment moments, diet was characterized according to macro- and micronutrients including FODMAPs intakes, with the objective to demonstrate the nutritional balance of the LFDs. Average FODMAP intake declined significantly between M1 and M2, when was followed the FODMAP restrictive period (M1 = 24.4 ± 12 g/day *vs.* M2 = 2.63 ± 5.4 g/day; $p < 0.01$). However there was no significant change in FODMAP intake between M2 and M3, after reintroduction of FODMAPs (M2-M3 = 3.5 g/day; $p > 0.05$). The amounts of FODMAPs consumed by participants at M2, compared with those calculated in assigned dietary plans (DP), did not differ significantly (M2 = 2.63 ± 5.4 *vs.* DP = 0.96 ± 1.14 g/day; p = 0.836) (Table IV). Reported compliance in following the assigned diet plans was 86%.

Mean daily energy need was 1,548 ± 121 kcal based on a normocaloric diet for adjusted weight. Introduction of a normocaloric-LFD (1,552 ± 119) to participants resulted in significant ($p < 0.01$) reduction of caloric intake between M1 and M2 (M1 = 1,958 ± 404 kcal/day *vs.* M2 = 1,625 ± 304 kcal/day, respectively). In this group of patients, there were no significant differences in micronutrient intake as calcium (Ca), magnesium (Mg) and vitamin D (Vit D) between M1, M2 and M3; although the intakes were always lower according the DRI in all assessments [M1 doses: Ca = 703 mg (daily intake recommendation –DRI = 1000 mg), Mg = 249 (DRI = 400 mg), and Vit D = 2,16 ug (DRI = 15 ug)]. About macronutrients, only was found significant changes in the glycosides consume, between M1 and M2 (233.7 g *vs.* 180 g; $p < 0, 01$), and of the lipids, between M1 and M3 (79.4 g *vs.* 57.8; $p < 0, 01$). Fiber and protein intake was not affected by changes in the diets (Table IV).

Table I. Participant body composition (n = 38)

Weight (kg)*	69 ± 12
BMI (kg/m^2)*	27.4 ± 4.6
*BMI classes***	
Normal weight	29%
Overweight	37%
Obesity	34%
Waist circumference (cm) *	84 ± 9
% Fat mass *	39.4 ± 7
% Fat free mass *	25.5 ± 3
Energetic needs*	1548 ± 121

**Value expressed as MEAN ± SD; **Expressed as a percentage value.*

SYMPTOMS

According to the IBS-SSS classification, this cohort presented only 2/38 (4%) of the participants with a score below 75 (without disease), and 33/38 (87%) classified as moderate to severe disease (score over 175); 25/36 of them (70%) presenting the sub-type constipated (IBS-C) (Table V). After introduction of LFDs, there were significant reductions in GI symptoms. The average improvement in IBS-SSS score was 132 ± 117, representing a significant 50% reduction after 4 weeks of LFDs (M1 = 275.3 *vs.* M2 = 137.4; $p < 0.01$) (Table III). The symptoms of Abdominal Pain and Distension also showed significant reductions after introduction of LFDs, between M1 and M2 (M1 = 5.0 *vs.* M2 = 2.4 and M1 = 6.9 *vs.* M2 = 2.8; $p < 0.01$; in pain and distension, respectively) (Table III). But, these declines were no longer significant after reintroduction of FODMAPS. There was also a significant reduction in constipation with LFDs during M1 and M2,

Table II. Comparison of repeated assessment of nutritional status between different assessment periods (M1, M2 and M3) of the trial (n = 31)

Parameter	M 1	M2	M3	p-value	(M1-M2)	(M2-M3)
Weight, kg	68.36	67.08	67.1	$p < 0.01^b$	*	ns
BMI, kg/m^2	27.2	26.8	26.8	$p < 0.01^b$	*	ns
WC (cm)	83.9	81.4	81.4	$p < 0.01^b$	*	ns
Fat mass, %	39.4	38.8	38.9	0.20^b	ns	ns
Fat free mass, %	25.5	25.7	25.9	0.33^b	ns	ns

*FODMAP: low fermentable oligo-, di-, mono-saccharides and polyols); BMI: body mass index; WC: waist circumference; *Significant. [a]p-value of Friedman test. [b]p-value of analysis of variance (ANOVA).*

Table III. Repeated assessments of symptoms scores (n = 31)

Parameter	M1	M2	M3	P value	M1-M2	M2-M3
FM Severity Score	21.8	16.9	17.0	$p < 0.01^a$	*	ns
IBS Severity Score	275.3	137.4	158.1	$p < 0.01^b$	*	ns
Distress Score	1.8	1.6	1.5	$p < 0.01^b$	*	ns
VAS generalize pain	6.6	4.9	5.4	0.000^a	*	ns
Muscle tension	6.1	4.6	4.7	0.002^a	*	ns
Asthenia	7.3	5.8	5.6	0.024^b	**	ns
Depression	5.1	4.2	4.0	0.043^a	**	ns
Sleep quality	6.6	5.1	5.0	0.017^b	**	ns
Memory	6.9	5.0	5.5	0.001^a	*	ns
Headache	4.9	3.8	4.0	0.046^a	**	ns
Abdominal pain	5.0	2.4	3.0	0.000^b	*	ns
Constipation	5.7	3.3	3.8	0.012^b	**	ns
Diarrhoea	2	0.8	1.5	0.019^b	**	ns
Bloating	6.9	2.8	3.8	0.000^b	*	ns

*[a]p-value ANOVA. [b]p-value of Friedman test. *Statistically significant differences between M1 and M2 ($p < 0.01$). **Statistically significant differences between M1 and M2 ($p < 0.05$).*

Table IV. Comparisons of nutritional intake between different assessment periods (M1, M2 and M3) of the trial (n = 31) and between LFD and DP

	M1	M2	M3	p-value	M1-M2	M2-M3	DP	M2-DP
FODMAPs, g	24.4	2.6	6.1	$p < 0.01^a$	*	ns	0.96	ns
Energy, kcal	1973	1615	1566	$p < 0.01^b$	*	ns	1556	ns
Glycosides, g	233.7	180.0	178.5	$p < 0.01^b$	*	ns	203	ns
Protein, g	74.1	71.8	68.1	$p = 0.295^b$	ns	ns	70.7	ns
Lipids, g	79.4	65.2	57.8	$p < 0.01^{a¥}$	ns	ns	53.9	ns
Fiber, g	22.7	21.1	20.7	$p = 0.29^b$	ns	ns	22.3	ns
Calcium ,mg	703	717	708	$p = 0.90^a$	ns	ns	817	ns
Magnesium, mg	249	223	242	$p = 0.30^a$	ns	ns	252	ns
Vitamin D, ug	2.16	3.06	2.71	$p = 0.96^a$	ns	ns	2.5	ns

*DP: dietary plan; LFD: low FODMAP diet. *Statistically significant difference between M1 and M2 ($p < 0.01$). ¥Statistically significant difference between M1 and M3 ONLY ($p < 0.01$). [a]p-value of Friedman test. [b]p-value of analysis of variance (ANOVA).*

Table V. Characterization of gastrointestinal symptoms of FM among participants prior to initiation of the trial

Score IBS-SSS[a]	275.3 ± 101	0 a 500
No disease/remission	4% (2/38)	< 75
Mild disease	9% (3/38)	75-175
Moderate disease	50% (19/38)	175-300
Serious illness	37% (14/38)	> 300
IBS-C	70% (25/36)	
IBS-M	22% (8/36)	
IBS-D	8% (3/36)	

[a]Expressed as mean ± SD. IBS-SSS: Irritable Bowel Syndrome symptom severity scale; IBS with constipation (IBS-C), with diarrhoea (IBS-D) and mist (IBS-M).

and a non-significant increasing after reintroduction of FODMAP, as assessed at M3 (M1 = 5.7, M2 = 3.3, M3 = 3.8; $p < 0.05$) (Table III).

There were significant declines (patient improvement) in all individual FM symptoms between M1 and M2, especially with scores on somatic pain (VAS) (M1 = 6.6, M2 = 4.9; $p < 0.01$) and muscle tension (M1 = 6.1, M2 = 4.9; $p < 0.01$) in accordance with the reduction in severity of FM (M1 = 22; M2 = 17; $p < 0.01$). No significant differences were noted after reintroduction of FODMAPs. The distress score throughout the trial and was not aggravated by reintroduction of FODMAPs (M1 = 1.8; M2 = 1.6; M3 = 1.5) (Table III).

It was found notable, positive correlations between improvements of somatic pain (declined VAS scores) with a number of

GI symptoms, including abdominal pain (rs = 0.443; $p < 0.01$), abdominal distension (rs = 0.386; $p < 0.05$) and with the improvement of IBS-SSS score (rs = 0.406; $p < 0.01$). Of particular note was "rate of satisfaction with improvement in symptoms" being strongly correlated (r = 0.650; $p < 0.01$) with "diet compliance rate", suggesting patients were conscious of LFDs lowering severity of symptoms. In concordance, was reported 77% of satisfaction with the diet in general and was observed 85% of compliance to diet plans.

DISCUSSION

This was the first clinical trial wherein a LFD intervention was experimented as a potential therapeutic approach for FM. The results of this pilot intervention with LFD, suggest beneficial influence on the outcome of somatic and visceral symptoms of FM (27). The study could prove that, the dietary plan implemented restricted in FODMAPs, was nutritionally balanced and provided a healthy diet, with benefits on weight status, at least for the period of the duration of the trial (4-8 week). Was found a very significative compliance to the assigned diets, comparing the participants FODMAPs intake with DP content.

There are some concerns regarding safety and nutritional balance of LFDs (28). LFDs prescribed in our study were helpful in providing a balanced intake of energy, macro- and micronutrients.

Our cohort exhibited nutritional status profiles similar to previous studies describing FM body composition (6) with a high prevalence of overweightness and high fat mass (29,30). The majority of research already done on FM, presents the weight loss as being crucial on alleviating its impact (7,31). We found a nutritional benefit provided by the prescribed LFDs, resulting in weight-loss without significant decrease in essential nutrient intake (protein, fiber, calcium, magnesium, vitamin D. The nutritional counselling promoted a tendency to improve the intake of important nutrients as calcium and vitamin D without, however, to be sufficient to achieve the recommended levels for the needs of these patients. The micronutrient intake was generally low in all assessed moments, which agrees with the data of publications describing the same pattern of nutritional deficiencies in FM (32,33).

The results of this trial have notable commonalities with other study's, where was implemented a LFD therapy for IBS treatment (16,18,28). LFD was found to alleviate symptoms of IBS in all published studies, providing an improvement of 75% in IBS cases. In IBS, LFD was found to be especially effective in relieving abdominal pain and distension, but was less effective in mitigating constipation (16,28). Also, we found this response among our cohort of FM patients, with alleviation of GI symptoms by LFD therapy and the most prominent response in abdominal pain and distension. These results reflect those published by Perez et al. where 31 IBS patients were treated with LFD for 21 days (34). Additional comparison between ours and Perez et al. results, shows reductions in VAS abdominal pain scores (6 to 2.8 *vs.* 5 to 2.4, respectively) and VAS distension scores (7.0 to 4.2 *vs.* 6.9 to 2.2, respectively).

The results of the intervention in the subgroup of FM constipated patients, are consistent with the Rao et al. opinion (28), about IBS patients treated with LFD. The study also found reduction in the global IBS score in IBS-C sub-type, when treatment of LFD was implemented. Thus, LFD can to be a potential therapy in FM patients suffering from constipation but, such therapy, needs to be accompanied by educating patients to strictly adhere to recommended levels of dietary fiber and water intake. Other studies report a large predominance of constipation (IBS-C sub-type 90%) in patients with FM (19,34). Our trial showed a 70% prevalence of constipation (25/36, IBS-C), 8% with diarrhoea (3/36, IBS-D) and 22% with mixed symptoms of diarrhoea and constipation (8/36, IBS-M). The prevalence of IBS-C in FM sufferers appears to be higher than in patients with only IBS, in general, where it is reported to be about 50% of cases (35). Another study of LFD therapy for IBS showed this same profile: 64.5% IBS-C, 22.6% IBS-D and 12.9% IBS-M (32). Authors (28) discuss the possibility that the reduced fiber intake of the LFD may contribute to constipation aggravation. Regarding the data from our study, we found that fiber intake was not significantly different throughout the trial and fiber consumption was always sufficient in relation to the daily needs in this trial. Based on these observations, we concluded fiber content did not contribute to any changes in FM symptoms in our study.

It should be noted that the reduction of prebiotic fiber, resulted from the fructo-oligosaccharide LFD restriction, is described as a possible risk factor to colon health and can contribute to constipation and colorectal cancer (28,36). However, these risks appear to be contradictory to the evident improvement of IBS symptomatology treated with LFD, as described by authors (16) and confirmed in our study with FM patients suffering from concomitant IBS. This contradiction has been described by authors as the "paradox of the LFD" (3). Furthermore, the eventual risk of lowering prebiotic fiber content could be avoided by concomitant inclusion of probiotics in LFD therapy. This hypothesis has already been proposed (16) but has yet to undergo study.

The more remarkable results of our study were the alleviation of FM symptoms as somatic pain, muscle tension and impact in the daily life of FM, after treatment with LFDs. Moreover, gradual improvement of distress score, throughout our study, was an added contribution of LFD therapy to symptomatic improvements. The positive correlation between reductions in somatic pain and GI disorders, in our study, is also notable. More extensive research is needed to discern the interconnection between these symptoms in FM patients.

There are many other aspects of LFD therapy open to future research. One is determining what role, if any, LFD-therapy plays in the neuro-enteric axis of FM patients. Also, cost/benefit analysis of implementing LFD-therapy for treating FM needs to be investigated, similar to what has already occurred for IBS.

CONCLUSION

FM is a disease that requires a treatment with multidisciplinary approach and nutrition approach has a strong potential. Our study is the first clinical trial that evaluate LFD-intervention integrated

into FM patient treatment. The diet therapy, LFD, prescribed in this study was shown to have positive impact on FM symptoms, especially with painful hypersensitivity, a mechanism commonly mediating symptoms of FM and IBS. Also, LFD contributed to weight loss in the cohort studied, an advantage in FM sufferers with a high prevalence of overweightness. Moreover, LFD demonstrated to be a balance diet without nutritional risk described in addition to symptomatic improvement of FM.

Overall, this pilot study shows that a LFD could be one option to use as a potential dietary approach to FM treatment but these limited results imply cautious optimism towards use of LFD therapy for FM and, at a minimum indicate, more extensive studies must be conducted to verify its efficacy and safety.

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STATEMENT OF AUTHORSHIP

Ana Paula Marum contributed to conception and design of the study, generation, collection, assembly, analysis and interpretation of data, and drafting article; Cátia Moreira contributed to dietary plans and nutritional quantifications, Pablo Tomas-Carus contributed to recruitment, critical revision of article, Fernando Saraiva contributed to recruitment and critical revision of article, Catarina Sousa Guerreiro contributed to concept/design, revising it critically for important intellectual content and final approval of the version to be submitted.

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Trabajo Original

Otros

Investigation on the endemic characteristics of *Metorchis orientalis* in Huainan area, China

Investigación sobre las características endémicas de Metorchis orientalis *en Huainan, China*

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Abstract

Objective: To investigate the endemic characteristics of *Metorchis orientalis (M. orientalis)* in the Huainan area, Anhui province, China.

Methods: The first-intermediate host, second-intermediate host and reservoir hosts were collected, and the endemic characteristics of *M. orientalis* were examined through field investigation and artificial infection.

Results: Investigation was completed in 89 domestic ducks, 156 domestic chicken, 41 domestic geese, 20 domestic cats and 19 dogs. The infection rate of *M. orientalis* was 18.0% (16/89) in ducks, 12.2% (19/156) in chicken, 9. 8% (4/41) in geese, 5.0% (1/20) in cats and 5.3% (1/19) in dogs. Sixty-seven cercariae of *M. orientalis* were identified in 1,000 *Parafossarulus striatulus,* with a natural infection rate of 6.7%, and 19 cercariae occurred in 300 *Pseudorasbora parva,* with a natural infection rate of 6.33%. The activity of the cercariae of *M. orientalis* was associated with light intensity and temperature. The full life cycle of *M. orientalis* ranged from 120 to 140 days; it occurred approximately in 89 days in snails, 28 days in fish and 20 days in ducks.

Conclusion: *M. orientalis* is prevalent in the Huainan area, and it may complete its life cycle in *Parafossarulus striatulus, Pseudorasbora parva* and natively raised ducks.

Key words:

Metorchis orientalis. Endemic characteristics. Huainan area.

Resumen

Objetivo: investigar las características endémicas del *Metorchis orientalis (M. orientalis)* en el área de Huainan, en la provincia de Anhui, China.

Métodos: fueron recogidos el primer huésped intermediario, el segundo huésped intermediario y el reservorio, y se examinaron las características endémicas del *M. orientalis* a través de investigación de campo e infección artificial.

Resultados: la investigación se llevó a cabo en 89 patos domésticos, 156 gallinas domésticas, 41 gansos domésticos, 20 perros y 19 gatos domésticos. La tasa de infección del *M. orientalis* fue del 18,0% (16/89) en patos, 12,2% (19/156) en pollos, 9,8% (4/41) en gansos, 5,0% (1/20) en gatos y 5,3% (1/19) en perros. Sesenta y siete cercarias de *M. orientalis* fueron identificadas en 1.000 *Parafossarulus striatulus,* con una tasa de infección natural del 6,7%, y 19 en 300 *Pseudorasbora parva,* con una tasa de infección natural del 6,33%. La actividad de las cercarias de *M. orientalis* se asoció con la intensidad de la luz y la temperatura. El ciclo de vida completo del *M. orientalis* osciló entre 120 y 140 días, y se produjo aproximadamente en 89 días en caracoles, 28 días en peces y 20 días en patos.

Conclusión: el *M. orientalis* es prevalente en el área de Huainan, y puede completar su ciclo de vida en *Parafossarulus striatulus, Pseudorasbora parva* y patos autóctonos.

Palabras clave:

Metorchis orientalis. Características endémicas. Área de Huainan.

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INTRODUCTION

Metorchis orientalis (M. orientalis) belongs to the family *Opisthorchiidae,* subfamily *Metorchiinae.* It was originally described in Japan, Russia and China, where the prevalence of *M. orientalis* was reported from Heilongjiang, Jilin, Beijing, Tianjin, Shanghai, Jiangsu, Zhejiang, Fujian, Jiangxi, Guangdong, Guangxi, Sha'anxi, Sichuan, Taiwan and Anhui province in China (1). *M. orientalis* occurs in wider hosts, and primarily parasitizes in the hosts' hepatic duct and gallbladder, consequently resulting in enlarged gallbladder, thickened cystic wall, desquamation of epithelium, vascular congestion and hemorrhage in internal organs of the infected hosts. Although this species involves wider hazards, its life cycle is less reported in China. The current study was undertaken to investigate the life cycle of *M. orientalis* and its epidemiological characteristics in the Huainan area of the Anhui province, China.

MATERIALS AND METHODS

SURVEY ON THE LOCAL ECOLOGICAL SYSTEM FOR *M. ORIENTALIS*

Investigation on the local ecosystems for *M. orientalis* was performed through interview with the local residents, field survey, sample collection, video and document recording, as well as observation on the surroundings of plants and animal feeding and practice of fishery, agriculture and livestock raising.

INVESTIGATION OF THE HOSTS

Samples of *Parafossarulus stritulus*, the first-intermediate host of *M. orientalis*, were collected from the waters (Luohe river, Yaohe river, Jiaogang lake and Gaotang lake) in the Huainan area with scoop net. Then, the individual snail was placed in the disposable dish and maintained in an eco-box at 18 °C ± 2 °C to observe escaping of the cercaria under the dissecting microscope once every 120 min. Cercariae were microscopically isolated from the host snails, and rinsed as previous technique (2) for next use.

Pseudorasbora parva, the second-intermediate hosts, were captured from the above lakes and rivers with net. The flesh parts of the fish were cut into fine pieces, washed and precipitated before microscopical isolation of the encysted cercariae. Then, the artificial pancreatic juice was applied to digest the bony parts and scales, which were subjected to repeated rinsing and precipitation for isolation. Finally, encysted cercariae of fluke were separated under microscope. The cercariae obtained from the previous samples were cleansed and maintained for their next use as described previously (3,4).

Selection of the definitive host or reservoir hosts was performed in terms of the epidemic characteristics of *M. oritentalis* with the previously described method (5-7). Sampling was carried out in 89 chicken, 156 ducks, 41 geese, 20 cats and 19 dogs that were raised by fishermen living along the areas of the Luohe and Yaohe rivers and Jiaogang and Gaotang lakes of the Huainan city. All animals were sacrificed, and the corresponding internal organs were taken for isolation of the parasites. The specimens were rinsed in saline, and maintained in 70% alcohol solution for next use.

ARTIFICIAL INFECTION EXPERIMENT

The eggs were obtained from the gallbladder of the ducks; the cercariae, from *Parafossarulus striatulus*; and the metacercaria, from the flesh of positive *Pseudorasbora parva.* The negative experimental animals, including young *Parafossarulus striatulus*, *Pseudorasbora parva*, and ducklings, were artificially infected following the procedures described in related documents (8). Eggs of *M. orientalis* were used for artificial infection with the first-intermediate host at a density of 80 ± 20 in water temperature of 18 °C ± 2 °C. The whole process, developing upon intake of the eggs by *Parafossarulus striatulus* into miracidiae, sporocysts, rediae and cercariae, took approximately 89 days, and by the 90th day, cercariae were obtained. Artificial infection of the second-intermediate hosts was performed in the cercariae that emerged from its snail hosts by a density of 100 ± 20 in the *Pseudorasbora parva.* Both the cercariae and the fish were maintained in a beaker containing 200 ml of water, and stored in an eco-box at 18 °C ± 2 °C by exposure to the daylight lamp. It took approximately 28 days for the cercariae to develop mature in the fish. Artificial infection with the definitive hosts was carried out in the domestic ducks by feeding them with the cercariae isolated from *M. orientalis* at a density of 60 for each animal. The feces of the infected ducks were collected after 20 days, and the younger ducks were microscopically dissected for isolation of the adult worms from their common bile ducts and hepatic ducts. Cercariae were also isolated from the *Parafossarulus striatulus.*

ACTIVITY PROFILE OF CERCARIAE AND THE INFLUENCE OF LIGHT ON CERCARIAE ESCAPING

Examination of the cercariae activity profile was performed in positively infected *Parafossarulus striatulus* by dividing them into two groups (n = 5 for each group). *Parafossarulus striatulus* in group A were maintained in a weighing bottle containing 50 ml of water; then, the bottle was stored in an eco-box at 1-32 °C with the daylight lamp on. The activity of cercariae was observed every two hours for determination of the duration of cercariae survival after emerging. Those in group B were also kept in a weighing bottle with 50 ml of water, which was placed outdoors and subjected to observation every two hours for determination of the effects of diurnal variation on cercaria escaping. The dish containing positive *Parafossarulus striatulus* was kept in an eco-box at 18 °C ± 2 °C for four hours with the daylight lamp on and off alternately in order to observe the quantity of the cercaria escaping and the effect of light on its escaping.

SPECIMEN PREPARATION

The specimens obtained in different stages, including cercariae, encysted cercariae and adults, were stained with carmalum solution, initially discolored in 1% hydrochloric acid solution, and rinsed in clean water. Then, the discoloration continued in the alcohol in gradient manner till 70%. The *M. orientalis* was compressed thinly and smoothly, and fixed in Bowen's fluid and dehydrated by 95% alcohol (where necessary, re-staining is required). Then, the specimens were subjected to dehydration in 100% alcohol. After transparency with oil of wintergreen, the specimens were moved onto the glass slide that was mounted with Canadian gum and dried in a drying oven for the next use.

SPECIES IDENTIFICATION

Morphological identification of the species was performed under the conventional microscope or dissecting microscope in compliance with the previous description (9-11). The data were maintained pertaining to the taxonomy, definitive host, parasitic sites and distribution of this species.

RESULTS

ECOLOGICAL ENVIRONMENT

The Gaotang lake, one of our sampling sites, is located between the Huainan city, Fengyang, Dingyuan and Changfeng county, and close to the Shangyao town of Huainan city. The whole natural water body covers approximately 100 hectares, and across the lake a dam was built, along which the local fishermen are living and practicing fisheries. Likewise, a large number of poultry and livestock are being raised, including ducks, geese, dogs, cats, pigs, cattle and sheep. Occasionally, some children are seen to graze the cattle on the lakeshore, where herds of poultry and livestock are also breeding freely at the dam or by the lake. A large quantity of hares, field mice and wild cats are living in the shrubs and weeds, and crowds of wild ducks and water fowls are seen flying over the lake or playing or seeking for foods in the water. A variety of aquatic plants or weeds, such as yellow water chestnut, and various freshwater shellfish, such as mussel, *Parafossarulus striatulus*, field snail, *Bithynia tentaculata, Radix swinhoei* and *Galba pervia,* are growing in the lake. In addition, the local villagers (fishermen and farmers) have planted plots of economic trees, including poplars and Chinese scholar trees, and farm crops along the lakeshores, which are also overgrown with shrubs and weeds, and crude latrines built by the villagers.

The second sampling field, the Yaohe river, bordering on the Gaotan lake, has a similar ecological environment. And the third sampling site, the Jiaogang lake, which covers some 1,000 hectares of water, lies to the north of the Fengtai county. The local farmers live by pisciculture in purse seine. A large quantity of freshwater shellfish, such as *Parafossarulus striatulus*, field snail, *Parafossarulus* and *Bithynia tentaculata*, breed in the water weeds, and herds of pigs and domestic ducks feed themselves on the lakeshores. This place has a similar ecosystem to the Gaotang lake. The ecosystem of the Luohe river, our fourth sampling site, is in general identical to that of the above three areas.

INFECTION OF THE INTERMEDIATE HOSTS

Cercariae of *M. orientalis* occurred in 67 of the 1,000 *Parafossarulus striatulus* (the first-intermediate host) detected in the Huainan area (Luohe river, Yaohe river, Jiaogang lake and Gaotanghu lake), and encysted cercariae of *M. orientalis* occurred in 19 of the 300 *Pseudorasbora parva* (the second-intermediate host). The natural infection rate was 6.7% (67/1,000) and 6.33% (19/300), respectively. Infection of the definitive hosts with *M. orientalis* was 18.0% (16/89) in domestic ducks, 12.2% (19/156) in chicken, 9.8% (4/41) in geese, 5.0% (1/20) in cats, and 5.3% (1/19) in dogs, in which the domestic ducks were most affected. The density of *M. orientalis* was 135 ± 2.38 in ducks, 110 ± 4.33 in chicken, 86 ± 2.06 in geese, 165 ± 4.27 in cats and 149 ± 1.78 in dogs on average.

ARTIFICIAL INFECTION OF THE HOSTS

In the artificial infection experiment with the first-intermediate, cercariae were detected in six of the 100 *Parafossarulus striatulus*, with an infection rate of 6.0%, from which six cercariae were isolated. After artificial infection of the second-intermediate in 30 days, we detected the encysted cercariae in 19 of the 60 *Pseudorasbora parva.* The infection rate was 31.7%, and 38 encysted cercariae on average were isolated from each host. Sixty domestic ducks were totally infected with *M. orientallis* (100%) by detection of the eggs in stool, and adults of *M. orientalis* were seen in the hepatobiliary systems in the domestic ducks, with an average of eleven for each ducks.

CERCARIA ACTIVITY REGULARITY AND THE EFFECT OF LIGHT ON CERCARIA ESCAPING

By observation of the behavior of *M. orientalis* cercaria, we found that cercariae escaping from the water outlet of the *Parafossarulus striatulus.* The survival time for cercariae in group A was negatively correlated with water temperature (Fig. 1), and the number of emerged cercariae in group B was higher in daytime (Fig. 2). One hundred and thirty-two cercariae emerged from the *Parafossarulus striatulus* with the light on, whereas no single cercaria occurred with the light off in the same ambient temperature, suggesting that light may greatly affect the activity of the cercariae.

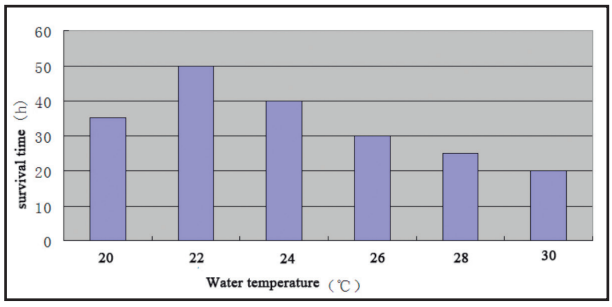

Figure 1.

Survival time (LD50) of cercaria of *M. orientalis* and water temperature.

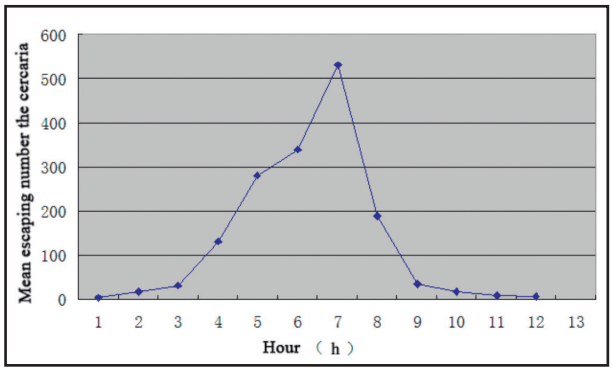

Figure 2.

Tendency for the quantity of *M.orientalis* cercariae emerging within 24 hours.

MORPHOLOGICAL CHARACTERISTICS FOR *M. ORIENTALIS*

The adult worms of *M. orientalis* are oval, shoe-like, with the back and abdomen flattened and densely distributed in small cuticular spines. The body measures 2.894-5.943 mm in length, 0.712-1.733 mm in width, with length to width ratio of 2.99~4.49 on average. The oral and ventral suckers look almost round and measure 0.204 mm × 0.211 mm and 0.189 mm × 0.209 mm, respectively. The oral sucker has well developed sarcoplasma, and arises from the anterior part. The ventral sucker anteriorly occurs at the 1/4 parts of its body, and the pharynx appears spherical, measuring 0.082 mm × 0.049 mm. The esophagus is short, and the two intestines run through both sides of the body. Two testises present generally in petaloid fashion, and arrange in tandem at the posterior 1/4 of the body. The ovary is located in front of the testis and has oval shape, measuring 0.196 mm × 0.261 mm. The seminal receptacle arises at the back of the ovary and is slightly curved, measuring 0.357 mm × 0.333 mm. The tubular uterus containing eggs twists through the ovary towards the gonopore, which is located at the anterior ventral sucker. The vitellaria is granular and bunchy, lying on both sides of the body. The egg, somewhat resembling that of *Clonorchis sinensis,* is oval and sized about 0.029 mm × 0.015 mm in diameter, with claybank color, egg cover, small spines at the rear end and miracidium in it.

DISCUSSION

Metorchis orientalis, belonging to the subfamily *Metorchiinae* and family *Opisthorchiidae,* lives in complex life cycles, and has *Parafossarulus striatulus* as its first-intermediate hosts. Its second-intermediate hosts involve freshwater fishes, such as *Pseudorasbora parva, Abbottina rivularis, Cichlasoma managuense* and *Pseudogobio rivularis*, as well as the definitive hosts, poultry, certain birds, dogs, cats and other mammals or occasional human beings. In the present study, we successfully isolated the cercaria, encysted cercariae and adults of *M. orientalis* from the *Parafossarulus striatulus*, *Pseudorasbora parva* and poultry collected in the Huainan area of the Anhui province, in China. The findings comply with the life cycle of this species. Huang et al. (9) described 232 species of flukes (95 genera under 24 families) in the Chinese poultry and livestock, and found that adults and larvae can live in livestock. Lu (15) reported 665 species that can parasitize in the poultry and livestock in the Anhui province through extensive literature review, in which 111 species were trematodes. Although only three species are associated with the Huainan area *(Clonorchis singnsis, Amphimerus anatis* and *Metorchis taiwanensis),* yet our results further confirmed that *M. orientalis* are prevalent in this area. Tao (1948) (25) used to hypothesize that *Biihynia* should be the first-intermediate host for *M. orientalis,* yet his artificial infection with this host was unsuccessful. In order to confirm the hypothesis, we failed to detect any cercariae of *M. orientalis* in the *Bithynia funhsiana,* and also failed to perform the artificial infection in this species. Zhang (1985) (26) reported natural infection of the cercariae of *M. orientalis* with the *Parafossarulus striatulus* that were collected in the suburb of Xiamen and Zhangzhou in the Fujian province, China. Our work showed that only *Parafossarulus striatulus* were infected with *M. orientalis*, and other freshwater snails, such as *Ramshorn, Lymnaea* and *Bithynia fuchsianus,* are immune to this species, which was also confirmed by our artificial infection. This findings suggest that the *M. orientalis* is specific to its first-intermediate host, and has unique epidemic characteristics. The second-intermediate hosts for *M. orientalis* are involved in *Pseudorasbora parva, Pseudogobio rivularis, Aphyocypris shantungensis* and *Puntius semifabsciatus*. Infection of these fish with *M. orientalis* is possibly associated with their behaviors, since cercaria *M. orientalis* tend to swim on the water surface, which makes more frequent contact of the fishes. Hong et al. (1964) (27) reported that 60% of *Pseudorasbora parva* were infected with *M. orientalis* in the Yushan area in Shanghai, China. This indicated that the second-intermediate hosts in this area were highly infected with *M. orientalis.* Worse enough, once digesting the fish containing encysted cercariae of *M. orientali,* the poultry would be infected. The definitive hosts for *M. orientalis* may include domestic chicken and geese, except for domestic ducks. In addition, *Stirix unalensis, Milvus korchun lineatus, Colymbus ruficollis, C. cristatus, Bubulcusibis coromandus, Phasianus torguatus, Eurystomus orientalis* and *Anas platyrhynchos,* as well as wild ducks and waterfowls, have also been reported as the definitive hosts for *M. orientalis,* which suggests that this species is not specific to selection for its definitive host (20-24).

The fact that domestic ducks are prone to infection with *M. orientalis* cannot be neglected, and high infection rate in certain areas can lead to heavy economic loss. Although low-grade infection with *M. orientalis* will not always cause death to the host, yet the parasitism occurs mostly in vital organs of the digestive system. This may result in lesions in the gallbladder and bile duct, inflammation, degenerated bile, congestion of the bile duct, hepatic pathological changes or serious damage to the liver function. Once the ducks are infected with such flukes, they tend to be emaciated due to poor digestion of the feeds, thus leading to reduced egg production. Terribly, if the endemic area is poorly managed, outbreak of the infection could be possible, and may eventually cause death of large amounts of animals (12,13). It had been reported that 198 of the 660 (30%) ducklings died from intake of the viscera of fish infected with *M. orientalis* in the Sheyang county of the Jiangsu province, China.

In our study, the poultry (chicken, geese and ducks) were purchased from the villagers and dissected by ourselves, and the internal organs of the livestock were ordered from the local butchers through field collection of the bile ducts, intestinal canals, oviducts and pancreatic ducts. These samples were brought back to our laboratory for isolation of the flukes with dissecting needle, spatula and hairbrush. This sampling method made hard to ensure the complete set of the internal organs in individual animals for measurement of the infection density. The sampling sites, including Luohe river, Yaohe river, Gaotang lake and Jiaogang lake, belong to the water system of the Huaihe river, and have their unique natural environment. A large quantity of phytoplankton, such as diatoms, green algae, yellow silk grass, *Myriophyllum spicatum* and yellow *Trapa bicornis*, and a variety of freshwater snails (such as *Parafossarulus striatulus*, field snails, *Bithynia tentaculata* and *Radix auricularia*) are growing or living in the river or lake (16,17). Apart from that, those water areas are critical habitats or wintering grounds for various kinds of waterfowls. The local fishermen and villagers have been living on the river bank or in their fishing boat, as well as raising a larger number of poultry and livestock, for a long time. Still, the villagers planted large quantities of economic plants such as poplar and Chinese scholar trees, under which massive shrubs and weeds are growing. In the recent years, the poultry and livestock industries show a trend towards rapid development in the Huainan area. Once the poultry and livestock are infected with the flukes, the animals will be prone to develop the symptoms, including anemia and weight loss, which will directly refrain the growth of young poultry and livestock, even resulting in death. In our investigation, we found that the infected species and infection rate in chicken, ducks and geese were relatively higher, especially in the free-ranged ducks along the river bank. This may be associated with the fact that free-ranged ducks have easy access to the freshwater snails containing encysted cercariae (18,19).

In compliance with the epidemiological characteristics of the *M. orientalis*, specificity to the first-intermediate host, blocking the transmission route, can rely on the eradication or reduction of the density of first-intermediate hosts by applying molluscicide. This can be appropriately done in the spring and summer seasons, when the *Parafossarulus striatulus* begin to multiply and are active (27), and the control effect can be effectively assessed. In addition, providing health education to the local fishermen and villagers could be important to reduce the infection of the flukes.

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Nutrición Hospitalaria

Trabajo Original

Otros

The effect of defatted cocoa powder on cholesterol-induced changes of serum lipids in rats

El efecto del polvo de cacao desgrasado en los cambios de colesterol inducidos de los lípidos séricos en ratas

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Abstract

Introduction: Cocoa has been known for many health benefits, but its lipid-lowering activity still remains unresolved.

Objectives: To investigate effects of varying amounts of defatted cocoa on serum lipids in cholesterol-fed rats.

Methods: Forty-eight male Sprague-Dawley rats were randomly assigned into four cholesterol-free (control) and four cholesterol-supplemented (experimental) diets containing 0, 1, 2 or 3% defatted cocoa (DC) and given *ad libitum* to the rats for ten weeks. Serum total cholesterol (TC), low- and very low-density lipoprotein cholesterol (LDL-C and VLDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were quantified, atherogenic index (AI) was calculated, and other biological parameters were assessed.

Results: Food intake and body weight did not respond to DC. Compared to 0% DC, 3% DC had the most prominent effect on serum lipids inducing significant fall in LDL-C and TG, and rise in TC/TG in cholesterol-deprived rats, and increase in VLDL-C and AI, and decrease in HDL-C in cholesterol-fed rats. Compared to cholesterol-deprived rats, 3% DC caused significant rise in VLDL-C, AI and TC/TG, and fall in TG in cholesterol-fed rats. This lipid-modifying effect was markedly substantiated by corresponding linear trend responses to DC. Differences in lipid variables of rats fed on DC diets were less evident.

Conclusions: Results suggest that, in contrast to cholesterol-free situations, defatted cocoa is seemingly incapable of counteracting the atherogenic effect of cholesterol in rats, perhaps in an interaction that is likely to have clinical implications in cardiometabolic conditions.

Key words:

Defatted cocoa. Cholesterol. Dyslipidemia. Cardiometabolic risks. Rats.

Resumen

Introducción: los beneficios del cacao para la salud se conocen desde hace muchos años, pero su actividad hipolipemiante aún permanece sin resolver.

Objetivos: investigar los efectos de cantidades variables de cacao desgrasado en los lípidos séricos en ratas alimentadas con colesterol.

Métodos: cuarenta y ocho ratas Sprague-Dawley macho fueron asignadas aleatoriamente en cuatro dietas libres de colesterol (control) y cuatro dietas con suplemento de colesterol (experimentales) que contenían 0, 1, 2 o 3% de cacao desgrasado (CD), suministradas a las ratas *ad libitum* durante diez semanas. Se cuantificaron el colesterol sérico total (TC), las lipoproteínas de baja o muy baja densidad (LDL-C y VLDL-C), las lipoproteínas de alta densidad (HDL-C) y los triglicéridos (TG), se calculó el índice aterogénico (IA), y se evaluaron otros parámetros biológicos.

Resultados: la ingesta de alimentos y el peso corporal no respondieron al CD. En comparación con el 0% de CD, la dieta con un 3% de CD tuvo el efecto más prominente en los lípidos séricos, produciendo una bajada significativa de LDL-C y TG y subida de TC/TG en ratas privadas de colesterol, y un aumento de VLDL-C y IA y descenso del HDL-C en ratas alimentadas con colesterol. En comparación con las ratas privadas de colesterol, la dieta con un 3% de CD causó un aumento significativo de VLDL-C, IA y TC/TG y un descenso de los TG en ratas alimentadas con colesterol. Este efecto modificador de los lípidos estuvo claramente reflejado en respuestas al CD de tendencia lineal. Las diferencias en las variables lipídicas de las ratas alimentadas con dietas con CD fueron menos evidentes.

Conclusiones: los resultados sugieren que, en contraste con situaciones libres de colesterol, el cacao desgrasado es aparentemente incapaz de contrarrestar el efecto aterogénico del colesterol en ratas, lo que sugiere una interacción que puede tener implicaciones clínicas en las condiciones cardiometabólicas.

Palabras clave:

Cacao desgrasado. Colesterol. Dislipidemia. Riesgos cardiometabólicos. Ratas.

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INTRODUCTION

Atherosclerosis is crucial to cardiovascular disease (CVD) and is strongly related to dyslipidemia (1). Classically, dyslipidemia includes high total cholesterol, high low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, and high triglycerides. In effect, cholesterol plaques are distinctive features of the atherosclerotic lesions (2). Dyslipidemia is also a target of CVD risk scoring for stratification and prevention (1). The epidemic of CVD is now a global phenomenon, and remains the highest cause of death worldwide (3). Given the several health risks and public health burdens of CVD (1,3), its prevention or management is becoming a major challenge. Therefore, identifying dietary factors that may favorably affect serum lipids is of great importance.

Current management of CVD involves various lifestyle changes, dietary and exercise regimes (4) and the use of drugs or medical interventions (2). Nowadays, there is growing interest in the use of plant foods for the prevention and management of CVD and other related disorders, with a special emphasis on cocoa and its products (5).

Cocoa (Theobroma cacao *L.*) is one of the most ancient cultivated human crops. It is originated in Mexico and is central to the local diet (6). Nowadays, cocoa is grown mainly in Indonesia, Sri Lanka and West Africa (6). Cocoa is traditionally consumed as a beverage with or without milk. However, it is now used on a much larger scale as a basic ingredient for numerous chocolate products and confectionaries (7). Consumption of cocoa is related to higher-quality diets, including higher intakes of protein, antioxidants and a number of vitamins and mineral elements (8). Cocoa intake is also associated with several beneficial health effects, particularly reduced risks of obesity, diabetes, hypertension and CVD (8,9).

Numerous cardioprotective effects of cocoa products have been reported, such as improved heart function, decreased oxidative susceptibility of LDL-cholesterol and reduced platelet activation, as shown by several comprehensive reviews (5,8,9). However, evidence for possible antihyperlipidemic activity of cocoa has been limited and mixed. Several studies have shown that cocoa products do not or variably affect lipid profile (10-15), whereas other studies failed to support this (13-19). In this regard, there are no animal studies. Here, it is important to strictly define cocoa and its products. Cacao is the natural product, and cocoa or cocoa powder is the processed product, whereas chocolate is the food prepared from a combination of cocoa, sugar, fat, milk and other ingredients (8). Thus, chocolate and cocoa are two different terms and are not interchangeable, and many of the proposed health effects of cocoa may not be applicable to chocolate (20). In essence, cocoa itself is a reasonable product to study or to recommend from the point of view of health, as chocolate contains several non-cocoa constituents.

The basic concern regarding cocoa products and CVD has been related to their high caloric load mostly due to the high fat content, the bulk of which is composed on average of 33% saturated stearic acid, 25% palmitic acid, and 33% monounsaturated oleic acid (8,20). The high fat content of cocoa may be viewed as a potential confounder affecting lipid assimilation and metabolism, the effect of which is not exactly known yet and may be unfavorable (20). In general, most of the nutritional and clinical studies linking cocoa with CVD have been mainly devoted to the effects of bioactive components such as polyphenols and flavonoids, and have often paid little or no attention to the cocoa fat as a possible mechanism for explaining such link. In fact, fats are the highest variable components of the diet both in quantitative and in qualitative terms, and they are the most relevant dietary factor affecting serum lipids, especially in cases with dyslipidemia (15). Nevertheless, controlled human or animal studies that link consumption of defatted cocoa and cholesterol with serum lipids and lipoproteins in particular are generally lacking. Therefore, we investigated whether the consumption of diets containing varying amounts of defatted cocoa with and without cholesterol had any effect on serum concentrations of total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides in rats fed on such a dietary regimen for a period of ten weeks.

MATERIALS AND METHODS

DEFATTED COCOA POWDER PREPARATION

One batch (10 kg) of medium fat alkalized cocoa powder (Cadbury®, Birmingham, England) was purchased from the local market in Amman, Jordan. The powder was defatted following the reference solvent extraction method (21). In this method, the powder was soaked with petroleum ether (boiling point 40-60 °C) in dark glass bottles (1:3, weight/volume), and was left at room temperature for 48 hours with occasional shaking. The mixture was allowed to stand and decanted to remove the solvent with its dissolved fat, and a fresh solvent was then added. This process was repeated three successive times. During the third time, a little amount of water was added to the mixture to facilitate separation and mixed slowly, and the fat-free cocoa powder was separated through a *malti* cloth. The defatted powder was air-dried and was blended in a stainless steel blender (Kenwood®, Hampshire, England) for 20 minutes to obtain homogenous powder. The resultant powder was placed in sealed dark polythene bags and kept refrigerated at 4 °C until further use. The macronutrient content of the whole and defatted cocoa powder as determined by the Weende method (21) is presented in table I.

EXPERIMENTAL DIETS

Eight isocaloric and isonitrogenous diets were prepared; four of them were cholesterol-free and differed in their content of defatted cocoa powder (0%, 1%, 2%, or 3%, w/w) while in the other four 1% cholesterol was added, at the expense of fat, to induce hyperlipidemia. The protein and carbohydrate contents of defatted cocoa powder were taken into consideration in the calculation of nutrient composition of the diets. Ingredient composition of the diets is described in table II. All diets contained the same amount

Table I. Macronutrient and energy content of cocoa powder

Component*	Whole cocoa powder (g.100g^{-1})	Defatted cocoa powder (g.100g^{-1})
Carbohydrate	53.2 ± 0.03	66.2 ± 0.02
Protein	15.4 ± 0.01	19.4 ± 0.02
Fat	20.4 ± 0.02	1.0 ± 0.01
Ash	6.5 ± 0.03	8.1 ± 0.02
Fiber	4.5 ± 0.05	5.4 ± 0.02
Energy (kcal. 100g^{-1})	458.0	351.4

**Mean of three determinations ± SEM, on dry matter basis.*

of calories, protein, carbohydrate, fat, vitamins and mineral elements. Dietary supplies of nutrients were in accordance with the dietary recommended allowances for rats from the American Institute of Nutrition (22). Macronutrient and energy contents of the diets are described in table II. Diets were freshly prepared once a week and placed desiccated in sealed dark polythene bags, and then kept refrigerated at 4 °C.

SAMPLE SIZE CALCULATION

The resource equation method was used to calculate the sample size (23). This method is particularly suited to factorial experiments, as in the present study, involving more than two groups and measuring many outcomes, and when no previous estimate of the standard deviation is available. In a completely randomized design, sample size is the total number of animals minus the number of treatment groups (23). In this study, two diets (cholesterol-free and cholesterol-containing), four levels of defatted cocoa powder (0%, 1%, 2%, or 3%, w/w), and six rats in each treatment group (as is common) were used. Thus, treatment groups were eight, and the calculated sample size was 42. For more precision, a sample size of 48 was adopted.

ANIMAL EXPERIMENTATION

Forty-eight male Sprague-Dawley rats were obtained from the Experimental Animal Unit of the Department of Nutrition and Food Technology of the University of Jordan, Amman, Jordan. The animals were acclimatized for eleven days before the experiment, during which they were fed on chow diet with free access to tap water. They were individually housed in plastic cages with stainless steel wire-mesh bottom (North Kent Plastic Cages Ltd., Dartford, England) under controlled temperature (22 ± 2 °C) and hygienic conditions with 12-hour light, 12-hour dark cycle. All the experiments involving animals were approved by the Institutional Animal Ethics Committee and carried out according to the recommended guidelines for animal care and use (24).

At the beginning of the experiment, animals weighed 239.6 ± 1.7 g and they were randomly assigned into the four cholesterol-free or four cholesterol-supplemented diets described above. During the experimental period, which lasted for ten weeks, experimental diets and tap water were given *ad libitum.* Body weight and food intake were monitored weekly. Food efficiency ratio as body weight gain (g) per 100 (g) food intakes was also calculated. On the termination day and after an overnight fast, animals were anesthetized using chloroform. Blood was collected by performing cardiac puncture and the serum was isolated and stored frozen at -20 °C until chemical analysis.

Table II. Composition of the experimental diets

Ingredient	Cholesterol-free diets (g.kg^{-1})				Cholesterol-containing diets (g.kg^{-1})			
Cocoa powder, defatted	0	10	20	30	0	10	20	30
Cholesterol	0	0	0	0	10	10	10	10
Cornstarch	657.0	650.4	643.8	637.1	657.0	650.4	643.8	637.1
Egg albumin	180.0	178.1	176.1	174.2	180.0	178.1	176.1	174.2
Corn oil	90	90	90	90	80	80	80	80
Vitamin mix (AIN-93)*	30	30	30	30	30	30	30	30
Mineral mix (AIN-93)*	40	40	40	40	40	40	40	40
DL-methionine	3	3	3	3	3	3	3	3
Tert-butylhydroquinone	0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.008
Carbohydrate (%)	65.7	65.7	65.7	65.7	65.7	65.7	65.7	65.7
Protein (%)	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0
Fat (%)	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
Energy (kcal.100g^{-1})	415.8	415.8	415.8	415.8	415.8	415.8	415.8	415.8

**AIN: American Institute of Nutrition (22).*

BIOCHEMICAL ANALYSIS

Concentrations of serum lipids and lipoproteins were determined by using commercial kits and in accordance to the manufacturer's instructions (Labkit, Spain and Syrbio, France). The lipid variables included total cholesterol, LDL-cholesterol, HDL-cholesterol, very low density lipoprotein (VLDL) cholesterol, and triglycerides. Analysis was performed at the Heteen Medical Laboratories, Zarqa, Jordan, using a pre-calibrated automated clinical chemistry analyzer (Humalyzer 2000, Human Gesellschaft für Biochemica und Diagnostica mbH, Wiesbaden, Germany). Atherogenic index ({total cholesterol minus HDL-cholesterol}/HDL-cholesterol), and ratios of total cholesterol/triglycerides and HDL-cholesterol/LDL-cholesterol were then computed (25,26).

STATISTICAL ANALYSIS

Data analysis was performed using statistical analysis software (SAS version 9, USA). Statistical significance was assessed by two-way ANOVA followed by the Duncan's multiple range tests, and the significance was set at $p < 0.05$. Data were expressed as means ± standard errors of the mean (SEM). Orthogonal polynomial comparisons were used to identify statistically significant trends. This test determines the nature of the response of the studied variables to increasing levels (0%, 1%, 2%, 3%) of defatted cocoa powder. Linear, quadratic and cubic trends were given as coefficient of determination (r^2) at $p < 0.05$.

RESULTS

The macronutrient composition of whole and defatted cocoa powders used in this study is given in table I. Whole cocoa powder was found to contain high content of fat (20.4 g/100 g) and energy (458 kcal/100 g). On dry matter basis, defatting process reduced fat and energy contents of the cocoa by almost 95% and 23% respectively. This process also resulted in marked increase in carbohydrate, protein, ash and fiber contents of the cocoa.

Table III presents body weight, food intake and food efficiency ratio of rats fed defatted cocoa powder with and without cholesterol. Initial body weights were essentially similar ($p \geq 0.05$) in all rats of the control and experimental groups. Compared to cholesterol-free control, cholesterol feeding did not significantly ($p \geq 0.05$) influence body weight, weight gain, and food efficiency ratio, but it induced a significant ($p < 0.05$) increase in food intake. In neither control nor experimental groups did defatted cocoa feeding affect these variables.

Concentrations and indexes of serum lipids and lipoproteins of rats fed defatted cocoa powder with and without cholesterol are shown in table IV. In contrast to control, cholesterol feeding resulted in significant ($p < 0.05$) increase in serum HDL-cholesterol and total cholesterol/triglycerides ratio, and decrease in triglycerides, whereas LDL- cholesterol, HDL- cholesterol/LDL-cholesterol ratio and atherogenic index were unaffected. Noteworthy, serum total cholesterol and VLDL-cholesterol were modestly but insignificantly ($p < 0.08$) increased by cholesterol feeding.

In cholesterol-free groups, compared to control, 3% defatted cocoa feeding produced significant ($p < 0.05$) decrease in LDL-cholesterol and triglycerides, and increase in total cholesterol/triglycerides ratio (Table IV). Compared to 1% and 2% defatted cocoa, 3% defatted cocoa feeding induced also significant ($p < 0.05$) decrease in triglycerides and increase in total cholesterol/triglycerides ratio. In cholesterol-containing groups, compared to control, 3% defatted cocoa feeding caused significant ($p < 0.05$) increase in atherogenic index and VLDL-cholesterol, and decrease in HDL-cholesterol. Noticeably, the decrease in triglycerides and the increase in total cholesterol/triglycerides ratio induced by cholesterol were essentially maintained throughout the various levels of defatted cocoa feeding.

In cholesterol-containing groups, compared to defatted cocoa feeding in cholesterol-free groups, 3% defatted cocoa feeding induced significant ($p < 0.05$) decrease in triglycerides and increase in VLDL-cholesterol, atherogenic index and total cholesterol/triglycerides ratio (Table IV). Furthermore, 1% and 2%

Table III. Body weight, food intake and food efficiency ratio of rats fed defatted cocoa powder for ten weeks

Variable	Cholesterol-free cocoa groups[$*]				Cholesterol-containing cocoa groups[$*]			
Cocoa powder (%)	0	1	2	3	0	1	2	3
Initial body weight (g)	239.9 ± 6.2[a]	239.1 ± 5.8[a]	239.4 ± 5.3[a]	239.5 ± 5.2[a]	239.4 ± 4.9[a]	239.6± 5.1[a]	239.6 ± 5.0[a]	240.3 ± 5.0[a]
Final body weight (g)	395.4 ± 15.3[a]	413.1 ± 12.8[a]	429.8 ± 16.6[a]	416.5 ± 13.1[a]	403.5 ± 19.3[a]	426.0 ± 16.2[a]	408.4 ± 24.4[a]	425.3 ± 22.1[a]
Weight gain ($g.day^{-1}$)	2.22 ± 0.15[a]	2.48 ± 0.19[a]	2.72± 0.19[a]	2.52 ± 0.15[a]	2.34 ± 0.27[a]	2.66 ± 0.24[a]	2.41 ± 0.29[a]	2.64 ± 0.28[a]
Food intake ($g.day^{-1}$)	13.91 ± 0.42[b]	14.65 ± 0.57[ab]	15.32 ± 0.38[a]	14.78 ± 0.37[ab]	14.45 ± 0.60[a]	15.35 ± 0.45[a]	14.95 ± 0.72[a]	15.98 ± 0.97[a]
Food efficiency ratio[#]	15.89 ± 0.64[a]	16.93 ± 1.08[a]	17.68 ± 1.00[a]	17.08 ± 0.85[a]	15.99 ± 1.28[a]	17.22 ± 1.22[a]	15.87 ± 1.16[a]	16.37 ± 0.94[a]

[$]Values are means ± SEM. [*]Values in rows with different superscripts are significantly different ($p < 0.05$). [#]Body weight gain (g)/100 g food intake.

Table IV. Serum lipid and lipoprotein concentrations and indexes of rats fed defatted cocoa powder for ten weeks

Variable[#]	Cholesterol-free cocoa groups[$*]				Cholesterol- containing cocoa groups[$*]			
Cocoa powder (%)	0	1	2	3	0	1	2	3
Total cholesterol ($mg.dl^{-1}$)	88.3 ± 8.6[a]	101.0 ± 7.6[a]	98.1± 6.1[a]	89.6 ± 5.9[a]	104.9 ± 7.6[a]	105.2 ± 10.6[a]	106.0 ± 6.3[a]	96.4 ± 6.3[a]
HDL-cholesterol ($mg.dl^{-1}$)	54.3 ± 5.8[b]	66.3 ± 6.1[b]	67.0 ± 4.9[b]	63.6 ± 2.4[b]	72.1 ± 5.3[a]	59.3 ± 6.8[ab]	61.0 ± 4.3[ab]	50.7 ± 3.9[b]
LDL-cholesterol ($mg.dl^{-1}$)	17.1 ± 2.1[a]	14.6 ± 3.4[ab]	10.3 ± 1.6[ab]	9.4 ± 0.8[b]	12.7± 2.8[a]	14.4 ± 2.8[a]	16.6 ± 2.9[a]	10.8 ± 2.5[a]
VLDL-cholesterol ($mg.dl^{-1}$)	17.0 ± 2.6[b]	20.1 ± 5.2[b]	20.9 ± 3.2[b]	16.7 ± 4.6[b]	20.0 ± 4.5[b]	31.5 ± 2.7[ab]	28.4 ± 5.1[ab]	34.9 ± 3.0[a]
Triglycerides ($mg.dl^{-1}$)	104.7 ± 7.2[a]	90.9 ± 4.8[a]	105.8 ± 12.7[a]	60.2 ± 6.0[b]	50.6 ± 4.0[c]	47.2 ± 5.9[c]	41.0 ± 4.5[c]	41.2 ± 5.3[c]
HDL-cholesterol/ LDL- cholesterol	3.31 ± 0.37[a]	6.46 ± 1.87[a]	7.28 ± 1.03[a]	7.11 ± 0.80[a]	6.97 ± 1.20[a]	4.60 ± 0.57[a]	4.37 ± 1.01[a]	5.50 ± 0.79[a]
Total cholesterol/ triglycerides	0.85 ± 0.06[b]	1.12 ± 0.10[b]	1.00 ± 0.14[b]	1.58 ± 0.20[a]	2.11 ± 0.17[a]	2.30 ± 0.19[a]	2.68 ± 0.20[a]	2.46 ± 0.22[a]
Atherogenic index[§]	0.65 ± 0.07[b]	0.56 ± 0.15[b]	0.48 ± 0.06[b]	0.41 ± 0.06[b]	0.47 ± 0.11[b]	0.79 ± 0.03[ab]	0.77 ± 0.14[ab]	0.92 ± 0.07[a]

[$]Values are means ± SEM. [*]Values in rows with different superscripts are significantly different ($p < 0.05$). [#]HDL: High-density-lipoprotein; LDL: Low-density-lipoprotein; VLDL: Very low-density-lipoprotein. [§]{(Total cholesterol-HDL-cholesterol)/HDL-cholesterol}.

defatted cocoa feeding in cholesterol-containing groups resulted in significant ($p < 0.05$) increase in total cholesterol/triglycerides ratio and decrease in triglycerides compared to those in cholesterol-free groups. In all groups, none of the other lipid variables were notably affected by defatted cocoa feeding.

Orthogonal polynomial trend analysis of studied variables of rats fed cholesterol-free and cholesterol-supplemented diets with increasing defatted cocoa powder for ten weeks is given in table V. In both control and experimental groups, none of the lipid and other biological variables did show quadratic or cubic trends in response to defatted cocoa feeding. In cholesterol-free groups, LDL-cholesterol, triglycerides and atherogenic index exhibited marked ($p < 0.05$) descending linear trends, whereas both ratios of HDL-cholesterol/LDL-cholesterol and total cholesterol/triglycerides exhibited ($p < 0.05$) ascending linear trends. In cholesterol-containing groups, descending linear trend ($p < 0.001$) was obtained for HDL-cholesterol, and ascending linear trends ($p < 0.05$) were seen for VLDL-cholesterol and atherogenic index. No linear trends were observed for the other studied variables.

DISCUSSION

The present study shows that in rats, the addition of varying amounts of defatted cocoa powder to cholesterol-free and cholesterol-containing diets did not affect body weight and food intake. There was a contradictory effect for defatted cocoa on serum lipid profile; this effect was seemingly favorable in rats fed cholesterol-free diet and unfavorable in those given cholesterol-containing diet. In effect, defatted cocoa was unable to counteract the untoward effects of cholesterol on serum lipids. The 3% defatted cocoa had the most prominent effect on serum lipids in all experimental groups. Furthermore, the recorded results were reinforced by remarkable corresponding orthogonal linear trends.

The energy and macronutrient composition of the whole cocoa powder used in this study was comparable to the literature range values (27). However, relative variability in the nutritional properties of cocoa powder has been reported. This variability may be attributed to a number of factors, such as differences in genotype, maturity stage, postharvest handling and storage conditions, product quality and analytical procedures (27). The presently obtained fat and energy values for defatted cocoa were consistent with those reported elsewhere (28).

Dietary cholesterol has been widely used in animals to modify lipid metabolism (25,26). Consistently, in this study, cholesterol feeding increased serum HDL-cholesterol and total cholesterol/triglycerides ratio, and decreased triglycerides. Cholesterol had some increasing effect on total cholesterol and VLDL-cholesterol, but this effect did not reach statistical significance. In line with these results, serum total cholesterol has been shown to increase or remain unchanged as a result of cholesterol feeding in animals (25). Furthermore, there is a general agreement regarding the triglyceride-reducing effect of cholesterol and the lack of its influence on body weight and food efficiency ratio (25,26), a matter that accords with the findings of the current study.

Table V. Orthogonal polynomial trend analysis of studied variables of rats fed defatted cocoa powder for ten weeks

Variable[#]	Cholesterol-free cocoa groups[$]			Cholesterol-containing cocoa groups[$]		
Polynomial trend	**Linear**	**Quadratic**	**Cubic**	**Linear**	**Quadratic**	**Cubic**
Weight gain	0.089	0.069	0.010	0.013	0.001	0.034
Food intake	0.107	0.083	0.013	0.076	0.000	0.032
Food efficiency ratio[§]	0.052	0.037	0.003	0.000	0.005	0.035
Total cholesterol	0.000	0.099	0.004	0.023	0.019	0.004
HDL-cholesterol	0.067	0.098	0.004	0.254**(D)	0.002	0.045
LDL-cholesterol	0.279**(D)	0.004	0.010	0.004	0.081	0.021
VLDL-cholesterol	0.000	0.040	0.001	0.198*(A)	0.014	0.066
Triglycerides	0.259**(D)	0.093	0.146	0.105	0.006	0.007
HDL-cholesterol/ LDL- cholesterol	0.201*(A)	0.074	0.003	0.051	0.144	0.001
Total cholesterol/ triglycerides	0.320**(A)	0.035	0.090	0.109	0.044	0.033
Atherogenic index[§§]	0.162*(D)	0.000	0.000	0.294**(A)	0.026	0.039

*[$]Values are coefficients of determination (r^2); *p < 0.05; **p < 0.01; [(A)] ascending; [(D)] descending. [#]HDL: High-density-lipoprotein; LDL: Low-density-lipoprotein; VLDL: Very low-density-lipoprotein. [§]Body weight gain (g)/100 g food intake. [§§]{(Total cholesterol-HDL-cholesterol)/HDL-cholesterol}.*

It is noteworthy that the currently recorded body weight and food intake were kept unchanged in all experimental groups. Several human studies have investigated the effect of cocoa or its products on body weight, but no animal studies are available. In agreement with our results, ingesting 100 g/day dark chocolate (70% cocoa) for seven days has not been shown to affect body weight in obese women (29). Similar results have been obtained in 49 healthy women following daily consumption of 41 g chocolate, 60 g almonds, or almonds and chocolate together for six weeks (30). Furthermore, no changes in body weight have been documented in men and women ingesting 50 g/day dark chocolate for three weeks (31).

There is a surprisingly large human literature on the relationship between cocoa and CVD, which has expanded rapidly since the 1990s. Despite this, there appears to remain a relative scarcity of the literature dealing with cocoa and CVD lipid markers (13-20), and findings also remain controversial. This might be due to the large discrepancy between the various experimental protocols used. In fact, the type and complexity of the cocoa source, genotype, manufacturing processes or chemical structure, the amount consumed, feeding duration, energy intake, basal diet composition and other lifestyle patterns are among many potential confounders that may contribute to this inconsistency. It may be also noticed that the aim of most of the previous studies was to evaluate the effect of whole cocoa or chocolate polyphenols, particularly flavonoids, in normal or pathological conditions. However, studies involving defatted cocoa inclusion to cholesterol-containing diets or those investigating such diets on serum lipids in humans and animals are generally scarce. This certainly limits the comparison of the present results with those of the other studies.

To the best of our knowledge, this study is perhaps the first demonstration that specifically links defatted cocoa with serum lipid parameters in the cholesterol-fed rats. It is generally accepted that this model has disturbed lipid metabolism (25,26). Under the present experimental conditions, the 3% defatted cocoa had the main impact on serum lipids. A significant fall in serum LDL-cholesterol and triglycerides, and a rise in total cholesterol/triglycerides ratio occurred in response to 3% defatted cocoa in rats fed cholesterol-free diet as compared to control. The decrease in triglycerides was obviously the reason behind the increase in total cholesterol/triglycerides ratio. On the other hand, in contrast to control, the 3% defatted cocoa induced an evident increase in serum VLDL-cholesterol and atherogenic index, and a decrease in HDL-cholesterol in rats fed cholesterol-containing diet. Moreover, the 3% defatted cocoa caused significant rise in VLDL-cholesterol, atherogenic index and total cholesterol/triglycerides ratio, and fall in triglycerides in rats fed cholesterol-containing diet compared to those fed cholesterol-free diet. Interestingly, the triglyceride-reducing action of cholesterol was maintained in rats fed cholesterol-containing diet without a noticeable effect of the different defatted cocoa levels. In essence, these results clearly demonstrate a favorable effect of defatted cocoa on serum lipid fractions in rats fed cholesterol-free diet, and an unfavorable effect in those fed cholesterol-containing diet. The reasons responsible for these findings and their physiologic and clinical significance are not clear. However, the following discussion will focus on the available literature.

In humans, consumption of 16-50 g dark or milk chocolate daily by healthy free-living normocholesterolemic individuals for periods of 2-4 weeks has been shown to increase HDL-cholesterol (10,31-34), decrease LDL-cholesterol (13-17,31) and tri-

glycerides (31,34), or to produce no effects on total cholesterol, LDL-cholesterol, VLDL-cholesterol and HDL-cholesterol/LDL-cholesterol ratio (10,33). Cocoa products have also been reported to increase HDL-cholesterol in hypercholesterolemic individuals (32). In obese women, ingesting 100 g/day dark chocolate containing 70% cocoa for seven days has been shown to increase HDL-cholesterol and decrease ratios of total cholesterol/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol (29). Furthermore, several comprehensive reviews examining the effects of consumption of cocoa or its products on serum lipids have shown that short-term ingestion of these products led either to decrease in LDL-cholesterol and total cholesterol with no major effects on HDL-cholesterol and triglycerides (13,14), or just to marginal effects on LDL-cholesterol and HDL-cholesterol (9). Apparently, some of these results are consistent with our findings; however, a remarkable variation in the experimental approaches still exists. It seems that the currently recorded favorable effect of defatted cocoa on serum lipid fractions in rats fed cholesterol-free diet somewhat accord with that reported in normocholesterolemic individuals (10,17,31,34). On the other hand, the effect of feeding cocoa and cholesterol together on serum lipids has not been yet investigated in humans or animals.

It may be noted that whole cocoa-containing chocolate was the study substance for the aforementioned human studies. In this respect, it has been stated that the great differences in the chocolate consumption in different population groups, and varied chocolate composition in terms of cocoa concentrations (15-85%), added food ingredients particularly milk, fat or sugar, or bioactive components such as polyphenols, carotenoids and phytosterols, make it rather difficult to evaluate the impact of chocolate on blood lipids in observational studies (8,15). Unlike these studies, we used solely defatted cocoa powder and incorporated it into a standardized rat diet. In view of these facts, in contrast to chocolate, cocoa itself has been recommended as a cardioprotective strategy (20).

The recorded results of the orthogonal polynomial linear trend analyses provided further substantiation for the discriminative effect of defatted cocoa on serum lipids in rats fed either cholesterol-free or cholesterol-containing diet. Marked descending linear trends for LDL-cholesterol, triglycerides and atherogenic index, and ascending linear trends for ratios of HDL-cholesterol/LDL-cholesterol and total cholesterol/triglycerides were demonstrated in the former rat group; whereas in the latter group, substantial descending linear trend for HDL-cholesterol, and ascending linear trends for VLDL-cholesterol and atherogenic index were obtained. Noteworthy, such data approaches have not been yet documented elsewhere.

However, some limitations to the present study need to be noted. The possible bioactive component in defatted cocoa neither was determined nor was its serum level assessed. Thus, the mechanisms by which defatted cocoa and cholesterol interact and affect serum lipids cannot be clearly explained. Nevertheless, we were able to report a favorable effect of defatted cocoa on serum lipid profile in rats fed cholesterol-free diet and unfavorable effect in those given cholesterol-containing diet.

CONCLUSIONS

Taken together, when incorporated into isocaloric and isonitrogenous diets in varying amounts, the particular 3% defatted cocoa appears to exert a profound favorable effect on serum lipids in cholesterol-deprived rats and, evidently, an unfavorable effect in cholesterol-fed rats. Defatted cocoa is seemingly ineffective to counteract the atherogenic effect of cholesterol in rats. It is also obvious that a sort of interaction between cholesterol and defatted cocoa took place, though it was not addressed. Thus, it would be of great importance to explore the mechanisms by which defatted cocoa and cholesterol interact and modify lipid assimilation and metabolism under cholesterol diet conditions. This could be useful to lessen the debate surrounding the claim that consumption of cocoa or its products can reduce the risk of dyslipidemia, atherosclerosis and CVD in man.

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Trabajo Original

Otros

Irisin is weakly associated with usual physical activity in young overweight women

La irisina se asocia débilmente con la actividad física habitual en mujeres jóvenes con sobrepeso

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Abstract

Purpose: To determine if irisin plasma levels are associated with regular physical activity, body composition and metabolic parameters in women subjected to calorie restriction.

Subjects and methods: We studied 42 women aged 34 ± 13 years with a body mass index of 27.7 ± 1.8 kg/m^2, who were subjected to a calorie restriction for three months. At baseline and at the end of the study, weight, waist and hip circumference, laboratory parameters, body composition by DEXA, resting and activity energy expenditure by indirect calorimetry and 72 hours actigraphy were measured. Fasting serum irisin was quantified using an ELISA kit.

Results: After the intervention period, participants lost 1.5 (0.4-3.4) kg and irisin levels did not change. Irisin baseline levels were positively but weakly correlated with the level of physical activity. This association was lost at the end of the intervention. No association was found between irisin levels and body composition or insulin sensitivity or their changes after calorie restriction. No association between serum irisin levels and PGC-1α expression in peripheral blood mononuclear cells and serum irisin was observed.

Conclusions: Fasting serum irisin was weakly associated with usual physical activity and did not change after calorie restriction.

Key words:

Irisin. Calorie restriction. PGC-1α.

Resumen

Objetivo: determinar si los niveles plasmáticos de irisina se asocian con la actividad física regular, composición corporal y parámetros metabólicos en mujeres sometidas a restricción calórica.

Material y métodos: estudiamos 42 mujeres de 34 ± 13 años con un índice de masa corporal de 27,7 ± 1,8 kg/m^2, quienes fueron sometidas a una restricción calórica durante tres meses. Al comienzo y final del estudio, se midieron peso, circunferencias de cintura y cadera, parámetros de laboratorio, composición corporal usando DEXA y gasto energético en reposo y en actividad mediante calorimetría indirecta y actigrafía. La irisina en ayunas se midió utilizando un kit ELISA.

Resultados: después del periodo de intervención, las participantes bajaron 1,5 (0,4-3,4) kg y los niveles de irisina no cambiaron. La irisina basal se relacionó de forma positiva pero débil con el nivel de actividad física de las participantes. Esta asociación se perdió al final de la intervención. No se encontró una asociación entre los niveles de irisina y la composición corporal o sensibilidad a insulina o el cambio de estos parámetros después del periodo de restricción calórica. No se observó asociación entre los niveles de irisina y la expresión de PGC-1α en monocitos periféricos.

Conclusiones: La irisina en ayunas se asoció débilmente con la actividad física habitual y no cambió después de la restricción calórica.

Palabras clave:

Irisina. Restricción calórica. PGC-1α.

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INTRODUCTION

In 2012, Boström et al. described (1) a new myokine, called irisin, which results from the cleavage of the type I membrane protein, fibronectin type III containing five domains (FNDC5). This cleavage is induced by the peroxisome proliferator-activated receptor γ (PPARγ) transcriptional co-activator PGC-1α (2). In humans, preliminary evidence showed that exercise increased its plasma levels (3). In murine models, On the other hand, irisin generates beige fat cells increasing mitochondria and the expression of uncoupling protein 1 (UCP1), thereby augmenting thermogenesis and energy expenditure (4-6). In humans, its plasma concentrations increase in the presence of metabolic diseases (7); they are associated with lean body mass (8) and inversely related to visceral fat mass (9). In obese young women irisin was found to be lower than in their normal weight counterparts (10). Other authors found no association with body composition (11).

Boström postulated that physical training in humans can double the plasma concentration of irisin (1). Other authors have described a temporary increase of irisin plasma levels during acute exercise phases that is not observed during chronic exercise (12) or during high intensity workouts (13). However, the majority of these studies focused exclusively on the intensity, frequency and duration of physical activity, without describing what happens during habitual physical activity.

Pardo et al. (14) concluded that plasma irisin correlated with usual energy expenditure and fat mass, the latter being its primary predictor. Recently, Al-Daghri et al. (15) found that healthy individuals had a positive association between irisin levels and habitual physical activity.

Thus, the purpose of this work was to evaluate the association of irisin with habitual physical activity and changes in body composition in a group of women before and after a period of calorie restriction used as an intervention that modifies body composition.

MATERIAL AND METHODS

We studied 47 healthy females aged between 25 and 40 years old, with a body mass index between 27 y 30 kg/m². We excluded participants who experienced weight fluctuations over the last six months (more than 2 kg), those who were taking medications of any type other than birth control measures, those who had any underlying disease, and those who exercised vigorously or competitively.

All participants signed an informed consent form and the study was approved by the Ethics Committee of the Institute of Nutrition and Food Technology. The study was registered at clinicaltrials.gov with the number NCT01508091.

At the beginning of the study, weight and height were measured. Their body composition was determined using dual-energy X-ray absorptiometry (DEXA) in a Lunar iDXA ME+200674 equipment.

Basal and activity energy expenditure were quantified combining indirect calorimetry in a Sensor Medics Vmax Encore 29 calorimeter, actigraphy and heart rate measurement using Actiheart® actigraphs. First, resting energy expenditure was assessed using a ventilated hood. Then, activity energy expenditure and heart rate were measured with a breath by breath technique while cycling in a braked cycle ergometer during ten minutes (or less if the participant reported exhaustion) using a 15 watt ramp to plot energy expenditure against heart rate. Finally, participants wore the actigraphs for 72 hours during weekdays. Using resting energy expenditure values and the heart rate/energy expenditure curve, results obtained with the actigraphs were individually calibrated to measure total energy expenditure (TEE), activity energy expenditure (AEE) and physical activity level (PAL) (Actiheart software version 4.0.32, www.camtech.com).

A fasting blood sample and serial samples for two hours after a 75 g oral glucose load were obtained. Peripheral blood mononuclear cells (PBMC) were isolated from the fasting sample. Routine blood chemistry was measured in a certified clinical laboratory, including insulin and blood glucose in the fasting post prandial blood samples. Plasma irisin was measured in samples stored at -80 °C, using an ELISA kit elaborated by AdipoGen Labs, with a sensitivity of 1 ng/ml, an intra assay precision between 4.8 and 6.7% and inter assay between 8 and 9.7%. All the samples were analyzed at the Institute of Nutrition and Food Technology one month after ending the study, on the same date. The expression of PGC1α in PBMC was measured by real time polymerase chain reaction using the following primers: forward: 5' GACGTGACCACTGACAATGA 3'; reverse: 5' GGGTTTGTTCTGATCCTGTG 3'.

Participants were then instructed to restrict their calorie intake by 25% of their measured TEE with actigraphy as described above, during the ensuing three months. The proportions of the meals were 50% carbohydrates, 25% lipids, 25% proteins, and 100% of micronutrient requirements according to daily recommended intakes (DRI) (16). Hypocaloric snacks were provided to the participants and they were controlled once a week by a dietitian. Immediately after the restriction period, the same measurements made on baseline were repeated. No specific instruction was given regarding exercise during the study period.

DATA AND STATISTICAL ANALYSIS

Using serial determinations of blood glucose and insulin levels before and after a glucose load, the Matsuda index for assessment of insulin sensitivity was calculated (17). Data was analyzed comparing parameters obtained at baseline and after the restriction period. The Shapiro-Wilk test was used to determine the variable distribution. Variables with a normal distribution are reported as mean ± standard deviation, otherwise as median (interquartile range). Differences between continuous absolute values were evaluated with Student or Kruskal Wallis tests. Paired testing of data at baseline and after the intervention was performed using paired t tests or Wilcoxon signed-rank test. Correlations were assessed using Pearson correlation coefficients. Statistical significance was set at a probability of less than 0.05. STATA v.12.1. program (Statacorp, Texas, USA) was used for the statistical analysis.

RESULTS

Five of the 47 women did not complete all the assessments at the end of the study, therefore data of 42 participants aged 34 ± 13 years with an initial body mass index of 27.7 ± 1.8 kg/m^2 are presented. Table I shows weight, waist and hip circumferences, blood pressure, body composition, and energy expenditure of participants at baseline and at the end of the study. Significant reductions in weight, fat mass, fat free mass and resting energy expenditure were observed. Significant increases in AEE and PAL were also observed after the intervention. Table II shows laboratory values. There was no significant change in irisin levels or PGC1α expression in PBMC after the calorie restriction period. Decreases in total cholesterol, triiodothyronine and thyroxine were observed.

Baseline physical activity level had a positive albeit weak correlation with irisin concentration (Fig. 1). This association was not present at the end of the intervention. No association between irisin levels and other parameters was observed at baseline or at the end of the study, including body composition measures, resting energy expenditure, serum lipid levels, Matsuda index or PGC1α expression in PBMC.

DISCUSSION

After the restriction period, participants reduced their body weight and fat mass. Irisin levels were only weakly associated with the physical activity level of participants at baseline. However, we did not observe any change in irisin levels after the calorie restriction period even though subjects increased their physical activity and their body composition changed.

We measured body composition, energy expenditure and metabolic parameters using accurate and adequate methods. For body composition, we used DEXA, a method that in our hands has a measurement error of less than 3% (18). For total energy expenditure we used a combination of indirect calorimetry and actigraphy in which actigraphs were calibrated with the individual heart rate/energy expenditure curves obtained during an incremental exercise test. This method provides reliable measures of total energy expenditure when compared with wearable indirect calorimeters (19,20). To assess insulin resistance we used the Matsuda index, which is the method with the best concordance with euglycemic insulin clamp (17).

Disappointingly, irisin was only weakly associated with baseline physical activity level, and this association was lost after the intervention. Despite the changes in fat and fat free mass achieved with calorie restriction, no change in irisin levels were observed. These results cast doubts about the real meaning of circulating irisin levels or the accuracy of the measurement methods used to determine this hormone. While Boström used Western Blot against a sequence of FNDC5 (21), later studies used different ELISA kits to quantify Irisin. Albrecht and colleagues recently evaluated the three more commonly used antibodies in ELISA kits for irisin and found that they have cross-reactions with plasma proteins different from irisin. However, the antibody used by AdipoGen Labs (which we used) marked a protein that weights 25kDa, which is within the weight range of irisin. However, this group concluded that the proteins these kits identified were not irisin (22). These results have been recently challenged by other authors (23). Even more, a recent report showed that irisin is a true circulating hormone, when measured by tandem mass spectrometry (24). However, the concerns about the accuracy of ELISA kits to measure irisin still persist.

To date, only two published studies mention a possible relationship between habitual physical activity and plasma concentration of irisin (14,15). However, the methods to measure physical activity used in these reports are less accurate than ours.

Table I. Anthropometry, body composition and energy expenditure of participants

	Baseline			End of study			p (paired analysis)
Anthropometry and blood pressure							
Weight (kg)	71.1	±	6.1	68.9	±	6.4	< 0.01
Waist circumference (cm)	94.2	±	6.3	90.0	±	6.7	< 0.01
Hip circumference (cm)	104.4	±	5.2	102.6	±	4.9	< 0.01
Systolic blood pressure (mm Hg)	117.0	±	14.6	109.5	±	9.7	< 0.01
Diastolic blood pressure (mm Hg)	75.2	±	9.8	70.0	±	7.3	< 0.01
Body composition by DEXA							
Total body fat (kg)	30.1	±	4.3	28.3	±	4.6	< 0.01
Total fat free mass (kg)	38.8	±	3.5	38.3	±	3.5	< 0.01
Energy expenditure							
Resting energy expenditure (kcal/24 h)	1,453.2	±	107.5	1,408.0	±	110.5	0.03
Activity energy expenditure (kcal/24 h)	591.9	±	240.9	716.5	±	370.3	0.04
Total energy expenditure (kcal/24 h)	2,282.3	±	298.8	2,352.4	±	400.3	NS
Physical activity level	1.6	±	0.2	1.7	±	0.3	0.03

Table II. Laboratory values of participants

	Baseline			End of study			p (paired analysis)
Blood glucose (mg/dl)	87.4	±	9.0	88.7	±	9.6	NS
Serum insulin (uU/ml)	8.5	±	4.6	8.9	±	6.0	NS
Matsuda index (arbitrary units)	5.7	±	4.0	6.1	±	5.2	NS
Total cholesterol (mg/dl)	181.4	±	34.7	172.2	±	32.2	NS
HDL cholesterol (mg/dl)	56.3	±	12.2	55.3	±	13.6	NS
Triacilglycerol (mg/dl)	114.2	±	65.7	101.9	±	50.2	NS
Creatinine (mg/dl)	0.7	±	0.1	0.7	±	0.1	NS
Thyroid stimulating hormone (uU/ml)	2.3	±	0.9	2.3	±	1.3	NS
Thyroxine (ug/dl)	9.0	±	2.1	8.4	±	1.9	< 0.01
Triiodothyronine (ng/ml)	1.5	±	0.4	1.4	±	0.3	< 0.01
Irisin (ug/ml)	2.0	±	1.4	2.0	±	1.2	NS
PGC-1α (arbitrary units)[§]	1.24 (0.37-3.88)			0.75 (0.25-5.85)			NS

[§]*Expressed as median (interquartile range)*

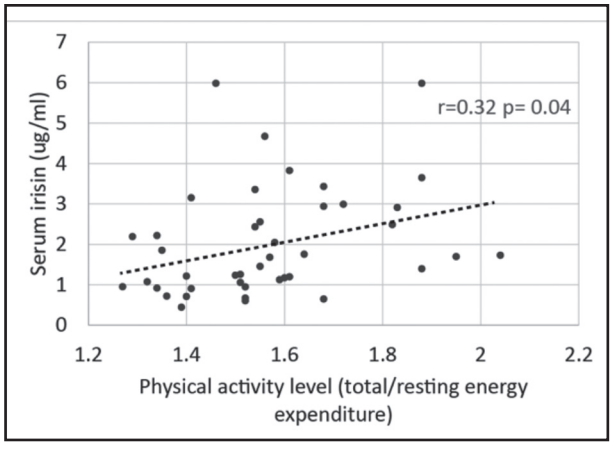

Figure 1.

Correlation between baseline irisin levels and physical activity level.

One group used accelerometers without individual calibration, and the other only used questionnaires. What is usually reported is that training, specifically resistance training, increases irisin levels, and that this increase correlates with the buildup in muscle mass (25).

Unlike other reports, we did not observe a change in irisin levels after weight loss (26), with thyroid function tests (27) or insulin (28,29). Unfortunately, we did not observe significant changes in insulin sensitivity at the end of the intervention period.

The upstream regulator of FNDC-5 cleaving and irisin liberation is PGC-1α (30,31). Therefore, we measured the expression of PGC1α in mRNA of PBMCs by rtPCR. Again, we found no association of its expression with irisin. It must be born in mind however that we did not measure the expression of the molecule in muscle, where it should have the direct effect, and that we obtained a great dispersion of values. Again, the lack of relationship between the precursor and the hormone causes us to wonder about the real value of the hormone as a marker of PGC-1α activation (32).

In summary, we only found a weak association of irisin with usual physical activity in these women, and we seriously doubt about the real physiological role of the hormone in muscle physiology.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Otros

Anorexia y bulimia nerviosas: difusión virtual de la enfermedad como estilo de vida

Anorexia and bulimia nervosa: virtual diffusion of the disease as a lifestyle

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Resumen

Introducción: la adolescencia es un periodo vulnerable para padecer trastornos de la conducta alimentaria (TCA) como la anorexia y la bulimia nerviosas. La insatisfacción corporal, uno de los factores precipitantes de los TCA, conduce a las adolescentes a la búsqueda de información sobre dietas en internet. En este contexto, las páginas pro-Ana (proanorexia) y pro-Mía (probulimia) difunden contenidos altamente perjudiciales para la salud relacionados con la pérdida de peso y los TCA.

Objetivos: en el presente trabajo se analizan la cantidad, el posicionamiento, la calidad y la difusión de las páginas pro-Ana y pro-Mía.

Métodos: se realizó una búsqueda de páginas web en el navegador Google Chrome con las palabras clave "anorexia", "bulimia", "trastornos de la conducta alimentaria (TCA)", "Ana y Mía", "pro-Ana y pro-Mía", "anorexic nation", "obesidad", "estilos de vida saludables" y "nutrición saludable". Se seleccionaron los 20 primeros resultados de cada búsqueda según los índices de posicionamiento de PageRank y se analizó la calidad de dichos recursos mediante un cuestionario. Para el estudio de la difusión de páginas pro-Ana y pro-Mía en redes sociales como Facebook y Twitter se utilizó el programa SharedCount.

Resultados: pro-Ana y pro-Mía dieron más de un millón de entradas, siendo páginas mal posicionadas, de tipo blog en su mayoría, con mayor difusión en Facebook y Twitter comparadas con otras de mejor calidad.

Conclusiones: pro-Ana y pro-Mía son recursos con una clara intencionalidad de contactar con personas que padecen un TCA o están en riesgo, con el fin de reforzar la comunicación entre ellas a través de la blogosfera.

Palabras clave:

Anorexia. Bulimia. pro-Ana. pro-Mía. Obesidad. Estilos de vida saludables. Nutrición saludable.

Abstract

Introduction: Adolescence is a vulnerable period for the onset of eating disorders (ED) such as anorexia and bulimia nervosas. Body dissatisfaction, a precipitating factor for ED, leads adolescents to seek information on the Internet about diets. In this context, pro-Ana (proanorexia) and pro-Mia (probulimia) are on-line pages that promulgate highly harmful contents for health related to weight loss and ED.

Objectives: The aim of this study was to analyze quantity, quality and social diffusion strategies used by pro-Ana and pro-Mia webpages.

Methods: A web search was done in the Google Chrome browser, using the keywords "anorexia", "bulimia", "eating disorders", "Ana and Mia", "pro-Ana and pro-Mia", "anorexic nation", "obesity", "healthy lifestyles" and "healthy nutrition". The top 20 results for each search were selected and analyzed according to positioning rates (PageRank, PR). The quality of these resources was analyzed by a previously published questionnaire. Finally, a study of the diffusion in social networks like Facebook and Twitter was performed for pro-Ana and pro-Mia pages using SharedCount.

Results: Searches for pro-Ana and pro-Mia reported more than a million entries. The pages were poorly positioned. Blog contents were the most shared between all the analyzed pages.

Conclusions: pro-Ana and pro-Mia are resources with a clear intention to establish a contact with people with an eating disorder or who are at risk for developing one, in order to strengthen the communication through the blogosphere.

Key words:

Anorexia. Bulimia. pro-Ana. pro-Mia. Obesity. Healthy lifestyle. Healthy nutrition.

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INTRODUCCIÓN

"Ana" y "Mía" no son personas reales, sino la denominación que toman las personas que padecen los trastornos de la conducta alimentaria (TCA) conocidos como anorexia nerviosa (AN) y bulimia nerviosa (BN). La AN es una enfermedad mental grave que se caracteriza por un miedo intenso a engordar y la búsqueda decidida de la delgadez mediante procedimientos voluntarios. Entre estos procedimientos están llevar una dieta restrictiva, estricta y autoimpuesta y, en algunos subtipos, desarrollar conductas purgativas (vómitos autoinducidos, abuso de laxantes, uso de diuréticos o ejercicio físico intenso) (1,2). En cuanto a la BN, la persona realiza ingestas excesivas de comida en un corto periodo de tiempo (atracones), acompañadas de conductas compensatorias inapropiadas de manera repetida (vómitos voluntarios y abuso de laxantes y diuréticos) que eviten el aumento de peso por los atracones (1,2).

Uno de los factores más decisivos para padecer un trastorno de la conducta alimentaria (TCA) es la insatisfacción corporal. Actualmente, el 70% de las adolescentes declara no sentirse a gusto con su cuerpo. El binomio "insatisfacción corporal + baja autoestima" suele desembocar en el seguimiento de una dieta restrictiva, que sin control médico puede conducir a personas vulnerables hacia el desarrollo de la AN (3-5). Estas personas, principalmente adolescentes, pueden poner en peligro su vida (5,6% muertes/década) debido, en parte, a los devastadores efectos que provoca la malnutrición en el organismo (6-8). Por otro lado, la implantación de conductas alimentarias extremas en la adolescencia se mantiene, al menos, durante diez años más (9), lo que contribuye a la cronicidad de la enfermedad (10,11). Médicos y especialistas en TCA indican que es importante alejar a los jóvenes de prácticas poco saludables para controlar el peso.

Por otro lado, el hábito de búsqueda en internet está muy extendido entre la población adolescente, siendo el área de la salud uno de los objetos de esas búsquedas (12). Un estudio realizado en 2012 con estudiantes de 12 a 18 años en Barcelona (España) mostró que el 75% de los encuestados utilizó internet para buscar información sobre salud, especialmente para consultar temas relacionados con el aspecto físico (36,1%), dietas y nutrición (27,8%) y problemas de alimentación (20,3%) (13), datos que coinciden con otros estudios (14). Si bien Google es la principal fuente de información sobre salud por parte de los adolescentes, los blogs y foros suponen un 24,8%, los chats un 9,3% y las redes sociales un 6,2% (15). Un dato reciente indica que el número de menores de 16 años que han accedido en 2015 a internet en España asciende a 31 millones (15). La exposición a contenidos peligrosos en un periodo vulnerable como es la adolescencia puede contribuir al inicio de un TCA. Algunas fundaciones en Estados Unidos estiman que existen más de un millón de sitios en internet que se dedican a fomentar estilos de vida sustentados en la anorexia y la bulimia, y a apoyar prácticas poco saludables. Estos sitios han experimentado un crecimiento del 470% durante el periodo 2006-2008 (16), incremento incluso mayor que el que han sufrido webs como Facebook o MySpace (cercano al 455%). Por ello, parece necesario establecer medidas de protección y prevención ante este tipo de contenidos.

En este contexto surgen pro-Ana (proanorexia) y pro-Mía (probulimia), grupos que promueven y apoyan la enfermedad como estilo de vida. En el espacio virtual, pro-Ana y pro-Mía son el objeto de innumerables mensajes en las redes sociales, blogs, foros y páginas webs, mostrando un innegable éxito en la difusión *on-line* de sus credos y máximas, acompañadas de consejos para lograr sus objetivos. El impacto que los recursos *on-line* tienen sobre la población adolescente se refleja en algunos estudios que indican que cerca del 60% de las pacientes con anorexia y bulimia realizaron una primera búsqueda en internet sobre contenidos no saludables que incluyen, entre otros, procedimientos para adelgazar rápidamente (17). Los profesionales consideran estas páginas altamente perjudiciales e influyentes, especialmente entre las adolescentes, que suelen consultarlas inicialmente para perder peso y quedan atrapadas en un estilo de vida tóxico.

El objetivo del presente trabajo es hacer un análisis cuantitativo, así como un estudio de las vías de difusión, posicionamiento y calidad de recursos *on-line* y la difusión en redes sociales de los contenidos pro-Ana y pro-Mía.

MÉTODOS

PROTOCOLO DE BÚSQUEDA EN GOOGLE MEDIANTE PALABRAS CLAVE

En mayo de 2015 se realizó una búsqueda en el navegador Google Chrome mediante palabras clave. Las palabras utilizadas en la búsqueda fueron: "anorexia", "bulimia", "trastornos de la conducta alimentaria (TCA)", "Ana y Mía", "pro-Ana y pro-Mía", "anorexic nation", "obesidad", "estilos de vida saludables" y "nutrición saludable". El número de resultados analizados se corresponde con el seleccionado para otros estudios (18).

Para las palabras "anorexia", "bulimia", "trastornos de la conducta alimentaria (TCA)", "Ana y Mía", "anorexic nation", "obesidad", "estilos de vida saludables" y "nutrición saludable", se seleccionaron las primeras 20 entradas, mientras que para la búsqueda "pro-Ana y pro-Mía" se seleccionaron 34 entradas al hacer un estudio más preciso de este tipo de webs.

ANÁLISIS DE POSICIONAMIENTO DE LOS RECURSOS *ON-LINE* PARA CADA PALABRA CLAVE

Para el análisis del posicionamiento se utilizó PageRank (PR) de Google. Para ello, se instaló en la barra de utilidades del navegador la herramienta SEOquake, que sirve para analizar la influencia de una página frente a otra, siguiendo diferentes índices de posicionamiento establecidos por Google. El PR es un valor numérico que oscila entre 1 y 10 y que Google asocia a una determinada web teniendo en cuenta los enlaces que recibe, la calidad de los mismos, así como la importancia de las webs de las que provienen dichos enlaces.

Se obtuvieron dos tipos de datos: por un lado, el número de páginas que presentaban valores de PR; por otro, se hizo un

análisis de los valores de PR calculando las medianas. Los datos obtenidos fueron exportados a un fichero ".csv".

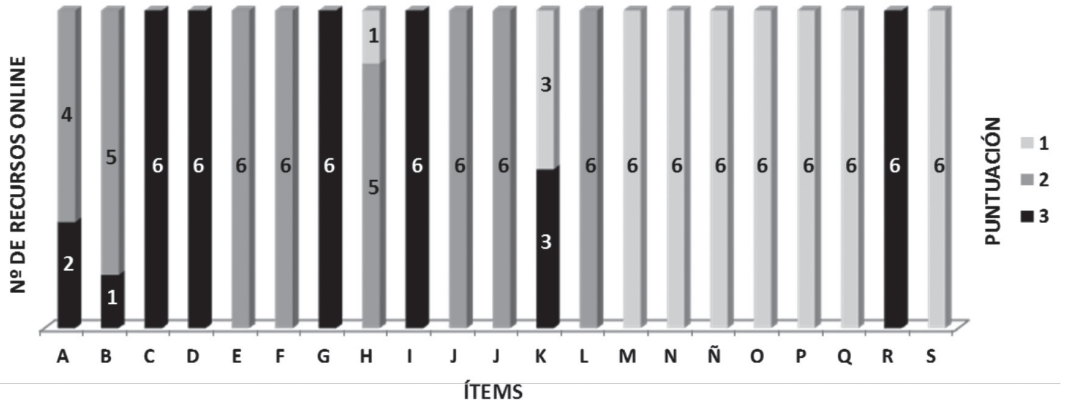
ANÁLISIS DE CALIDAD DE LAS PÁGINAS PRO-ANA Y PRO-MÍA

Para el estudio de la calidad de los recursos web se analizó la aplicabilidad de varios ítems incluidos en cinco variables, siguiendo una modificación a partir del cuestionario propuesto por Bermúdez-Tamayo (19,20). Las cinco variables son: transparencia y ausencia de conflicto de intereses, autoría, protección de datos personales, responsabilidad y accesibilidad. Cada una de estas variables contiene una serie de ítems (un total de 21 nombrados de la A a la S) que se describen en la tabla I. Los ítems comprendidos entre A y O se valoraron con tres niveles de *aplicabilidad* (donde 1 equivale a "no aplica"; 2, a "aplicación parcialmente dudosa"; y 3, a "sí aplica"). Para los ítems comprendidos entre P y S se valoró la *accesibilidad*

Tabla I. Análisis de calidad

A		Ítem	Descripción de los ítems
ANÁLISIS DE CALIDAD	TRANSPARENCIA Y AUSENCIA CONFLICTO INTERESES	A	Nombre de la persona/organización
		B	Dirección electrónica/física del responsable
		C	Especificación del propósito/objetivo
		D	Especificación de la población a la que se dirige
		E	Especificación de la financiación para su desarrollo/mantenimiento
	AUTORÍA	F	Declaración de las fuentes de información de los documentos
		G	Fecha de publicación de los documentos
	PROTECCIÓN DATOS PERSONALES	H	Indicación de la forma de protección de la información o aviso legal
		I	Se especifica la fecha de actualización de la información
		J	Descripción del procedimiento de actualización de la información
	RESPONSABILIDAD	K	¿Hay posibilidad de contacto (e-mail/otros)?
		L	Si hay consultas *on line,* ¿se identificaran al responder?
		M	Declaración del procedimiento usado en la selección del contenido
		N	Indican de dónde procede/cómo se obtuvo el enlace de calidad
	ACCESIBILIDAD	Ñ	Facilidad de encontrar contenidos
		O	Facilidad de encontrar búsquedas
		P	Facilidad de lectura
		Q	Lenguaje adaptado a destinatario
		R	Presencia de sellos de calidad

B



A. Descripción de las cinco variables y de los ítems para cada variable que constituyen el cuestionario adaptado de Bermúdez-Tamayo (19). B. Análisis de blogs pro-Ana y pro-Mía. El número de blogs que obtienen las puntuaciones 1, 2 o 3 se muestra en el interior de las barras. 1: no aplica; 2: aplicación dudosa; 3: aplica. Dirección de los blogs: http://prinzessinloreleiwannabeana.blogspot.com/; http://amigasanaymia.blogspot.com/; http://princesnikky.blogspot.com/; http://listadeblogsactualizadosanaymia.blogspot.com/; http://pro-anaymia.blogspot.com/; http://eatisforweaks.blogspot.com/.

con cinco niveles en orden creciente del 0 al 4, donde 0 equivale a "nada accesible o de muy difícil accesibilidad"; 1, a "poco accesible"; 2, a "medianamente accesible"; 3, a "bastante accesible"; y 4, a "totalmente accesible". La escala de valoración de estos ítems es mayor debido a la valoración subjetiva de dichos ítems o gusto personal (facilidad de lectura, color y letra, lenguaje adecuado, etc.).

ANÁLISIS DE DIFUSIÓN DE RECURSOS PRO-ANA Y PRO-MÍA

El estudio sobre la difusión de las páginas encontradas en la búsqueda "pro-Ana y pro-Mía" se llevó a cabo utilizando la herramienta SharedCount, que permite conocer la repercusión de un recurso web en las distintas redes y herramientas sociales y valorar el potencial de difusión del mismo. La herramienta muestra cuánto se comparte una URL y explica, por tanto, su aparición en las primeras posiciones en los motores de búsqueda como Google. En este trabajo se han seleccionado 34 entradas de la búsqueda "pro-Ana y pro-Mía" para analizar el tipo de recurso y la repercusión social, principalmente a través de Facebook y Twitter.

ANÁLISIS ESTADÍSTICO DESCRIPTIVO

Para el análisis estadístico de los datos se ha utilizado el programa Excel y se han calculado media y mediana para cada ítem del cuestionario.

RESULTADOS

RESULTADOS DE LA BÚSQUEDA

La búsqueda en Google con las palabras clave "anorexia", "bulimia", "trastornos de la conducta alimentaria (TCA)", "Ana y Mía", "pro-Ana y pro-Mía", "anorexic nation", "obesidad", "estilos de vida saludables" y "nutrición saludable" dio un total de 62.373.00 resultados. El número de entradas para cada búsqueda se muestra en la figura 1A, mientras que en la figura 1B se muestra el porcentaje de cada búsqueda relativo al total. La búsqueda en Google arroja un resultado cuantitativamente muy superior para "anorexia" (42%) que para el resto de palabras clave, indicando que existe en la red más información relacionada con este trastorno que con otros como la bulimia. Así, la "obesidad" (26%) y la "bulimia" (18%) son las que ocupan el segundo y tercer puesto respectivamente.

ANÁLISIS DE POSICIONAMIENTO MEDIANTE PAGERANK (PR)

Los resultados de posicionamiento de PageRank (PR) de Google, correspondientes a las 20 primeras entradas por palabra clave, mostraron que las búsquedas de "obesidad" y "nutrición saludable" dieron un número alto de páginas con valores de PR (17 de las 20 analizadas), mientras que las búsquedas "pro-Ana y pro-Mía" y "anorexic nation" arrojaron un número de páginas mucho menor (Fig. 2).

Por otro lado, los valores de las medianas de los PR son muy bajos en las páginas "Ana y Mía", "pro-Ana y pro-Mía" y "anorexic nation", lo que hace referencia a su bajo posicionamiento, es decir, reciben pocos links de páginas bien posicionadas. Por el contrario, las páginas "anorexia", "bulimia", "TCA", "obesidad", "estilos de vida saludables" y "nutrición saludable" mostraron PR de 3 y 4, lo cual indica que son recursos de calidad en su nicho.

ANÁLISIS DE CALIDAD DE LOS RECURSOS

El análisis de calidad se ha restringido a los seis recursos mejor posicionados relacionados con "pro-Ana y pro-Mía", que fueron los que mostraban características básicas para el análisis; el resto eran vídeos de YouTube o noticias en prensa. Los resultados del análisis de estos recursos, que se exponen en la tabla I, indican que los valores más bajos en aplicabilidad se observan en los ítems de "accesibilidad", exceptuando el que corresponde a "lenguaje adaptado a destinatario" (R). En la variable "transparencia y ausencia de conflicto de intereses", los ítems correspondientes a "especificación

A

Búsqueda	Número de entradas
Anorexia	25.900.000
Obesidad	16.400.000
Bulimia	11.100.000
Ana y Mía	5.420.000
Pro-Ana y pro-Mía	1.130.000
Nutrición saludable	927.000
Estilos de vida saludable	692.000
TCA	499.000
Anorexic nation	305.000

B

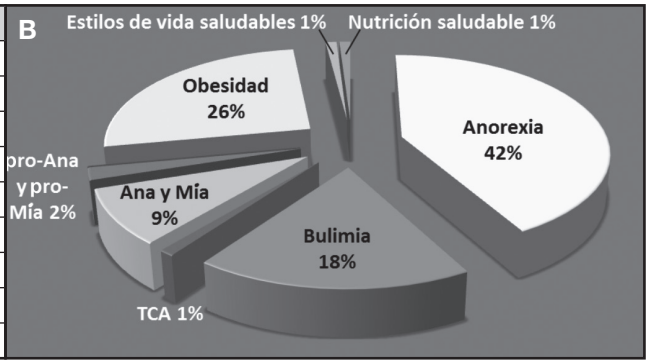


Figura 1.

A. Número de entradas para cada palabra clave. B. Porcentaje relativo.

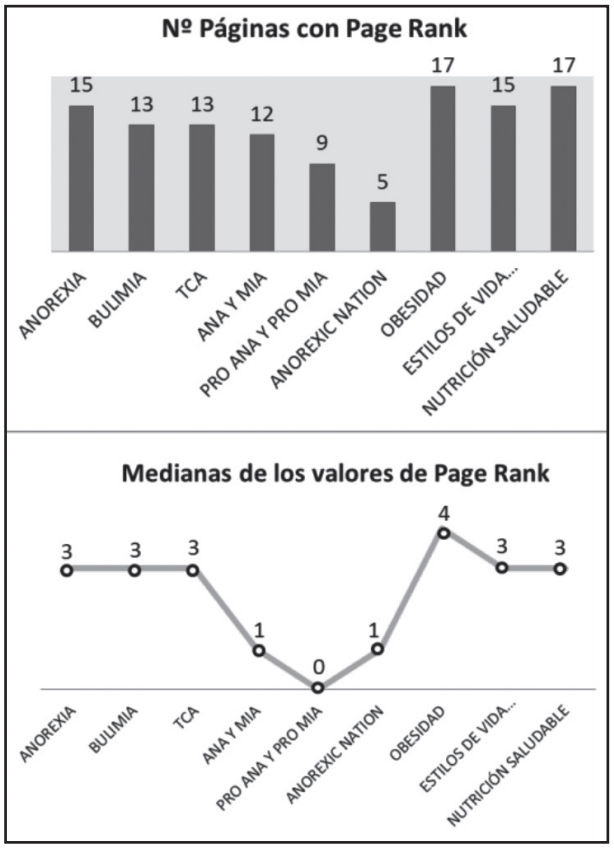


Figura 2.

Análisis de calidad con PageRank de los recursos obtenidos en las búsquedas con palabras clave.

de propósito" y "especificación de la población a la que se dirige" (C y D respectivamente) fueron los que obtuvieron mayor puntuación (3 = "sí aplica"). Por el contrario, la aparición del nombre de la persona y su dirección de correo electrónico no es clara en la mayoría de las ocasiones. Dentro de la variable "autoría", el ítem "fecha de publicación de los documentos" sí aplica, pero la declaración de las fuentes de información es dudosa. Los valores de los ítems pertenecientes a la variable "protección datos personales" indican que los recursos especifican adecuadamente la "fecha de actualización de la información". Dentro de la variable "responsabilidad", los ítems M y N obtuvieron la menor puntuación, indicando que no declaran el procedimiento usado en la selección del contenido ni presentan enlaces de calidad. Por otro lado, dentro de esta variable no está claro que haya posibilidad de contacto mediante correo electrónico u otros medios con la persona/organización, ni si existe identificación cuando se responde a consultas *on-line* (ítems K y L).

ANÁLISIS DEL TIPO DE RECURSO Y DIFUSIÓN EN LAS REDES SOCIALES DEL CONTENIDO DE PÁGINAS PRO-ANA Y PRO-MÍA

Para el estudio de la difusión en redes sociales se han considerado las puntuaciones obtenidas por cada recurso en Facebook y Twitter, por ser las más populares en la actualidad. Se han analizado 34 recursos *on-line* procedentes de la búsqueda "pro-Ana y pro-Mía", de los cuales se han eliminado aquellos con poca o ninguna difusión social según el número de puntos totales en Facebook y Twitter. Los resultados con difusión fueron 27, distribuidos en tres categorías (Tabla II): a) contenidos pro-Ana y pro-Mía; b) campañas de denuncia de estas plataformas; y c) páginas informativas de estas enfermedades.

Todos estos recursos se han analizado mediante la herramienta SharedCount, que permite saber cuántas veces se ha compartido un enlace en internet, lo cual da una idea de su difusión en las redes sociales. Se han tenido en cuenta las puntuaciones totales (suma de *likes, shares* y comentarios) para Facebook y Twitter, cuyos resultados se muestran en la tabla III.

Con objeto de profundizar en la estructura de los recursos, se han establecido unos rangos para la puntuación en Facebook y otros para los *tweets.* Los resultados, en la figura 3, muestran que un número alto de los recursos analizados con contenido pro-Ana y pro-Mía se difunden tanto mediante Facebook (15 de 22) como mediante Twitter (17 de 22). Sin embargo, cada recurso tiene poca puntuación total (rango 10-100 para Facebook y 0-50 para Twitter), lo que contrasta con la difusión de las páginas informativas, que presentan puntuaciones altas, si bien aparecen muy pocas páginas en la búsqueda.

DISCUSIÓN

RESULTADOS DE LA BÚSQUEDA

Realizar una búsqueda en Google con la palabra "anorexia" proporciona una gran cantidad de resultados, que en nuestro caso fue un 57% superior a los obtenidos con la palabra "bulimia". Ambas palabras se refieren a los dos TCA más comunes. Sin embargo, los resultados indican que en internet existe más información relacionada con la anorexia. Según la "guía de recursos para el tratamiento de los trastornos del comportamiento alimentario" publicada en 2008 por el Instituto de Nutrición y Trastornos Alimentarios Consejería de Sanidad de la Comunidad de Madrid (INUTCAM) (21), uno de los rasgos característicos que presentan las personas con anorexia es la pérdida notoria de peso, que se acompaña de cambios de humor y aislamiento social que no pasan inadvertidos a familiares y amigos. Sin embargo, las personas con bulimia se dan atracones, generalmente en privado, y debido a las conductas purgativas no muestran cambios drásticos sobre el peso. La mayor visibilidad de la anorexia y la estigmatización de las personas que la padecen pueden llevar a una mayor preocupación y a generar gran cantidad de información disponible en internet. La relación con la conciencia de enfermedad que la anorexia despierta puede explicar que esta genere los mayores resultados en nuestra búsqueda y casi un 40% mayor que la búsqueda con la palabra "obesidad". En este sentido, los adolescentes perciben la obesidad o sobrepeso principalmente como un problema estético, teniendo un bajo conocimiento de las consecuencias

Tabla II. Recursos pro-Ana y pro-Mía

Categoría	Recursos web
1. Contenidos pro-Ana y pro-Mía	http://prinzessinloreleiwannabeana.blogspot.com.es/
	http://comenzandoarenacerconanaymia.blogspot.com.es/
	http://anaymia.esforos.com/
	http://princessanamiaperfect.blogspot.com.es/
	http://mianaly.blogspot.com.es/
	http://amigasanaymia.blogspot.com.es/
	http://amigasanaymia.blogspot.com/
	http://comenzandoarenacerconanaymia.blogspot.com
	http://princessanamiaperfect.blogspot.com
	http://noeatbyme.blogspot.com/
	http://mianaly.blogspot.com
	http://listadeblogsactualizadosanaymia.blogspot.com
	http://pro-anaymia.blogspot.com
	http://proanaymiaforever.blogspot.com
	http://www.youtube.com/watch?v=8TnRqxrz8sI
	http://www.antxoa.com/blog/princesitas-de-porcelana-pro-ana-pro-mia-como-vomitar-sin-que-se-enteren-tus-padres-y-como-ganar-la-carrera-de-kilos/
	http://kidsandteensonline.com/2015/01/22/proana/
	http://www.muydelgada.com/pro.html
	http://empezando-a-ser-ana.blogspot.com.es/
	http://ligeracomounapluma.blogspot.com
	http://empezando-a-ser-ana.blogspot.com
	http://pro-anaymia.blogspot.com/2007/12/pro-ana-y-pro-mia-tips.html
2. Plataformas de denuncia	https://www.change.org
3. Páginas informativas de estas enfermedades (Wikipedia, organismos oficiales y portales de salud o sociedades científicas)	http://es.wikipedia.org/wiki/Pro-Ana, http://www.elperiodico.com/es/noticias/sociedad/madre-pide-changeorg-prohibir-webs-anorexia-bulimia-3902115,
	http://www.eldiario.es/hojaderouter/internet/paginas-ana-mia-anorexia-bulimia-leyes-espana_0_298170489.html,
	http://comeconsalud.com/alimentacion-nutricion/ana-y-mia-princesas/

Categorías de los recursos pro-Ana y pro-Mía utilizados en el análisis de difusión en las redes sociales. La mayor parte de ellos (16 recursos) eran blogs, mientras que el resto fueron webs (11 recursos) (Fig. 4).

Tabla III. Difusión en redes sociales

Redes sociales	Pro-Ana y pro-Mía	Informativas
Facebook*	884	2.878
Tweets*	78	273

*Puntuaciones obtenidas en Facebook y Twitter mediante SharedCount. *Valor promedio.*

reales sobre su salud (22). En adultos, la percepción se refina y es la obesidad la percibida como una enfermedad, mientras que el sobrepeso se entiende como un problema de estética (23). Esta situación es potencialmente peligrosa, ya que si bien el sobrepeso no es en sí una enfermedad, es una condición que predispone al desarrollo de enfermedades. Por ejemplo, conforme aumentan el peso y el perímetro de la cintura, se produce un fenómeno que conocemos como "resistencia a la insulina", por el cual las células responden peor a la insulina, apareciendo el síndrome metabólico (24).

ANÁLISIS DE POSICIONAMIENTO MEDIANTE PAGERANK (PR)

Los resultados de posicionamiento de PageRank (PR) de Google mostraron (Fig. 2) que los recursos obtenidos con las palabras "obesidad" y "nutrición saludable", así como con "anorexia" y

Facebook	Ana y Mía	Informativas
10-100	15	2
101-500	3	0
501-1.000	1	0
1.001-1.500	1	0
1.501-3.000	0	1
3.001-4.000	1	0
4.001-8.000	0	1
8.001-10.000	0	1
> 10.000	1	0

Tweets	Ana y Mía	Informativas
0-50	17	2
51-100	1	0
101-200	1	1
201-300	2	0
301-500	0	0
501-1.000	1	2

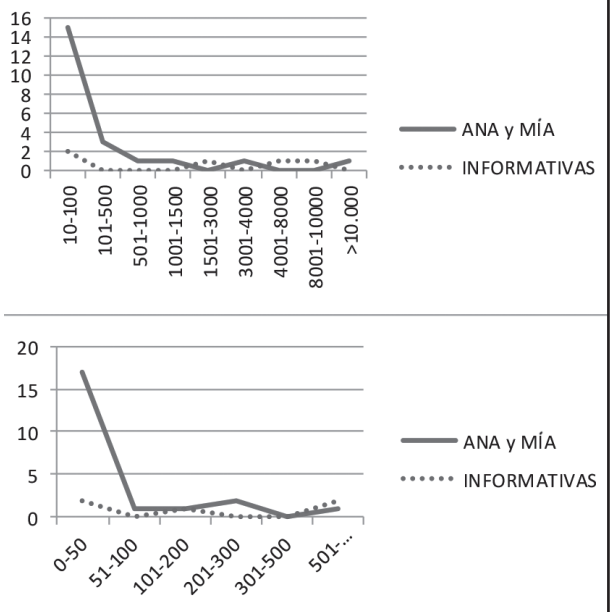


Figura 3.

Distribución de las puntuaciones en Facebook y Twitter en páginas con contenidos pro-Ana y pro-Mía, frente a las páginas informativas sobre estas.

"estilos de vida saludables", fueron páginas que en su mayoría (17 de 20 para las dos primeras y 15 de 20 para las dos segundas) tenían valores de PR de 3 y 4, lo que indica que son recursos de calidad (25). Este resultado es coherente con el hecho de que estas búsquedas ofrecieron mayoritariamente resultados correspondientes a páginas oficiales, organizaciones, asociaciones o portales de salud y medicina. Por el contrario, solo 9/20 páginas y 5/20 páginas procedentes de la búsqueda con las palabras clave "pro-Ana y pro-Mía" y "anorexic nation", respectivamente, mostraban valores de PR. Además, los valores de PR para estas páginas son muy bajos, lo cual hace referencia a que reciben pocos links de páginas bien posicionadas, es decir, de calidad, y/o son de carácter personal. Así, la búsqueda con la palabra "pro-Ana y pro-Mía" pone en contacto al usuario con una información con pocos links y sin contrastar, algo típico del formato blog. Los resultados indican que estas webs son utilizadas por grupos de internautas aislados.

ANÁLISIS DE CALIDAD DE LOS RECURSOS

Los seis recursos obtenidos con la búsqueda de "pro-Ana y pro-Mía" en los que se analizó la aplicabilidad de cinco variables muestran de forma contundente que en todos ellos se especifica el objetivo o propósito del mismo (ítem C), se especifica la población a la que se dirige (ítem D), se muestra la fecha de publicación de los contenidos (ítem G), se especifica la fecha de actualización (ítem I) y muestran un lenguaje adaptado al destinatario (ítem R). Sin embargo, el nombre de la persona aparece de forma dudosa en la mayoría de los casos. Todos estos ítems confieren al recurso una clara intencionalidad y propósito de alcanzar el objetivo de contactar con personas que están o pudieran llegar a estar inmersas en la anorexia, con el fin de reforzar la comunicación entre ellas. De hecho, en muchas ocasiones se advierte al entrar en el blog que el contenido puede no ser del interés del visitante, destacando el carácter restrictivo de estos recursos que publican contenidos altamente peligrosos para la salud, donde no suele aparecer la fuente de información y la responsabilidad del autor es nula, dejando al internauta a merced de los intereses de las personas que los publican.

Los resultados obtenidos con "pro-Ana y pro-Mía" son específicos del contenido y contrastan con los obtenidos en el análisis de páginas web relacionadas con la nutrición y los TCA (20), donde la mayoría de los recursos (búsquedas con las palabras clave "dieta", "anorexia", "bulimia", "nutrición" y "obesidad") muestran claramente el nombre de la persona u organización responsable de la web, existe posibilidad de contacto por correo electrónico, pero no muestran la fecha de publicación o actualización de los documentos. En ambos estudios, las fuentes de información encontradas en estas páginas son dudosas y los datos sobre la accesibilidad indican que encontrar contenidos y efectuar búsquedas en las mismas no es fácil. Sin embargo, en los blogs pro-Ana y pro-Mía sí hay un interés por que el mensaje llegue al destinatario, reflejado en la aplicabilidad en todos los blogs estudiados del ítem R, hecho que no se ha observado previamente (20). Estos blogs carecen de sellos de calidad.

ANÁLISIS DEL TIPO DE RECURSO Y DIFUSIÓN EN REDES SOCIALES DEL CONTENIDO DE PÁGINAS PRO-ANA Y PRO-MÍA

Las TIC (tecnologías de la información y las comunicaciones) se han convertido en un elemento importante en los procesos de socialización de las generaciones más jóvenes, dando lugar a dinámicas que se crean en los propios entornos *on-line* y anteponiéndose incluso a la familia y la escuela. Por un lado, las interacciones sociales son la razón más común para usar internet por parte de los jóvenes; por otro, internet, incluido el acceso móvil, se emplea con profusión para la búsqueda de información no sólo cultural, social o de ocio y compras, sino también en el área de la salud. Las redes sociales se están configurando como el lugar de comunicación entre iguales y el vehículo de multitud de iniciativas que aglutina colectivos unidos por un interés, una meta y un deseo de reivindicación comunes. A las redes sociales ya no las define el hecho de compartir un "territorio" sino compartir una misma "red interconectada", la pertenencia a un grupo virtual dentro de una red social (12,13,26).

La búsqueda con la palabra clave "pro-Ana y pro-Mía" pone en contacto al usuario con recursos que fueron mayoritariamente blogs (Fig. 4). Estos son espacios de creación personal, en los que el autor puede publicar libremente y de forma gratuita contenidos de varios tipos, incluyendo ideas propias y opiniones de terceros, con el objetivo de compartirlos con otros. Este objetivo es importante, ya que el sistema de comentarios incluido en los blogs permite a los lectores establecer una conversación con el autor y entre ellos acerca de lo publicado, creando comunidades cuyos miembros interactúan y conversan libremente entre sí, formando parte de una blogosfera. De hecho, es muy frecuente que dispongan de una lista de enlaces a otros blogs. Un punto importante a tener en cuenta en el fenómeno de difusión de los TCA es que la blogosfera es el hábitat en el que el individuo se siente parte de un grupo, donde se siente apoyado y comprendido a través de conversaciones con otros miembros del grupo sin restricciones ni censuras. Los blogueros experimentan los efectos positivos de la auto-expresión, la catarsis y el apoyo social que requieren para hacer frente a una enfermedad estigmatizante como la AN. Por otro lado, estas características pueden llevar asociado el peligro de carecer de rigor en los contenidos.

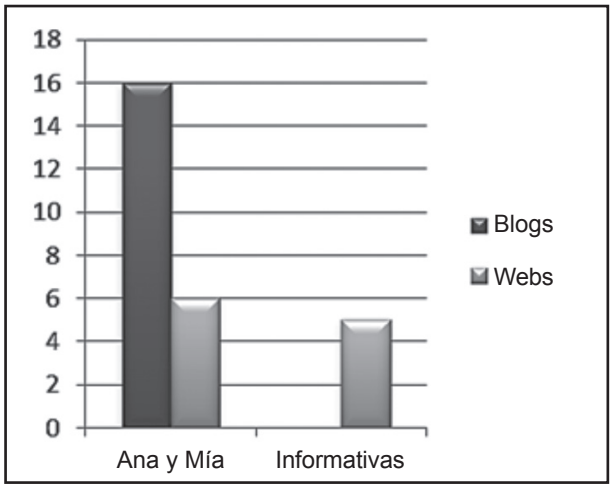


Figura 4.

Distribución de las páginas obtenidas de la búsqueda pro-Ana y pro-Mía dentro de la categoría blog o web.

Acerca de la difusión en redes sociales, nuestros resultados indican que las páginas y blogs analizados optan por la difusión a través de Facebook y Twitter (Tabla III). Facebook es la red social más conocida y popular de internet. Es una herramienta social para conectar personas, descubrir y crear nuevas amistades, subir fotos y compartir vínculos de páginas externas y vídeos. Tanto los contenidos como los perfiles pueden ser visibles para cualquier persona que tenga permiso de acceso por parte del usuario o bien ser públicos. Facebook posee una clasificación de 1 en Alexa y un PageRank de 10, lo cual lo convierte en el sitio más visitado de internet después de Google.

Anorexic nation es una verdadera red de fotografías, donde cada una conecta con otros blogs, dentro de los cuales hay cientos de fotos y mensajes cortos. Utiliza Tumblr como plataforma que permite a sus usuarios publicar textos, imágenes, vídeos, enlaces, citas y audio en forma de una especie de cuaderno de notas breves y personales que no admite comentarios ni intromisiones a pesar de ser público. Enfatiza la expresión libre. Los usuarios pueden "seguir" a otros usuarios registrados y ver las entradas de estos conjuntamente con las suyas, por lo cual Tumblr puede ser considerado como una herramienta social. Las teorías conductuales y de comunicación (27) sugieren que uno de los componentes más perjudiciales es la exhibición de imágenes, en este caso de personas extremadamente delgadas, que se fomentan a nivel social como signo de éxito.

CONCLUSIÓN

En este trabajo se han analizado los resultados de una búsqueda con las palabras clave "anorexia", "bulimia", "trastornos de la conducta alimentaria (TCA)", "Ana y Mía", "pro-Ana y pro-Mía", "Anorexic nation", "obesidad", "estilos de vida saludables" y "nutrición saludable". El resultado sobre el número de páginas indica que el número de entradas para "anorexia" es muy superior al resto, lo que prueba que existe una gran cantidad de información disponible en internet. El análisis de posicionamiento muestra que las páginas encontradas con la palabra clave "anorexia" tienen en su mayoría valores de PR y estos indican que están bien posicionadas, mientras que los recursos encontrados con la palabra "pro-Ana y pro-Mía" no están bien posicionados. Así, la búsqueda con "pro-Ana y pro-Mía" lleva al usuario a recursos que reciben pocos links de páginas bien posicionadas, lo que coincide con el hecho de que mayoritariamente estos corresponden a blogs. Por su estructura, es fácil diseminar en estos blogs información tóxica para la salud donde se promueve la enfermedad como estilo de vida. Particularmente peligrosa es la exposición a estas páginas por adolescentes que quieren bajar

de peso, donde se propone seguir dietas y se dan trucos para adelgazar que, sin control médico y en caso de vulnerabilidad, pueden conducir al desarrollo de un TCA. El análisis de calidad refleja que todos los blogs muestran un lenguaje y propósitos muy claros y dirigidos a alcanzar sus objetivos, que, junto a la difusión social, mayoritariamente por Facebook, pueden proporcionar un apoyo grupal entre los usuarios muy buscado y valorado por los adolescentes frente a la familia e instituciones, hecho que puede facilitar permanecer en la enfermedad. Desde las instituciones y asociaciones se trabaja en dos vertientes para proteger a los adolescentes del acceso a estas páginas: el cierre de estas páginas y generar páginas de calidad. Sin embargo, las redes sociales no tienen competencia en cuanto a poder de difusión, por lo que es más difícil llegar a los adolescentes a través de páginas de calidad si estas son escasas en número.

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Trabajo Original

Otros

Lactobacillus rhamnosus GG reduces hepatic fibrosis in a model of chronic liver disease in rats

El Lactobacillus rhamnosus *GG reduce la fibrosis hepática en un modelo de enfermedad hepática crónica en ratas*

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Abstract

Background: The intestinal dysbiosis is common in chronic liver disease and can induce to inflammatory responses and mediate the collagen deposition in the liver.

Aim: To evaluate the probiotic *Lactobacillus rhamnosus* GG (LGG) for the treatment of liver fibrosis in a model of chronic cholestatic liver disease in rats.

Methods: Male adult Wistar rats (n = 29) were submitted to common bile duct ligation (BDL groups) or manipulation of common bile duct without ligation (Ctrl groups).Two weeks after surgery, each group was randomly divided to receive 1 ml of PBS (Ctrl and BDL) or PBS containing 2.5 x 10^7 CFU of LGG (Ctrl-P and BDL-P) through gavages for 14 days. Euthanasia occurred 33 days after surgery when samples of blood and liver tissue were collected.

Results: The hepatic gene expression of *Tlr*4, *Tnf*α, IL-6, *Tgf*β, and metalloproteinase-2 and -9 were higher in the BDL groups in comparison to Ctrl. The ductular reaction evaluated by immunocontent of cytokeratin-7 (CK7) and the content of collagen were increased in BDL groups. Also, there was an imbalance in the antioxidant defenses (superoxide dismutase and catalase) and an increase in the oxidative stress marker sulfhydryl in BDL groups. The treatment with LGG significantly reduced gene expression of IL-6, collagen deposition, and ductular reaction in hepatic tissue of animals from BDL-P groups.

Conclusion: The treatment with the probiotic LGG was able to reduce liver fibrosis, ductular reaction, and hepatic gene expression of IL-6 in a model of cholestatic liver disease in rats.

Key words:

Probiotics. Liver fibrosis. Bile duct-ligated rats. *Lactobacillus rhamnosus.*

Resumen

Introducción: la disbiosis intestinal es común en la enfermedad hepática crónica y puede inducir respuestas inflamatorias y mediar la deposición hepática de colágeno.

Objetivo: evaluar el efecto del probiótico *Lactobacillus rhamnosus* GG (LGG) en el tratamiento de la fibrosis hepática en un modelo de enfermedad hepática colestásica en ratas.

Métodos: se sometió a ratas Wistar macho adultas (n = 29) a ligadura del conducto biliar común (grupo BDL) o a manipulación del conducto biliar sin ligadura (grupo Ctrl). Dos semanas después, cada grupo se dividió aleatoriamente para recibir 1 ml de PBS (Ctrl y BDL) o PBS con 2,5 x 10^7 UFC de LGG (Ctrl-P y BDL-P) durante 14 días. Se aplicó la eutanasia 33 días después de la cirugía y se recogieron muestras de sangre y de tejido hepático.

Resultados: las expresiones hepáticas de *Tlr*4, *Tnf*α, IL-*6*, *Tgf*β, metaloproteinasa-2 y -9 fueron mayores en los grupos BDL. La reacción ductular evaluada por el inmunocontenido de citoqueratina 7 (CK7) y el contenido de colágeno se aumentó en los grupos BDL. Además, hubo un desequilibrio en las defensas antioxidantes (superóxido dismutasa y catalasa) y un aumento en el estrés oxidativo (sulfhidrilo) en los grupos BDL. El tratamiento con LGG redujo la expresión génica de IL-*6*, la deposición de colágeno y la reacción ductular en el hígado de los animales del grupo BDL-P.

Conclusión: el tratamiento con LGG redujo la expresión génica de *IL*-6 en el hígado, la fibrosis hepática y la reacción ductular en un modelo de enfermedad hepática colestásica en ratas.

Palabras clave:

Probióticos. Fibrosis hepática. Ligadura del conducto biliar. *Lactobacillus rhamnosus.*

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INTRODUCTION

Liver fibrosis is characterized by excessive accumulation of extracellular matrix, mostly collagen type I, in response to acute or chronic liver injuries (1). The causes of fibrosis include viral hepatitis, steatohepatitis for alcohol or obesity, autoimmune or metabolic disease, drug exposition, and others (1). The etiology of liver injury defines the pattern of fibrosis progression and the involvement of the different populations of myofibroblasts (2).

Although portal myofibroblasts are common in biliary fibrosis, myofibroblasts originated from activation of hepatic stellate cell (HSC) are also important in this process (3). The activated-HSC is the principal cell involved in collagen production. Its activation results in an intense pro-inflammatory and pro-fibrogenic response, which can be induced by apoptotic bodies, reactive oxygen species (ROS), and bacterial endotoxins (4).

Gut-derived bacterial products, like lipopolyssacharides, reach the liver through portal vein and can mediate several immune responses with participation of inflammatory cytokines (5). Bacterial endotoxins can bind to Toll-like receptor 4 (TLR4) present in hepatic cells, which triggers the release of TNFα, IL-6, IL1β, and other inflammatory cytokines (5). This signaling promotes the production of collagen by activated-HSC, mediated by *Tgf*β (6). Because of the importance of gut-liver axis in fibrosis progression, it has been hypothesized that the modulation of intestinal microbiota using probiotics could improve the gut barrier and reduce inflammatory and fibrogenic response in liver disease (7,8). Probiotics are live micro-organisms that, when consumed in adequate amounts, confer a health benefit on the host (9).

The *Lactobacillus rhamnosus* GG (LGG) is a commensal Gram-positive bacteria widely used as a probiotic strain because of its beneficial effects on the intestinal barrier and inflammatory profile (10,11). The therapeutic use of LGG is safe and has been extensively studied in allergies, diarrhea, fatty liver disease and other conditions (12-14). Bajaj et al. found a reduction in endotoxemia and an improvement in gut dysbiosis in cirrhotic patients treated with LGG (15). However, the effect of this strain in hepatic fibrosis was not studied. Therefore, the aim of this study was to evaluate the effect of *Lactobacillus rhamnosus* GG in hepatic fibrosis in a model of chronic cholestatic liver disease in rats.

METHODS

ETHICS STATEMENT

All procedures were conducted according to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication number 85-23, revised 1996) of the National Guidelines on Animal Care. In addition, the experimental protocols were approved by the local Ethics Committee of the Hospital de Clínicas de Porto Alegre (Comissão de Ética no Uso de Animais do Hospital de Clínicas de Porto Alegre – no. 12 0312).

ANIMALS AND STUDY DESIGN

Twenty-nine adult male Wistar rats (two months old, 300 g ± 43 g) were obtained from the Experimental Animal Unit of the Research Center of Hospital de Clínicas de Porto Alegre. The rats were allocated four animals per cage and maintained in a controlled environment (room temperature 20 °C ± 2 °C, standard light/dark cycle of 12 hr-lights on at 07:00 am). Standard food and water were provided *ad libitum*. Animals were randomly distributed into two surgical groups: bile duct-ligated (n = 17) or sham-operated (n = 12). The bile duct ligation procedure was conducted as previously described (16). Rats were anaesthetized with ketamine (90 mg/kg) and xylazine (12 mg/kg) intraperitoneally. After laparotomy, the bile duct was double ligated with non-absorbent surgical sutures and resected between the two ligatures. The sham-operated rats underwent the same surgical procedure with exception of bile duct ligation and resection. Before returning to home-cages, all animals received a subcutaneous injection of tramadol (5 mg/kg).

Two weeks after surgery, the two experimental groups were randomly subdivided into two groups, which received the probiotic *Lactobacillus rhamnosus* GG ATCC 53103 (LGG) or phosphate buffered saline (PBS). Six sham-operated (Ctrl-P) and eight bile duct-operated (BDL-P) rats received 2.5 x 10^7 colony-forming units of LGG (Culturelle™, Amerifit, USA) in 1 ml of PBS through gavages (12). The other six sham-operated (Ctrl) and nine bile duct-operated (BDL) rats received gavages containing just 1 ml of PBS.

The treatment was performed daily, always during the same period of the day, for two weeks (from the third to the end of the forth week post-surgery). After that time, treatment was discontinued for five days until the sacrifice (33 days after surgery).

SAMPLE COLLECTION

Rats were anesthetized as previously described, blood samples were withdrawn by cardiac puncture from the left ventricle and centrifuged (five minutes at 5,000 × *g*), and plasma was stored at -80 °C until analysis of the biochemical markers of liver dysfunction. Subsequently, rats received 0.1 ml of heparin (5,000 U/ml) and were perfused with 50 ml (500 ml/h) of PBS at 4 °C, using an infusion pump with a cannula inserted into the heart left ventricle. Liver samples were taken from the median lobe (approximately 50 mg each) and stored at -80 °C for further investigation of gene expression and oxidative stress. The remaining of the liver tissue was stored in a 10% formaldehyde buffered solution for histological examination.

OXIDATIVE STRESS ANALYSES

To determine the reduced thiol (SH) groups present in liver samples, a protocol according to Soszynski et al. (17) was performed. Briefly, free sulfhydryl groups in the liver homogenates samples (40 µl) reacted with 10 µL of 10 mM DTNB (Sigma-Aldrich D8130) (diluted in ethanol), and the formation of the yellowish

2-nitro-5-thiobenzoate was measured by spectrophotometer, at 412 nm. The concentration of color complex protein was determined using the linear equation obtained with a standard curve of reduced glutathione. Results were presented as nmol of SH/mg of protein.

The analysis of catalase (CAT) activity was based on the sample ability in consuming hydrogen peroxide compared to a standard curve built with purified catalase (Sigma-Aldrich C9322). The reaction was followed at 240 nm and expressed as unit/mg protein (18). The superoxide dismutase (SOD) catalyzes the reaction of two superoxide anions resulting in the formation of hydrogen peroxide, which is less reactive and can be degraded by enzymes such as CAT. The analysis of SOD is based on the ability of the sample to inhibit the superoxide-mediated adrenaline oxidation (19). One unit of SOD activity was defined as the amount of enzyme required to inhibit the reaction of oxidation by 50%, measured by absorbance at 480 nm, and was expressed as unit/mg protein. All analyses were normalized by protein content estimated by Bradford method (Bio-Rad #500-0201) (20).

QUANTITATIVE REAL TIME POLYMERASE CHAIN REACTION (q-PCR)

Total RNA from liver samples (50 mg) were isolated using TRIzol® reagent (Invitrogen, Carlsbad, CA), according to the manufacturer's instructions. First strand cDNA was synthesized from 1.25 µg of total RNA using High Capacity cDNA reverse Transcription Kit (Invitrogen™, Life Technologies™, Carlsbad, CA, USA) according to the manufacturer's protocol. Gene expression analysis was performed in duplicate, in 48 well StepOne™ system (Applied Biosystems®, Life Technologies™, Carlsbad, CA, USA) using TaqMan® Gene Expression Assays (Life Technologies™, Carlsbad, CA, USA). The following genes were investigated: tumor necrosis factor alpha (*Tnf*α: Rn01525859_g1), interleukin 6 (IL-*6*: Rn00561420_m1), Toll-like receptor 4 (*Tlr4*: Rn00569848_m1), transforming growth factor beta (*Tgf*β: Rn00572010_m1), matrix metalloproteinases 2 and 9 (*Mmp2:* Rn01538170_m1*; Mmp9*: Rn00579162_m1), and beta-actin (β-actin: Rn00667869_m1) as endogenous control. Each reaction contained 5 µl of TaqMan® Gene Expression PCR Master Mix (Life Technologies™, CA, USA), 0.5 µl of the probe for each target gene, 2 µl of diluted cDNA (100 ng) in 10 µl of final reaction mixture. The two-step PCR conditions were two minutes at 50 °C, ten minutes at 95 °C, 40 cycles with ten seconds at 95 °C, and one minute at 60 °C. All samples were analyzed in duplicate and gene expression was quantified using the $2^{-\Delta\Delta Ct}$ (threshold cycle) method using the control group as the reference (21).

HISTOLOGICAL AND IMMUNOHISTOCHEMICAL ASSESSMENT

Livers were fixed in 10% buffered formalin for 48 hours, paraffin embedded, and sectioned (3 µm). Five-micrometer-thick sections were used for both immunohistochemistry and picrosirius red staining. To assess biliary ductular reaction, immunohistochemistry assay was performed to label a cytokeratin 7 (CK7), a marker of biliary epithelium in outlining biliary structures (22). Sections were incubated with mouse anti-CK7 primary antibody (Abcam, Cambridge, UK, Ab9021; dilution 1:100), and immunolabeling was amplified using the avidin-biotin-peroxidase complex, as previously described (23). As secondary antibody, a multispecies reagent was used (EasyPath; Erviegas Ltd, São Paulo, Brazil). Picrosirius red was performed in order to evaluate the fibrosis extent.

Three images were photographed (10-fold magnification) for each liver section using Q Capture Pro Software v.5.1.1.14 (Q Imaging Co. Burnaby, BC, Canada) and were quantified using Adobe® Photoshop® CS3 software. To quantify the positivity CK7 presence and collagen deposition, the color depicting positivity, red for picrosirius staining and brown for CK7 immunohistochemistry, was selected. Color representing the liver parenchyma (green or blue for picrosirius and CK7 immunohistochemistry, respectively) was set as background. The absolute number of pixels of the color of interest and the background were taken, and total positivity was calculated by dividing the total pixels of each image by the number pixels of the color of interest (24).

SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSES

Sample size calculation was based on collagen quantification in liver using picrosirius staining in a pilot study. A sample of five animals was calculated to detect a reduction of 20% in hepatic content of collagen in BDL-P compared to BDL, considering 80% power and 5% significance (Winpepi 11.44).

Statistical analyses were performed by using Prism 5 (Graph Pad, San Diego, USA). Distributions were first tested for normality using the Shapiro-Wilk test. Multiple comparisons were performed using 1-way ANOVA with Tukey-Kramer post hoc tests. Data are presented as mean ± standard deviation. Results with $p < 0.05$ were considered as significant.

RESULTS

LGG DO NOT AFFECT CLINICAL AND BIOCHEMICAL PARAMETERS OF CHOLESTATIC DISEASE

At the fourth week after surgery, BDL and BDL-P rats exhibited signs of chronic cholestatic liver disease: hepatic enlarged abdomen, yellowish fur and tail, hepatomegaly, and splenomegaly. Plasma biochemical analyses confirmed these findings (Table I). Rats submitted to the bile duct ligation, BDL or BDL-P groups, exhibited higher plasma levels of total bilirrubin, alkalin phosphatase, and gamma glutamyl transferase, accompanied by a reduction of body weight and albumin levels when compared to control groups.

Table I. Biochemical analyses and body weight at the end of the study

	Ctrl	Ctrl-P	BDL	BDL-P	p
Weight (g)	413.7 ± 72.8	413.2 ± 25.5	311.23 ± 17.9*#	323.3 ± 27.2*#	< 0.001
Weight gain (g)[a]	93.9 ± 14.5	99.1 ± 12.1	34.0 ± 33.2*#	30.8 ± 29.6*#	< 0.001
Albumin (mg/dL)	3.7 ± 0.2	3.7 ± 0.3	3.1 ± 0.5*#	3.1 ± 0.4*	0.017
Total bilirrubin (mg/dL)	0.3 ± 0	0.3 ± 0	10.1 ± 0.8*#	10.4 ± 0.8*#	< 0.001
Alkalin phosphatase (U/L)	155 ± 33.3	138.4 ± 44.2	275 ± 58.1*#	307.4 ± 61.5*#	< 0.001
Gamma glutamyl transferase (U/L)	1.8 ± 1.6	1.6 ± 1.3	66.4 ± 32.3*#	61.9 ± 28.4*#	< 0.001

To test differences among groups, ANOVA were used (p < 0.05). [a] *Weight gain was calculated by a difference between the final weight and the weight at the beginning of the experimental. *Difference* versus *Ctrl. #Difference* versus *Ctrl-P.*

EFFECT OF LGG ON OXIDATIVE STRESS PARAMETERS

The hepatic oxidative stress was evaluated by determining activities of SOD and CAT and by measuring of SH groups (Fig. 1). Bile duct ligation induced a significant reduction in CAT activity when compared to the Ctrl ($p < 0.001$) (Fig. 1A) and Ctrl-P ($p < 0.001$) (Fig. 1A) but no difference was detected between BDL and BDL-P. In contrast, no changes were found for SOD activity among groups ($p = 0.1025$) (Fig. 1B). Increased SOD/CAT ratio can be

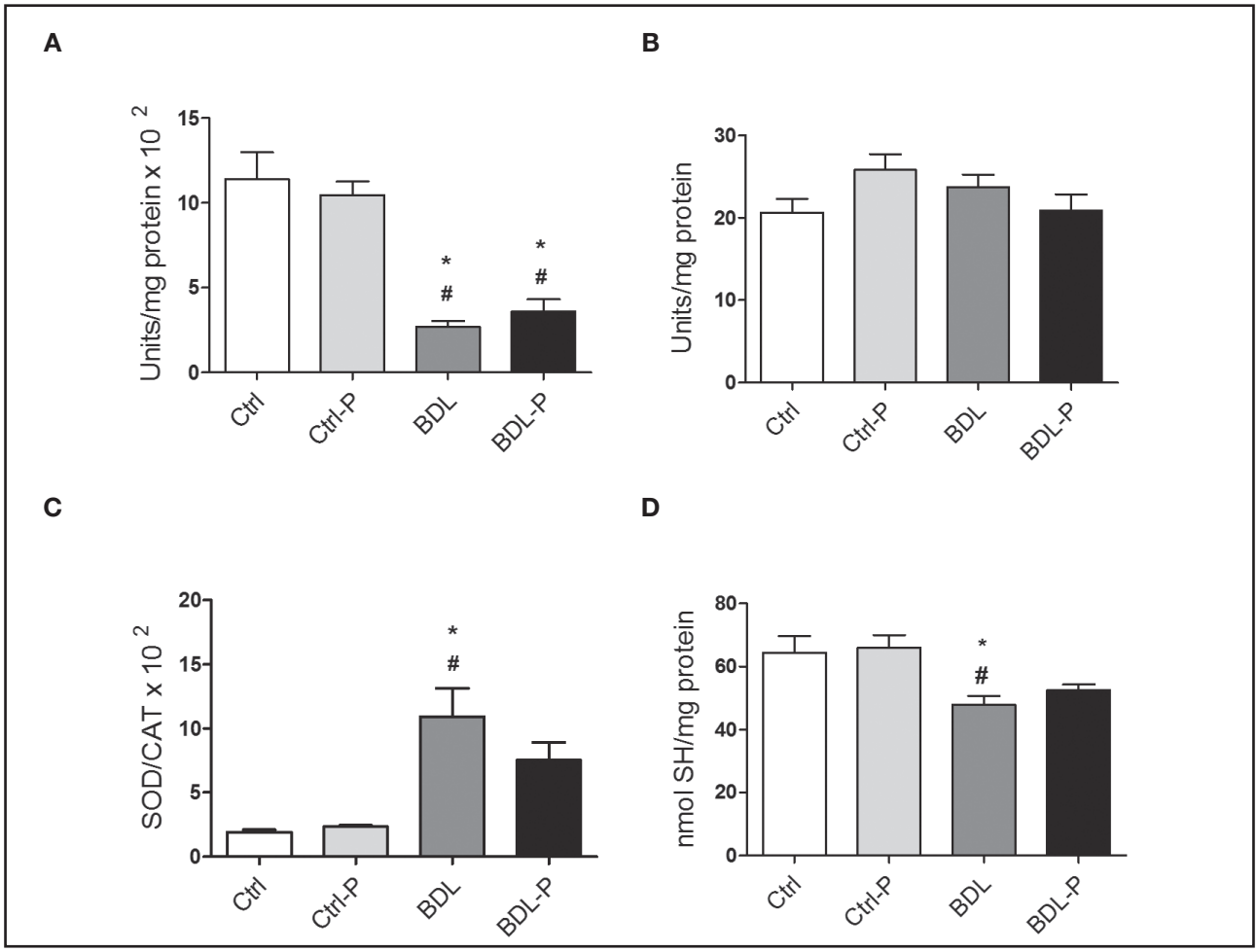

Figure 1.

The effect of LGG on oxidative stress parameters.

The antioxidant defenses were measured by determining activities of SOD (A) and CAT (B). The SOD/CAT ratio (C) was used to evaluate the pro-oxidative status and the measuring of SH groups (D) to measure the oxidative damage. To test differences between groups, ANOVA followed by the Tukey test was used ($p < 0.05$). *Difference *versus* Ctrl. #Difference *versus* Ctrl-P.

related to a pro-oxidative status because hydrogen peroxide, the product of SOD reaction, is not fully transformed in H_2O and O_2. The BDL group had a higher SOD/CAT ratio when compared to Ctrl ($p < 0.05$) (Fig. 1C) and Ctrl-P ($p < 0.01$) (Fig. 1C). The treatment with LGG promoted a reduction of about 30% in SOD/CAT ratio in comparison to BDL group, albeit not significant ($p = 0.398$) (Fig. 1C). SH levels were higher in the BDL group compared to Ctrl ($p < 0.05$) (Fig. 1D) and Ctrl-P ($p < 0.01$) (Fig. 1D), without any difference between BDL-P in comparison to both control groups.

LGG ALTERS INFLAMMATORY PATHWAYS IN HEPATIC TISSUE

The mRNA expression of liver inflammatory and fibrosis markers was not altered in Ctrl animals treated with LGG (Fig. 2). However, BDL model consistently presented increased levels of *Tlr*4 (1.5-fold, $p < 0.05$) (Fig. 2A), *Tnf*α (3.9-fold, $p < 0.001$) (Fig. 2B), IL-6 (12.8-fold, $p < 0.01$) (Fig. 2C), *Tgf*β (1.8-fold, $p < 0.01$) (Fig. 2D), *Mmp*2 (3.2-fold, $p < 0.05$) (Fig. 2E), and *Mmp*9 (3.5-fold, $p < 0.05$) (Fig. 2F). When the BDL group was treated with LGG (BDL-P group), no reduction could be seen for all markers but IL-6, which was 30% less expressed in BDL-P than in BDL group ($p < 0.05$) (Fig. 2C).

LGG REDUCES HEPATIC COLLAGEN DEPOSIT AND DUCTULAR REACTION

As expected, the content of collagen increased 12-fold in the BDL group in comparison to the Ctrl group ($p < 0.01$) (Fig. 3). The treatment with LGG significantly promoted a reduction of 32% in hepatic collagen deposition in comparison with BDL group ($p < 0.05$) (Fig. 3). Concerning the ductular reaction, the BDL group had a higher (29-fold) immunocontent of CK7 when compared to Ctrl ($p < 0.001$) (Fig. 4). LGG treatment reduced CK7 in 39% in relation to the BDL group ($p = 0.036$) (Fig. 4).

DISCUSSION

In this study, the effects of the LGG treatment on the fibrosis progression and ductular reaction in a model of cholestatic disease are shown. Our data support the hypothesis that probiotic treatment can reduce collagen deposition, CK7 content, and IL-6 expression in the liver.

Here, LGG treatment started after 14 days of bile duct ligation to investigate the effect of probiotic on an established cholestatic liver disease. As previously showed by Georgiev et al., liver changes

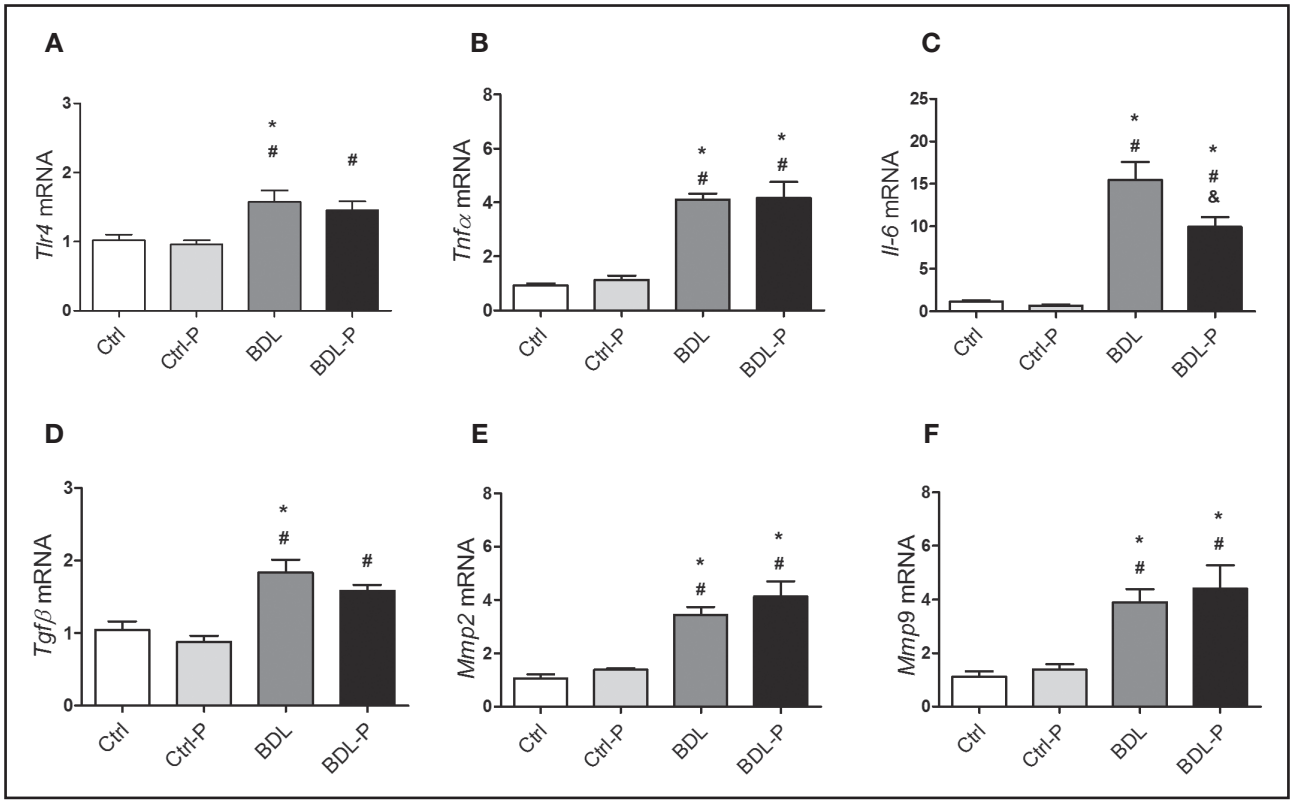

Figure 2.

The effect of LGG treatment on genes involved in inflammatory and fibrogenic pathways in hepatic tissue.
The gene expression of *Tlr4* (A), *Tnf*α (B), *Il-6* (C), *Tgf*β (D), *Mmp2* (E), *and Mmp9* (F) were determined by q-PCR and are expressed $2^{-\Delta\Delta Ct}$. Differences were tested by ANOVA followed by the Tukey ($p < 0.05$). *Difference *versus* Ctrl. #Difference *versus* Ctrl-P. &Difference *versus* BDL.

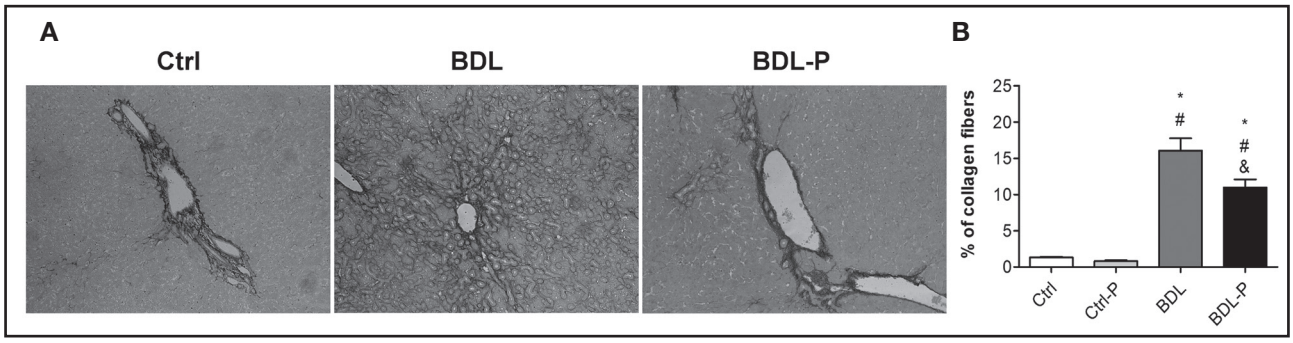

Figure 3.

The effect of LGG on collagen deposition.

Liver sections were stained with Picrosirius Red (original magnification 400×). A. Representative photomicrographs of liver sections of Ctrl, BDL, and BDL-P group, respectively. The quantification of stained collagen is shown in B. To test differences between groups, ANOVA followed by the Tukey test was used ($p < 0.05$). *Difference *versus* Ctrl. #Difference *versus* Ctrl-P. &Difference *versus* BDL.

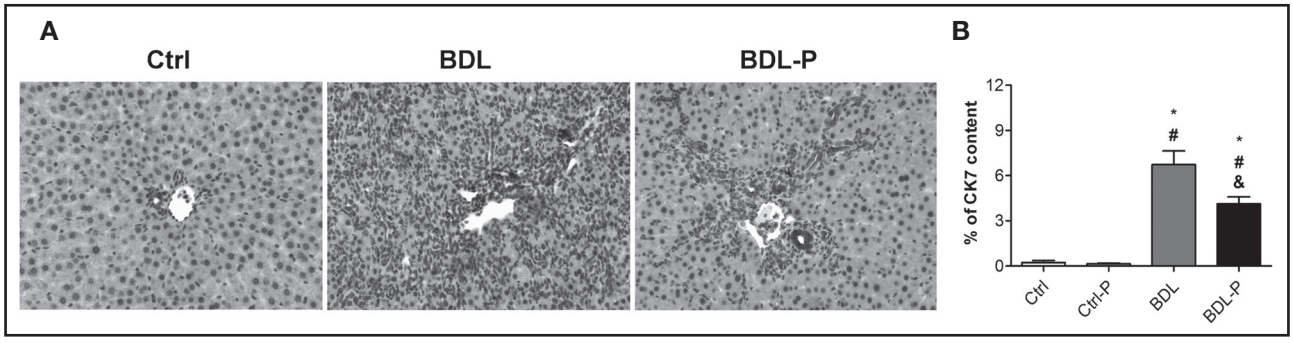

Figure 4.

The effect of LGG on ductular reaction.

The ductular reaction was evaluated by CK7 immunohistochemistry. All images were captured at 400× final magnification. A. Representative photomicrographs of liver sections of Ctrl, BDL, and BDL-P group, respectively. The quantification of immunocontent of CK7 is shown in B. To test differences between groups, ANOVA followed by the Tukey test was used ($p < 0.05$). *Difference *versus* Ctrl. #Difference *versus* Ctrl-P. &Difference *versus* BDL.

caused by BDL model occurred within the firsts 14 days, with no further significant collagen accumulation after that time, demonstrating that this time period is suitable for the study of cholestatic chronic disease (25). As expected, a significant increase in classical markers of cholestasis in rats subjected to bile duct ligation were found (25). Nonetheless, the treatment with probiotic did not lead to changes in the overall clinical manifestation or in the biochemical parameters of biliary flow. Zhou et al. found decreased levels of total bilirrubin evaluated in portal serum of bile duct-ligated rats (for ten days) after treatment with 2×10^8 CFU/ml of *L. plantarum* (26). However, we evaluated plasma parameters in blood collected by cardiac puncture in rats with advanced liver disease (33 days after ligation). The difference found in the blood collection site and the stage of the disease could explain why we did not find similar results to Zhou et al.

According to Lee et al., damages in hepatocyte or biliary epithelium is a *sine qua non* condition to the development of a chronic hepatic disease that is followed by an intense inflammatory and fibrogenic response (1). As portal fibroblasts are located adjacent to bile duct epithelia, they are mostly implicated in biliary cirrhosis and known as the first responders in the obstructive liver disease (3,27). Portal fibroblasts produce and secrete *Tgf*β and inflammatory cytokines that can induce the transdifferentiation of HSC into myofibroblasts, which are responsible for a later cellular response in cholestatic disease (3,27,28). Myofibroblasts can directly contribute to the persisting inflammation by releasing pro-inflammatory mediators or acting as a target of ROS, cytokines or endotoxins (2). In our study, animals subjected to a BDL procedure have increased oxidative stress, as seen by the reduction of CAT activity and SH content. SOD and CAT act coordinately to control ROS levels and the SOD/CAT activity ratio gives an idea of enzymatic antioxidant equilibrium (29). The BDL group had a SOD/CAT ratio five times higher than control groups, showing a potentially oxidative environment, as confirmed by the decrease in SH levels. LGG treatment presented slight improvement in SOD/CAT ratio, although not statistically significant, which can be related to the decrease of activated inflammatory cells.

Intestinal dysbiosis and bacterial overgrowth are common in chronic liver disease and can contribute to inflammatory response by activation of the *Tlr* family, especially by lipopolysaccharides (1). Indeed, we found an increase in *Tlr*4, *Tnf*α, and Il-*6* gene expression in liver of BDL rats, as previously reported (30-32). Some studies have demonstrated that probiotic treatment decreases *Tlr4, Tnf*α, and Il-*6* expression in animal model of CCl_4 induced-fibrosis (30,31). In the same way, a reduction in plasma TNFα and IL-1α levels in a BDL model with administration of probiotic VSL#3 (50 billion bacteria/kg of body weight/day) was demonstrated (32). It is important to note that these studies started probiotic treatment at the onset of the disease. On the contrary, we used probiotics to treat an established liver disease, which could lead to more slight results. Furthermore, the treatment with probiotics was discontinued for five days before the sacrifice in our study. We chose this design in an attempt to find out which cytokines would be expressed even after the end of the treatment, however, this may have hidden some pathways activated by LGG use. These strategies used in our experimental design may have affected the magnitude of the results since it was not possible to show a significant decrease in inflammatory markers, except for Il-*6* gene expression.

Bacterial compounds derived from the gut can activate Kupffer cells to produce IL-6 in the periportal region, leading to HSC activation and liver fibrosis (33-35). We suggest that LGG treatment can reduce the gut delivered endotoxins, decreasing an exposure of Kupffer cells and, consequently, reducing Il-*6* expression. Nonetheless, IL-6 has a controversial role in fibrosis. Although serum and hepatic levels of IL-6 are higher in patients and animals with acute or chronic liver disease, this cytokine has been associated with protective functions during hepatic fibrogenesis (36). This idea is supported by studies where Il-*6*-deficient animals presents an uncommon higher liver fibrosis, which is restored after IL-6 administration (33). However, in humans with biliary fibrosis, IL-6 mediates the ductular reaction and is released specifically by biliary epithelia and portal fibroblasts in contrast to other forms of fibrosis (3). In addition, *in vitro* experiments found that IL-6 derived from Kupffer cells promotes survival and proliferation of HSC, followed by enhancement of liver fibrosis (37,38). Wang et al. (37) suggested that IL-6 can positively or negatively regulate liver fibrosis via targeting different types of liver cells, since IL-6 receptors are broadly expressed in hepatic cells. Despite that, in the present study reduction of Il-6 was observed in the BDL-P group, which was accompanied by a decrease in collagen deposition and ductular reaction.

Myofibroblasts are the major cells responsible for excess deposition of extracellular matrix in response to *Tgf*β released by Kupffer cells and HSC (2). Also, cells involved in the ductular reaction in human chronic biliary diseases can express *Tgf*β (39). We showed that BDL groups had an increase of about 75% in *Tgf*β expression, which was accompanied by a significant increase in hepatic fibrosis (12-fold) and ductular reaction (29-fold) when compared with control. The treatment with LGG in BDL animals promoted a significant reduction in the collagen deposition and ductular reaction. In the same way, *Tgf*β was 25% less expressed in BDL-P in comparison with the BDL group, albeit not statistically significant.

Some limitations of this study should be addressed. First, this study is descriptive in nature and causal relations should be drawn with care. However, for the first time, we showed that LGG treatment could be used to attenuate ductular reaction and fibrosis in a model of established liver disease. Second, we suggest that LGG may impair gram-negative bacteria overgrowth, which in turn would increase HSC activation and fibrosis. Unfortunately, endotoxin measurement could not be presented in this study.

In the present study we demonstrated that LGG administration was effective in attenuating fibrosis in a model of established cholestatic liver disease in rats. The reduction in pro-inflammatory cytokine Il-6 might be related to the mechanisms by which probiotics exert their beneficial effects. However, further investigation is necessary to better understand these pathways. Based on our results, we suggest that *Lactobacillus rhamnosus* GG can be a promising therapy for adjuvant treatment of hepatic fibrosis.

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Nutrición Hospitalaria

Revisión

Consumo de huevo y enfermedad cardiovascular: una revisión de la literatura científica

Egg intake and cardiovascular disease: a scientific literature review

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Resumen

El huevo es un alimento que aporta proteína de alta calidad y numerosos nutrientes con potenciales beneficios para la salud. Sin embargo, la aparición de la enfermedad cardiovascular como importante causa de morbilidad y mortalidad en el mundo, junto con la identificación de los niveles elevados de colesterol plasmático como factor de riesgo para esta patología, llevó, en los años 70, a profesionales e instituciones de salud a limitar el consumo de colesterol y, por tanto, de huevo en la población. Hasta la fecha, los análisis de cohortes prospectivas tienden a mostrar que el consumo de hasta un huevo diario no aumenta significativamente el riesgo cardiovascular en la población sana. Sin embargo, esta evidencia no es clara en los pacientes diabéticos y pone en duda que este alimento consumido en cantidades elevadas sea del todo inocuo en esta población en particular. Asimismo, estudios de intervención a corto plazo han mostrado que, en general, el consumo de huevo no afecta negativamente los factores de riesgo cardiovascular en individuos sanos así como en aquellos con enfermedad cardiometabólica. Además, estos estudios sugieren que la incorporación del huevo en la dieta podría traer beneficios adicionales, promoviendo un perfil lipídico menos aterogénico.

Palabras clave:

Huevo. Dieta. Enfermedad cardiovascular.

Abstract

Eggs are a highly nutritive food. They contain high quality protein and several nutrients with potential health benefits. Nevertheless, the appearance of cardiovascular disease as an important public health issue, with high morbidity and mortality rates worldwide, along with the identification of high blood cholesterol levels as a risk factor for this disease, was responsible for the advice to limit dietary cholesterol (and, therefore, eggs) that was promoted by health care professionals and institutions during the 70s. To date, several cohort studies show that the intake of one egg a day does not increase cardiovascular risk in the general population. However, this evidence is not clear among diabetic patients, and raises the question whether its consumption in large quantities is entirely safe in this particular population. Additionally, intervention studies have shown that egg consumption does not adversely affect cardiovascular risk factors neither in healthy individuals nor in those with cardiometabolic disease. Moreover, these studies suggest that the incorporation of egg to the diet could bring additional benefits such as promoting a less atherogenic lipid profile.

Key words:

Egg consumption. Diet. Cardiovascular disease.

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INTRODUCCIÓN

El surgimiento de la enfermedad cardiovascular (ECV) como una epidemia real en los años 1950-1960, junto con la identificación de los niveles elevados de colesterol plasmático como factor de riesgo de eventos cardiovasculares, determinó que las instituciones de salud pública diseñaran e implementaran estrategias destinadas a disminuir el consumo de colesterol dietario en la población para la prevención de esta enfermedad. De esta manera, la American Heart Association (AHA), en la década de 1990, recomendó un consumo de colesterol inferior a 300 mg al día (1). Desde entonces y hasta la actualidad, la idea de que el colesterol dietario es nocivo para la salud y que debe limitarse su ingesta se ha instalado como un paradigma, transformándose frecuentemente en una recomendación rutinaria y generalizada de profesionales e instituciones de salud. Sin embargo, en las últimas décadas ha surgido controversia en torno a este tema debido a numerosos estudios observacionales y de intervención que ponen en duda la asociación entre el contenido de colesterol de la dieta y el riesgo de ECV.

El objetivo de esta revisión es efectuar un análisis crítico y objetivo de la evidencia científica reciente respecto al consumo de huevo en la dieta y sus efectos en salud humana, con especial énfasis en la salud cardiovascular y en aquellos aspectos que han causado mayor polémica en el ámbito científico.

EL HUEVO, UN ALIMENTO ALTAMENTE NUTRITIVO

El huevo es un alimento de bajo costo y altamente nutritivo que lo hace un valioso contribuyente de una dieta balanceada y saludable con un bajo aporte calórico (75 calorías por cada unidad de tamaño mediano). En promedio, el contenido de macronutrientes del huevo incluye escasa cantidad de carbohidratos y aproximadamente 12 g de proteína de óptima calidad por cada 100 g de huevo. El contenido de lípidos corresponde en su mayor parte a ácidos grasos monoinsaturados con una escasa cantidad de grasas saturadas, a la vez que constituye una las principales fuentes de colesterol de la dieta (aproximadamente 220 mg de colesterol por cada unidad de huevo de tamaño mediano (2).

El huevo aporta proteínas de elevado valor biológico, ricas en aminoácidos esenciales, que podrían promover la síntesis y mantención de la masa musculoesquelética. Esta propiedad puede ser de relevancia para atletas y adultos mayores, ayudando en estos últimos a contrarrestar el proceso de sarcopenia propio del envejecimiento. La principal proteína de la clara es la ovoalbúmina, seguida por la ovotransferrina y otras como la lisozima (3). Se postula que las diferentes proteínas del huevo podrían tener un impacto favorable frente a procesos de inflamación así como propiedades antimicrobianas, inmunoprotectoras, antihipertensivas y antioxidantes (3,4). Por otro lado, se sugiere que los lípidos de la yema también poseen numerosos beneficios nutricionales y para la salud, incluyendo propiedades antimicrobianas. Además, la yema contiene inmunoglobulina Y (Ig Y), equivalente funcional de la inmunoglobulina G y uno de los principales anticuerpos en los mamíferos. Tanto *in vitro* como *in vivo*, la Ig Y inhibe el desarrollo de infecciones por patógenos gastrointestinales como rotavirus, *Escherichia coli* y otros (3). Por otro lado, los lípidos y fosfolípidos presentes en la yema han mostrado tener efectos antioxidantes y han sido estudiados en la prevención de la oxidación de ácidos grasos insaturados. Un fosfolípido en especial, la fosfatidilcolina, es fuente importante de colina, un nutriente importante para el desarrollo cerebral, la función hepática y la prevención del cáncer.

El huevo es también una de las principales fuentes de vitamina D en la dieta y aporta otros numerosos nutrientes como riboflavina, folato, selenio, vitamina A y vitamina B12, entre otros (5) (Tabla I). Algunos de estos nutrientes (como zinc, selenio, retinol y tocoferoles) son deficitarios en personas que consumen una dieta occidental. Dada la capacidad antioxidante de estos nutrientes, podrían ser potenciales protectores frente a la ECV (2). En la tabla II puede observarse el aporte relativo de diferentes nutrientes según las recomendaciones diarias de ingesta (RDA) a partir del huevo (6). Por otro lado, el huevo aporta carotenoides como luteína y zeaxantina, los cuales tienen propiedades antioxidantes y podrían proteger contra las cataratas y la degeneración macular, causas importantes de ceguera en la vejez. Asimismo, se ha postulado que las características antioxidantes y antiinflamatorias de estas biomoléculas podrían también ejercer efectos cardioprotectores.

COLESTEROL DIETARIO, COLESTEROL PLASMÁTICO Y RIESGO CARDIOVASCULAR

Existe evidencia significativa que vincula la presencia de niveles elevados de colesterol plasmático con riesgo cardiovascular (RCV)

Tabla I. Composición nutricional del huevo (5)

Componente	Cantidad por huevo mediano (58 g/unidad)
Energía	78 kcal
Proteína	6,5 g
Colesterol	227 mg
Grasas saturadas	1,7 g
Grasas monoinsaturadas	2,3 g
Vitamina D	0,9 µg
Riboflavina	0,24 mg
Vitamina B12	1,3 µg
Selenio	6 µg
Fosforo	103 mg
Hierro	1 mg
Folato	26 µg
Retinol	98 µg

Tabla II. Aporte relativo de nutrientes derivados del consumo de dos huevos grandes según las recomendaciones (RDA) diarias para un adulto (6)

Nutriente	% Valor recomendado/día
Calorías	6%
Proteína	20%
Vitamina K	62%
Vitamina D	12%
Riboflavina	30%
Vitamina B12	16%
Selenio	34%
Fosforo	16%
Hierro	8%
Folato	12%

(7,8). Sin embargo, es importante considerar que los estudios que inicialmente asociaron el nivel de colesterol de la dieta con riesgo cardiovascular (RCV) correspondieron a modelos animales experimentales en los que se aportaron dosis suprafisiológicas de colesterol (9) y a estudios epidemiológicos en los que no se consideró el concomitante aporte de grasas saturadas (con efectos deletéreos sobre el perfil lipídico y RCV) de los alimentos ricos en colesterol. Adicionalmente, varios estudios observacionales y de intervención recientes han mostrado que el efecto de una restricción de colesterol dietario sobre los niveles plasmáticos de colesterol es en general de baja magnitud y menor que el impacto derivado de una baja ingesta de grasas saturadas y ácidos grasos transesterificados. A base de esta nueva evidencia, algunos paneles de expertos de diferentes asociaciones, como la American College of Cardiology/American Heart Association (ACC/AHA) (10), y las recomendaciones alimentarias del DGAC (Dietary Guidelines Advisory Committee) de Estados Unidos (11) del año 2015 han retirado la recomendación que limita el consumo de colesterol dietario y enfatizan otras que promueven una dieta saludable alta en fibra y baja en grasas saturadas y ácidos grasos transesterificados. Sin embargo, otras guías de prevención cardiovascular y manejo de dislipidemias, como la International Atherosclerosis Society (IAS) (12), el National Cholesterol Education Program (NCEP) (13) y la European Society of Cardiology/European Atherosclerosis Society (14) todavía recomiendan una limitación en el consumo de colesterol.

CONSUMO DE HUEVO Y COLESTEROL PLASMÁTICO

Consistente con el efecto promedio del contenido global de colesterol en la dieta, el consumo de huevo tiene un impacto de baja magnitud sobre los niveles de colesterol plasmático. En un metaanálisis, Weggemans (15) observó que por cada aumento de 100 mg de colesterol aportado por huevo en la dieta, los niveles de colesterol total en el plasma aumentaron en 2,2 mg/dl; el colesterol HDL (c-HDL), en 0,3 mg/dl; y la razón colesterol total/c-HDL, un conocido marcador de RCV, en 0,02 unidades. Aunque este estudio sugiere que el perfil lipídico resultante podría tener un efecto adverso en términos de RCV, los autores destacan que aquellos individuos que consumían una dieta baja en grasas saturadas presentaron un aumento menos aparente en el nivel de colesterol plasmático, lo que pone en relevancia el efecto modulador de la calidad global de la dieta en que se inserta el consumo de huevo. Por otro lado, estudios de intervención publicados con posterioridad a este metaanálisis han encontrado resultados variables, incluyendo algunos que no detectaron asociación entre consumo de huevo y cambios en los niveles de colesterol total, c-LDL (16,17), c-HDL (17) ni en la relación colesterol total/c-HDL (18).

La variabilidad en la sensibilidad de los individuos frente al aporte de colesterol dietario está determinada por la presencia de variaciones genéticas en genes que modulan el metabolismo de las lipoproteínas. Así, la variante genética E4 de la apolipoproteína (apo) E y los polimorfismos en los genes de apo CIII y apo B, entre otros, han sido asociados con un fenotipo hiperrespondedor de los niveles de colesterol plasmático ante la ingesta de colesterol. Asimismo, variantes en el gen NPC1L1 también regulan el efecto del colesterol dietario sobre el colesterol plasmático (20). Adicionalmente, otros factores clínicos como la obesidad y la resistencia a la insulina han sido asociados con una respuesta colesterolémica atenuada frente al consumo de colesterol en la dieta (21).

Es importante destacar también que el potencial RCV de los individuos no depende solamente de los niveles totales de lipoproteínas plasmáticas, sino que existen perfiles más o menos aterogénicos dependiendo de las características intrínsecas de las diferentes subclases de partículas lipoproteicas. Es así como las partículas de LDL pequeñas y densas son menos afines por el receptor de LDL y más susceptibles a procesos oxidativos y, por tanto, resultan más aterogénicas (22). En este sentido, estudios de intervención han mostrado que el consumo de huevo promueve la aparición de partículas de LDL y HDL de mayor tamaño (23,24). Asimismo, dos revisiones recientes (19,25) coinciden en que la evidencia actual sugiere que el contenido de colesterol de la dieta tendría no solamente un efecto modesto sobre el colesterol plasmático, sino que también aumentaría el tamaño de las partículas de LDL y disminuiría el número de partículas de LDL pequeñas, favoreciendo de esta manera un perfil lipídico menos aterogénico. Con respecto al c-HDL, el colesterol de la dieta elevaría sus niveles plasmáticos, aumentando también el tamaño de estas partículas lipoproteicas con un probable aumento concomitante en el transporte reverso de colesterol (26). Adicionalmente, la relación c-LDL/c-HDL se mantendría estable, aunque, como se mencionó previamente, algunos estudios muestran que la relación entre colesterol total/c-HDL tendería a elevarse (15).

IMPACTO DEL CONSUMO DE HUEVO SOBRE ENFERMEDAD CARDIOVASCULAR: EVIDENCIA DE ESTUDIOS OBSERVACIONALES Y COHORTES PROSPECTIVAS

El efecto del consumo de huevo sobre ECV es aún un tema controvertido y no existen, hasta la fecha, grandes estudios que hayan testeado esta hipótesis en protocolos de intervención prospectivos, randomizados y controlados. Por lo tanto, esta conexión ha sido esencialmente evaluada en estudios de diferentes cohortes epidemiológicas.

Ya antiguos reportes de la década de 1980 basados en la cohorte de Framingham (27) no demostraron una asociación significativa entre la ingesta de colesterol dietario aportado por el consumo de huevo, los niveles de colesterol plasmático y la incidencia de eventos coronarios. Los estudios observacionales más importantes de las últimas dos décadas que asocian consumo de huevo y ECV o mortalidad pueden observarse en la tabla III. Los estudios prospectivos de Burke (28) y Mann (29), junto a un metaanálisis reciente (30), han reportado asociaciones positivas entre consumo de huevo y eventos o mortalidad cardiovascular. Asimismo, Nettleton (31) y Djoussé (32) describieron una asocia-

Tabla III. Estudios observacionales prospectivos de las últimas dos décadas que han evaluado la relación entre consumo de huevo, factores de riesgo y enfermedad cardiovascular

Autor/año/país/ referencia	Diseño	Resultados
Mann et al., 1997, Inglaterra (29)	Seguimiento promedio de 13,3 años de 10.802 hombres y mujeres (16 a 79 años de edad)	Mayor mortalidad cardiovascular con mayor consumo de huevo (> 6/semana)
He et al., 2003, Estados Unidos (65)	Seguimiento durante 14 años de 43.732 hombres profesionales de la salud de 40-75 años de edad	El consumo de grasa total, colesterol y huevo no se asoció a incidencia de infarto cerebral
Houston et al., 2011, Estados Unidos (44)	Seguimiento durante nueve años de 1.941 adultos mayores de 70 y 79 años de edad provenientes del estudio *Health ABC*	El consumo de huevo se asoció a mayor RCV (HR 1,68; IC 95%, 1,12-2,51). Sin embargo, el análisis por subgrupos mostró que los pacientes sin diabetes no presentaron mayor riesgo y el subgrupo de pacientes diabéticos presentó mayor incidencia de eventos coronarios (HR 5,02; IC 95%, 1,63-15,52), comparando el tercil de mayor consumo (≥ 3 huevos/semana) *versus* aquel de menor consumo (< 1/semana)
Zazpe et al., 2011, España (42)	Seguimiento durante 6,1 años de 14.185 adultos graduados universitarios pertenecientes al estudio *SUN*	No se observó asociación entre consumo de huevo e incidencia de ECV (comparando ingesta > 4 huevos a la semana con < 1 huevo semanal)
Qureshi et al., 2007, Estados Unidos (43)	Seguimiento durante 20 años de 9.734 adultos de 25 y 74 años de edad participantes del estudio de seguimiento epidemiológico de NHANES I (NHEFS)	No se observó asociación entre consumo de ≥ 6 huevos a la semana y RCV ni mortalidad. En el subgrupo de diabéticos, el consumo de ≥ 6 huevos a la semana se correlacionó con mayor riesgo de infarto cardiaco, pero no de origen cerebral (RR 2,0, IC 95%, 1,0-3,8)
Djoussé and Gaziano, 2008, Estados Unidos (32,39)	Seguimiento por 20 años de 21.327 participantes hombres de 40 y 85 años de edad que forman parte del *Physician's Health Study*	El consumo de huevo no se asoció a incidencia de eventos coronarios o infarto cerebral, pero el consumo de ≥ 7 huevos a la semana se correlacionó con mayor riesgo de mortalidad total (HR 1,23; IC 95%, 1,11-1,36). Esta asociación fue de mayor magnitud y con un patrón dosis dependiente en pacientes diabéticos (HR 2,01; IC 95%, 1,26-3,20). En un segundo análisis, el consumo de ≥ 7 huevos a la semana se asoció a mayor riesgo de insuficiencia cardiaca
Hu et al., 1999, Estados Unidos (35)	37.851 hombres de entre 40 y 75 años de edad pertenecientes al Health Professionals Follow-up Study seguidos ocho años y 80.082 mujeres de entre 34 y 59 años pertenecientes al Nurses Health Study seguidas 14 años	No se observó asociación entre consumo de huevo y ECV en ambas cohortes. En el análisis por subgrupos se observó un mayor riesgo de infarto cardiaco entre los diabéticos (en hombres diabéticos comparando consumo de > 1 huevo/día con < 1 huevo a la semana RR 2,02; IC 95%, 1,05-3,87; en mujeres diabéticas RR 1,49; IC 95%, 0,88-2,52)
Nakamura et al., 2004, Japón (40)	Seguimiento a 14 años de 5.186 mujeres y 4.077 hombres ≥ 30 años de edad	A mayor consumo de huevo se observaron mayores niveles de colesterol plasmático de manera dosis dependiente solamente en mujeres ($p < 0,001$). En mujeres, pero no en hombres, se evidenció menor mortalidad total con un consumo de 1-2 huevos/semana comparado con ingesta de 1 huevo/día (RR 0,78; IC 95%, 0,63-0,96)

(Continua en la página siguiente)

Tabla III (Cont.). Estudios observacionales prospectivos de las últimas dos décadas que han evaluado la relación entre consumo de huevo, factores de riesgo y enfermedad cardiovascular

Autor/año/país/ referencia	Diseño	Resultados
Nakamura et al., 2006, Japón (47)	Seguimiento promedio de 10,2 años de 90.735 adultos (19.856 hombres y 21.408 mujeres de 40 a 59 años de edad en la cohorte I; 23.463 hombres y 26.008 mujeres de 40 a 69 años de edad en la cohorte II)	No se observó asociación significativa entre consumo de huevo y eventos coronarios en la población total ni en el análisis por subgrupos (diabéticos, hipercolesterolémicos, individuos en dietas bajas en colesterol, etc.)
Trichopoulou et al., 2006, Grecia (45)	Seguimiento promedio de 4,5 años de 1.013 adultos diabéticos participantes del estudio EPIC	El consumo de huevo se asoció a mayor mortalidad total (HR 1,31; IC 95%, 1,07-1,60) y cardiovascular (HR 1,54; IC 95%, 1,20-1,97) en este grupo de individuos diabéticos
Goldberg et al., 2014, Estados Unidos (66)	1.429 hombres y mujeres (hispanos, afroamericanos y blancos) con seguimiento medio de once años	Por cada huevo consumido a la semana, el riesgo de ateroesclerosis disminuyó un 11% (IC 95%, 3%-18%). No se observó asociación entre consumo de huevo y ECV clínica
Nettleton et al., 2008, Estados Unidos (31)	Seguimiento por 13 años de 14.153 adultos afroamericanos y blancos de entre 45 y 64 años de edad provenientes del estudio ARIC	El riesgo de insuficiencia cardiaca fue mayor con un mayor consumo de huevo (RR 1,23; IC 95%, 1,08-1,41 para el consumo de 1 huevo/día)
Burke et al, 2007, Australia (28)	Seguimiento por 14 años de 256 mujeres y 258 hombres, aborígenes australianos de entre 15 y 88 años	El consumo de huevos (> 2 veces por semana) se asoció a mayor riesgo de infarto cardiaco (HR 2,59; IC 95%, 1,11-6,04)
Sauvaget, 2003, Japón (37)	Seguimiento durante 16 años de 15.350 hombres (edad promedio 54 años) y 24.999 mujeres (edad promedio 58 años)	El consumo diario de huevo se asoció a un riesgo menor de mortalidad por infarto cerebral (HR 0,70; IC 95%, 0,51-0,95)
Scrafford et al., 2011, Estados Unidos (36)	Seguimiento durante casi nueve años de 6.833 hombres y 8.113 mujeres > 17 años de edad pertenecientes a NHANES III	No se observó asociación entre consumo elevado de huevo (> 7 huevos/ semana) y mortalidad cardiovascular en la población general ni en el subgrupo de diabéticos. Asociación inversa entre consumo elevado de huevo y mortalidad por infarto cerebral en hombres (HR 0,27; IC 95%, 0,10-0,73)

ECV: enfermedad cardiovascular; RCV: riesgo cardiovascular; HR: hazard ratio; IC: intervalo de confianza.

ción positiva entre consumo de huevo e insuficiencia cardiaca. Por otro lado, la mayoría de los estudios prospectivos de grandes cohortes y otros metaanálisis recientes (33,34) no han encontrado asociación entre el consumo de hasta un huevo al día y la incidencia de infarto cardiaco y cerebral en población sana.

En el estudio prospectivo de Hu (35), conocido como *Harvard Egg Study*, se analizaron datos de dos cohortes: el *Health Professionals Follow Up Study* (HPFUS), con el seguimiento de 51.529 hombres durante ocho años, y el *Nurse's Health Study,* con el seguimiento de 121.700 mujeres durante 14 años. Estos estudios no demostraron una asociación entre el consumo de huevo (hasta una unidad al día) con un mayor RCV, a excepción del subgrupo de diabéticos, en que el consumo de esta cantidad de huevo se correlacionó con una mayor incidencia de ECV.

Hasta la fecha, tres metaanálisis han evaluado la información proveniente de estos estudios prospectivos. En el metaanálisis de Rong (34), que incluyó ocho estudios de cohortes, no se observó asociación general entre el consumo de hasta un huevo al día con la incidencia de infarto cardiaco o cerebral. Sin embargo, un mayor (> 1 huevo al día) *versus* un menor consumo de huevo se asoció a un riesgo elevado de patología coronaria entre los diabéticos (RR 1,54; intervalo de confianza [IC] 95%, 1,14-2,09). Resultados similares se encontraron en un segundo metaanálisis de 22 cohortes independientes (33): la muestra global mostró que el consumo de uno o más huevos al día no determinaba más eventos coronarios ni infarto cerebral que una ingesta de menos de un huevo a la semana. Consistente con otros estudios, este análisis observó que los diabéticos que consumían más de un huevo/día tenían un incremento del 69% en el riesgo de desarrollar enfermedad coronaria con respecto a aquellos diabéticos que consumían menos de un huevo a la semana (*hazard ratio* [HR] 1,69; IC 95%, 1,09-2,62). En otro metaanálisis (30), la detección de un mayor riesgo de eventos coronarios en la subpoblación de diabéticos (RR 1,83; IC 95%, 1,42-2,37) coincidió con un mayor riesgo cardiovascular en la población general (RR 1,19; IC 95%, 1,02-1,38), siendo el efecto de tipo dosis dependiente en ambas poblaciones. Los resultados de estos tres metaanálisis son discordantes y deben ser interpretados con precaución ya que los criterios de inclusión y exclusión de las cohortes analizadas difieren significativamente entre ellos.

Adicionalmente, el metaanálisis de Rong (34) observó un menor riesgo de infarto cerebral hemorrágico en asociación con un mayor consumo de huevo (RR 0,75; IC 95%, 0,57-0,99). Otros estudios han encontrado también una relación inversa entre consumo de huevo y riesgo de infarto cerebral, como ocurre con el análisis de Scrafford (basado en los datos de NHANES III [36]) (Tabla III), en donde se observó una menor mortalidad por infarto cerebral en hombres, como también lo reporta el estudio de Sauvaget realizado en japoneses (37) (Tabla III).

Por último, una revisión sistemática y metaanálisis reciente (38) concluye que no existe asociación entre el consumo de colesterol de la dieta (de cualquier fuente, no solamente aportado como huevo) y ECV, pero dada la gran heterogeneidad y falta de rigurosidad metodológica de los estudios incluidos, los autores no consideran sus resultados como definitivamente concluyentes.

A base de los 16 análisis de estudios prospectivos reportados hasta la fecha (Tabla III), solo seis de ellos han mostrado posibles efectos adversos cardiovasculares derivados del consumo de huevo en población general. En cuatro de estos trabajos, este efecto se observó solamente con ingestas iguales o superiores a un huevo al día (31,32,39,40), y solo en dos se detectó esta asociación con ingestas inferiores (28,29). Las discordancias entre los estudios pueden deberse a que muchos de estos análisis no consideraron otras posibles variables confundentes derivadas de la dieta, como consumo de otras fuentes de colesterol o la ingesta de grasas saturadas, grasas transesterificadas, fibra y calorías totales. Este punto es fundamental ya que el RCV global es modulado en forma importante por la calidad del patrón dietario general (41). De hecho, varios de estos estudios prospectivos han mostrado una asociación entre consumo elevado de huevo con dietas y estilos de vida poco saludables (35,36,39,42), los cuales podrían ser los verdaderos determinantes primarios de los resultados observados.

En resumen, la evidencia disponible muestra que no habría una asociación entre el consumo de hasta un huevo al día con la aparición de ECV en población sana. Esto podría explicarse por el escaso efecto promedio que exhibe el nivel de ingesta de colesterol dietario sobre los niveles de colesterol plasmático en la mayoría de las personas. Por otro lado, el consumo de huevo tiende a elevar simultáneamente los niveles de c-LDL y c-HDL, manteniendo sin cambios significativos la razón c-LDL/c-HDL, lo que podría explicar su escaso efecto sobre el RCV ateroesclerótico. Adicionalmente, es importante considerar que el huevo es un alimento rico en otros nutrientes y componentes bioactivos que podrían tener un efecto cardioprotector antiateroesclerótico, contrarrestando, al menos en parte, los potenciales efectos del colesterol dietario sobre el sistema cardiovascular.

Por otro lado, es importante destacar que varios estudios observacionales prospectivos de grandes cohortes (35,39,43-45), tres metaanálisis (30,33,34) y una revisión sistemática (46) han reportado una asociación positiva entre el consumo de huevo y ECV o mortalidad en población diabética, aunque existen otros estudios que no han llegado a las mismas conclusiones (36,47). Estos resultados son más difíciles de interpretar y los mecanismos fisiopatológicos subyacentes a esta asociación no han sido definidos.

EFECTOS DEL CONSUMO DE HUEVO SOBRE EL RIESGO CARDIOVASCULAR ATEROESCLERÓTICO: EVIDENCIA DE ESTUDIOS CLÍNICOS DE INTERVENCIÓN

Hasta la fecha, no existen estudios de intervención randomizados y controlados que evalúen primariamente el impacto del consumo de huevo sobre la incidencia de eventos cardiovasculares. Los estudios de intervención disponibles son de pequeño tamaño y miden resultados intermedios, principalmente marcadores bioquímicos y factores de riesgo clínicos asociados a un mayor RCV.

CONSUMO DE HUEVO Y LÍPIDOS PLASMÁTICOS

Consumo de huevo en individuos normocolesterolémicos

En un estudio randomizado, Katz y cols. (48) observaron que el consumo de dos huevos al día durante seis semanas no produjo alteraciones en los niveles de colesterol total, c-LDL, c-HDL ni función endotelial en 49 individuos normocolesterolémicos sanos. Por otro lado, Herron (49) evaluó la respuesta lipídica de individuos normocolesterolémicos frente a la ingesta de huevo según su clasificación como hipo o hiperrespondedores a la exposición a colesterol dietario. En este estudio, 40 hombres sanos sometidos a una dieta *Step 1* del NCEP de Estados Unidos fueron randomizados alternadamente a dos periodos de 30 días consumiendo tres huevos al día y luego placebo (sustituto de huevo, sin colesterol) separados por un periodo de tres semanas de lavado o blanqueo de la intervención inicial. Al término del estudio, los hiporrespondedores (62,5% de los participantes) no presentaron cambios en colesterol-total, c-LDL, c-HDL ni razón c-LDL/c-HDL en ninguna de las dos dietas. Por otro lado, los hiperrespondedores exhibieron elevaciones en colesterol total, c-LDL, c-HDL y en la razón c-LDL/c-HDL, aunque este último parámetro no alcanzó un nivel considerado de mayor RCV, durante el periodo de dieta suplementada con huevo. Adicionalmente, el grupo hiperrespondedor mostró aumento en la actividad de LCAT y CETP, enzimas remodeladoras de las partículas de HDL, lo que sugiere un aumento en el transporte reverso de colesterol. Este mismo grupo de investigadores había reportado previamente resultados similares en mujeres premenopáusicas, aunque en este último caso no se observó aumento en la razón c-LDL/c-HDL en aquellas mujeres clasificadas como hiperrespondedoras al aporte de colesterol dietario (50).

Posteriormente, el mismo equipo de trabajo evaluó la respuesta a una carga de colesterol en un grupo de 42 adultos mayores sanos. Los participantes fueron randomizados alternadamente a una dieta con tres huevos diarios o placebo por 30 días y separados por tres semanas de blanqueo entre las intervenciones (18). En este estudio se observaron aumentos de c-LDL y c-HDL durante el periodo de ingesta de la dieta con huevo, pero las razones c-LDL/c-HDL y colesterol-total/c-HDL se mantuvieron constantes.

Adicionalmente, se observó un aumento en el tamaño de las partículas de LDL y una mayor actividad de LCAT en los hiperrespondedores (18). Finalmente, un estudio chileno, que incluyó a 36 hombres normolipémicos o con hipercolesterolemia aislada, observó que el aporte de un huevo al día por cuatro semanas en el contexto de una dieta habitual no produjo elevaciones en los valores de colesterol total ni c-LDL, independiente de los niveles basales de colesterol plasmáticos o del genotipo de apo E (51).

Consumo de huevo en individuos hipercolesterolémicos

Knopp (52) evaluó la respuesta al consumo de huevo en individuos hipercolesterolémicos (HC) o con dislipidemia mixta. En este estudio randomizado doble ciego, 162 individuos con niveles de c-LDL entre 130 y 190 mg/dl o dislipidemia mixta que adherían a la dieta *Step I* baja en grasas saturadas del NCEP recibieron dos huevos al día o placebo. Después de 12 semanas se observó que solo aquellos participantes con dislipidemia mixta sometidos a la dieta con huevo presentaron elevaciones significativas del c-LDL (aumento absoluto de 12 mg/dl), y que tanto los individuos HC como los dislipidémicos mixtos presentaron aumento del c-HDL con el consumo de huevo. Asimismo, Njike (53) observó que el aporte de dos huevos al día por seis semanas no producía elevaciones en colesterol total, c-LDL ni c-HDL ni alteraciones en la función endotelial en individuos hipercolesterolémicos, aunque la función endotelial mejoró en aquellos asignados al grupo control. Sin embargo, tres estudios previos han mostrado que el consumo de colesterol dietario en forma de huevo aumenta los niveles de colesterol total y c-LDL en individuos moderadamente hipercolesterolémicos, incluso en presencia de una restricción de grasas saturadas en la dieta (54-56).

Consumo de huevo en individuos con ECV ateroesclerótica

Recientemente, Katz (57), en un estudio randomizado controlado simple ciego, analizó las consecuencias de la ingesta de un desayuno con dos huevos al día en comparación con uno elevado en carbohidratos o un sustituto de huevo durante seis semanas en 32 individuos con ateroesclerosis establecida (estenosis arterial coronaria > 50%) y que llevaban una dieta *ad libitum.* Este estudio encontró que el consumo de huevo no alteró los niveles de colesterol total, c-LDL, c-HDL ni presión arterial, ni modificó la función endotelial en comparación con los otros desayunos.

CONSUMO DE HUEVO Y FACTORES DE RIESGO CARDIOVASCULAR EN POBLACIÓN DIABÉTICA

Hasta la fecha, solo tres estudios han evaluado el efecto del consumo de huevo en individuos diabéticos. Pearce (58) evaluó el papel del huevo asociado a una dieta hipocalórica hiperproteica sobre el control metabólico y de factores de RCV. En este protocolo, 65 participantes diabéticos o intolerantes a la glucosa fueron randomizados a una dieta elevada en colesterol (dos huevos/día) o baja en colesterol, aunque isoproteica (con aporte de proteína magra de origen animal). Al cabo de 12 semanas, ambos grupos mantuvieron los niveles de c-LDL y mostraron una disminución del c-no HDL, apo B y presión arterial, sin diferencias entre los grupos. Sin embargo, el grupo que consumió huevo mostró una mayor elevación en los niveles de c-HDL. Adicionalmente, ambos grupos exhibieron mejorías en el control glicémico y HOMA-IR. Asimismo, el estudio australiano DIABEGG *(Diabetes and Egg Study)* randomizó a 140 prediabéticos o diabéticos a una dieta elevada en huevo (aproximadamente 12 huevos/semana) o baja en huevo (< 2 huevos/semana) en el contexto de una dieta baja en grasas saturadas y elevada en grasas poli- y monoinsaturadas, sin restricción calórica (59). Al cabo de tres meses, no se observaron diferencias significativas en cuanto al perfil lipídico, glicemia de ayuno, hemoglobina glicosilada ni presión arterial entre ambos grupos. Sin embargo, casi la mitad de los participantes en este estudio usaba estatinas, por lo que sería esperable que exhibieran una respuesta plasmática atenuada frente a un aumento del contenido de colesterol dietario (60). Por otro lado, en México, Ballesteros (61) no encontró diferencias en el perfil lipídico, control glicémico, PCR ni niveles de LDL oxidadas en pacientes diabéticos sometidos a un desayuno con un huevo al día en comparación con un desayuno isocalórico con avena. Adicionalmente, se detectó una disminución en los niveles sanguíneos de transaminasas y del factor de necrosis tumoral alfa en relación al consumo del desayuno con huevo, evidenciando una disminución en la inflamación subclínica de bajo grado que suele caracterizar a estos pacientes.

En base a estos estudios, es posible concluir que el consumo de huevo en el contexto de una dieta hipocalórica o baja en grasas no tendría consecuencias negativas sobre los factores de riesgo cardiovascular (FRC) de diabéticos. Aunque los estudios descritos muestran potenciales beneficios o ausencia de daño al adicionar huevo a las recomendaciones dietéticas para individuos diabéticos o con SM, es importante considerar que los niveles de colesterol sanguíneo en ayunas no reflejan cabalmente el potencial RCV aterosclerótico asociado a diabetes mellitus (60). Adicionalmente, existe una discordancia entre estos hallazgos derivados de estudios de intervención a corto plazo y basados en efectos intermedios con lo observado en los estudios de grandes cohortes, donde se detectó una mayor incidencia de ECV en poblaciones diabéticas (35,39,43-45) así como una mayor incidencia de diabetes en asociación al consumo de huevo en la población general (62-64).

Es posible plantear que lo observado en los estudios de intervención está influenciado, en gran parte, por el contexto dietético global en el que se desarrollan las intervenciones con suplemento de huevo. Así, en los estudios observacionales, el elevado consumo de huevo podría ser meramente un marcador de una dieta y estilo de vida poco saludables, pero no un factor etiológico directo,

que conduce a un mayor riesgo de enfermedades crónicas. Este factor confundente es eliminado en los estudios de intervención, ya que la mayoría de ellos modifican las características de la dieta basal de los individuos, favoreciendo patrones más saludables (como la dieta *Step I* del NCEP u otras restringidas en carbohidratos o hipocalóricas). Esta situación sugiere que los efectos del consumo de huevo sobre la salud de las personas, en especial de aquellas con un mayor RCV, serían diferentes dependiendo del patrón dietético global en el cual este alimento es consumido.

CONCLUSIONES

Teniendo en cuenta la alta calidad nutritiva del huevo, junto con su aporte de numerosos compuestos bioactivos beneficiosos para la salud humana, este alimento puede ser considerado como un constituyente importante en la dieta de personas en todas las etapas del ciclo vital, pero podría jugar un rol aún más significativo en etapas de mayor demanda nutricional, como la infancia o el embarazo, o en aquellos más vulnerables, como los adultos mayores.

Con respecto a los resultados discordantes derivados de diferentes estudios epidemiológicos, es importante considerar que muchos de estos estudios tienen limitaciones metodológicas o no ofrecen el diseño necesario para obtener conclusiones definitivas de tipo causa-efecto. Muchos de ellos no ajustan sus análisis por otras variables de la dieta, como la ingesta de grasas saturadas y fibra, o sus encuestas de consumo de alimentos solo se realizan al inicio del seguimiento longitudinal, sin considerar los cambios en los hábitos alimentarios que podrían ocurrir con el paso de los años hasta que se presentan los desenlaces clínicos finales.

En cuanto a los estudios de intervención disponibles hasta la fecha, son de corta duración y pequeño tamaño muestral, y miden resultados intermedios. Aunque hasta la fecha sus resultados muestran que el consumo de huevo no es deletéreo para el perfil lipídico ni el RCV de las personas, esta evidencia es insuficiente para concluir con certeza que el consumo regular de huevo, sin restricciones cuantitativas, es seguro para toda la población. Para esto serían necesarios estudios mayores, randomizados y controlados (al menos en poblaciones de alto riesgo) que midan el efecto del consumo de huevo sobre efectos clínicos de relevancia como la incidencia y/o la mortalidad por enfermedades crónicas, incluidos ECV, DM2 y cáncer.

Por otro lado, un factor fundamental a considerar cuando se pretende hacer una recomendación en torno a la ingesta de huevo, o de cualquier otro alimento específico, es el patrón dietético global en el que el alimento es consumido. Dada la evidencia disponible, se puede concluir que el consumo de huevo, en el contexto de una dieta y estilo de vida globalmente saludables, podría ser recomendado en cantidades de hasta una porción diaria para la población sana. En población diabética o de elevado riesgo cardiovascular, en honor al principio de precaución y considerando que la evidencia no es concluyente aún, parece prudente no recomendar un consumo regular de huevo, o al menos evitar el consumo de su yema.

CONFLICTOS DE INTERÉS

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Nutrición Hospitalaria

Revisión

Efficacy of enteral nutritional support after hospital discharge in major gastrointestinal surgery patients: a systematic review

Eficacia del soporte nutricional enteral tras el alta hospitalaria en pacientes con cirugía digestiva: revisión sistemática

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Abstract

Introduction: Nutritional support for malnourished patients undergoing gastrointestinal surgery reduces the complication rate and shortens the length of stay. The efficacy of nutritional support after hospital discharge was analyzed in this systematic review.

Methods: The search strategy (nutrition OR "enteral nutrition" OR "nutritional supplements" OR "oral nutritional supplements" OR "sip feed" OR "sip feeding" OR "dietary counseling") AND ("patient discharge" OR discharge OR postdischarge) AND (surgery OR operation OR "surgical procedure") was followed in Medline, CENTRAL, and Trip databases. Inclusion criteria comprised: type of study (randomized controlled trial), language (English, Spanish), and subjects (patients undergoing gastrointestinal surgery). The risk of bias was assessed by using the Cochrane methodology.

Results: Five studies which were published in six different articles and recruited 446 patients were included. A high risk of bias was detected for most of them. Nutritional support improved energy intake and protein intake when high-protein oral supplements were provided. The intervention was associated with better weight prognosis, but the data about body composition were inconsistent. In most of the trials, nutritional intervention did not enhance functional capacity or quality of life. None of the studies analyzed the effects on complications after discharge.

Conclusion: Nutritional support provided at discharge may increase dietary intake and improve body weight, but the low quality of studies can weaken the validity of results.

Key words:

Malnutrition. Nutritional support. Oral nutritional supplements. Surgery. Length of stay. Hospital discharge.

Resumen

Introducción: el soporte nutricional en pacientes desnutridos sometidos a cirugía gastrointestinal reduce la tasa de complicaciones y acorta la duración de la estancia. En esta revisión sistemática se analiza su eficacia después del alta hospitalaria.

Métodos: la estrategia de búsqueda *(nutrition OR "enteral nutrition" OR "nutritional supplements" OR "oral nutritional supplements" OR "sip feed" OR "sip feeding" OR "dietary counseling") AND ("patient discharge" OR discharge OR postdischarge) AND (surgery OR operation OR "surgical procedure")* se introdujo en las bases Medline, CENTRAL y TripDatabase. Fueron criterios de inclusión: tipo de estudio (RCT), idioma (inglés, español) y población del estudio (pacientes sometidos a cirugía gastrointestinal). El riesgo de sesgo se evaluó mediante la metodología Cochrane.

Resultados: se incluyeron cinco estudios (446 pacientes), publicados en seis artículos diferentes. Se detectó un alto riesgo de sesgo en la mayoría de ellos. El soporte nutricional mejoró la ingesta de energía y el consumo de proteínas cuando se proporcionaron suplementos orales hiperproteicos. La intervención se asoció con un mejor pronóstico de peso, pero los datos sobre la composición corporal fueron inconsistentes. En la mayoría de los estudios, la intervención nutricional no mejoró la capacidad funcional o la calidad de vida. Ninguno de los estudios analizó los efectos sobre las complicaciones después del alta.

Conclusión: el soporte nutricional proporcionado después del alta puede aumentar la ingesta y mejorar el peso corporal, pero la baja calidad de los estudios debilita la validez de los resultados.

Palabras clave:

Desnutrición. Soporte nutricional. Suplementos nutricionales orales. Cirugía. Estancia hospitalaria. Alta hospitalaria.

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INTRODUCTION

The tight relationship among malnutrition, surgery, and poorer outcomes was for the first time established by the classic study of Studley, published in 1936 (1). Eighty years later, malnutrition is a common condition in surgical patients, with a prevalence ranging from 20 to 40% (2,3). The deterioration of nutritional status during hospitalization has been associated with longer hospital stay, an increase in morbidity, and a higher economic burden (4).

Preoperative nutrition provided to malnourished surgical patients has been related to the reconstitution of immune function and significant reductions in complications (5,6). The supply of immunonutrition in the perioperative period reduces the infection rate and shortens the length of stay, although a significant reduction in mortality has not been demonstrated (7). This improvement in the prognosis is associated with a significant reduction in the economic expenditure derived from hospitalization, which exceeds the cost of the intervention (8). Following this evidence, current clinical guidelines encourage active screening for malnutrition in surgical patients and the perioperative provision of nutritional support (9).

Nevertheless, the efficacy of nutritional support beyond hospital discharge has received less attention, in spite of the fact that some changes due to surgery can persist for weeks. In this way, an increase in resting energy expenditure has been observed in patients with peritonitis until 23 days after the injury, accompanied by the reduction in skeletal muscle and visceral protein (10). Furthermore, severe losses of weight, muscle mass, and grip strength have been described 180 days after major surgery (11). Dietary restrictions, anorexia, and gastrointestinal symptoms such as nausea, vomiting, abdominal pain, and diarrhea may persist for a long time after major surgery, compromising an adequate feeding.

A systematic review was performed to test the current evidence about the effects of nutritional support on nutritional status, complication rates, and quality of life, when administered after hospital discharge in patients who underwent gastrointestinal surgery.

METHODS

The systematic review was conducted following the principles of the PRISMA declaration (12).

SEARCH STRATEGY

A bibliographic search was performed in February 2015 using the Medline (PubMed), Trip Database, and Central (Cochrane Library) databases. The following strategy was used for this purpose: ("nutrition" OR "enteral nutrition" OR "nutritional supplements" OR "oral nutritional supplements" OR "sip feed" OR "sip feeding" OR "dietary counseling") AND ("patient discharge" OR discharge OR postdischarge) AND (surgery OR operation OR "surgical procedure").

INCLUSION CRITERIA

The eligibility criteria for including studies in the review were the type of assay (randomized, double-blinded, controlled studies), type of patients (patients undergoing either elective or urgent major gastrointestinal surgery), patients' age (adults), type of nutritional intervention (either dietary counselling, oral nutritional supplements, or enteral nutrition provided after hospital discharge, independently if any nutritional intervention was provided during hospitalization or not), and language (English, Spanish).

EXCLUSION CRITERIA

Non-randomized or non-controlled studies, trials including patients receiving home parenteral nutrition, trials providing nutritional support only during hospitalization, studies in which patients underwent surgical procedures other than gastrointestinal (e.g., cardiovascular, orthopedic, head and neck), and studies that did not fulfil the inclusion criteria were excluded.

TYPE OF INTERVENTION

Any kind of nutritional support that included dietary counselling, oral nutritional supplements (ONS), and/or enteral nutrition provided at hospital discharge. The control group should include no nutritional support or the usual care of the center. Home parenteral nutrition (HPN) was not considered for the purpose of this review. HPN is a complex modality of nutritional support used in a very specific group of patients with intestinal failure. The aim of this systematic review was to evaluate the utility of oral or enteral nutrition in the common surgical patient. The efficacy and effectiveness of HPN has been recently reviewed (13). Nutritional support exclusively provided during the perioperative period was excluded from this review as several previous trials and meta-analysis have evaluated its efficacy.

OUTCOMES

The outcomes of interest were the daily intake of energy and protein (comprising dietary intake and oral or enteral nutrition); nutritional status, assessed either with validated structured tools (e.g., Subjective Global Assessment, NRS-2002, Malnutrition Screening Tool, etc.), anthropometric measures (weight, body mass index, body circumferences, skinfold thickness), body composition (e.g., muscle mass or fat mass measured with bioelectrical impedance), or muscle strength (e.g., grip strength measured with dynamometry); complication rate at discharge, including infections, mechanical complications of surgery (e.g., anastomotic leak), mortality, and re-hospitalization; quality of life measured with any validated survey; and the cost-effectiveness of the intervention (e.g., incremental cost-effectiveness ratio).

DATA COLLECTION

Data were collected from the selected trials by the authors in an independent manner using a common structured form. Outcome measures were recorded as mentioned in the publication, either as intention to treat analysis or per protocol.

ASSESSMENT OF QUALITY AND RISK OF BIAS

The identified randomized, controlled trials were considered as suitable for revision if they matched the initial inclusion criteria. Quality was assessed following the methodology proposed in the *Cochrane handbook for systematic review of interventions,* version 5.1.0 (14). Each identified study was independently evaluated for inclusion by two reviewers who were blinded to authors, institutions, and journals during the selection process. When several papers from the same study were found, the publication with higher methodological quality was selected. Any disagreement between the reviewers was resolved by consensus discussions with the other members of the team.

SYNTHESIS OF DATA AND STATISTICAL ANALYSIS

Due to the use of different measures of outcomes and the lack of a complete reporting of results in various publications, there was no possibility of performing a meta-analysis. Results are presented in a narrative manner.

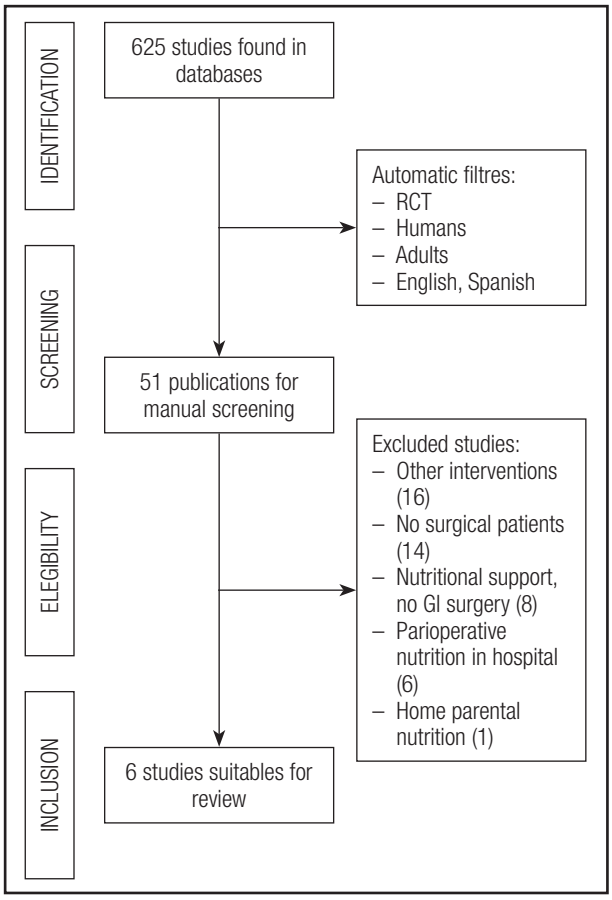

Figure 1.

Flow char of the study selection process (RCT: Randomized, controlled trials; GI: Gastrointestinal).

RESULTS

ELIGIBLE STUDIES

After the selection process, six publications with a total of 446 patients were included in the review (15-20). One study presented results in two different publications, and it was treated as one single study (7,8). The selection process is presented in figure 1, and the characteristics of these studies are summarized in table I.

CHARACTERISTICS OF THE SELECTED STUDIES

All but one of the studies were developed in a single center: the study by Smedley et al. took place in three different hospitals in the UK (18). Only two trials provided nutritional support exclusively after hospitalization (15,16,19), while the others offered perioperative nutritional support to any of the groups. The trial by Keele et al. included four arms of intervention: no nutritional support, nutritional support in the postoperative period and at discharge, nutritional support only in the postoperative period, and nutritional support only at discharge (14). Patients recruited in the trial by Beattie et al. received ONS during the postoperative period and at home, or the usual care (which was not described in the text) (17). The study by Smedley et al. also included four arms: usual care (progressive oral diet), preoperative ONS, perioperative ONS and at discharge, and postoperative ONS and at discharge (18). In the study by Carey et al., usual care was compared with nutritional support, both provided at discharge. The usual care included dietary advice provided by the ward dietitian in a single session of 45 minutes, with written information and recommendations about the use of ONS. The intervention group included regular phone calls from a dietitian, face-to-face interviews, and ONS or enteral nutrition, if necessary (19). The duration of the follow-up ranged between four and 24 weeks.

In four trials, specific commercially available ONS were provided to patients, in three of them a hypercaloric standard ONS (Fortisip™, NV Nutricia, Zoetermeer, The Netherlands; Ensure Plus™, Abbott Laboratories, Lake Forest, USA) was provided, and in the remaining, a combination of low-fat and non-fat, high-protein ONS (Top up special™ and Plus one™, Ferrosan, Søborg, Denmark) was provided (14-18).

Table I. Summary of the selected articles

Study	n	Age (yr)	Gender (M/F)	Type of surgery	Intervention groups	Time of intervention	Type of intervention	Follow-up (weeks)
Keele et al., 1997	86	60-64.7	48/38	Colon, stomach	4	Postop + discharge	ONS	16
						Postop	ONS	
						No intervention	Usual care	
						Discharge	ONS	
Jensen et al., 1997	53	53-64	28/25	Colorectal	2	Discharge	Dietary counselling + ONS	16
							Usual care	
Beattie et al., 2000	101	54.4-62.4	60/41	GI	2	Postop + discharge	ONS	10
						Postop + discharge	Usual care	
Smedley et al., 2004	179	55-63	100/79	Colorectal	4	Periop + discharge	ONS	4
						Preop	ONS	
						Postop + discharge	ONS	
						No intervention	Usual care	
Carey et al., 2013	27	65.1-65.7	21/6	Gastrectomy, esophagectomy, pancreatoduodenectomy	2	Discharge	Dietary counselling + ONS + EN	24
							Usual care	

Yr: Years; M: Male; F: Female; GI: Gastrointestinal; Postop: Postoperative; Periop: Perioperative; Preop: Preoperative; ONS: Oral nutritional supplements; EN: Enteral nutrition.

The risk of bias is summarized in table II and figure 2. For randomization, two studies used sealed envelopes (16,18), one used a computer-generated table of random numbers (17), and another, a randomization table (19). In the other trials the method for randomization was not specified in the text. None of the studies blinded personnel and participants, and only two studies blinded the outcomes assessment (17,18). Only in the study by Carey et al. were data analyzed in an intention-to-treat mode (19).

Table II. Risk of bias summary of each selected study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of personnel (performance bias)	Blinding of outcome assessment (detection bias)	Intention to treat analysis	Incomplete outcome data (reporting bias)	Selective reporting (reporting bias)	Other bias
Keele, 1997	–	–	–	–	–	?	–	?	+
Jensen, 1997	?	?	–	–	?	?	–	?	+
Beattie, 2000	+	–	–	–	+	–	+	+	+
Smedley, 2004	–	–	?	–	+	?	–	?	+
Carey, 2013	–	–	–	–	?	+	+	?	+

PATIENT CHARACTERISTICS

The number of patients recruited for each trial ranged from 27 to 179, with an age of 53 to 66 years. Most patients were male (257/461). Three studies included patients who underwent programmed major gastrointestinal surgery (6,9,10), the study developed by Jensen et al. included emergency surgery (7,8), and another study did not report this characteristic (11). All of the studies except one (Jensen et al.) reported the nutritional status of the patients, although it was evaluated with different methods. The study by Keele et al. found 14% of patients with severe nutritional risk according to the Nutritional Risk Index, Beattie et al. reported 3% of patients with low body mass index, and Carey et al. found malnutrition in 62.9% using the Subjective Global Assessment. In the study by Smedley et al., 34% of patients had nutritional risk, but the method used to detect it was not described.

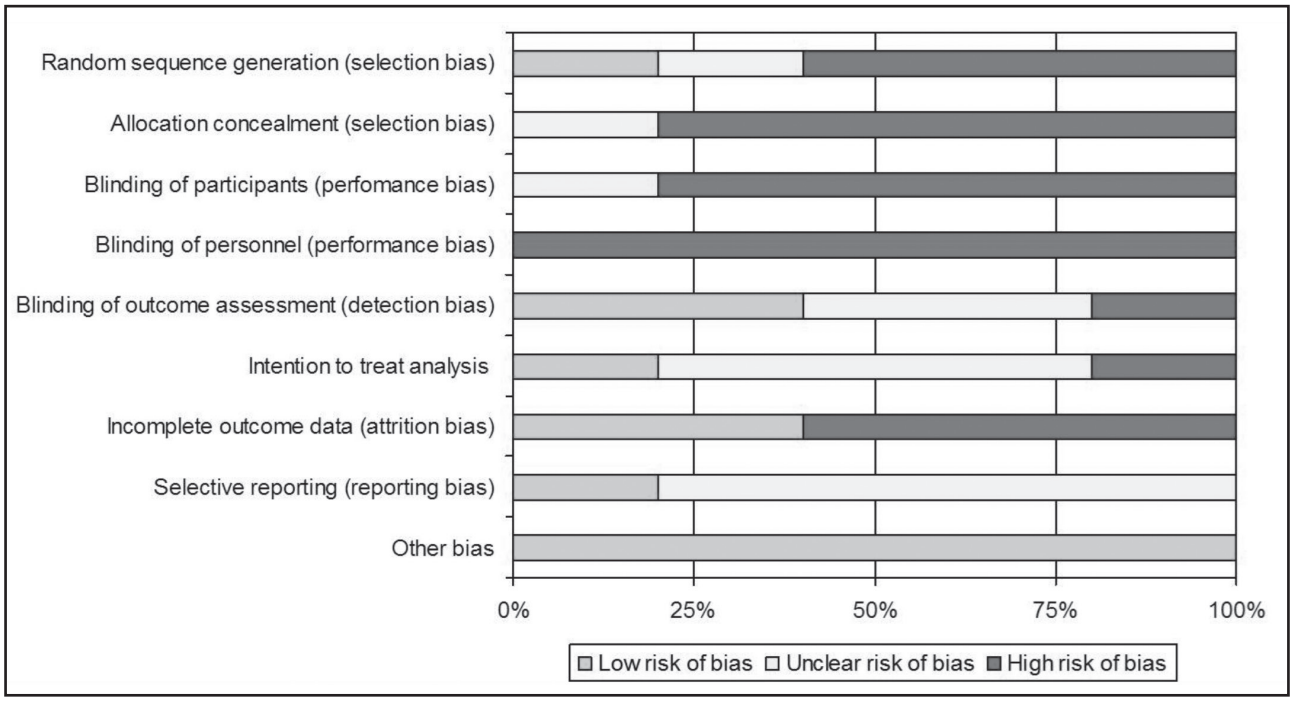

Figure 2.
Risk of bias graph.

EFFECTS ON ENERGY AND PROTEIN INTAKE

Oral intake was measured in all but one study (Beattie et al.). Three of these studies found a positive effect of the intervention on energy or protein intake. In the study by Keele et al., one month after discharge the patients who received ONS in the postoperative period and at discharge ate more calories than those receiving only postoperative ONS or no nutritional support (14). Two months after hospital discharge, ONS at discharge was related to higher energy intake than nutritional support limited to hospitalization. There were no differences in protein intake (14).

Jensen et al. described higher energy (57.8 kcal/kg muscle mass *vs* 47.3 kcal/kg muscle mass, $p = 0.022$) and protein (1.5 g/kg *vs* 1 g/kg, $p = 0.002$) intake in the intervention group (15). A similar result was found by Smedley et al.: patients with nutritional support ate 2,133 kcal and the control group, 1,791 kcal ($p < 0.05$) (19). Nevertheless, Carey et al. did not find significant differences in energy (control 1,956 kcal *vs* intervention 1,723) or protein intake (control 91 g *vs* intervention 69 g) (19).

EFFECTS ON WEIGHT

Weight was assessed in all of the studies, and three of them found positive results with nutritional support (15,17,18). Keele et al. did not detect significant differences in weight among the four arms of the trial (14). The other trial with four different arms detected a better weight maintenance and recovery in subjects who received ONS pre and postoperatively compared with the other groups (18). At the end of the study by Jensen et al., weight gain was significantly better with nutritional support (+4.6 kg *vs* +1.9 kg, $p = 0.014$), and in the trial by Beattie et al. the intervention diminished weight loss (-1.5 kg *vs* -5.9 kg, $p < 0.001$) (15,17). The most recent publication found no differences between groups (-0.9 kg *vs* -3.2 kg, $p > 0.05$) (19).

EFFECTS ON ANTHROPOMETRY AND BODY COMPOSITION

All studies determined anthropometry, but different methodologies were followed. Keele et al. measured mid-arm circumference (MAC), mid-arm muscle circumference (MAMC), and triceps skinfold thickness (TST), but without differences among groups (14). A similar methodology was used by Beattie et al., with favorable results associated with intervention in MAC (-0.42 cm *vs* -1.28 cm, $p < 0.001$) and TST (-0.16 mm *vs* -0.82 mm, $p < 0.001$), and by Smedley, without finding any beneficial result (17,18). Carey et al. described similar changes in arm muscle area among patients allocated to the intervention (+0.4 cm^2) or control (+0.3 cm^2). Nutritional intervention produced a better gain of muscle mass (+3.1 kg *vs* +1.7 kg, $p = 0.014$), measured with dual-energy X-ray absorptiometry (DXA) in the study by Jensen et al. (15).

EFFECTS ON MUSCLE FUNCTION

The effects of nutritional support on body function were assessed in the five studies. Grip strength was the most common

Table III. Main findings of the studies included in the systematic review

Studies	Oral intake	Weight	Body composition	Body function	Complications	QoL	Cost
Keele et al., 1997	Higher energy intake 1-2 months after discharge	NS	NS	NS	NA	NA	NA
Jensen et al., 1997	Higher energy and protein intake with intervention	Higher weight gain with intervention	Higher gain of muscle mass with intervention	NS	NA	NS	NA
Beattie et al., 2000	NA	Less weight loss with intervention	Less loss of muscle and fat mass with intervention	Less loss of grip strength with nutritional support	Less use of antibiotics with intervention	Better physical and mental score with intervention	NA
Smedley et al., 2004	Higher energy intake with intervention	Better evolution with supplementation	NS	NS	Lower complication rate with intervention	NS	NS
Carey et al., 2013	NS	NS	NS	NS	NA	NS	NA

QoL: Quality of life; NA: Not assessed; NS: No significant differences among groups.

method in the studies, but only the study by Beattie et al. found a positive result (14,16,17,19). Those patients randomized to nutritional support lost less muscle strength than controls (-0.82 kg/m^2 *vs* -1.93 kg/m^2, respectively; $p < 0.001$). Jensen et al. measured expiratory forced volume and a fatigue score without finding benefits related to nutritional supplementation (16). A visual analogue scale of fatigue was used by Smedley et al., and there were no favorable results from the intervention (18).

EFFECTS ON QUALITY OF LIFE

Quality of life was evaluated in four studies (16-19). In two cases more than a single questionnaire was used (16,18). Two studies used the SF-36 (17,18), and the General Well Being and Quality of Life (16), EuroQOL (18), and EORTC-QLQ30 were used in the others (19). Two of the studies provided numerical results. Nutritional support yielded a significantly better evolution of the physical (+21.1 pts *vs* +4.1 pts) and mental (+16.0 pts *vs* +0.9 pts) scores of SF-36 (17). There were no significant differences in quality of life measured with EORTC-QLQ30 between the controls and intervention (64% *vs* 58%, $p > 0.05$) in the study by Carey et al. (19).

EFFECTS ON CLINICAL OUTCOMES

None of the selected publications studied clinical outcomes, such as mortality or readmission, after hospital discharge. Fewer patients required antibiotic treatment during hospitalization in the group that received nutritional support than in the control group to nutritional support in the trial by Beattie et al. (7/52 *vs* 15/49, $p < 0.05$) (17). The global rate of complications was inferior when ONS were provided in the study by Smedley et al. (15/35 *vs* 34/44, $p < 0.05$) (18).

COST ANALYSIS

Only one study analyzed the resources consumption (18). The use of ONS tended to reduce costs by 15% per patient episode. The mean cost per patient was £2,289 with ONS before and after surgery, £2,286 with ONS only before surgery, £2,324 with postoperative ONS, and £2,618 in the no-intervention group. These differences were not significant.

DISCUSSION

MAIN FINDINGS

This review analyzed the disposable evidence about the utility of nutritional support in surgical patients when provided after hospitalization. A PICOS strategy was followed and risk of bias systematically assessed for this purpose. The comprehensive search of the literature obtained a very limited number of studies when compared with the extensive research that exists about this issue during hospitalization.

The more consistent result through the different publications was that nutritional support increased energy intake. An increase in protein intake was only described in the study that provided high-protein ONS, but the oral supplements most commonly used in the studies were hypercaloric (15). In addition to this, most trials described a better weight evolution with nutritional intervention that resulted either in more weight gain or in less weight loss during the follow-up. The evolution of weight seemed

to improve when the nutritional intervention included hospitalization and home care. The data about changes in body composition were inconsistent, and the intervention did not enhance muscle strength or quality of life. Only the study of Beattie et al. found positive effects on these parameters of the administration of ONS in the postoperative period and at home (17).

The trials included in this systematic review did not consider clinical outcomes after discharge. In the two studies that analyzed complications during hospitalization, nutritional support reduced antibiotic use and the overall complications in the hospital (17,18). Therefore, the effects of nutritional intervention on readmission, mortality, or other ambulatory outcomes such as infection remain unknown. Finally, the only study that researched the cost-effectiveness of this intervention did not find significant differences in costs with the control group.

Of the included studies, the one by Carey et al. stands out for its complete lack of positive results in any of the measured outcomes (19). This trial stands out for the nutritional care proposed to each group. The usual care provided to the control group consisted of dietary advice and probably included the administration of ONS, whereas the intervention group received more personal and intensive nutritional support. So, the control group probably received a similar nutritional support than intervention groups of the other trials, which can explain the absence of benefits of the provided care.

Two previous meta-analyses have studied if the use of ONS improved outcomes after hospitalization. The first included six trials which recruited mainly elderly patients with an acute disease who were not specifically undergoing surgery. ONS reduced readmissions with an odds ratio of 0.591 (CI 95%, 0.434 to 0.804, $p = 0.001$), independently of age (21). The second included six trials with patients older than 65 years who received ONS after hospitalization due to a medical disease or orthopedic surgery. The intervention caused a significant improvement in nutritional intake and status, but there were no benefits regarding readmission and mortality (22).

LIMITATIONS OF THE REVIEW

This review highlights the shortcomings of the research that has been carried out until now about the utility of nutritional support in surgical patients beyond their hospital stay. Regardless of the number of studies, the analysis of the methodology pointed out severe limitations in the development of the studies. Most studies have a high risk of bias, especially in the items of blinding. If the concealment of intervention in oral nutrition is in practice impossible, the blinding of collaborators, outcomes assessment, and data analysis has to be guaranteed. Furthermore, an intention-to-treat analysis is almost mandatory in a clinical intervention like nutritional support in which compliance can definitively influence results.

A critical point when analyzing the efficacy of nutritional support is the initial nutritional status of patients. Only one of the studies used a validated tool for nutritional assessment like the Subjective Global Assessment (19). The other trials used unsatisfactory methods to evaluate malnutrition (e.g., BMI, NRI), so the obtained results could be influenced by recruiting well-nourished patients. Regarding the measurement of outcomes, several limitations can be signaled. Weight changes can be masked by intravenous fluid administration and edema, which tend to improve after discharge. The assessment of nutritional status by means of circumference and skinfold thickness measurement is subjected to a high inter and intraobserver variability. Only one study used DXA, a more accurate method, for body composition study.

Finally, it is difficult to separate the effects of nutritional support administered during hospitalization and at discharge, as most studies combined both interventions. The study by Smedley et al., who included four different arms with a relatively large sample size, detected a better evolution of weight when ONS were administered during the complete process. Two studies included nutritional support only at discharge. The study by Jensen et al. detected favorable effects on energy intake, weight, and body composition, and was less affected by risk of bias (15,16). The other study, published by Carey et al., has been previously discussed.

FUTURE RESEARCH

New studies should cover the gaps described in the studies of this review. First of all, it is necessary to correctly identify the nutritional status of the patients at the moment of discharge, as well-nourished patients can hardly benefit from nutritional support. Second, nutritional intervention at discharge has to be integrated with nutritional support during hospitalization, a well-established care supported by evidence and several clinical guidelines. Third, a more comprehensive evaluation of nutritional status should be ensured using well-validated and universally recognized tools.

CONCLUSIONS

The methodological limitations of the studies included in this systematic review prevent us from offering firm recommendations about the utility of nutritional support in surgical patients after hospitalization. Nutritional care can ameliorate energy intake and weight, but there are insufficient data about its efficacy on clinical outcomes and quality of life. New studies with a high-quality design are greatly needed.

AUTHORSHIP

AVC performed the search for articles. ACF, RVT, AHM, BPM, and MDBP assessed the articles, extracted the data, and revised the manuscript.

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Nutrición Hospitalaria

Revisión

Nonalcoholic fatty liver disease (NAFLD) pathophysiology in obese children and adolescents: update

Fisiopatología de la enfermedad del hígado graso no alcohólica (EHGNA) en niños y adolescentes obesos: actualización

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Abstract

Objective: Although the nonalcoholic fatty liver disease was first identified in 1980, it presents multifactorial and unclear pathophysiology. In this review, we intend to update the pathophysiological mechanisms of a high morbidity and mortality associated disease that is affecting obese children worldwide.

Data sources: The PubMed and the Cochrane Library databases were used in the search strategy for articles related to nonalcoholic fatty liver disease and published in the last three decades.

Data summary: This review describes the current knowledge on the different mechanisms related to the pathophysiology of nonalcoholic fatty liver disease focused on histological, anatomical and biochemical aspects involved in triggering steatohepatitis and leading to cirrhosis.

Conclusions: The clinical research and advanced technological resources demonstrated several determinants pathophysiological mechanisms of nonalcoholic fatty liver disease trying to assist in their treatment and change its natural course.

Key words:

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

Resumen

Objetivo: aunque la enfermedad de hígado graso no alcohólico se identificó por primera vez en 1980, presenta una fisiopatología multifactorial y mal definida. En esta revisión, tenemos la intención de actualizar los mecanismos fisiopatológicos de esta enfermedad con alta morbilidad y mortalidad asociadas que está afectando a niños obesos en todo el mundo.

Fuentes de datos: las bases de datos PubMed y la Biblioteca Cochrane se utilizaron en la estrategia de búsqueda de los artículos relacionados con la enfermedad de hígado graso no alcohólico publicados en las últimas tres décadas.

Resumen de datos: esta revisión describe el conocimiento actual acerca de los diferentes mecanismos relacionados con la fisiopatología de la enfermedad de hígado graso no alcohólico, con especial énfasis en aspectos histológicos, anatómicos y bioquímicos implicados en el desencadenamiento de la esteatohepatitis y conducentes a la cirrosis.

Conclusiones: la investigación clínica y los recursos tecnológicos avanzados han demostrado diversos mecanismos fisiopatológicos determinantes de la enfermedad de hígado graso no alcohólico, tratando de ayudar en su tratamiento y cambiar su curso.

Palabras clave:

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

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Continuous scientific medical advances in the last decades provide new insights on the pathophysiology of some intriguing health problems such as nonalcoholic fatty liver disease (NAFLD). First described in 1980 (1), NAFLD is a disease characterized by the accumulation of fat in the cytoplasm of hepatocytes, not related to alcohol, causing the so called fatty liver (2). The presence of at least 5% of affected hepatocytes in biopsies' fragments provides the histopathologic diagnosis of fatty liver (3). This condition is characterized as a spectrum ranging from liver steatosis to steatohepatitis (characterized by inflammation and fibrosis), and finally cirrhosis. It is, therefore, a serious condition that can cause liver failure in a short period of time (4). NAFLD is now the most common form of chronic liver disease and its prevalence is rapidly growing around the world (5). The real prevalence of NAFLD in the pediatric population is still unknown and variable, with a range of prevalence from 3.0 to 60.3% in obese children and adolescents. Its physiopathological mechanisms are not yet fully understood, although it is recognized to be increasing especially among overweight children and adolescents, with at least 50% of them presenting some degree of NAFLD (6). NAFDL prevalence is variable depending on the region, surveyed population and the mode of NAFLD diagnosis. In Europe, the prevalence of NAFLD is estimated to be 25% (7). In the United States it is estimated to be 34% in adults (8) and 10-20% in children (9). In Asia, rates about 30% are reported, despite the lower body mass index (BMI) (10). The available evidence on NAFLD-associated morbidity and mortality demonstrates that children affected by NAFLD are at increased risk of death or undergoing a liver transplant when compared to children of the same age and sex but without the disease (11). The natural history of NAFLD in children reveals a progressive evolution of the disease, leading to the development of liver cirrhosis in an expressive percentage of this population (12). NAFLD is closely related to obesity, environmental/nutritional factors, and genetic predisposition (3). Obesity, a chronic and prevalent nutritional disorder in the world, is often associated with fatty liver, hypertension, insulin resistance and dyslipidemia (13). It affects several age groups, including children and adolescents. In a murine model, obesity-induced steatosis led to an increased oxidative stress, as well as chronic inflammation of the liver (14). Insulin resistance, a frequent condition in obese patients, has a key role in the pathophysiology of NAFLD (15). Similarly, the high food intake common to obesity can cause changes in the intestinal flora, with lipid metabolism injury causing fatty liver (16). Laboratory findings in obese individuals showed increased levels of inflammatory markers, acute phase inflammation proteins, hormones, free radicals and other endothelial activation factors. This fact demonstrates the existence of an underlying inflammatory condition, determining the onset of NAFLD (17). In this review, current and comprehensive data to explain the pathophysiology of NAFLD, especially in obese children and adolescents, are described. In this population the evolution of NAFLD is more insidious than in adults, probably due to the fact that this age group does not present proper mechanisms of adaptation to metabolic changes caused by obesity. On the other hand, this population is supposedly more susceptible to therapeutic interventions, making them a candidate to new treatment strategies to prevent evolution to end-stage liver disease.

METHODS

We reviewed the literature related to the topic of obesity and nonalcoholic fatty liver disease (NAFLD) available in the PubMed database, published in Portuguese and English by 2016, using the following descriptors: "non-alcoholic fatty liver disease; "fatty liver"; "obesity". The articles included involved children and adolescents of both sexes, exogenous obesity carriers and some of its comorbidities. Coincident articles and those who did not contribute methodologically to the scope of this research were excluded. The search strategy in SciELO and Medline databases using the same descriptors did not result in articles of interest for review. Thus, the search resulted in 53 articles, and after reading them, 40 were selected because they were closer to the scope of this article, which focused on two important pediatric metabolic disorders, NAFLD and obesity.

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) PATHOPHYSIOLOGICAL ASPECTS RELATED TO OBESITY IN CHILDREN AND ADOLESCENTS

The exact mechanism that determines NAFLD remains unknown, although evidence shows that this disorder develops from primary metabolic abnormalities determined by inflammatory cytokines, insulin resistance and oxidative stress commonly found in obese patients (18). In a broader approach, obesity alters hepatic metabolism triggering one histopathological sequence of events characterized by the death of steatotics liver cells and release of enzymes that culminate in focal and non-specific inflammation (19). Additionally, in NAFLD, an accumulation of lipids in the cytoplasm of hepatocytes in the form of vacuoles which are organized by determining the fatty infiltration of the liver known as steatosis occurs, which in turn progresses to an inflammatory frame (steatohepatitis), with resulting fibrosis and liver cirrhosis (20). In the long run, NAFLD may progress to hepatocellular carcinoma (21).

According to the consensus published by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition 2012 (22), NAFLD is defined as follows:

- *NAFLD:* the simplest form of steatosis, with moderate levels of inflammation.
- *Nonalcoholic steatohepatitis (NASH):* accumulation of macrovacuolar intra hepatocyte with periportal inflammation, hepatocellular ballooning and perisinusoidal fibrosis.
- *Cirrhosis:* fibrosis in advanced stage with loss of liver structure.

The natural history of NAFLD shows that different mechanisms contribute in parallel to the development of NAFLD and its evolution to inflammation and fibrosis (23). Basically, the disease is the

result of the imbalance between supply and use of triglycerides and free fatty acids (FFA) in the liver and impairment of beta-oxidation of free fatty acids, which causes lipid deposits in the cytoplasm of hepatocytes (24).

Below, we summarize some of these mechanisms.

OBESITY

Obesity, especially central obesity, often progresses to hepatic steatosis. In obese individuals we see a chronic, low grade, inflammatory condition mediated by inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), as well as leptin and adiponectin, which add a significant contribution (25). Fatty liver impairment disrupts homeostasis by increasing in release of inflammatory and non-inflammatory cytokines (26). This triggers a cascade of hepatocyte injury, with production of more inflammatory mediators that leads to an impairment of liver metabolic capacity.

INSULIN RESISTANCE

Insulin resistance is a key mechanism for the development of NAFLD in both adults and children. It is observed that in children, insulin resistance is associated with compensatory hyperinsulinemia. The association of hepatic insulin resistance with hyperinsulinemia impairs the mitochondrial oxidation process of free fatty acids and lipid peroxidation, and results in the formation and accumulation of toxic lipid metabolites such as reactive oxygen species (ROS), which causes oxidative stress and hepatocellular injury (27). Dietary factors such as high glycemic index intake and high intake of fatty meals that would jeopardize the metabolism of carbohydrates are theories proposed to explain the complex mechanism by which insulin resistance could cause the appearance of fatty liver in obesity. This diet elicits insulin release, resulting in increased plasma and hepatocellular concentrations of free fatty acids (FFA) (28). NAFLD in children would be aggravated by decreased plasma adiponectin. Adiponectin attenuates insulin action on insulin receptors through its anti-inflammatory action, preventing hepatocellular damage by free fatty acids. On the other hand, the high TNF-α leads to increased insulin resistance and mitochondrial production of reactive oxygen species (ROS), as well as decreased plasma levels of antioxidants such as glutathione peroxidase (29).

GUT MICROBIOTA (INTESTINAL FLORA)

The normal intestinal flora is made up of a multitude of bacteria living in balance, performing important functions, including the immune defense. Disruption of this balance *(dysbiosis)* would increase the passage of toxins into the portal circulation, causing local inflammation, with release of inflammatory markers (30). The intestinal microbiota also influences the secretion of biliary acids, which have a regulatory function in the digestion and metabolism of nutrients such as carbohydrates and lipids (31,32). Some available evidence suggests that alterations in the intestinal flora can lead to the development of NAFLD, and that the expression of the disease would be influenced by biliary acids (33). Studies indicate that *dysbiosis* secondary to obesity could act as a determinant of the pathophysiology of NAFLD in children and adults (34-36).

GENETIC FACTORS

The influence of genetic factors determining NAFLD is not well elucidated, although the role of interaction between genes and environment on the onset of metabolic diseases is recognized. Genetic polimorfirms (PAI-I 6754G/5G and PPAR-γ2 Pro12Ala, among others) indicate a potential association with insulin resistance and obesity in children (37). Genetics plays a key role in Wilson's disease, an inherited disorder of copper metabolism in which children present predominantly hepatic manifestations (38). Ethnic background explains the variable predisposition to the development of NAFLD, which has a clearly greater frequency among Hispanics and Asians while it is lower among children of African origin (39).

OTHER NAFLD MECHANISMS

Hereditary hemochromatosis, autoimmune hepatitis, and α1-antitrypsin deficiency are also implicated in the pathogenesis of NAFLD (40).

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Nutrición Hospitalaria

Revisión

Efectos del té verde y su contenido de galato de epigalocatequina (EGCG) sobre el peso corporal y la masa grasa en humanos. Una revisión sistemática

Effects of green tea and its epigallocatechin (EGCG) content on body weight and fat mass in humans: a systematic review

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Resumen

La prevalencia e incidencia del sobrepeso y la obesidad continúan en aumento a nivel mundial, así como las enfermedades relacionadas con estas condiciones. Ello se atribuye a un incremento en la ingesta de energía y una disminución en el gasto de la misma. El consumo de té verde se ha relacionado con una reducción en la grasa y el peso corporal. Sin embargo, las investigaciones realizadas con el té verde han sido muy diversas. Esta revisión sistemática explora las investigaciones que se han realizado con té verde y su contenido de galato de epigalocatequina (EGCG) evaluando su efecto sobre la grasa y el peso corporal en humanos. Se realizó una búsqueda en las bases de datos PubMed y Web of Science que dio como primer resultado un total de 424 artículos potenciales. Fueron excluidos 409, por lo que se utilizaron 15 artículos para esta revisión sistemática. Las investigaciones han sido muy diversas; sin embargo, el consumo diario de té verde con dosis de EGCG entre los 100 y los 460 mg/día ha mostrado mayor efectividad sobre la reducción de masa grasa y peso corporal en periodos de intervención de 12 semanas o más. Además, la utilización de dosis de cafeína entre 80 y 300 mg/día ha mostrado ser un factor de importancia para los efectos obtenidos, siempre y cuando los participantes no tuviesen previo a la intervención una ingesta habitual de cafeína alta (> 300 mg/día).

Palabras clave:

Té verde. Galato de epigalocatequina. Peso corporal. Composición corporal. Cafeína. Masa grasa.

Abstract

The prevalence and incidence of overweight and obesity worldwide continues to increase, as well as diseases related to these conditions. This is attributed to an increase in energy intake and a decrease in energy expenditure. Consumption of green tea has been linked to a reduction in body fat and body weight. However, research on green tea has been very diverse. This review assesses the investigations that have been made with green tea and its epigallocatechin gallato (EGCG) content, evaluating its effect on body fat and body weight in humans. A search was made in the PubMed and Web of the Science databases that gave a first total result of 424 potential articles; 409 were excluded and 15 articles were used for this systematic review. Research has been very varied, however, daily consumption of green tea with doses of EGCG between 100 and 460 mg/day has shown greater effectiveness on body fat and body weight reduction in intervention periods of 12 weeks or more. In addition, the use of caffeine doses between 80 and 300 mg/day has been shown to be an important factor for this effects, when the participants did not have a high caffeine intake (> 300 mg/day) prior to the intervention.

Key words:

Green tea. Epigallocatechin gallate. Body weight. Body composition. Caffeine. Body fat.

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INTRODUCCIÓN

La incidencia y prevalencia de sobrepeso y obesidad a nivel mundial se incrementan con características epidémicas (1). Algunos autores señalan que las causas de la obesidad son múltiples, y proponen diversos factores de riesgo para el desarrollo de esta condición (2,3). Estos factores de riesgo llevan a un balance energético positivo que es resultado de una ingesta energética cada vez mayor y un gasto energético reducido.

Se ha propuesto que el té verde *(Camellia sinensis)* tiene un efecto en la reducción del peso corporal (4) que está relacionado con su contenido de catequinas: epigalocatequina-3-galato (*epigallocatechin-3-gallate* EGCG), epigalocatequina (*epigallocatechin* EGC), epicatequina galato (*epicatechin gallate* ECG), y epicatequina (*epicatechin* EC), siendo el EGCG el más abundante, además de ser el compuesto más activo farmacológicamente (5-7). Adicionalmente, se ha descrito que el EGCG inhibe la proliferación y diferenciación de adipocitos en estudios *in vitro* (7).

El té verde contiene además cafeína, la cual también ha sido asociada a la disminución y control del peso corporal en humanos, por medio de la estimulación de la termogénesis y la oxidación de las grasas (8). Esta bebida que se prepara con las hojas de la planta *Camellia sinensis,* se consume ampliamente en el mundo (9). Las investigaciones que involucran la utilización de té verde o EGCG son muy variadas, han utilizado diversas dosis de extracto de té verde, EGCG, cafeína, etc. Además, en su realización han participado sujetos con diversas características en periodos de intervención diferenciales. El objetivo de esta revisión fue evaluar la literatura existente respecto de los efectos del té verde y su contenido de EGCG sobre la masa grasa y el peso corporal en humanos.

MÉTODO DE BÚSQUEDA DE LITERATURA

Para la elaboración de esta revisión, se llevó a cabo una búsqueda de artículos durante cuatro meses (enero a abril de 2016) a través de las bases de datos PubMed y Web of Science, sin utilizar ningún criterio temporal para la búsqueda. Se utilizaron los términos MeSH: *"tea" AND "body weight" OR "adipose tissue" OR "body composition".* Adicionalmente, se realizaron búsquedas con los términos *"epigallocatechin gallate" OR "epigallocatechin 3 gallate" AND "caffeine" AND "body weight" OR "adipose tissue" OR "body composition".*

Además, la selección de artículos se llevó a cabo considerando los siguientes criterios de inclusión: a) debían ser ensayos clínicos; b) haberse realizado en humanos; c) ser originales; d) ser aleatorizados; e) haber utilizado té verde o extracto de té verde en al menos uno de sus grupos; y f) reportar la dosis de EGCG utilizada.

De los 199 artículos identificados en PubMed originalmente, se excluyeron: a) 61 por no ser relevantes para la temática; b) 50 por no ser artículos originales (revisiones, revisiones sistemáticas y metaanálisis); c) 18 por utilizar combinaciones de sustancias (guaraná, taurina, etc.); d) 33 por estar duplicados; e) 12 debido a que utilizaban un tipo de té diferente al té verde; f) siete por no especificar dosis de EGCG; y g) cuatro por presentar investigaciones sobre efectos agudos que comprendían de algunas horas a un par de días y no presentar, por tanto, efectos sobre peso o composición corporal, contando al final con 14 artículos de esta base de datos.

En cuanto a la búsqueda en la base de datos Web of Science, de los 225 artículos identificados originalmente, se excluyeron: a) 192 por no ser relevantes para la temática; b) 13 por ser repetidos; c) dos por presentar efectos agudos; d) tres por utilizar combinaciones de sustancias (guaraná, taurina, etc.); e) dos por ser de modelos animales; f) cinco por no especificar dosis; g) seis por no ser originales; y h) uno por no ser ensayo clínico. Por lo tanto, se tomó en cuenta un artículo de esta base de datos.

Para la realización de esta revisión sistemática se contó con 15 artículos originales (Fig. 1). Aunque no se utilizó ningún criterio temporal para la búsqueda, después de excluir los artículos por los criterios mencionados, los documentos restantes se encontraron en el periodo de tiempo comprendido entre el año 2004 y el 2015.

RESULTADOS DE LOS ESTUDIOS REVISADOS

INDIVIDUOS ESTUDIADOS

De los 15 estudios analizados (Tabla I) más de la mitad (nueve) (5,9,10-16) incluyeron hombres y mujeres, cinco (7,17-20) se enfocaron específicamente en mujeres y uno (6), solo en hombres.

La investigación que comprendió la mayor cantidad de participantes fue la de Nagao y cols., (15) con 240 individuos, seguida de la de Brown y cols., (6) con 135. De los 15 estudios que comprendió esta revisión, 14 tuvieron participantes con obesidad y/o sobrepeso; de estos 14 estudios, uno incluía, además, entre las características de los sujetos el presentar síndrome metabólico (5).

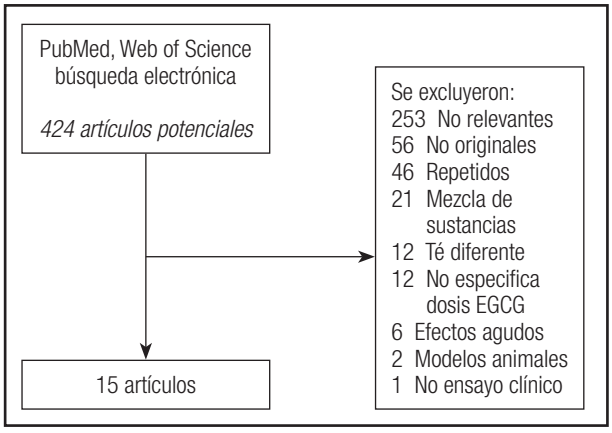

Figura 1.

Cuadro de flujo de la selección de estudios respecto a los efectos del té verde sobre el peso y la composición corporal.

Tabla I. Investigaciones que evaluaron el efecto del té verde y su contenido de EGCG sobre el peso y la composición corporal en humanos

Referencia	Tipo de estudio (duración de la intervención)	Condición de individuos	Grupos (n) Mujeres/ Hombres	Edad promedio	Dieta	Suplementación y dosis diaria			Cambios al finalizar el estudio				
						Suplemento	EGCG (mg/ día)	Cafeína (mg/ día)	Grasa corporal (%)	Grasa corporal (kg)	Circunferencia cintura (cm)	IMC (kg/m²)	Peso corporal (kg)
Auvichayapat y cols., 2008	Aleatorizado, paralelo (12 s)	Obesidad	PLAC (30) 21/9	48,95 ± 4,96	Thai: 65% CH 15% PS 20% LPS	3 cápsulas PLAC	0	0	↓2,77	NE	↓4,23	↓1,88	↓2
			GTE (30) 21/9	48,53 ± 5,50		3 cápsulas GTE	100,74	86,58	↓3,8	NE	↓3,86	↓2,47	↓2,7*#
Basu y cols., 2010	Aleatorizado, paralelo, simple-ciego (8 s)	Obesidad + MeS	Control (12) 10/2	44,6 ± 3,2 (25-63)	Dieta y estilo de vida habitual	4 tazas agua	0	0	NE	NE	NE	NE	NE
			GT (13) 10/3	42,8 ± 2,6 (28-59)		4 tazas GT	440,00	8,96	↓0,3 ± 0,9	NE	↑1 ± 2,3	↓0,9 ± 0,3**	↓2,5 ± 0,7**
			GTE (10) 7/3	39,5 ± 3,0 (27-52)		4 tazas agua + 2 cápsulas GTE	460,00	3,60	↑0,2 ± 1,3	NE	↓4,1 ± 2,5	↓0,7 ± 0,2*	↓1,9 ± 0,6*
Brown y cols., 2011	Aleatorizado, control placebo, doble ciego, cruzado (6 s cada periodo)	Sobrepeso/ obesidad	PLAC (69) 0/69	49,4 ± 5,6	Dieta y estilo de vida habitual	PLAC	0	0	NE	NE	NE	NE	↑ 0,53± 1,9
			DGT (66) 0/66	49,5 ± 5,6		DGT	212	0	NE	NE	NE	↓0,327 ± 1,89*	↓0,64 ± 2,2
Chan y cols., 2006	Aleatorizado, paralelo (3 m)	Obesidad + PCOS	PLAC (16) 16/0	34,8 ± 4,2	Libre de cafeína	6 cápsulas PLAC	0	0	↑1,6	NE	NE	↑0,7	↑1
			GT (18) 18/0			6 cápsulas GT	540	158,7	↓0,2	NE	NE	↓0,3	↓1,8
Diepvensy cols., 2006	Aleatorizado doble ciego, paralelo (87 días)	Sobrepeso	PLAC (23) 23/0	41,6 ± 10,0	LED	9 cápsulas PLAC (maltodextrina)	0	236,7	↓3#	↓3,9##	↓3,6##	↓1,5##	↓4,2##
			GT (23) 23/0	41,7 ± 8,6		9 cápsulas GTE	595,8	236,7	↓3,2##	↓3,8##	↓4,5##	↓1,5##	↓4,2##
Dostal y cols., 2015	Aleatorizado, paralelo, doble ciego, control placebo (12 m)	Sobrepeso/ obesidad + Postmenopausia	PLAC (60) 60/0	60,0 ± 0,65	NE	2 cápsulas PLAC	0	0	↓0,15± 0,16	↓0,12 ± 0,15	NE	↓0,05 ± 0,11	NE
			GTE (61) 61/0	60,7 ± 0,60		2 cápsulas DGTE	843	< 16	↓0,15 ± 0,17	↓0,30 ± 0,16	NE	↓0,13 ± 0,11	NE
Hsu y cols., 2008	Aleatorizado, paralelo, doble ciego (12 s)	Obesidad	PLAC (37) 37/0	43,9 ± 12,6	Dieta habitual	3 cápsulas Placebo	0	0	NE	NE	↓1,3	↓0,006	↓0,03
			GTE (41) 41/0	43,0 ± 11,1		3 cápsulas 400 mg GTE	302	27,3	NE	NE	↓1,7#	↓0,06	↓0,15

(Continúa en la página siguiente)

Tabla I (Cont.). Investigaciones que evaluaron el efecto del té verde y su contenido de EGCG sobre el peso y la composición corporal en humanos

Referencia	Tipo de estudio (duración de la intervención)	Condición de individuos	Grupos (n) Mujeres/ Hombres	Edad promedio	Dieta	Suplementación y dosis diaria			Cambios al finalizar el estudio				
						Suplemento	EGCG (mg/ día)	Cafeína (mg/ día)	Grasa corporal (%)	Grasa corporal (kg)	Circunferencia cintura (cm)	IMC (kg/m^2)	Peso corporal (kg)
Hursel y cols., 2009	Aleatorizado, control placebo, doble ciego, paralelo (16 s)	Sobrepeso/ obesidad	AP + PLAC (20) 11/9	44 ± 2	VLED (4 s) + 50-60g proteína/ día (3 m)	Placebo	0	0	↓2	↓3,1	↓4,1	↓1,6	↓4,1
			HP + PLAC (20) 11/9		VLED (4 s) 100-120 g proteína/ día (3 m)	Placebo	0	0	↓4,2	↓5,4	↓7	↓2,4	↓6,6
			AP + GTE (20) 11/9		VLED (4 s) + 50-60g proteína/ día (3 m)	GTE	270	150	↓4,2	↓5,9	↓7,2	↓2,6	↓7,1
			HP + GTE (20) 11/9		VLED (4 s) 100-120 g proteína/ día (3 m)	GTE	270	150	↓4,1	↓4,3	↓7,2	↓2,4	↓6,6
Kovacs, y cols., 2004	Aleatorizado, paralelo (17 s)	Sobrepeso/ obesidad	PLAC (53) 41/11	18-60	VLED (4 s) + WM (13 s)/ placebo	Placebo	0	0	↓3,8#	↓5,1#	↓7,1#	↓2,1#	↓5,9#
			GT (51) 36/15		VLED (4 s) + WM (13 s)/GT	GT	323	104	↓2#	↓2,9#	↓4,6#	↓1,5#	↓4,1#
Maki y cols., 2009	Aleatorizado, doble ciego (12 s)	Sobrepeso/ obesidad Sedentarismo	Control (63) 28/35	49,0 ± 1,3	Evitar té, alimentos y suplementos que contengan catequinas	Cafeína	0	39	NE	↓3,5%	NE	NE	↓1
			Catequinas (65) 33/32	47,0 ± 1,3		Catequinas + cafeína	214,4	39	NE	↓5,2%	NE	NE	↓2,2
Mielgo-Ayuso y cols., 2014	Randoizado, doble ciego, paralelo (12 s)	Obesidad	Control (40) 40/0	18-49	LED (55% CH, 30% LPS, 15% PS) RMR-600 Kcal	PLAC	0	0	NE	↓4,6	↓4	↓3	↓7,7
			EGCG (43) 43/0			GTE	300	0	NE	↓4,9	↓5	↓3	↓7,6
Nagao y cols., 2007	Aleatorizado doble ciego, paralelo multi-centro (12 s)	Sobrepeso/ obesidad	Control (117) 49/68	41,7 ± 9,9	Ingesta dietética y actividad física habitual	Bebida enlatada con 96 mg catequinas	16	75	↓0,7 (2,8)*	↓0,5 (2,3)	0,0 (2,5)	↓0,0 (0,6)	↓0,1 (1,7)
			Catequinas (123) 51/62			Bebida enlatada con 583 mg catequinas	100	72,3	↓ 2,5 (3,3)*	↓2,3 (2,6)	↓2,5 (2,2)	↓0,6 (0,6)	↓1,7 (1,5)

(Continúa en la página siguiente)

Tabla I (Cont.). Investigaciones que evaluaron el efecto del té verde y su contenido de EGCG sobre el peso y la composición corporal en humanos

Referencia	Tipo de estudio (duración de la intervención)	Condición de individuos	Grupos (n) Mujeres/ hombres	Edad promedio	Dieta	Suplementación y dosis diaria			Cambios al finalizar el estudio				
						Suplemento	EGCG (mg/ día)	Cafeína (mg/ día)	Grasa corporal (%)	Grasa corporal (kg)	Circunferencia cintura (cm)	IMC (kg/m²)	Peso corporal (kg)
Nagao y cols., 2009	Aleatorizado controlado, doble ciego, paralelo (12 s)	Normopeso/ sobrepeso + DM2 + no recibe insulina	Control (20) 10/10	62,8 ± 2,2	NE	96,3 mg catequinas	16	75	↑0,8 (0,3)	NE	↑0,1 (0,5)	↑0,1 (0,1)	↑0,2 (0,3)
			Catequinas (23) 15/8	64,9 ± 1,6		582,8 mg catequinas	100	72,3	↑0,2 (0,3)	NE	↓3,3 (1,1)	↓0,1 (0,2)	↓0,2 (0,5)
Suliburska y cols., 2012	Aleatorizado, doble ciego, control placebo (3 m)	Obesidad	PLAC (23) 11/12	52,26 ± 7,71	NE	1 cápsula PLAC	0	NE	NE	NE	↑0,04	↓0,09	NE
			GTE (23) 12/11	48,56 ± 8,81		1 cápsula: 379 mg GTE	208	NE	NE	NE	↓0,63	↓0,36	NE
Yang y cols., 2012	Aleatorizado, controlado (8 s)	Obesidad/ sobrepeso	Control (15) 8/7	25,5 ± 1,5	7.531-8.368 kJ/día	Bebida control (8,5 g GT) (650 ml/día) + inulina	81	NE	NE	↓0,3	0	↓0,1	↑0,1
			Experimental (15) 8/7	27,6 ± 2,1		Bebida experimental (28 g GT) (650 ml/día)	267	NE	NE	↓1,4#	↓2	↓0,6#	↓1,29#

*AP: adecuada en proteína; CH: carbohidratos; PS: proteínas; LPS: lípidos; DGT: extracto de té verde descafeinado; DGTE: extracto de té verde descafeinado; DM2: diabetes mellitus tipo 2; EGCG: galato de epigalocatequina; GT: té verde; GTE: extracto de té verde: HP: alta en proteína; IMC: índice de masa corporal; KJ: kilojulio; LED: dieta baja en energía; m: meses; MeS: síndrome metabólico; NE: no evaluado; PCOS: síndrome de ovario poliquístico; PLAC: placebo; RMR: taza metabólica basal; s: semanas; Thai: tailandesa; VLED: dieta muy baja en energía; WM: mantenimiento del peso. *Las diferencias entre grupos fueron estadísticamente significativas (p < 0,05). **Diferencias entre grupos estadísticamente significativas (p < 0,01). #Diferencias estadísticamente significativas a los valores presentados en línea base (p < 0,05). ##Diferencias estadísticamente significativas a los valores presentados en línea base (p < 0,01).*

En otra investigación, realizada exclusivamente con mujeres (4), se incluía la característica de que las participantes presentaban síndrome de ovario poliquístico. El último estudio se llevó a cabo con pacientes que presentaban diabetes mellitus tipo 2 y no recibían insulina, en este estudio cabe mencionar que al inicio de la intervención el grupo control presentaba un índice de masa corporal (IMC) promedio de 24, es decir, normopeso, mientras que el grupo experimental presentaba un IMC promedio de 25,6, que se clasifica en grado de sobrepeso (14).

DISEÑOS DE LOS ESTUDIOS Y DURACIÓN

Los estudios seleccionados para la realización de la presente revisión fueron en su totalidad aleatorizados. De ellos, 14 tuvieron un diseño paralelo (1-5,7-15) y uno tuvo diseño cruzado (6). La duración de las investigaciones fue desde seis semanas cada periodo de intervención (6), encontrando dos estudios con una duración de ocho semanas (5,9), uno con una duración de 87 días (18), ocho (más de la mitad) con una duración de 12 semanas (7,10,13-17,20), uno llevado a cabo durante 16 semanas (11), y otro, durante 17 semanas (12), hasta llegar al de mayor duración, que comprendía 12 meses (19).

TRATAMIENTOS CONTROL Y DE INTERVENCIÓN

El té verde y su contenido de EGCG fueron administrados en diferentes presentaciones y dosis. Algunas investigaciones utilizaron extracto de té verde y otras, extracto de té verde descafeinado (6,19). Las dosis de EGCG fueron desde 100 mg (14,15) hasta 843 mg por día (19) en los grupos de intervención, mientras que en los grupos control fueron de 0 mg por día (5-7,10-13,16-20) y dos estudios refirieron dosis de 16 mg (14,15) por día. Por otro lado, en cuanto al contenido de cafeína, Basu y cols. (5) realizaron un estudio con un producto descafeinado que, sin embargo, contenía 8,96 y 3,6 mg de cafeína para los grupos experimentales, mientras que en las investigaciones que no utilizaron té verde o extracto de té verde descafeinado, el contenido de cafeína consumido con el suplemento proporcionado en los grupos experimentales fue de 39 a 236,7 mg/día. Si bien se muestran efectos de las intervenciones aun en investigaciones donde se utilizaron suplementos descafeinados (6), las tendencias a la disminución en el peso y la masa grasa corporales se observan mayores con la combinación del EGCG y la cafeína (11,18,15). Sin embargo, respecto a la adición de cafeína, autores como Kovacs y cols. (12) refirieron que el efecto del EGCG puede incrementarse en los participantes al combinarlo con cafeína, siempre y cuando los participantes no hubiesen tenido, previa a la intervención, una ingesta habitual de cafeína alta (> 300 mg/día). Si tal es el caso y la dosificación de cafeína durante la intervención resulta menor que la ingesta previa, el restringir o disminuir la cafeína durante la intervención en estos participantes puede enmascarar o disminuir el efecto de la combinación EGCG-cafeína.

DIETAS

El aspecto del control dietético, al igual que otros descritos previamente, fue muy variable. Así, observamos que seis investigaciones (5-7,13,15,17) indicaron a los participantes dieta habitual; sin embargo, a pesar de esta recomendación, entre ellas algunas especificaron características restrictivas como evitar té, alimentos y suplementos que contienen catequinas (13) o dieta libre de cafeína (17), mientras que dos investigaciones no especificaron ningún tipo de dieta o restricción dietética (14,16). Las investigaciones que controlaron la ingesta fueron la de Diepvens y cols., (18) en la cual se proporcionó una dieta baja en energía; la de Hursel y cols., (11) donde se proporcionó dieta muy baja en energía; y la de Yang y cols., (9) en la cual se proporcionaron de 7.531 a 8.368 kJ/día.

DIFERENCIAS ENTRE GRUPOS

Las diferencias entre grupos controles y experimentales solo se reportaron estadísticamente significativas en cinco de los estudios (5,6,10,14,15); sin embargo, esta significancia no se reportó en todas las variables medidas. Así, de manera específica, en la investigación de Auvichayapat y cols. (10) solo se reportó diferencia estadísticamente significativa respecto al peso corporal, con menores valores en el grupo expuesto al extracto de té verde (GTE), mientras que en el estudio de Basu y cols. (5) se reportó para el IMC y peso corporal final de los grupos expuestos al té verde (GT) y GTE, al compararlos con el grupo control. En la investigación de Brown y cols. (6) se reportó diferencia significativa en el IMC final, mientras que en el estudio de Nagao y cols. (15) se reporta para el porcentaje de grasa corporal y en el de Nagao y cols., (14) en la circunferencia de cintura.

Además, es de suma importancia subrayar que en numerosas investigaciones, las cuales se especificarán enseguida, se reportó la diferencia significativa intragrupo, es decir, diferencias estadísticamente significativas al comparar los valores finales de cada grupo con los registrados por el mismo grupo en la línea base. Así, Auvichayapat y cols. (10) reportaron diferencia significativa en el peso corporal final del grupo GTE al compararlo con los valores de la línea base. Diepvens y cols. (18) reportaron estas diferencias significativas intragrupo en ambos grupos (placebo y GT) en peso corporal, IMC, circunferencia de cintura, kilogramos y porcentaje de masa grasa, al comparar los valores iniciales con los finales. Hsu y cols. (7) reportaron estas diferencias significativas intragrupo en circunferencia de cintura del grupo experimental. Kovacs y cols. (12) reportaron diferencias significativas en los valores de porcentaje y kilogramos de masa grasa, circunferencia de cintura, índice de masa corporal y peso corporal al comparar los valores al término de la intervención con los valores en línea base, tanto en el grupo experimental como en el control. Yang y cols. (9) reportaron estas diferencias significativas en los valores finales de grasa corporal, IMC y peso corporal solo del grupo experimental al compararlos con sus valores en la línea base.

DISCUSIÓN

Las investigaciones con té verde han sido muy variadas, sin embargo, las dosis que han mostrado mayor efectividad sobre la grasa y el peso corporal se encuentran en el rango entre los 100 mg/día, cuando la dieta es controlada y se utiliza el suplemento por un mínimo de 12 semanas (10), y los 460 mg/día (5), aunque la recomendación dietética se limite al mantenimiento de la dieta habitual. Además, la utilización de dosis de cafeína no se presenta como indispensable para el efecto (10), aunque se le puede atribuir un efecto sinérgico cuando se presenta en dosis que van desde 80 mg/día (10) hasta 200 mg/día (18) aproximadamente. Adicionalmente, en cuanto a la cafeína, cabe mencionar que algunos investigadores como Kovacs y cols. (12) han referido que la ingesta alta habitual de cafeína (> 300 mg/día) de los participantes, previo a la intervención con té verde, puede tener un efecto, reduciendo la eficacia de tratamiento.

CONCLUSIONES

Las investigaciones que se han realizado respecto al efecto del consumo de té verde y su contenido de EGCG sobre la composición y el peso corporal han sido muy variadas. Se han utilizado diversas dosis, tanto de té como de su contenido de EGCG y de cafeína. Además, las características de los participantes, incluidos sexo, edad, condiciones patológicas o de salud, peso corporal inicial y otras, han sido también diversas. Sin embargo, es evidente que las intervenciones de 12 semanas o más muestran una mayor tendencia hacia una disminución de peso y grasa corporal, siempre y cuando las dosis de EGCG se mantengan entre 100 y 460 mg/día. Asimismo, la adición de cafeína entre los 80 y los 300 mg/día pudo incrementar el efecto del té verde, siempre y cuando los participantes no hubiesen tenido previo a la intervención una ingesta habitual de cafeína alta (> 300 mg/día). Sin embargo, sería importante analizar la tolerancia a la cafeína en los pacientes antes de la intervención para evitar efectos adversos.

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Nutrición Hospitalaria

Artículo Especial

La red de promotores de salud como estrategia de educación alimentaria: el ejemplo del Programa EDALNU (1963-1994)

The health educator network as a nutrition education strategy: the example of the EDALNU programme (1963-1994)

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Resumen

La educación en alimentación y nutrición es una herramienta fundamental para garantizar la salud. En 1961, se puso en marcha el Programa de Educación en Alimentación y Nutrición (EDALNU), que ayudó a la población española a completar su transición alimentaria y nutricional. El objetivo de este trabajo es analizar las características de la red de promotores de salud que se desarrolló en el marco del programa.

Recibieron formación relacionada con alimentación y nutrición 46.752 personas, el 94% de ellas mujeres. El 89,54% obtuvo el título de iniciado y el 8,80%, el de diplomado. Se realizaron 1.407 acciones y en 1979 se alcanzó el momento más álgido, con 131 cursos y 4.029 alumnos. Madrid, con el 26,65% de cursos; Valencia, con el 7,60%; Murcia, con el 7,53%, y Málaga, con el 6,75%, fueron las provincias más activas. El Ministerio de Cultura y Educación fue el encargado de organizar el mayor número de cursos (26,23%), seguido de Sección Femenina (11,16%) y Acción Católica (5,12%). La duración y los contenidos formativos de los cursos eran de 160 horas para los diplomados y 40 para los iniciados.

La acción formativa desarrollada estuvo sometida a los cambios que experimentó el Programa y a los que afectaron a la estructura administrativa y política española. La investigación ha mostrado las desigualdades territoriales que acompañaron el desarrollo de la red de formadores, su componente de género y el carácter plural de las instituciones que organizaron los cursos.

Palabras clave:

Educación alimentaria y nutricional. Educación para la salud. Promoción de la salud. Políticas de salud pública. Políticas y programas de nutrición. Historia. España siglo XX.

Abstract

Food and nutrition education is an essential tool to ensure public health. The year 1961 saw the launch of the Food and Nutrition Education Programme (EDALNU), which helped Spanish population to complete their nutrition transition. The aim of this study was to analyze the characteristics of the health education network which was created as part of the program.

A total of 46,752 people, 94% of whom were women, received training on food and nutrition. Of these, 89.54% obtained the basic certificate, and 8.80% were awarded the diploma. Some 1,407 courses were given, reaching a peak in 1979 with 131 courses and 4,029 students. The most active provinces were Madrid, with 26.65% of the courses; Valencia, with 7.60%; Murcia, with 7.53%, and Malaga, with 6.75%. The Spanish Ministry of Culture and Education organized the largest number of courses (26.23%), followed by the Women's Section (11.16%) and Catholic Action (5.12%). Diploma courses were taught for 160 hours, while basic courses lasted 40 hours.

The training delivered was affected by changes in the EDALNU program and the Spanish administrative and political structure. Our research revealed that the development and gender balance of the network of trainers presented regional inequalities, and that a wide range of institutions were involved in delivering the courses.

Key words:

Food and nutrition education. Health education. Health promotion. Public health policies. Nutrition policies and programs. History. 20th century Spain.

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INTRODUCCIÓN

Como se ha señalado en los trabajos que se han ocupado de analizar las políticas de salud relacionadas con las cuestiones alimentarias y nutricionales, durante el primer franquismo se produjo un retroceso al priorizar las iniciativas que primaban los aspectos asistenciales en detrimento de las destinadas a la prevención y a la promoción de la salud (1). La recuperación de un cierto grado de institucionalización de la nutrición comunitaria y de políticas y programas relacionados con la educación en alimentación y nutrición llegaría de la mano de los acuerdos firmados con Estados Unidos, la Organización de las Naciones Unidas para la Alimentación y la Agricultura (FAO) y UNICEF en las décadas de 1950 y 1960 (2,3).

Fue en 1961, con la ayuda técnica de la FAO y el soporte económico de UNICEF, cuando se puso en marcha el programa de Educación en Alimentación y Nutrición (EDALNU) (4). Unos años antes, en 1954, se había puesto en marcha el Servicio Escolar de Alimentación y Nutrición (SEAN) con el objetivo básico de distribuir entre los escolares el complemento alimenticio que comportó la ayuda social americana (2).

El Programa EDALNU, en línea con lo que estaba ocurriendo en el contexto internacional (5), intentaba responder a los retos que planteaba la transición nutricional y alimentaria española (6-8). En las décadas de 1950 y 1960 persistían problemas de desnutrición o malnutrición por defecto, al mismo tiempo que empezaban a emerger los problemas ligados a un creciente sobrepeso y obesidad (9,10). Se trataba de mejorar los conocimientos y los hábitos alimentarios en los niños y en los adultos, favorecer el nivel nutricional de las familias españolas y estimular el consumo de alimentos locales. También se intentaba mejorar la utilización de los recursos con que contaban las familias e interesar a la población en general en los problemas de alimentación y nutrición (11,12).

Para poder desarrollar todos aquellos objetivos, con el fin de capacitar, informar y divulgar a todos los niveles en cuestiones alimentarias y nutricionales, la Oficina Técnica del Programa EDALNU creó una red de formadores, los conocidos como diplomados e iniciados en educación en alimentación y nutrición, que tenían como principal función formar en dicha materia a distintos grupos de población (4).

En diciembre de 1972, el Programa EDALNU, que desde su puesta en marcha había estado adscrito fundamentalmente a la Dirección General de Enseñanza Primaria del Ministerio de Educación, fue transferido a la Dirección General de Sanidad (12). De acuerdo con los datos proporcionados por Consuelo López Nomdedeu (una de las máximas responsables del programa), a pesar de dichos cambios se siguieron realizando actividades formativas relacionadas con la educación alimentaria y nutricional, aunque estas no alcanzasen las dimensiones que habían mostrado en la década de 1960 y los primeros años de 1970 (13). En cualquier caso, la progresiva desactivación del Programa EDALNU adquiere cierta relevancia si tenemos en cuenta su coincidencia temporal con el incremento de los efectos no deseados de la transición nutricional y más concretamente, como ocurrió en el caso español, con el aumento de la incidencia de sobrepeso y/u obesidad (14).

En un momento en el que una adecuada educación en alimentación y nutrición resulta fundamental para garantizar la salud individual y colectiva (15,16), con el objeto de reforzar iniciativas como la estrategia NAOS (Nutrición Actividad Física y Prevención de la Obesidad) puesta en marcha por el Ministerio de Sanidad en 2005 (17), parece oportuno recuperar y adaptar a las circunstancias actuales políticas de salud y de nutrición como las que permitieron a la población española, a través del Programa EDALNU, intentar alcanzar un equilibrio nutricional óptimo.

La presente investigación, a través de un análisis descriptivo histórico de su estructura y planificación, analiza las características de la red de promotores de salud que puso en marcha el Programa EDALNU con la formación de sus diplomados e iniciados en educación en alimentación y nutrición.

La explotación de la base de datos donde se recoge la información referida a todas aquellas personas que recibieron algún tipo de capacitación puede ayudar a poner en valor la dimensión que alcanzó el mayor esfuerzo en materia de educación en alimentación y nutrición desarrollado en España en el siglo XX (2).

Se trata, en definitiva, de profundizar en las claves de una transición alimentaria y nutricional en la que la población española fue capaz de superar las dificultades ligadas a la desnutrición pero no pudo evitar los problemas asociados a la sobrealimentación y a una alimentación inadecuada y que tan preocupantes resultan en el contexto epidemiológico nutricional actual (18).

MATERIAL Y MÉTODO

La información que ha permitido desarrollar la investigación procede, básicamente, de los libros de registro de los diplomados e iniciados EDALNU que se encuentran depositados en el Ministerio de Sanidad, Servicios Sociales e Igualdad y documentación custodiada en la Escuela Valenciana de Estudios en Salud (EVES).

Los datos proporcionados por estas fuentes han permitido conocer las características de quienes participaron en las actividades formativas, las organizaciones que las llevaron a cabo, dónde se realizaron, o los contenidos y características de las mismas, además de complementar los resultados obtenidos por los trabajos que se han ocupado hasta la fecha del Programa EDALNU (2,4,9,11,12).

RESULTADOS Y DISCUSIÓN

Con el Programa EDALNU se consiguió disponer de una red de promotores de salud (diplomados, iniciados y monitores) integrada por 46.752 personas con formación relacionada con la educación en alimentación y nutrición. Los diplomados EDALNU que recibían el curso de mayor duración eran los encargados de formar a los iniciados. Como se puede ver en la figura 1, el 89,54% obtuvo el título de iniciado.

La formación que recibían el diplomado y el iniciado se diferenciaba principalmente en la duración del curso y el contenido del mismo (Fig. 2). Los cursos de diplomados EDALNU tenían una

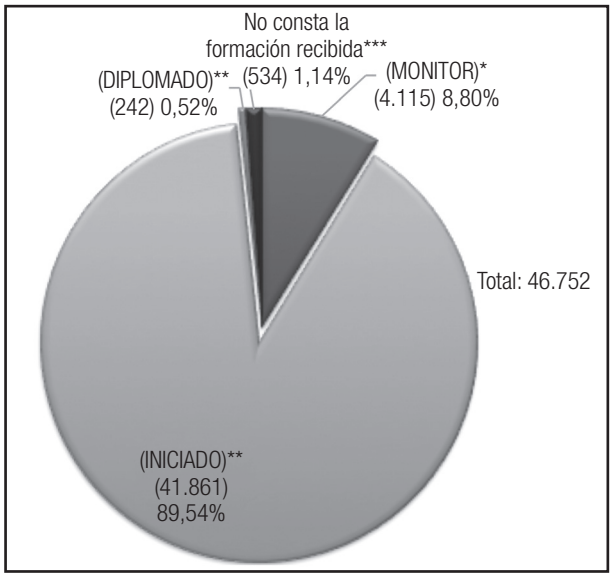

Figura 1.

Título obtenido y personas formadas en la red de promotores de salud del Programa EDALNU. Fuente: Elaboración propia a partir de los datos recogidos en los libros de registro de los diplomados e iniciados EDALNU (1964-1994), depositados en el Ministerio de Sanidad, Servicios Sociales e Igualdad (MSSSI). *Corresponde a una formación de 2-3 meses. Ver contenidos en figura 2. **Corresponde a una formación de 15 días. Ver contenidos en figura 2. ***La formación no consta en las fuentes.

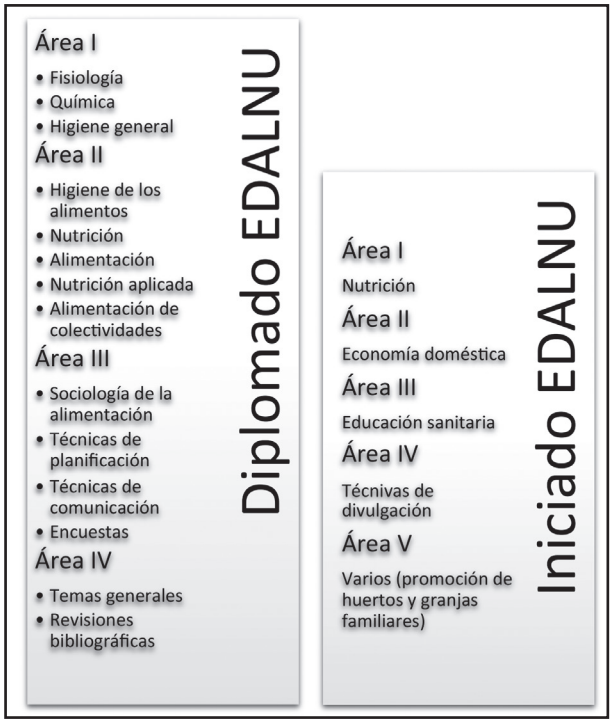

Figura 2.

Contenidos de los cursos de formación destinados a los promotores de salud del programa: Iniciados y Diplomados EDALNU. Fuente: elaboración propia a partir de los documentos: Normas del Ministerio de Sanidad, Servicios Sociales e Igualdad (MSSSI) (no consta fecha) para convocar y llevar a cabo los cursos de diplomados e iniciados EDALNU (Educación en Alimentación y Nutrición).

duración de 160 horas (120 de tipo teórico y 40 de carácter práctico) y estaban orientados a personas que estuviesen al menos en posesión de un título de grado medio o universitario de primer grado, como ocurría con los maestros, asistentes sociales, ayudantes técnicos sanitarios e instructoras de sanidad, peritos agrícolas, diplomados de economía doméstica rural, etc. Sus puestos de trabajo o ámbitos de actuación debían estar relacionados con programas de desarrollo comunitario, educación al consumidor o promoción de la salud, o con las escuelas hogar, los comedores escolares, las colonias de vacaciones o las guarderías infantiles, entre otros.

Quienes obtenían el diploma podían colaborar en la realización de encuestas de consumo actuando como "dietistas", en la "investigación del peso y talla de la población escolar", en la orientación de las minutas de los "centros de alimentación colectiva", en la divulgación de temas de alimentación (educación nutricional) a través de "charlas y reuniones organizadas en diferentes asociaciones y por medio de campañas de radio y prensa local", además de participar en la preparación y desarrollo de los cursos de iniciados EDALNU. No se trataba, en cualquier caso, de formar especialistas en nutrición, sino de proporcionar conocimientos sobre nutrición básica, higiene, alimentación práctica y educación nutricional.

En relación con las cuatro áreas en las que se agrupaban los contenidos teóricos del curso para diplomados EDALNU (Fig. 2), la primera de ellas tenía como principales objetivos ayudar a entender la necesidad de una nutrición correcta, las funciones de los nutrientes, así como las relaciones entre nutrición, salud y desarrollo, y las características de los diferentes alimentos, su valor nutritivo y sus formas de presentación.

En el caso de la segunda de las áreas, se buscaba que los diplomados fuesen capaces de entender la cadena alimentaria en toda su complejidad: "desde la producción al consumo familiar o institucional, con las implicaciones que los diferentes procesos tienen en la economía, la sanidad y el valor nutritivo de los alimentos". Así mismo, debían adquirir los conocimientos y habilidades necesarias para llevar a cabo la sustitución de alimentos, teniendo en cuenta su valor nutritivo, pero también los hábitos alimentarios de cada grupo y el tipo de alimentación habitual en cada zona.

Esta segunda área también contemplaba los objetivos de la materia de nutrición aplicada, destacando el papel que se otorgaba a la economía doméstica y a la "educación del consumo". El diplomado debía aprender a manejar las dimensiones económicas, sociales y nutritivas de los alimentos y las repercusiones de los mismos en la economía familiar y conocer distintos métodos de preparación y cocción de alimentos y sus repercusiones sobre el valor nutritivo de los mismos. Por último, en esta área se incluían también aspectos relacionados con la restauración colectiva.

En la tercera de las áreas se trataban cuestiones relacionadas con la sociología de la alimentación a través del análisis de los comportamientos alimentarios y los contrastes socioculturales que generaban, la elaboración y el diseño de programas formativos, y el adiestramiento en el manejo de medios audiovisuales adaptados a los distintos grupos y situaciones.

Por último, se capacitaba a los alumnos en el análisis de la comunicación y sus elementos y en el desarrollo de las técnicas de promoción comunitaria. Los contenidos teóricos se completaban con unas unidades que estaban destinadas a conocer los recursos bibliográficos en materia de nutrición comunitaria, la estructura y organización del Programa EDALNU y la dimensión internacional que tenían los programas de aquella naturaleza y su interrelación con los sectores económicos, sanitarios, educativos y de la producción y consumo de alimentos.

Las 40 horas de actividad práctica se concretaban en visitas a centros relacionados con las temáticas del curso, con la participación en talleres audiovisuales y análisis de programas de educación nutricional, con la elaboración de formularios para encuestas, con el estudio de minutas de centros de alimentación colectiva de diferentes características (niños, ancianos, obreros, etc.) y con la elaboración de menús tipo para familias de diferentes ingresos. Finalmente, para obtener el título, los alumnos debían realizar un trabajo de campo supervisado y relacionado con alguna de las temáticas abordadas en el curso.

En el caso de los cursos de iniciados EDALNU, que tenían una duración de 40 horas teóricas-prácticas divididas en cinco áreas (Fig. 3), los cursos estaban orientados a personas que estuviesen al menos en posesión del graduado escolar, el bachillerato elemental o un título de formación profesional o equivalente. Al igual que ocurría con los diplomados, se seleccionaba prioritariamente a aquellas personas relacionadas con programas de desarrollo comunitario, educación al consumidor, comedores escolares, guarderías, etc. y, en concreto, a profesionales como "los auxiliares de clínica, las divulgadoras rurales (de la Sección Femenina), maestros, etc.".

El área dedicada a la nutrición se componía de 19 temas en los cuales se impartían conceptos básicos sobre los distintos grupos de alimentos, el manejo de tablas de composición de los mismos y el cálculo de las necesidades energéticas. En la segunda área, dedicada a la economía doméstica, los alumnos aprendían en ocho temas buenas prácticas de compra, gestión de los recursos del hogar, almacenamiento y conservación de alimentos y planificación de dietas. En el área de educación sanitaria se abordaba la higiene en la manipulación de alimentos, las enfermedades que se podían transmitir a través de los mismos y la prevención de toxiinfecciones. Con los contenidos del área de técnicas de divulgación se buscaba formar a los iniciados en las técnicas divulgativas y métodos de educación informal, además del manejo de los medios audiovisuales.

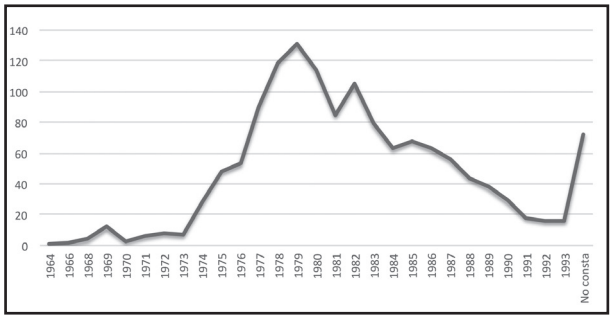

Figura 3.

Número de cursos destinados a los promotores de salud del Programa EDALNU por año. Fuente: elaboración propia a partir de los datos recogidos en los libros de registro de los diplomados e iniciados EDALNU (1964-1994), depositados en el Ministerio de Sanidad, Servicios Sociales e Igualdad (MSSSI).

Los diplomados responsables de impartir los cursos para iniciados debían completar todas aquellas actividades en función de las características del grupo al que iba dirigida la formación. Se pretendía fomentar la producción de alimentos en función de la zona geográfica y de las posibilidades del mercado y para ello se promovía la creación de huertos o granjas familiares. El curso se completaba con un seminario final que pretendía fijar los conceptos estudiados.

Los diplomados y los iniciados EDALNU recibían de manera gratuita diverso material didáctico (libros, manuales, diapositivas, folletos, carteles, fichas, etc.) editados por los organismos de los que dependía el programa y que permitían alcanzar sus objetivos. Tanto el curso de diplomados como el de iniciados no podían superar los 50 alumnos. Hay que indicar, sin embargo, que según la base de datos algunos de los cursos no cumplían las horas ni el número máximo de personas por curso.

En relación con los organismos responsables, la distribución geográfica y evolución temporal de las actividades formativas y el número de personas formadas, hay que indicar que aunque el Programa EDALNU inició sus actividades formativas en 1962 (13), los primeros registros de iniciados y diplomados datan de 1964. Fue a finales de la década de 1970, en concreto en 1979, cuando se convocó el mayor número de cursos, un total de 131 (Fig. 3). A partir de dicha fecha, las actividades formativas empezaron a declinar. Se trató de un cambio de tendencia que guardaba relación con las transferencias de las competencias sanitarias, y especialmente en promoción de la salud, a las comunidades autónomas (12). Como ya se ha señalado, en 1972 el Programa EDALNU había pasado a depender de la Dirección General de Sanidad.

En cuanto a las instituciones y organismos que se responsabilizaron de las actividades formativas, destaca el número de cursos organizados o coordinados por el Ministerio de Cultura o Educación, con un total de 369 de los 1.407 que se organizaron, lo cual representa el 26,2%. Cabe destacar, asimismo, la actividad formativa que llevaron a cabo instituciones como la Sección Femenina, organizadora del 11,1% de los cursos, y Acción Católica, responsable del 5,12%, sobre todo en los primeros años de la puesta en marcha del Programa EDALNU. En ambos casos, muchos de los cursos se realizaron en colaboración con instituciones y organismos como la Dirección General de Sanidad, la Dirección General de Desarrollo Comunitario o el ya citado Ministerio de Cultura o Educación. También destacan, por la importancia que tuvieron en la realización de cursos para diplomados e iniciados, instituciones y organismos como los servicios de Extensión Agraria, las escuelas de Puericultura o asociaciones de amas de casa de diversa naturaleza. Asimismo, a partir de la década de 1980, coincidiendo, como ya se ha indicado, con las transferencias sanitarias a las comunidades autónomas, aparecen

como organizadores de cursos, aunque en menor número, las jefaturas provinciales de Sanidad, las consejerías de Sanidad, las direcciones generales de Salud Pública, centros socioculturales, centros de salud, ayuntamientos e institutos de Formación Profesional y colegios.

Al analizar la naturaleza pública o privada y el tipo de institución u organismo responsable de los cursos y su evolución temporal (Fig. 4), se puede observar que fueron las de carácter educativo público las que organizaron el mayor número de cursos, sustituyendo a las de carácter privado, que prácticamente monopolizaron las desarrolladas durante el primer quinquenio.

En cuanto a la distribución geográfica de las actividades formativas que se llevaron a cabo, destaca Madrid como la provincia con mayor número de cursos realizados con un total de 380 (Fig. 5), es decir, el 26,6% y 12.173 personas formadas. Esta circunstancia podría estar explicada por la propia estructura organizativa del Programa EDALNU, por encontrarse en dicha ciudad su oficina técnica y por estar ubicadas en la capital algunas de las principales instituciones y organismos que impartieron los cursos o figuraban como responsables, tal como ocurría con el Ministerio de Cultura o Educación.

Del resto de provincias destacan, por el número de cursos organizados, Valencia, Murcia y Málaga, con 107, 106 y 95 (Fig. 5), es decir, el 7,6, el 7,5 y el 6,7%, llegando a formar a 4.351, 4.061 y 3.633 personas respectivamente. Para explicar la importancia que alcanzaron las actividades del programa en estas provincias, hay que mencionar el papel que pudieron jugar algunas circunstancias de carácter local, además de la descentralización que conllevó el citado traspaso de competencias a las comunidades autónomas en materia de promoción de la salud.

En el caso de Valencia hay que subrayar el papel que jugaron en el desarrollo del programa profesionales vinculados a la Conselleria de Sanidad y, en concreto, al Instituto Valenciano de Estudios en Salud Pública (IVESP), y que contaban con una sólida formación en materia de educación en alimentación y nutrición y nutrición aplicada, como era el caso de la maestra Pilar Espí,

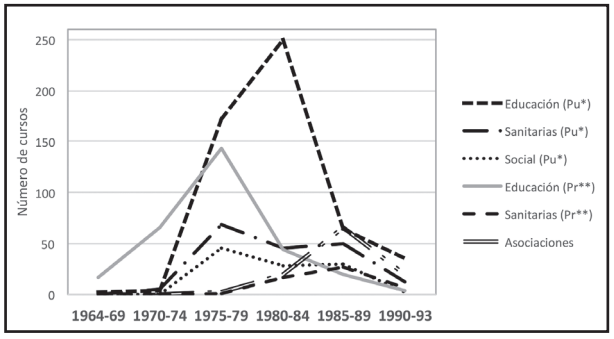

Figura 4.

Distribución del número de acciones formativas destinadas a los promotores de salud del Programa EDALNU según su titularidad: pública (*) o privada (**). Fuente: elaboración propia a partir de los datos recogidos en los libros de registro de los diplomados e iniciados EDALNU (1964-1994), depositados en el Ministerio de Sanidad, Servicios Sociales e Igualdad (MSSSI).

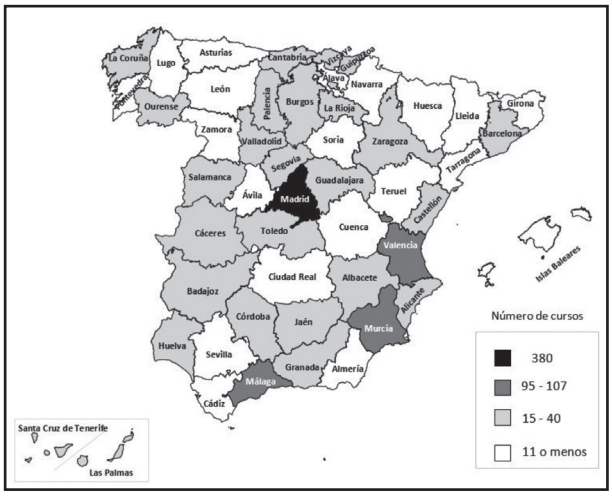

Figura 5.

Distribución geográfica del número de acciones formativas destinadas a promotores de salud del Programa EDALNU por provincia (1963 a 1994). Fuente: elaboración propia a partir de los datos recogidos en los libros de registro de los diplomados e iniciados EDALNU (1964-1994), depositados en el Ministerio de Sanidad, Política Social e Igualdad (MSPSI).

ligada desde sus inicios al programa EDALNU, o del especialista en epidemiología nutricional José Aranda Pastor.

En Madrid, Acción Católica fue la entidad organizadora más activa, con 45 cursos, seguida de Sección Femenina, con 36; los institutos de Bachillerato, con 33; la Escuela Javerianas, con 23; la Escuela de Puericultura, con 22; el Servicio de Extensión Agraria, con 17; y el Ministerio de Cultura o Educación, con 15.

En el caso de Valencia, las entidades más activas fueron las asociaciones de amas de casa, con 45 cursos, y Sección Femenina, con 10. En Murcia, el Ministerio de Cultura o Educación y la Consejería de Sanidad organizaron 34 y 20 cursos respectivamente, y en Málaga, el Ministerio de Cultura o Educación y la Escuela de Puericultura fueron responsables de 26 cursos cada uno y Sección Femenina, de 13.

Se trata de resultados que muestran la diversidad de instituciones y organizaciones que colaboraron en la creación de la red de formadores, pero también las diferencias que marcaban las características socioeconómicas y culturales de las distintas provincias. Llama la atención la poca actividad que desarrolló el Programa EDALNU en materia de formación de formadores en la provincia de Barcelona, una de las más pobladas de España y con un potencial sanitario y científico destacable. Solo se impartieron 20 cursos y se formó a un total de 388 personas.

Como se puede apreciar en el histograma de la figura 6, fue en el quinquenio 1980-1984 cuando se alcanzó el máximo número de personas que recibieron formación como iniciados o diplomados EDALNU. Los datos reflejan que fue a finales de la década de los 70 y principios de los 80 cuando se alcanzó la mayor actividad formativa, produciéndose a partir de 1985 un progresivo declive.

Por último, los resultados del análisis de la base de datos muestran una feminización del colectivo que recibió formación como

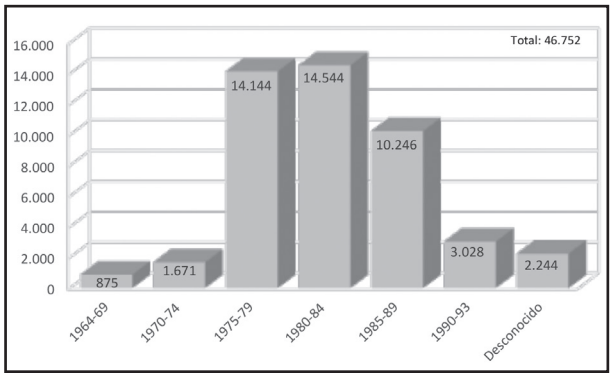

Figura 6.

Distribución del número de promotores de salud del Programa EDALNU formados según quinquenio (1963-1994). Fuente: elaboración propia a partir de los datos recogidos en los libros de registro de los diplomados e iniciados EDALNU (1964-1994), depositados en el Ministerio de Sanidad, Política Social e Igualdad (MSPSI).

diplomados o iniciados EDALNU, ya que las mujeres alcanzaron el 94% del total de titulados. Para explicar esta circunstancia, hay que recordar el contexto histórico en el que se desarrollaron las actividades formativas y los objetivos del propio programa (2,4). Como se ha puesto de manifiesto en investigaciones previas (11), uno de los objetivos fundamentales del EDALNU era el de mejorar el nivel nutricional de la familia española a través de la difusión de conocimientos en alimentación, promocionar mejores hábitos alimentarios y estimular el consumo de alimentos locales. Para ello era necesario educar a la población y, concretamente, capacitar al ama de casa como principal responsable de la alimentación y el bienestar familiar. Todo ello, sin olvidar el papel que pudo jugar en aquella feminización el hecho de que hubiese una presencia mayoritaria de mujeres en los colectivos a los que iban dirigidas muchas de las actividades formativas y especialmente las relacionadas con los cursos de diplomados (maestras, enfermeras, etc.).

CONCLUSIÓN

Como se ha podido comprobar al analizar las características y el volumen de la red de promotores de salud que impulsó el Programa EDALNU, se trató de una acción formativa de alcance que estuvo, sin embargo, sometida a los cambios que experimentó el propio programa, a los que afectaron a la estructura administrativa y política española y, más concretamente, a aquellos que acompañaron a la creación de las autonomías.

A pesar de las limitaciones que ofrecen las fuentes consultadas, la investigación ha permitido mostrar las desigualdades territoriales que acompañaron la formación de la red de formadores, su fuerte componente de género y, en consonancia con la propia estructura del programa (2,4,9,11,12), el carácter plural de las instituciones que organizaron los cursos orientados a la formación de los diplomados o iniciados.

Los resultados también ponen de manifiesto la continuidad que tuvieron las actividades formativas del Programa EDALNU, a pesar de la progresiva desactivación del mismo tras el traspaso de su competencia desde el ámbito del Ministerio de Educación al de Sanidad. En cualquier caso, la red de promotores fue decisiva para poder desarrollar el importante volumen de actividades educativas que llevó a cabo el Programa EDALNU tanto en el ámbito escolar y familiar como en el comunitario (2,4,9,11,12), y que ayudaron a mejorar los hábitos alimentarios de la población española.

El hecho de que la desactivación del programa coincidiese con la aparición de los efectos no deseados de la transición alimentaria y nutricional y, más concretamente, con la emergencia de la epidemia de sobrepeso y obesidad (10,14) debería servir para insistir en la necesidad de dar continuidad a políticas de salud y programas de nutrición aplicada como los que estaban detrás del EDALNU.

La experiencia histórica analizada también ofrece importantes elementos de reflexión que pueden ayudar en el abordaje de los retos alimentarios y nutricionales que tiene planteados en la actualidad la población española y en la puesta en marcha de políticas como la que conlleva el desarrollo de la Estrategia NAOS (16) o el Programa PERSEO (19,20), sin olvidar el interés que pueden ofrecer las redes de promotores de la salud para la consecución de sus objetivos.

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Nutrición Hospitalaria

Grupo de Trabajo SENPE

Guía de práctica clínica SENPE/SEGHNP/SEFH sobre nutrición parenteral pediátrica

Pediatric parenteral nutrition: clinical practice guidelines from the Spanish Society of Parenteral and Enteral Nutrition (SENPE), the Spanish Society of Pediatric Gastroenterology, Hepatology and Nutrition (SEGHNP) and the Spanish Society of Hospital Pharmacy (SEFH)

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Resumen

Introducción: la nutrición parenteral (NP) en la infancia es un tratamiento cuyas características son muy variables en función de la edad y la patología que presente el paciente.

Material y métodos: el grupo de Estandarización y Protocolos de la Sociedad Española de Nutrición Parenteral y Enteral (SENPE) es un grupo interdisciplinar formado por miembros de la SENPE, Sociedad Española de Gastroenterología, Hepatología y Nutrición Pediátrica (SEGHNP) y Sociedad Española de Farmacia Hospitalaria (SEFH) que pretende poner al día este tema. Para ello, se ha realizado una revisión pormenorizada de la literatura buscando las evidencias que nos permiten elaborar una Guía de Práctica Clínica siguiendo los criterios del Oxford Centre for Evidence-Based Medicine.

Resultados: este manuscrito expone de forma resumida las recomendaciones en cuanto a indicaciones, vías de acceso, requerimientos, modificaciones en situaciones especiales, componentes de las mezclas, prescripción y estandarización, preparación, administración, monitorización, complicaciones y NP domiciliaria. El documento completo se publica como número monográfico.

Conclusiones: esta guía pretende servir de apoyo para la prescripción de la NP pediátrica. Constituye la base para tomar decisiones en el contexto de la evidencia existente. Ninguna guía puede tener en cuenta todas las circunstancias clínicas individuales.

Palabras clave:

Nutrición parenteral.
Niños. Neonato.
Estandarización.

Abstract

Introduction: Parenteral nutrition (PN) in childhood is a treatment whose characteristics are highly variable depending on the age and pathology of the patient.

Material and methods: The Standardization and Protocols Group of the Spanish Society for Parenteral and Enteral Nutrition (SENPE) is an interdisciplinary group formed by members of the SENPE, the Spanish Society of Gastroenterology, Hepatology and Pediatric Nutrition (SEGHNP) and the Spanish Society of Hospital Pharmacy (SEFH) that intends to update this issue. For this, a detailed review of the literature has been carried out, looking for the evidences that allow us to elaborate a Clinical Practice Guide following the criteria of the Oxford Center for Evidence-Based Medicine.

Results: This manuscript summarizes the recommendations regarding indications, access routes, requirements, modifications in special situations, components of the mixtures, prescription and standardization, preparation, administration, monitoring, complications and home NP. The complete document is published as a monographic number.

Conclusions: This guide is intended to support the prescription of pediatric PN. It provides the basis for rational decisions in the context of the existing evidence. No guidelines can take into account all of the often compelling individual clinical circumstances.

Key words:

Parenteral nutrition.
Child. Newborn.
Standardization.

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INTRODUCCIÓN

Los niños que necesitan nutrición parenteral (NP) constituyen un grupo heterogéneo tanto por la enfermedad de base que presentan como por su edad, ya que esta última determina las características fisiológicas y los requerimientos para el crecimiento. Todo ello influye de manera decisiva en la composición de la NP.

En el año 2007, el grupo de Estandarización y Protocolos de la Sociedad Española de Nutrición Parenteral y Enteral (SENPE) publicó el *"Documento de consenso SENPE/SEGHNP/SEFH sobre nutrición parenteral pediátrica"* (1), planteándose en la actualidad su revisión y puesta al día.

Para ello, se ha realizado una revisión pormenorizada de la literatura buscando las evidencias que nos permiten elaborar una Guía de Práctica Clínica siguiendo los criterios del Oxford Centre for Evidence-Based Medicine (2). El texto completo se publicará en un número monográfico de Nutrición Hospitalaria y este artículo constituye la versión corta de la Guía.

INDICACIONES

La NP puede ser utilizada en todo niño desnutrido o con riesgo de desarrollar desnutrición aguda o crónica cuando sus necesidades nutricionales no logren ser administradas completamente por vía enteral (1,3,4). De este modo se dará cobertura a sus necesidades de energía y nutrientes para mantener o recuperar su salud y crecimiento. Se recomienda potenciar al máximo la ingesta por la vía digestiva ya que mantiene el trofismo intestinal y disminuye la incidencia de complicaciones secundarias a la NP (5). En la tabla I se muestran las indicaciones de NP.

Los niños son particularmente sensibles a las restricciones nutricionales debido a sus necesidades para mantener un crecimiento óptimo, fundamentalmente en las épocas de máximo desarrollo. Por ello, la NP estará indicada en:

- Todo paciente pediátrico en el que no sea posible la vía enteral entre cinco y siete días (GdE 2) (6) o antes si el paciente ya estaba desnutrido.
- En el recién nacido pretérmino (RNPT) la NP debe administrarse precozmente (en las primeras 24 horas) para evitar la desnutrición temprana (GdE 1) (7).

La NP debe mantenerse hasta que se consiga una adecuada transición a la nutrición enteral (NE) y dichos aportes alcancen al menos 2/3 de los requerimientos nutricionales estimados.

VÍAS DE ACCESO

Las vías de acceso venoso para NP pueden ser periféricas y centrales. La elección dependerá del tiempo previsto de tratamiento, de los requerimientos nutricionales del paciente, de la enfermedad de base, del estado nutricional y de los accesos vasculares disponibles.

Tabla I. Indicaciones de nutrición parenteral*

Patología digestiva
– *Intervenciones quirúrgicas*
• Resección intestinal
• Malrotación y vólvulo
• Alteraciones de la pared abdominal (gastrosquisis, onfalocele, etc.)
• Enfermedad de Hirschsprung complicada o extensa
• Atresia intestinal (incluido síndrome de apple peel)
• Resecciones intestinales amplias: síndrome de intestino corto
• Enfermedad de Crohn grave o con múltiples resecciones con afectación del crecimiento
• Trasplante intestinal
– *Malabsorción intestinal*
• Displasia intestinal
• Enfermedad por inclusión de microvilli
• Enterostomía proximal
• Diarrea grave prolongada
• Fístula enterocutánea
• Inmunodeficiencias
– *Alteraciones de la motilidad intestinal*
• Peritonitis plástica
• Enteritis rádica
• Aganglionosis intestinal (segmento largo de enfermedad de Hirschsprung)
• Pseudoobstrucción intestinal crónica idiopática
– *Otros*
• Enterocolitis necrosante
• Isquemia intestinal
• Vómitos incoercibles
• Sangrado intestinal masivo
• Enfermedades inflamatorias intestinales
• Pancreatitis aguda grave, fístula pancreática
• Vasculitis con grave afectación digestiva
• Íleo meconial
• Mucositis o enteritis grave por quimioterapia
• Insuficiencia hepática grave
Patología extradigestiva
– Todo paciente desnutrido o con riesgo de desnutrición secundaria a cualquier patología
– Displasia broncopulmonar
– Oxigenación con membrana extracorpórea
– Perioperatorio en paciente desnutrido grave
– Trasplante de órganos y médula ósea
– Pacientes en cuidados intensivos con diversas patologías: traumatismo craneoencefálico (fase precoz), politraumatismos, sepsis, cirugía, quemados críticos, fracaso multiorgánico
– Caquexia cardiaca
– Insuficiencia renal grave
– Inestabilidad hemodinámica grave
– Recién nacidos prematuros
– Errores innatos del metabolismo (en el debut y en descompensaciones)
– Pacientes oncológicos con mucositis intensa o trombopenia grave (plaquetas < 25.000) que contraindique la nutrición enteral

**Modificado de Gomis Muñoz et al., 2007 (1).*

ACCESOS VENOSOS PERIFÉRICOS

Se sitúan en venas subcutáneas, a través de las cuales pueden infundirse soluciones con una osmolaridad máxima de 850 mOsm/l (GdE 3) (8) y, por tanto, con un aporte de nutrientes limitado, por el riesgo de flebitis. Los catéteres venosos percutáneos periféricos largos *(midline catheters)* se pueden utilizar en el medio hospitalario para la administración de NP normocalórica durante periodos de varias semanas (GdE 2) (9). La NP por vía periférica se utiliza solo como medida temporal, cuando los requerimientos del paciente son bajos por ser un complemento de la NE o porque no se pueden lograr accesos venosos centrales.

ACCESOS VENOSOS CENTRALES

Los catéteres venosos centrales (CVC) se pueden clasificar según el tiempo durante el que vayan a ser utilizados:

- *NP a corto plazo (hasta tres semanas):* se insertan percutáneamente directamente en una vía central (vena subclavia, yugular interna, vena innominada o vena femoral). Están pensados para un uso continuado y solo deben ser utilizados en pacientes hospitalizados por cortos espacios de tiempo (de días a semanas) (GdE 3) (10).
  En cuanto a los catéteres umbilicales en el recién nacido (RN), deben retirarse antes del día 14 los venosos y antes del quinto día los arteriales (GdE 1) (11).
- *NP a medio plazo (de tres semanas a tres meses):* CVC no tunelizados para un uso discontinuo o transitorio. Los hay de dos tipos, los catéteres venosos centrales de inserción periférica (PICC) en una vía del brazo, tórax o cuello, y los CVC percutáneos no tunelizados, tipo Hohn. Se pueden utilizar tanto en pacientes hospitalizados como domiciliarios hasta tres meses, aunque no son una solución óptima para la administración de nutrición parenteral domiciliaria (NPD) (GdE 2) (9).
- *NP a largo plazo (más de tres meses) (10):* especialmente para pacientes en NPD. Requieren CVC tunelizados y fijados tipo Broviac, Hickman, etc. (GdE 2).
  Los catéteres totalmente implantados subcutáneamente tipo Port-a-Cath no son idóneos para la administración de NPD (GdE 3).

En la tabla II se indican los calibres recomendables de los CVC y PICC en función del peso y edad de los pacientes. Los catéteres pueden tener una o varias luces.

La técnica de elección para la colocación de una vía central es la canulación percutánea guiada por ecografía (GdE 1) (12). En caso contrario, es necesario un control radiológico para confirmar la localización de la punta y descartar iatrogenia durante la inserción (GdE 2).

COLOCACIÓN Y MANIPULACIÓN DE LAS VÍAS (ASEPSIA)

La colocación de los CVC se debe realizar con técnica estéril. Se deben seguir estrictas medidas antisépticas tanto en el lavado de las manos como en la manipulación de las conexiones al manipular los CVC (GdE 1) (12).

Tabla II. Calibres de los catéteres en función de la edad y peso del paciente

Calibre del CVC		
Edad	**Peso**	**Calibre**
0-6 meses	< 10 kg	4 Fr
6 meses-4 años	10-20 kg	4,5-5 Fr
4 años-12 años	20-40 kg	5 Fr
> 12 años	> 40 kg	7 Fr
Calibre PICC		
Peso		**Calibre**
< 5 kg		2 Fr
5-10 kg		3 Fr
10-50 kg		4 Fr
> 50 kg		5 Fr

Fr: french; 1 Fr: 0,3 mm diámetro externo.

REQUERIMIENTOS EN NUTRICIÓN PARENTERAL PEDIÁTRICA

REQUERIMIENTOS ENERGÉTICOS

Clásicamente, la principal preocupación a la hora de prescribir una NP era el no alcanzar las necesidades energéticas del paciente; sin embargo, actualmente, el problema se centra más en las consecuencias negativas a las que conduce el exceso o desequilibrio de los diversos nutrientes. La estimación de las necesidades energéticas en los niños con NP precisa considerar los distintos componentes del gasto energético y el hecho de que la mayoría de ellos están hospitalizados, inactivos, con o sin alimentación enteral concomitante y con diversos grados de estrés metabólico (1,13).

El cálculo de los requerimientos energéticos debe realizarse de forma individualizada, según edad, estado nutricional y enfermedad subyacente. En pacientes con enfermedades que conlleven alto riesgo de desnutrición**,** el mejor método es el cálculo del gasto energético en reposo (GER) corregido por un factor que incluye la actividad y el grado de estrés. La forma idónea de conocer el GER es mediante calorimetría indirecta. Sin embargo, la mayoría de los clínicos no disponen de esta técnica y, por tanto, precisan estimar las necesidades energéticas con cálculos orientativos mediante ecuaciones de predicción, siendo la más aceptada la fórmula de Schofield (14).

Una vez calculado el GER tal como se indica en la tabla III se corregirá por un factor que tenga en cuenta el estrés de la enfermedad y la actividad física. Generalmente, para evitar la sobrealimentación se suele emplear un factor de multiplicación 1,1-1,2 en niños con enfermedad de moderada intensidad (GdE 4) (15).

Tabla III. Ecuaciones de predicción para el cálculo de los requerimientos energéticos en NP (kcal/día) y relación kcal no proteicas por gramo de nitrógeno

Cálculo del GER	Schofield		OMS
	Con el peso	Con el peso y la talla	
Niños:			
0-3 años	(59,5 x P) - 30,3	(0,17 x P) + (1.516,1 x T) - 617	(60,9 x P) - 54
3-10 años	(22,7 x P) + 504	(19,6 x P) + (130 x T) + 415	(22,7 x P) + 495
10-18 años	(17,7 x P) + 658	(16,2 x P) + (137,1 x T) + 515	(17,5 x P) + 651
Niñas:			
0-3 años	(58,3 x P) - 31	(16,2 x P) + (1.022,3 x T) - 413	(61 x P) - 51
3-10 años	(20,3 x P) + 486	(16,9 x P) + (161,7 x T) + 370	(22,4 x P) + 499
10-18 años	(13,4 x P) + 692	(8,4 x P) + (465,2 x T) + 200	(12,2 x P) + 746

P: peso (kg); T: talla (m); GER: gasto energético en reposo. Requerimientos energéticos totales (kcal/día): GER x factor (1,1-1,2). Relación kcal no proteicas/gramo de nitrógeno: 150-200 kcal no proteicas por cada g nitrógeno. En críticos, 100-130 kcal no proteicas por cada g nitrógeno.

No hay razones para incrementar la energía en casos de cirugía no complicada (GdE 2) (15). En situaciones de NP prolongada y desnutrición grave este factor se puede incrementar hasta 1,3-1,5 (GdE 4) (15). En la tabla IV se recogen las cantidades aproximadas de energía según la edad (1,13,15-17).

Una vez calculada la energía total diaria es fundamental que su aporte en principios inmediatos esté equilibrado, para conseguir una adecuada retención nitrogenada y evitar alteraciones metabólicas (18). El cálculo de los requerimientos de proteína debe realizarse siempre en primer lugar y es el que determina el resto del aporte calórico no proteico. Se recomienda 100-200 kcal no proteicas por cada gramo de nitrógeno (Tablas IV y VI) (1,13,19,20).

Tabla IV. Necesidades energéticas aproximadas en NP según la edad

Edad (años)	Kcal/kg peso/día
Recién nacido pretérmino*	1º día 60 1ª semana 90 3ª semana 120
< 1 mes	110
1-3 meses	95-100
4-12 meses	80
1-3 años	60
4-10 años	45-55
11-14 años	35
15-18 años	30

**Ref. 17; resto de las edades modificado de ref. 16.*
Para menores de un año las recomendaciones se basan en el GET incluyendo el crecimiento (16).
A partir de un año las cifras de energía/kg/d que se muestran corresponden al GER (Schofield) (14) para cada uno de los rangos de edad. En ellos y en función de la situación clínica del niño estas cifras se multiplicarán por un factor 1,1-1,2 o por el que se considere adecuado.

REQUERIMIENTOS PROTEICOS

Las proteínas se suministran en forma de soluciones de aminoácidos (AA) y son esenciales para mantener la masa corporal magra. Los aportes recomendados según la edad se recogen en la tabla V (1,13,15). Estudios recientes sustentan la importancia de alcanzar rápidamente las dosis máximas incluso en el neonato pretérmino siempre que se guarde la relación nitrógeno/kcal no proteicas (21) (Tabla VI).

REQUERIMIENTOS DE LÍPIDOS

Los lípidos deben formar parte de las soluciones de NP por su elevada densidad calórica, por ser fuente de ácidos grasos esenciales (AGE), por disminuir la osmolaridad de la solución y por evitar los efectos negativos de la sobrecarga de glucosa. Se recomienda que constituyan del 25 al 40% de las calorías no proteicas (13,15). Los aportes máximos diarios recomendados en NP se resumen en la tabla VII (13,15). Deben controlarse las cifras de triglicéridos, que no deben superar la concentración de 150 mg/dl en pretérminos, 250 mg/dl en lactantes y 400 mg/dl en los niños mayores (15,22).

Tabla V. Necesidades de aminoácidos en NP según la edad

Edad	Gramos/kg peso/día Pacientes estables	
	Límites	Recomendaciones
Recién nacido pretérmino	1,5-4	3-4
Recién nacido a término	1,5-3	2,3-3
2º mes a tres años	1,0-2,5	2,0-2,5
3-5 años	1,0-2,0*	1,5-2
6-12 años	1,0-2,0*	1-1,5
Adolescentes	1,0-2,0	1-1,5

**En pacientes críticos se puede incrementar hasta 3 g/kg/día.*

Tabla VI. Necesidades de energía y proteínas a alcanzar en NP en el pretérmino según el peso al nacer

Peso (g)	Proteína g/kg/d	Energía kcal/kg/d	Proteína/E g/100 kcal	Nitrógeno*/E g/100 kcal
500-700	4,0	105	3,8	0,61
700-900	4,0	108	3,7	0,59
900-1.200	4,0	119	3,4	0,54
1.200-1.500	3,9	125	3,1	0,50
1.500-1.800	3,6	128	2,8	0,45
1.800-2.200	3,4	131	2,6	0,42

*E: energía; *g nitrógeno = g proteína (AA)/6,25.*

Tabla VII. Requerimientos de lípidos en NP según edad

Edad	Aportes máximos g/kg/d	Ritmo de infusión g/kg/hora
Lactantes (incluidos RNPT)	3-4	0,13-0,17
Niños	2-3	0,08-0,13

RNPT: recién nacido pretérmino. Nota: no debe superarse el ritmo de infusión cuando se cicle la NP.

Tabla VIII. Requerimientos de glucosa en NP según edad

Edad	Dosis inicial mg/kg/minuto g/kg/d	Dosis máxima mg/kg/minuto g/kg/d
Recién nacido pretérmino	4-8 6-12	11-12 16-18
Lactantes y niños hasta dos años	5-7 7- 10	11-12 16-18
Resto de edades	3-5 4-7	8-10 10-14

En algunas circunstancias, hay que tener precaución y reducir los aportes (0,5-1 g/kg/día), garantizando el aporte de AGE: infecciones graves, hiperbilirrubinemia neonatal, trombocitopenia < 100.000/mm^3, insuficiencia hepática y enfermedades pulmonares (19,20). En pretérminos de muy bajo peso al nacer, su inicio en los dos primeros días de vida es seguro (GdE 1) (23).

REQUERIMIENTOS DE GLUCOSA

Su aporte no debe exceder el 60-75% de las calorías no proteicas (1,13,15). El ritmo de infusión (mg/kg/minuto) debe ser progresivo y dependiente de la edad, tal y como se detalla en la tabla VIII, para evitar la hiperglucemia y la diuresis osmótica. En los neonatos, especialmente en los RNPT, se recomienda poner especial énfasis en evitar la hipoglucemia y en tratarla sistemáticamente en caso de presentarse (GdE 1) (24). Se sugiere, además, que la glucemia no sobrepase los 150 mg/dl (GdE 5) (24) ya que se asocia con mayores complicaciones, particularmente en los RNPT y/o de bajo peso al nacer. El uso de insulina debe restringirse a casos de difícil control de la hiperglucemia.

REQUERIMIENTOS DE AGUA Y ELECTROLITOS

Se calcularán en función de la edad, el tamaño corporal, el estado de hidratación, los factores ambientales, la enfermedad subyacente y el estado nutricional, especialmente en el RN (1,13,15,17). Se resumen en las tablas IXA y IXB.

REQUERIMIENTOS DE MINERALES Y OLIGOELEMENTOS

Varían según la edad y el peso corporal. Para conseguir una mejor retención fosfo-cálcica se recomienda una relación calcio:fósforo molar de 1,3/1 o una relación por peso de 1,3-1,7/1 (1,13,19,20). Los oligoelementos suelen administrarse de forma conjunta, aunque es posible proporcionar algún elemento aislado como el zinc (Tablas X y XI).

REQUERIMIENTOS DE VITAMINAS

Las recomendaciones según ASPEN en vitaminas para el RNPT y resto de las edades se recogen en la tabla XII, que constituye una síntesis de las principales recomendaciones (1,13,25).

MODIFICACIONES EN SITUACIONES ESPECIALES

Entre los pacientes pediátricos que precisan NP existen una serie de circunstancias que hacen necesario matizar las conside-

Tabla IX.A. Aportes de agua y electrolitos en NP* de recién nacidos

	Agua (ml/kg/día)			Sodio (mEq/kg/día)			Potasio (mEq/kg/día)		
	Fase transición	Fase intermedia	Fase estable	Fase transición	Fase intermedia	Fase estable	Fase transición	Fase intermedia	Fase estable
RNT	60-120	140	140-170	0-3 (5)**	2-5	2-3	0-2	1-3	1,5-3
RNPT > 1.500 g	60-80	140-160	140-160	0-3 (5)**	3-5	3-5 (7)**	0-2	1-3	2-5
RNPT < 1.500 g	80-90	140-180	140-180	0-3 (5)**	2-3 (5)**	3-5 (7)**	0-2	1-2	2-5

**Incluye el aporte progresivo por vía enteral. **Fase poliúrica (valores entre paréntesis). RNT: RN a término. RNPT: RN pretérmino.*

Tabla IX.B. Aportes de agua y electrolitos en NP

Electrolitos	> 1er mes-1 año/ kg/d	> 1 año-12 años/ kg/d
Agua (ml)	100 ml (más las pérdidas)	Holliday-Segar* (más las pérdidas)
Sodio (mEq)	2-3	2-3
Cloro (mEq)	2-3	2-3
Potasio (mEq)	1-3	1-3

**Holliday-Segar (mantenimiento):*
- *Hasta 10 kg, 100 ml/kg (total 1.000 ml);*
- *Entre 10 y 20 kg = 1.000 ml por los primeros 10 kg más 50 ml/kg por los segundos 10 kg (total 1.500 ml);*
- *A partir de 20 kg = 1.500 ml por los primeros 20 kg más 20 ml/kg por los kilos que superen 20 kg. Máximo 2.000-2.500 ml/24 horas.*

Tabla XI. Aportes de oligoelementos en NP

Elemento	RNPT mcg/kg/d	RNT - 1 año mcg/kg/d	Resto edades mcg/kg/d
Fe	200	50-100	50-100
Zn	450-500	< 3 meses: 250 > 3 meses: 50	50 (máx. 5.000 mcg/d)
Cu	20	20	20 (máx. 300 mcg/d)
Se	2-3	1-3	2 (máx. 30 mcg/d)
Cr	0-6 meses: 0,0006 7-12 meses: 0,012		1-3 años: 0,22 4-8 años: 0,3 9-13 años: 0,5 chicos; 0,4 chicas 14-18 años: 0,7 chicos; 0,48 chicas
Mn	1	1	1 (máx. 50 mcg/d)
Mo	1	0,25	0,25 (máx. 5 mcg/d)
I	1	1	1 (máx. 50 mcg/d)

RNPT: RN pretérmino; RNT: RN a término.

Tabla X. Aportes de minerales en NP

		RNPT/kg/d	RNT/kg/d	< 1año/kg/d	1-11 años/kg/d	12-15 años/kg/d
Calcio	mg	60-80	40-60	20-25	10-20	4,5-9
	mM	1,5-2	1-1,5	0,5-0,6	0,25-0,5	0,12-0,2
	mEq	3- 4	2-3	1-1,2	0,5-1	0,2-0,4
Fósforo	mg	45-70	30-45	10-30	8-22	5-10
	mM	1,45-2,25	1-1,5	0,3-1	0,25-0,7	0,16-0,3
	mEq	2,9-4,5	2-3	0,6-2	0,5-1,5	0,3-0,6
Magnesio	mg	4-7	3-6	3-6	3-6	2,5-4,5
	mM	0,17-0,3	0,12-0,25	0,12-0,25	0,12-0,25	0,1-0,2
	mEq	0,34-0,6	0,25-0,5	0,25-0,5	0,25-0,5	0,2-0,4

RNPT: RN pretérmino; RNT: RN a término. Calcio: 1 mM = 40 mg = 2 mEq (gluconato Ca 10%: 100 mg = 9 mg Ca); Fósforo: 1 mM = 31 mg = 2 mEq (relación calcio/fósforo = 1,3/1); Magnesio: 1mM = 24 mg = 2 mEq.

Tabla XII. Recomendaciones y preparados de vitaminas en NP

Vitamina	RNPT (dosis/kg/día)	Lactante (dosis/kg/día)	Niño (dosis/día)	Soluvit® + Vitalipid Infantil® 3,77 + 10 ml	Soluvit® + Vitalipid Infantil® 10 + 10 ml[1]	Infuvite Pediatric® 5 ml[2]	Cernevit 5 ml[3]	Soluvit® + Vitalipid Adultos® 10 + 10 ml[1]
A (mcg)[4, 6]	210-455	150-300	150	700	700	700	1.060	1.000
E (mg)	2,8-3,5	2,8-3,5	7	6,4	6,4	7	10,2	9,1
K (mcg)	10	10	200	200	200	200	0	150
D (mcg)[5]	1-4	3,2	10	40	40	40	22	20
C (mg)	15-25	15-25	80	37,7	100	80	125	100
B_1 (mg)	0,2-0,35	0,35-0,5	1,2	0,94	2,5	1,2	3,51	2,5
B_2 (mg)	0,15-0,2	0,15-0,2	1,4	1,35	3,6	1,4	4,14	3,6
B_6 (mg)	0,15-0,2	0,15-0,2	1	1,5	4	5	4,53	4
B_3 (mg)	4-6,8	4-6,8	17	15,08	40	17	46	40
B_5 (mg)	1-2	1-2	5	5,65	15	5	17,25	15
Biotina (mcg)	5-8	5-8	20	22,62	60	20	69	60
Folato (mcg)	56	56	140	150,8	400	140	414	400
B_{12} (mcg)	0,3	0,3	1	1,88	5	1	6	5

[1]El Soluvit® es un vial de vitaminas hidrosolubles liofilizadas que se disuelven en 10 ml y el Vitalipid Infantil® contiene vitaminas liposolubles en emulsión lipídica en ampollas de 10 ml. [2]Infuvite®. Dos viales multidosis; uno de 1 ml con folato, biotina y vitamina B_{12}, y otro de 4 ml con el resto de vitaminas. La dosis recomendada es 1 ml + 4 ml. Medicamento extranjero. Dosis: RNPT < 1 kg: 1,5 ml; 1-3 kg peso: 3 ml; resto edades: 5 ml. [3]El Cernevit es un vial de liofilizado que se recomienda disolver en 5 ml de agua estéril. [4]Equivalencia: 1 mcg de vitamina A = 3,3 UI. [5]Equivalencia: 1 mcg de vitamina D = 40 UI. [6]RNPT (recién nacido pretérmino) con enfermedad pulmonar: 450-850 mcg. B_1 (tiamina); B_2 (rivoflabina); B_3 (niacina); B_5 (pantoténico); B_6 (piridoxina).

raciones sobre requerimientos que se han expuesto anteriormente. En la tabla XIII se resumen las más importantes.

COMPONENTES DE LAS MEZCLAS DE NP PARA PEDIATRÍA

AMINOÁCIDOS

En pacientes pediátricos, y especialmente en neonatos, está recomendado el uso de soluciones de AA específicas debido a la inmadurez de sus sistemas enzimáticos (GdE 5) (47). No existen estudios sobre la adecuación de estas soluciones a niños de mayor edad, aunque tampoco sobre la idoneidad de las soluciones para adultos.

HIDRATOS DE CARBONO

Se utilizan exclusivamente soluciones estériles de D-glucosa.

LÍPIDOS

Se recomienda el uso de emulsiones lipídicas al 20%. La composición de sus triglicéridos varía según su fuente única o combinada (aceite de soja, coco, oliva y pescado), aunque ninguna ha demostrado una superioridad clara y definitiva sobre las otras (23,48). En tanto se dispone de estudios con evidencia suficiente sobre los efectos de las soluciones mixtas con w3, consideramos que por su composición (equilibrio de AGE, ausencia de fitosteroles y contenido en vitamina E) parecen las más recomendables. El uso rutinario de heparina no está recomendado.

ELECTROLITOS Y MINERALES

El mayor problema para poder añadir en la bolsa de NP todos los electrolitos que requiere el paciente pediátrico es la precipitación calcio-fosfato. Esta se puede disminuir con la utilización del glicerofosfato sódico (49). Es indispensable el uso de filtros de 1,2 micras en la administración de mezclas ternarias, y de filtros de 0,22 micras para mezclas binarias en el sistema de administración para evitar los posibles precipitados (GdE 5) (13,15,20).

OLIGOELEMENTOS

Existen soluciones de oligoelementos intravenosos (IV) específicos para pediatría. En pacientes con NP a largo plazo es importante que no haya exceso de manganeso o cromo.

VITAMINAS

Existen multivitamínicos IV diseñados para pediatría por sus necesidades específicas (25).

Tabla XIII. Consideraciones sobre las principales situaciones especiales

Patología	Inicio	Volumen	Energía (kcal/kg/d)	Aminoácidos (g/kg/d)	Glucosa	Grasa (g/kg/d)	Otros
RNPT (1,15,17,21-29)	Precoz (< 24 horas) (GdE 1)	Ajustado a fase evolutiva	Inicio: 60 A la semana: 100 o más Que asegure crecimiento	Fórmula para RN Inicio: 2,4 (GdE 1), aumento posterior Glutamina no beneficio (GdE 1)	Ajustado a fase evolutiva No insulina de rutina	Inicio precoz (GdE 1) La mejor emulsión lipídica no se conoce (GdE 1)	Ca/P adecuados, control estrecho Suplemento Zn (GdE 3) Vitaminas y oligoelementos
Críticos (1,13,15,30-34)	No consenso precoz *vs.* tardío (> 8 d): evitar sobrealimentación Potenciar vía enteral	No indicaciones especiales	Medición por CI (GdE 1) Ajustado a necesidades, evitar sobrealimentación (GdE 2)	Mínimo 1,5 (GdE 3), pocos estudios adolescentes No uso rutinario de arginina ni glutamina (GdE 2)	Evitar hiperglucemia (GdE 2)	Mínimo 0,5 (emulsión de soja) para asegurar AGE No uso rutinario w3 (GdE 2)	
Hepática (1,15,35-38)	Candidatos a trasplante hepático: soporte agresivo para mejorar pronóstico (GdE 3)	Restringido	EHC: medición por CI (GdE 1)	EHA: no restricción sistemática, solo si inestabilidad clínica y encefalopatía (GdE 5) No evidencia uso AA ramificados	EHA: glucosa para prevenir hipoglucemia (GdE 4)	Cuidado si colestasis	Colestasis: suspender Cu y Mn (GdE 3) Electrolitos según situación clínica (limitación Na, etc.)
Renal (1,15,39-42)		Ajustado	IRA: como críticos ERC 2 a 5: similar a población general (GdE 2)	ERC 2 a 5: no restricción, recomendaciones según edad + 0,5-1 si diálisis peritoneal y 0,4 si hemodiálisis (GdE 4) Fórmula normal	Según aporte de grasa	ERC: dislipemia frecuente que puede limitar aporte calórico (GdE 4)	Controlar Zn y suplementar en hemodiálisis (GdE 4) Controlar vitamina A y retirar en diálisis (GdE 4) IRA y ERC: alteraciones electrolíticas frecuentes
Trasplante de progenitores hematopoyéticos (1,15,43-46)		Restringido	Medición por CI (GdE 1) Evitar sobrealimentación	Proteína suficiente para evitar la pérdida de masa magra (GdE 3) No glutamina		Emulsión oliva y w3 seguras, beneficios antioxidantes (GdE 2)	

AA: aminoácidos; AGE: ácidos grasos esenciales; CI: calorimetría indirecta; EHC: enfermedad hepática crónica; ERC: enfermedad renal crónica; FHA: fallo hepático agudo; RN: recién nacido.

CARNITINA

No existe evidencia de que la incorporación de carnitina aporte efectos beneficiosos, aunque tampoco nocivos. Se sugiere su adición en RNPT y NP de duración superior a cuatro semanas.

PRESCRIPCIÓN Y ESTANDARIZACIÓN

La prescripción de NP es un proceso susceptible de errores. Un impreso de prescripción bien diseñado, así como la informatización de la prescripción, puede disminuir la incidencia de errores y aumentar la eficiencia del procedimiento (15,51). Estos beneficios pueden aumentarse con el uso de soluciones estandarizadas. La prescripción de la NP ha de hacerse a diario tanto si es estándar como individualizada.

Para lograr la estandarización es necesario un rango amplio de soluciones de NP que se ajuste a los diferentes requerimientos de macronutrientes, electrolitos y volumen de los pacientes. Cuando estos no puedan alcanzarse, se emplearán nutriciones individualizadas. En pediatría existe poca experiencia en el uso de soluciones estandarizadas.

PREPARACIÓN

La preparación de la NP está centralizada en los servicios de Farmacia para poder garantizar las condiciones de asepsia y validar la compatibilidad, estabilidad y adecuación de los requerimientos prescritos. Se trabaja en cabina de flujo laminar horizontal cumpliendo estrictamente una normativa de trabajo y es importante realizar controles microbiológicos periódicamente (GdE 5) (52).

Todas las bolsas preparadas deben ir identificadas con el nombre del paciente y su ubicación, la composición exhaustiva de la mezcla y otros datos que puedan ayudar en la administración (GdE 5) (52).

Las soluciones de NP "todo en uno" necesitan menor manipulación tanto en la preparación como en la administración, suponen menor gasto de material fungible y de personal, solo precisan una bomba de administración y son peor caldo de cultivo para microorganismos que los lípidos separados. Por estas razones, si la estabilidad de la emulsión lo permite, esta es la forma ideal de administración (53). Para evitar la desestabilización de la NP es importante seguir un orden de adición de los componentes (siempre los AA primero) y vigilar la concentración final de AA (mayor de 2-2,5%), glucosa y lípidos (GdE 5) (52,53).

La precipitación calcio-fosfato es el mayor problema de compatibilidad de las mezclas de NP. Se produce a rangos de concentración compatibles con las necesidades del paciente, especialmente en niños, ya que tienen altos requerimientos de estas sustancias. Las sales orgánicas de calcio y fosfato son mucho menos proclives a precipitar que las inorgánicas (49), por lo que se recomienda su uso (GdE 5) (52). Los fosfatos orgánicos tienen una buena tolerancia y son una fuente eficaz de fósforo.

Se recomienda el aporte diario de vitaminas y oligoelementos, los cuales se pueden aportar juntos en la misma bolsa. La degradación de vitaminas se puede minimizar utilizando NP "todo en uno", bolsas multicapa y bolsas exteriores de fotoprotección (GdE 5) (52-54).

La generación de peróxidos es de especial importancia por su efecto deletéreo en neonatología. Para prevenirla es fundamental evitar la luz y el contacto con el oxígeno. Se recomienda su fotoprotección con sobrebolsas fotoprotectoras y la utilización de sistemas de administración que eviten el paso de la luz (GdE 1) (55).

El aluminio se puede acumular en el cuerpo y producir efectos nocivos. Es importante conocer el contenido de aluminio de los distintos componentes de la NP para intentar disminuir su aporte. Es preferible utilizar electrolitos en envases plásticos que en cristal (56).

Solamente se pueden incluir en la bolsa de NP los medicamentos compatibles con los componentes de la NP y que no desestabilicen la emulsión.

ADMINISTRACIÓN

Para la administración (57) de NP en pediatría se precisan contenedores preferiblemente multicapa y sobrebolsa fotoprotectora. Idealmente, los sistemas de infusión deberán ser opacos. Los dispositivos protectores tipo Segur-Lock o válvulas herméticas sin aguja son de gran utilidad, ya que evitan tener que pinzar la vía durante la manipulación o desconexión de la línea y los pinchazos accidentales. Además, desinfectados antes y después de su uso de forma adecuada podrían disminuir el riesgo de infección.

Los filtros impiden la entrada de aire y partículas en el torrente circulatorio. Se recomienda el uso de sistemas de administración que tengan incorporado el filtro de 1,2 µm si la NP contiene lípidos y de 0,22 µm si no los lleva (GdE 5) (57). Si no es posible su utilización rutinaria, se aconseja al menos emplearlos en los recién nacidos, en los pacientes en los cuales se prevé un tratamiento largo (especialmente en nutrición parenteral domiciliaria), en los enfermos con enfermedad respiratoria y en las infusiones con alto contenido en partículas (medicamentos que requieren preparación de reconstitución) o con peligro de desestabilizarse.

Las soluciones de NP deben ser administradas con un preciso control de la velocidad de infusión mediante bombas volumétricas. El sistema de infusión debe ser regularmente controlado. Las infusiones a través de una vía periférica deben ser frecuentemente controladas para detectar signos de extravasación. Las bombas de infusión deben tener sistemas de prevención de libre flujo si se abren durante su uso (GdE 5) (57).

La manipulación de las vías debe realizarse con la máxima asepsia, por lo que es imprescindible realizar siempre un lavado antiséptico de las manos, usar guantes estériles y establecer un campo estéril.

Para prevenir la oclusión del catéter es importante infundir suero fisiológico al finalizar la administración.

La infusión puede ser continua, a lo largo de 24 horas, o intermitente en periodos más cortos de tiempo. La administración cíclica es habitual en pacientes con tratamientos de larga duración y en domicilio.

Es deseable administrar la NP por una luz del catéter exclusiva para ello. No se recomienda usar el catéter para extracciones. No se debe administrar ningún fármaco en "Y" con la NP excepto si existen estudios sobre su compatibilidad.

MONITORIZACIÓN

La monitorización de la NP comprende una valoración inicial completa antes de su inicio, en la que se incluirán la propia indicación de la NP, el estado nutricional del niño, el tipo de acceso venoso y una serie de controles analíticos que se detallan en la tabla XIV (GdE 5) (15). La frecuencia con la que se deben realizar estos últimos dependerá de la situación clínica y de la duración del soporte nutricional. Se deben seguir algoritmos de soporte nutricional para la solicitud y monitorización de la NP (GdE 5) (15).

Cuando se trata de pacientes con NPD o prolongada, además de las determinaciones habituales, se monitorizarán niveles de vitaminas y elementos traza (GdE 5) (15).

Se deberían realizar medidas antropométricas y una evaluación clínica en pacientes que reciben NP, 2-3 veces por semana, por parte de un profesional experto (GdE 5) (15).

COMPLICACIONES

ASOCIADAS A LOS CVC

Pueden ser de varios tipos: complicaciones técnicas en relación con la *inserción* del catéter (neumotórax, laceración de un vaso, arritmias, perforación cardiaca con taponamiento, embolismo aéreo, lesión de un plexo nervioso o localización anómala del catéter), mucho menos frecuentes cuando la colocación se dirige mediante ecografía (GdE 1) (12); *rotura o desplazamiento* accidental, oclusión, trombosis venosa e infección.

Tabla XIV. Monitorización de la NP en niños

A. Control clínico
– Balance hídrico diario
– Antropometría (peso, longitud/talla, perímetro craneal)
B. Control analítico
– Hemograma con recuento diferencial
– Electrolitos
– Urea/creatinina
– Glucosa en sangre
– Equilibrio ácido-base
– Calcio/fósforo
– Proteínas totales/albúmina
– Prealbúmina
– Enzimas hepáticas y bilirrubina
– Colesterol y triglicéridos
– Glucosa, electrolitos y cuerpos cetónicos en orina

Estos parámetros deben realizarse al inicio de la NP y posteriormente con frecuencia variable según la situación clínica del paciente (por ejemplo, dos o tres veces a la semana inicialmente). Si la NP se prolonga durante meses hay que monitorizar también oligoelementos, vitaminas, mineralización y edad ósea y estudio de coagulación (estudio de factores de riesgo trombótico).

La *oclusión* consiste en la obstrucción parcial o completa de un catéter que limita o impide la posibilidad de extraer sangre o infundir a su través. Es una complicación frecuente sobre todo en niños. Para prevenirla se recomienda infundir suero fisiológico (3-5 ml) después de la administración de medicaciones o tras la extracción de sangre (GdE 3) (15,58). El lavado con heparina a baja concentración no aporta ninguna ventaja frente al suero salino (GdE 2) (58). El empleo de heparina, catéteres impregnados de heparina, heparina de bajo peso molecular o warfarina de forma profiláctica no ha demostrado ser una medida eficaz en la prevención de trombosis venosa (GdE 2) (59).

La actuación dependerá de la causa que se sospeche (10). Antes de iniciar un tratamiento farmacológico, deberá descartarse oclusión no trombótica causada por precipitados de fármacos o minerales que pueden ser disueltos con hidróxido sódico o ácido clorhídrico (GdE 3), depósitos de lípidos que se disuelven con etanol (GdE 3) o malposición del CVC (60).

En las oclusiones trombóticas el coágulo puede formarse como una vaina de fibrina en el extremo distal del catéter o como un trombo en la pared externa del CVC o en la pared del vaso en el que se sitúa el catéter. En estos casos puede usarse estreptoquinasa, uroquinasa o factor activador del plasminógeno (alteplasa) (GdE 3) (61). Los datos con el empleo de otros agentes trombolíticos (alfimeprasa, tenecteplasa) en niños son muy limitados (GdE 4).

La *trombosis de una vena central* puede ser asintomática, manifestarse como dolor o edema local en la extremidad afecta o incluso como un tromboembolismo potencialmente fatal. Un ecocardiograma o una ecografía-*doppler,* un escáner torácico o una venografía pueden confirmar el diagnóstico. La trombosis aguda puede tratarse con agentes trombolíticos, pero la forma más habitual de tratamiento es la anticoagulación. En pacientes con necesidad de NP prolongada o con alto riesgo de tromboembolismo puede ser interesante el uso de antagonistas de la vitamina K o de heparinas de bajo peso molecular (59-61).

Las *infecciones,* bacteriemias asociadas a catéter (BC), son una de las complicaciones más comunes y potencialmente graves. Las dos principales puertas de infección son el punto de inserción en la piel (en los catéteres de corta duración) o el cabezal del catéter (en los catéteres permanentes) (62). Los gérmenes más frecuentes son: *Staphylococcus epidermidis, Enterobacter spp, Escherichia coli, Klebsiella pneumoniae, Pseudomona aeruginosa, Staphyloccus aureus, Enterococcus (E. faecalis, E. faecium)* y *Candida albicans* u otros hongos.

Debe sospecharse una infección asociada a catéter si el niño presenta fiebre > 38,5 °C, acidosis metabólica, trombocitopenia o inestabilidad en la homeostasis de la glucosa, en ausencia de otro foco en la exploración. Deben realizarse hemocultivos simultáneos de sangre periférica y central, extraídos a través de cada una de las luces del catéter, y proceder a su cultivo cuantitativo (GdE 1)

(10-12,62,63). Tras ello, se comenzará con antibioterapia empírica (GdE 2) que cubra el germen más frecuentemente implicado en las BC (estafilococo plasmocoagulasa negativo) y los bacilos Gram negativos, incluida *Pseudomona aeruginosa.* Una vez conocido el resultado del hemocultivo y del antibiograma se modificará la pauta antibiótica. La duración del tratamiento dependerá del germen aislado (10-12,62,63).

La retirada del catéter es el tratamiento de elección ante una BC, en especial en los catéteres de corta duración (GdE 3) (10-12,62,63). En los casos de BC en un catéter de larga duración podemos intentar evitar la retirada del mismo asociando a la antibioterapia sistémica un sellado (63,64) con antibióticos *(antibiotic-lock)* (GdE 4) o con taurolidina.

La inserción del catéter y su manipulación con técnica aséptica disminuyen el riesgo de BC (GdE 1) (10-12,63). El punto clave en su prevención es el cumplimiento de la técnica aséptica en el manejo del catéter, incluyendo el lavado de manos (GdE 1) (63).

COMPLICACIONES METABÓLICAS

Están derivadas del déficit o del exceso de alguno de los componentes individuales de la solución de NP o de la presencia de contaminantes. Hay que ser extremadamente cuidadoso en la alimentación de niños desnutridos para evitar el síndrome de realimentación, en especial en el paciente crítico (65).

ENFERMEDAD METABÓLICA ÓSEA (OSTEOPOROSIS, OSTEOMALACIA)

Ocurre en pacientes con NP de muy larga duración, especialmente si se asocia a fracaso intestinal (66). El origen es multifactorial.

COMPLICACIONES HEPÁTICAS

La elevación de las enzimas hepáticas (sobre todo GGT) y de la bilirrubina es frecuente en niños con NP de duración superior a 15 días (67). El origen es desconocido y en su aparición pueden influir distintos factores como la disminución del circuito enterohepático, el empleo de soluciones pobres en taurina y ricas en glicina, la composición de las emulsiones lipídicas, la sobrealimentación y las infecciones, entre otras (68). Son importantes en la NP de larga duración, en especial en el seno de un fracaso intestinal, y pueden manifestarse como litiasis biliar o alteración hepática variable (esteatosis, cirrosis, colestasis, etc.). La suspensión de los lípidos intravenosos de la NP y el empleo de una emulsión de aceite de pescado al 10% (Omegaven®, Fresenius-Kabi), 1 g/kd/día por un tiempo limitado, han conseguido mejorar o revertir la colestasis relacionada con el fracaso intestinal (GdE 4) (68).

La prevención de las complicaciones hepáticas debe considerar todos los factores potenciales de riesgo.

PROBLEMAS PSICOSOCIALES

La enfermedad de base, las hospitalizaciones repetidas y prolongadas, la dependencia de máquinas y la sobreprotección de los padres pueden perturbar el desarrollo normal de algunos niños con NP prolongada. Hemos de procurar enviar a los niños con NP prolongada lo antes posible a su domicilio (69).

NUTRICIÓN PARENTERAL DOMICILIARIA

La NPD, aquella que se administra en el domicilio del paciente, es una alternativa a la hospitalización prolongada. Sus objetivos son: mejorar o mantener el estado nutricional del paciente, facilitar la adaptación intestinal, reducir el riesgo de complicaciones relacionadas con la hospitalización (infecciones), mejorar la calidad de vida del niño y su familia y disminuir los costes del tratamiento, evitando hospitalizaciones (69,70).

Para implantar una NPD es necesaria la participación de un equipo multidisciplinar. La familia debe ser adecuadamente entrenada para poder realizar el tratamiento de forma segura y el paciente debe estar en una situación clínica estable. No merece la pena iniciar una NPD si se prevé una duración inferior a 30 días. Debe valorarse el impacto de la NPD en la vida social y laboral de la familia y facilitarse el contacto con personal experto durante las 24 horas del día.

INDICACIONES

La indicación más frecuente es el fracaso intestinal prolongado o permanente (71). La causa más común es el síndrome de intestino corto, seguido por los trastornos de motilidad y la diarrea grave rebelde. Las indicaciones extradigestivas comprenden las complicaciones de los procesos tumorales y las inmunodeficiencias primarias o secundarias.

Las características de la familia y de su entorno social son críticas para iniciar un programa de NPD (69,72). Hay que comprobar que la familia puede y quiere hacerse cargo del cuidado del niño y que tiene los recursos materiales adecuados para llevarlo a cabo.

ACCESOS VASCULARES

La NPD requiere un acceso venoso central adecuado (12). La *composición* de la NPD se adapta a las necesidades individuales del paciente, no difiere de la NP hospitalaria y va a depender, sobre todo, de la edad del paciente y de los aportes tolerados por vía digestiva (1,15,19,68).

ENTRENAMIENTO DE LAS FAMILIAS Y SEGUIMIENTO

La formación tiene como objetivo adquirir los conocimientos y habilidades necesarios para efectuar los cuidados que requiere la

NPD, así como prevenir y reconocer las complicaciones (69,72). Debe comenzarse lo antes posible, implicar a todos los miembros del equipo y proporcionar las instrucciones orales y escritas hasta asegurar su correcta realización. Es imprescindible la evaluación periódica.

Antes del alta, el equipo de NPD tiene que contactar con el pediatra del paciente y el hospital más cercano a su domicilio para conseguir un seguimiento (Tabla XIV) y tratamiento más eficaces (15,69,72). La preparación de la NPD se realizará en dicho hospital, en el de origen o por un servicio de *catering.*

COMPLICACIONES DE LA NPD

No difieren de las observadas en la NP hospitalaria, excepto en lo que se refiere a su frecuencia en relación con la duración más prolongada del tratamiento, sobre todo las infecciones, la trombosis venosa y la hepatopatía. Existe una serie de factores de riesgo que pueden contribuir a su fracaso y a la necesidad de valoración del paciente como posible candidato a trasplante (Tabla XV). La remisión adecuada y precoz a unidades de Rehabilitación Intestinal y Trasplante puede mejorar el pronóstico y la evolución (73) (Tabla XVI).

Tabla XV. Factores de riesgo para el fracaso de la NPD en niños con fallo intestinal crónico (73)

– Lactantes pretérmino o de poca edad
– Alteración mucosa, isquemia intestinal
– Pérdida de válvula ileocecal
– Intestino remanente < 25 cm
– Diarrea intratable
– Infecciones de catéter precoces (< 3 meses)
– Más de tres infecciones relacionadas con el catéter o más de una al mes
– Aporte excesivo de grasa en NP (> 3,5 g/kg/día)
– Intolerancia a la alimentación enteral
– Seguimiento no especializado

Tabla XVI. Criterios de remisión a Unidad de Rehabilitación Intestinal (73)

– Disfunción hepática o alto riesgo de desarrollarla:
• Pretérminos con resección intestinal
• Hiperbilirrubinemia persistente (3-6 mg/dl)
– Problemas clínicos complejos:
• Diagnóstico incierto
• Intervenciones de alargamiento intestinal
– Limitación de accesos venosos centrales:
• Dificultad de colocación o mantenimiento
• Trombosis venosa extensa (2/4 accesos venosos superiores)
• Sepsis por catéter frecuente, sobre todo si alteración hepática

CALIDAD DE VIDA

Los indicadores de calidad de vida de los pacientes con NPD son significativamente peores que los observados en los controles sanos, pero la situación es significativamente mejor cuando la comparación se establece con pacientes en hospitalización prolongada (74).

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