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C/ Castelló, 128, 1.º - 28006 Madrid - Tel. 91 782 00 30 - Fax: 91 561 57 87
e-mail: suscripc@grupoaran.com

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C/ Castelló, 128, 1.º - 28006 Madrid - Tel. 91 782 00 30 - Fax: 91 561 57 87
e-mail: nutricion@grupoaran.com
www.nutricionhospitalaria.org
www.grupoaran.com

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SOCIEDAD ESPAÑOLA DE NUTRICIÓN CLÍNICA Y METABOLISMO

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Nutrición Hospitalaria

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¿Tiene justificación el aporte de fibra con prebióticos en enfermedad renal crónica? Influencia sobre las toxinas urémicas. Utilidad o ficción

Is the contribution of fiber with prebiotics justified in chronic kidney disease? Influence on uraemic toxins. Utility or fiction

La enfermedad renal crónica (ERC) constituye un importante problema de salud mundial que desafía a los pacientes y a las autoridades necesidades sanitarias. El consumo de fibra beneficia a los enfermos renales al actuar de forma preventiva sobre los factores de riesgo asociado, mejorando la composición de la microbiota intestinal o reduciendo la acidosis metabólica y la inflamación (1). El enfoque convencional en el manejo dietético en ERC, que abarca malnutrición, sarcopenia, desgaste proteico energético y sobrecarga de volumen, se está expandiendo hacia el mantenimiento de la salud intestinal. La razón que soporta este manejo dietético en la ERC se deriva del rol emergente de la población bacteriana intestinal, denominada microbiota intestinal, como un factor de riesgo importante en la ERC (2). Cada vez se presta más atención a la modulación de la microbiota intestinal modificando la composición de la dieta para incorporar un número más significativo de alimentos vegetales (3).

Es por ello que el manejo nutricional en la ERC ha cambiado en los últimos años, pasando de dietas restrictivas a la nutrición de precisión, buscando una correcta ingesta de macro y micronutrientes que mejoran el estado nutricional del paciente.

El aumento de los productos bacterianos circulantes de origen intestinal activa la inmunidad innata, promueve la inflamación y aumenta la incidencia de enfermedades cardiovasculares y mortalidad (4). Se ha establecido, en varios estudios, una estrecha correlación entre la alteración de la comunidad microbiana y la progresión de la ERC (5). Además se evidenció una importante diferencia en el perfil fecal entre pacientes con ERC y población sana (6). Cada vez es más relevante la importancia de las toxinas generadas por el metabolismo de la microbiota intestinal. Aproximadamente 10 g de proteínas llegan diariamente al colon, donde son procesadas por bacterias intestinales a metabolitos como amonio, aminas, tioles, fenoles e indoles (7).

Los productos de fermentación colónica se eliminan en gran parte a través de las heces, aunque una parte es absorbido y eliminado por vía renal. En el contexto de la ERC, estos productos pueden, por lo tanto, acumularse (8). Varias moléculas han sido identificadas como toxinas urémicas, como indol sulfato (IS), P-cresol sulfato (PCS) y fenil sulfato (FS) (7). IS y PCS son las dos toxinas urémicas más estudiadas por su toxicidad cardiovascular. Estas no pueden ser eliminadas por las membranas de diálisis, pero son parcialmente excretadas en pacientes con función renal residual mediante secreción en el túbulo proximal (8). En la ERC se elevan los niveles de los productos avanzados de la glicación (AGE) porque su excreción renal está reducida, y la formación endógena puede aumentar debido al estrés oxidativo y, en pacientes con diabetes *mellitus,* derivan de la hiperglucemia. La ingesta de fibra puede reducir los niveles séricos de

editorial

AGE y la velocidad de la onda del pulso (pwv), y esta reducción podría ayudar a prevenir eventos cardiovasculares (9,10).

Varias intervenciones terapéuticas han sido exploradas para mejorar la disbiosis intestinal y así reducir la absorción de toxinas urémicas y el paso de endotoxinas desde la luz intestinal (11). Las toxinas urémicas podrían reducirse mediante el aumento selectivo de las bacterias sacarolíticas (que digieren la fibra dietética) y la disminución de bacterias proteolíticas (proteínas y aminoácidos fermentadores) en el colon.

Las fibras dietéticas se dividen en dos grupos: a) fibras insolubles, que son, en general, menos procesadas durante la digestión y contribuyen más a agregar volumen a la masa fecal y a la mejora de la motilidad intestinal; y b) fibras solubles, carbohidratos fermentables que son fuente de varios metabolitos importantes derivados de la microbiota como ácidos grasos de cadena corta (AGCC), ácidos biliares, poliaminas, iones, fenoles y vitaminas, todos con distintas acciones en las células huésped (12).

Una dieta rica en fibra proporciona energía a la flora intestinal y permite a los aminoácidos que llegan al colon incorporarse a las proteínas bacterianas y excretarse en vez de ser fermentados en solutos urémicos (13). En la ERC existe una relación directa entre la proporción de proteína dietética/fibra y concentraciones de PCS y IS, por lo que una dieta con una baja proporción de proteínas/fibra puede ser beneficiosa (14). Una alta ingesta de fibra se ha asociado con niveles plasmáticos más altos de adiponectina antiinflamatoria y niveles más bajos niveles de interleucina-6 y proteína C reactiva (PCR). Según los resultados del Nacional Encuesta de Examen de Salud y Nutrición (NHANES III), con 14.533 participantes, una alta la ingesta de fibra reduce los niveles de PCR mucho más marcadamente en los pacientes renales que en el resto (38 % por cada 10 g/día de aumento en la ingesta total de fibra frente al 11 % en personas sin enfermedad renal). Además, en la población con ERC, una mayor ingesta de fibra se asoció con menor mortalidad, mientras que en personas sin enfermedad renal no tuvo efectos sobre la mortalidad (13).

La restauración de la microbiota intestinal con suplementación de prebióticos, probióticos o simbióticos ha emergido como un importante potencial terapéutico en la ERC (14). En la actualidad no hay estudios de intervención a larga escala con calidad sobre eventos clínicamente relevantes para apoyar el uso generalizado de estos suplementos dietéticos (15). Estudios con tamaño muestral pequeño han demostrado que la administración de *Bifidobacterium longum* en cápsulas entéricas a pacientes con ERC tuvo efectos mínimos sobre la progresión de la enfermedad renal (13).

La inulina, un polisacárido de fructano de almacenamiento natural, sin sabor, con un grado de polimerización de 2 a 60, que consta de una cadena lineal de unidades de fructosa, con unidades de glucosa en el extremo final, fibra dietética soluble en agua que proporciona varios beneficios para la salud, como regular la glucosa en sangre, reducir la obesidad y la prevención de enfermedades cardiovasculares, ha sido estudiado en diferentes poblaciones (15,16). La fuente natural de la inulina es la achicoria y la alcachofa de Jerusalén en la familia *Asteraceae*. Las raíces de la achicoria contienen 40 % de inulina y los tubérculos de la alcachofa de Jerusalén un 18 %. Además existen preparados comerciales para uso dietético (17-19).

En este número de la revista *Nutrición Hospitalaria*, Liyang Chang y cols. (20) publican los resultados de un elegante estudio aleatorizado, controlado, placebo-control, en 54 pacientes con ERC 3b-5ND, aleatorizados, en dos grupos, valorando la ingesta proteica dietética mediante un diario dietético de 3 días y niveles de nitrógeno en orina de 24 horas, con periodo de intervención de 12 semanas. Este estudio tuvo como objetivo evaluar si una dieta baja en sal (< 100 meqv/día) y baja en proteínas (06-08 g/kg/día) suplementada con 10 g de inulina, como prebiótico, podría reducir los niveles séricos de toxinas urémicas IS y PC en pacientes con ERC, al objeto de aportar evidencia para el ajuste de las prescripciones dietéticas de pacientes hospitalizados y de pacientes ambulatorios. Secundariamente los autores evaluaron sus efectos sobre los marcadores inflamatorios, estado nutricional y función renal. Los autores encontraron un descenso de los niveles séricos de IS y PCS en el grupo tratado. La correlación de la reducción del nivel de IS y PCS fue similar entre la población de estudio ($r = 0{,}570$, $p < 0{,}05$). Los niveles de marcadores inflamatorios en ambos grupos disminuyeron después de la intervención. Se observó una disminución significativa en los niveles de IL6 en el grupo que recibió inulina en comparación con el grupo que solo recibió LPD ($p = 0{,}029$). No encontraron diferencias en los marcadores nutricionales ni variaciones significativas en la función renal.

Sus resultados mejoran nuestra comprensión sobre la posible utilización de Inulina como prebiótico en la reducción de las toxinas urémicas, IS, PCS unidas a proteínas en la ERC.

En resumen, las toxinas urémicas se han asociado con aumento de la inflamación, estrés oxidativo y han sido implicadas en varias complicaciones relacionadas con la ERC, incluyendo enfermedades cardiovasculares, anemia, alteraciones del metabolismo óseo-mineral y la progresión de la ERC.

El uso de una dieta rica en vegetales, técnicas culinarias adecuadas, y uso de prebióticos, probióticos, o los simbióticos, junto con el consejo dietético, podrían muy bien mejorar la disbiosis y/o el aumento de la permeabilidad intestinal, reduciendo la formación de toxinas urémicas y mejorando la microbiota intestinal (21).

Conflictos de interés: el autor declara no tener conflicto de interés.

Secundino Cigarrán Guldrís
Servicio de Nefrología. Hospital Ribera Polusa. Lugo

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ARÁN

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Trabajo Original

Nutrición artificial

Evaluación sensorial de un suplemento nutricional oral específico para diabetes con aceite de oliva virgen extra en pacientes en riesgo nutricional y diabetes *mellitus* tipo 2: ensayo clínico doble ciego, aleatorizado, cruzado y multicéntrico (DIACARE)

Organoleptic evaluation of a diabetes-specific oral nutritional supplement with extra virgin olive oil in patients at nutritional risk and type 2 diabetes mellitus: *double-blind, randomized, crossover and multicenter clinical trial (DIACARE)*

Isabel M.ª Vegas Aguilar[1], Cristina Porca Fernández[2], Tamara Casañas Quintana[3], Alicia Calleja Fernández[3], Cristina Tejera Pérez[2], Francisco Tinahones Madueño[1], Diego Bellido Guerrero[2], José Manuel García Almeida[1]

[1]Servicio de Endocrinología y Nutrición. Hospital Universitario Virgen de la Victoria. Málaga. [2]Servicio de Endocrinología y Nutrición. Complejo Hospitalario Universitario de Ferrol. Ferrol, A Coruña. [3]Departamento Médico. Adventia Pharma. Las Palmas de Gran Canaria

Resumen

Introducción: las fórmulas nutricionales específicas para diabetes (FED) suelen presentar una composición que favorece simultáneamente su palatabilidad y el control glucémico y metabólico.

Objetivo: comparar la aceptación sensorial de un FED respecto a un suplemento nutricional oral estándar (FE) en pacientes en riesgo de desnutrición con diabetes *mellitus* tipo 2.

Método: ensayo clínico, aleatorizado, doble ciego, cruzado, multicéntrico y controlado. Se evaluó, a través de una escala del 1 al 4, el olor, el sabor y la textura percibida de un FED y de un FE.

Resultados: se reclutaron a 29 pacientes y 58 evaluaciones sensoriales de los suplementos. Se observó una mejor valoración de la FED respecto a la FE, aunque no se alcanzaron diferencias estadísticamente significativas: olor, 0,04 (IC 95 %), de -0,49 a 0,56 ($p = 0,092$); sabor, 0,14 (IC 95 %), de -0,35 a 0,63 ($p = 0,561$); textura, 0,14, (IC 95 %), de -0,43 a 0,72 ($p = 0,619$). No se encontraron diferencias cuando se analizaron por orden de aleatorización, sexo, grado de desnutrición, mayor o menor grado de complejidad, mayor o menor tiempo de evolución de la diabetes, ni por ser más o menos mayores.

Conclusiones: el suplemento nutricional específico para paciente con diabetes, formulado con aceite de oliva virgen extra, EPA y DHA, una mezcla específica en hidratos de carbono, fibra soluble e insoluble, presentó una adecuada aceptación sensorial del paciente desnutrido con diabetes *mellitus* tipo 2.

Palabras clave:

Diabetes *mellitus* tipo 2. Desnutrición relacionada con la enfermedad. Suplemento específico para diabetes. AOVE. Sensorial.

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Vegas Aguilar IM, Porca Fernández C, Casañas Quintana T, Calleja Fernández A, Tejera Pérez C, Tinahones Madueño F, Bellido Guerrero D, García Almeida JM. Evaluación sensorial de un suplemento nutricional oral específico para diabetes con aceite de oliva virgen extra en pacientes en riesgo nutricional y diabetes *mellitus* tipo 2: ensayo clínico doble ciego, aleatorizado, cruzado y multicéntrico (DIACARE). Nutr Hosp 2023;40(4):686-691

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Correspondencia:

Alicia Calleja Fernández. Departamento Médico. Adventia Pharma. C/ Viera y Clavijo, 30, 2.º. 35002 Las Palmas de Gran Canaria
e-mail: a.calleja@adventiapharma.com

Abstract

Introduction: oral nutritional supplements specific for diabetes (DSF) usually have a composition that favors their palatability and simultaneous glycemic and metabolic control.

Objective: to compare the sensory acceptability of a DSF with respect to a standard oral nutritional supplement (STF) in patients at risk of malnutrition with type 2 diabetes *mellitus.*

Method: randomized, double-blind, crossover, multicenter, controlled, double-blind clinical trial. Odor, taste and perceived texture of a DSF and a STD were evaluated using a scale of 1 to 4.

Results: twenty-nine patients were recruited and 58 organoleptic evaluations of the supplements were registered. A better evaluation of DSF was observed with respect to STD, although no statistically significant differences were reached: odor, 0.04 (CI 95 %) -0.49 to 0.56 ($p = 0.092$); taste, 0.14 (CI 95 %), -0.35 to 0.63 ($p = 0.561$); texture, 0.14 (CI 95 %), -0.43 to 0.72 ($p = 0.619$). No differences were found when analyzed by order of randomization, sex, degree of malnutrition, greater or lesser degree of complexity, greater or lesser time of evolution of diabetes, or by being older or younger.

Conclusions: the specific nutritional supplement for diabetic patients formulated with extra virgin olive oil, EPA and DHA, a specific mixture of carbohydrates, and fiber, presented an adequate sensory acceptance by malnourished patients with type 2 diabetes *mellitus.*

Keywords:

Diabetes *mellitus* type 2. Disease-related malnutrition. Oral nutritional supplement. EVOO. Organoleptic.

INTRODUCCIÓN

La diabetes *mellitus* (DM) es una enfermedad crónica con una prevalencia que oscila entre el 4,0 % y 6,0 % de los adultos en todo el mundo (1). Las guías de la American Diabetes Association (ADA) 2022 establecen unas recomendaciones de alimentación saludable, siguiendo un patrón de dieta mediterránea. De forma concreta, recomiendan una dieta rica en ácidos grasos monoinsaturados a partir del aceite de oliva, ácidos grasos poliinsaturados (omega-3) y fibra y controlada en sodio. Respecto a la carga y al índice glucémico, las guías de la ADA sugieren su individualización según la situación clínica del paciente (2).

La desnutrición relacionada con la enfermedad (DRE) en la diabetes es una complicación que muchas veces pasa desapercibida. El estudio VIDA, realizado en pacientes ancianos diabéticos hospitalizados, puso de manifiesto que la prevalencia de malnutrición es superior a la de pacientes no diabéticos: alcanza unas tasas de malnutrición del 21,2 % y de riesgo de malnutrición del 39,1 % (3,4). La DRM en el paciente diabético supone un incremento de la mortalidad (5).

El tratamiento nutricional del paciente desnutrido tiene como base el consejo dietético, incidiendo en el fortalecimiento de la ingesta dietética, especialmente energética y proteica, y su combinación con la pauta de suplementos nutricionales orales (SNO) o el uso de nutrición enteral por sonda cuando las circunstancias clínicas impiden alcanzar los requerimientos nutricionales por vía oral. De forma concreta, los SNO se reconocen cada vez más como parte integral de la estrategia global de tratamiento de la desnutrición de los pacientes, tanto a nivel hospitalario como comunitario (6). Diferentes estudios han demostrado que el uso de los SNO resulta eficaz para incrementar la ingesta nutricional, mejorar la evolución clínica del paciente y ser coste-eficaces (6).

Los pacientes diabéticos desnutridos pueden beneficiarse de SNO específicos que favorezcan su control glucémico y metabólico. Para ello, suelen formularse siguiendo las recomendaciones generales de las guías ADA y de los diferentes estudios desarrollados en este grupo de pacientes (7-14). En su mayoría, las fórmulas específicas para diabetes (FED) presentan un mayor porcentaje de grasa (en torno al 40 %), con un elevado componente de ácidos grasos monoinsaturados (> 20 %, VCT); un moderado aporte de hidratos de carbono (en torno al 40 %) a partir de polisacáridos (almidón resistente), oligosacáridos de bajo índice glucémico (dextrinas), fructosa e isomaltulosa (isómero de la glucosa); un porcentaje de proteínas del 15-20 % a partir de proteína láctea (lactosuero, caseinato) o proteína vegetal, y fibra, habitualmente a partir de una mezcla soluble e insoluble o solo soluble (15). Teniendo en cuenta que los pacientes diabéticos suelen presentar frecuentemente alteraciones del gusto (16), las FED suelen presentar una composición que favorece simultáneamente su palatabilidad y el control glucémico y metabólico.

El objetivo principal del estudio fue comparar la aceptación sensorial de un suplemento nutricional líquido específico para diabetes con la de un suplemento nutricional oral estándar en pacientes en riesgo de desnutrición con diabetes *mellitus* tipo 2 (DM2).

MATERIAL Y MÉTODOS

Ensayo clínico, aleatorizado, doble ciego, cruzado, multicéntrico y controlado realizado desde marzo de 2019 hasta abril de 2022. El estudio se registró en ClinicalTrials.gov con el identificador NCT05423938.

PACIENTES

Se reclutaron pacientes adultos con diagnóstico de DM2 (confirmado por el uso de hipoglucemiantes orales durante al menos dos meses) en riesgo de desnutrición o desnutridos (diagnosticados con valoración global subjetiva [VGS]). Se excluyeron pacientes con DM1, DM2 en tratamiento con insulina y DM secundaria a esteroides, pacientes en tratamiento con inhibidores de la alfaglucosidasa, IMC > 35 kg/m^2, neoplasia maligna, enfermedad renal crónica avanzada (filtrado glomerular < 30 ml/min), hepatopatía y gastroparesia graves, enfermedad infectocontagiosa crónica (tuberculosis activa, hepatitis B o C o VIH), embarazadas o lactantes o que presentasen una alergia o intolerancia a alguno de los ingredientes de las fórmulas.

MÉTODO

En la visita inicial, el paciente fue valorado nutricionalmente. Se realizó un diagnóstico nutricional con VGS. Tras la aleatorización del orden de ingesta de los suplementos a estudio, el paciente se tomó el primer suplemento nutricional oral (SNO) de 200 ml en presencia del investigador. Tras su ingesta completa, se realizó una valoración sensorial en la que se evaluó el olor, el sabor y la textura percibida, que se puntuaron en una escala del 1 al 4. Las respuestas se clasificaron de forma cualitativa en: muy malo, malo, regular, bueno o muy bueno. En el día 8 se realizó la segunda visita, en la que se repitió el mismo procedimiento que en la visita inicial, pero el SNO que se tomó el paciente fue la segunda fórmula a estudio.

FÓRMULAS A ESTUDIO

- FED (Bi1 DIACARE® hp/hc, Adventia Pharma). Suplemento nutricional oral (SNO) específico para diabetes, polimérico, hipercalórico e hiperproteico, con fibra.
- FE (Bi1 CONTROL®, Adventia Pharma): SNO estándar, polimérico, hipercalórico e hiperproteico, sin fibra.

La información nutricional de las fórmulas nutricionales se detalla en la tabla I. Los SNO se presentaron en un envase Tetra Pak® de 200 ml en blanco exactamente iguales para ambas fórmulas. Cada envase se etiquetó con un código numérico como única diferenciación entre ambos productos para que el paciente recibiese el suplemento experimental (FED) o el control (FE).

ALEATORIZACIÓN

El procedimiento de aleatorización lo realizó el responsable del análisis estadístico del estudio a través de una tabla numérica. Cada paciente recibió un número de participante que le hizo comenzar el estudio por un producto u otro de forma cruzada (experimental [FED]; control [FE]).

ASPECTOS ÉTICOS

El estudio se llevó a cabo en consonancia con la declaración de Helsinki. El protocolo del estudio, la hoja de información del paciente y el consentimiento informado fueron aprobados por el Comité de Ética de Investigación Provincial de Málaga con fecha 21/2/2019 y código JGA-DIACARE-2018-01.

A todos los pacientes se les informó de las condiciones de participación y accedieron a participar tras firmar el consentimiento informado.

ANÁLISIS ESTADÍSTICO

Se empleó la prueba de t de Student para variables continuas y la prueba de χ^2 para variables categóricas. Las diferencias entre grupos para las variables continuas se resumen mediante el intervalo de confianza del 95 % de la diferencia de medias y la desviación estándar. Se consideró estadísticamente significativa una $p < 0,05$.

Tabla I. Composición de macronutrientes e ingredientes de las fórmulas por 100 ml

	FED (A)	FE (B)
Energía (kcal)	150	150
Proteínas: g / VCT %, (ingredientes)	7,5 g / 20 % (lactosuero, caseinato y proteína vegetal)	7,5 g / 20 % (caseinato)
Hidratos de carbono: g / VCT %, (Ingredientes) Azúcares	13 g / 42 % (dextrina, maltodextrina e isomaltulosa) 1,9 g (1,3 g isomaltulosa)	34,5 g / 46 % (maltodextrina y sacarosa) 6,8 g (0 g isomaltulosa)
Grasas: g / VCT % (ingredientes) AGS (VCT %) AGMI (VCT %) AGPI (VCT %) EPA y DHA (mg)	7,0 g / 36 % (AOVE, canola y pescado) 7,4 % 25,4 % 9,4 % 75 mg	5,6 g / (34 %) (girasol) 5,7 % 11,3 % 17,0 % -
Fibra Soluble Insoluble	2,3 g 1,6 g 0,7 g	-
Aroma	Natural vainilla	Natural vainilla
Edulcorante	Acesulfamo K (E-950) Sucralosa (E-955)	Sacarosa Acesulfamo K (E-950) Sucralosa (E-955)

AGS: ácidos grasos saturados; AGM: ácidos grasos monoinsaturados: AGP: ácidos grasos poliinsaturados; AOVE: aceite de oliva virgen extra; FED: fórmula específica para diabetes; FE: fórmula estándar; VCT %: porcentaje respecto al valor calórico total. A: Bi1 diacare hp-hc®, Adventia Pharma S. L., España; B: Bi1 control hp-hc®, Adventia Pharma S. L., España.

RESULTADOS

PARÁMETROS DEMOGRÁFICOS Y DE EVOLUCIÓN DE LA DM TIPO 2

Se incluyeron 29 pacientes en el estudio, de los que el 51 % fueron mujeres. La edad media fue de 68,84 años (DE 11,37). El índice de complejidad de Charlson fue de 4,14 (DE 1,57). Los participantes presentaron un tiempo de evolución de su diabetes *mellitus* tipo 2 de 8,66 años (DE 6,89), una HbA1c de 6,29 (DE 1,12) % y el tratamiento recibido mayoritariamente fue la metformina (93,1 %), combinado, en algunos casos, con análogos del GLP1 e IDPP-IV.

Respecto al estado nutricional, el 86,2 % presentó riesgo de desnutrición (VGS = B) y el 13,8 %, una desnutrición grave (VGS = C). Los resultados se detallan en la tabla II. El porcentaje de peso perdido fue del 8,66 % (DE 5,76), con un IMC de 24,88 kg/m^2 (DE 4,52).

Respecto a la valoración sensorial cuantitativa, se observó una mejor valoración de la FED respecto a la FE (Fig. 1), aunque no se alcanzaron diferencias estadísticamente significativas: olor, 0,04 (IC 95 %), de -0,49 a 0,56 (p = 0,092); sabor, 0,14 (IC 95 %), de -0,35 a 0,63 (p = 0,561); textura, 0,14 (IC 95 %), de -0,43 a 0,72 (p = 0,619), ni cuando se agruparon las valoraciones en un sumatorio 0,39 (IC 95 %), de -1,35 a 2,13 (p = 0,653). No se encontraron diferencias estadísticamente significativas cuando se analizaron por orden de aleatorización, sexo, grado de desnutrición, mayor o menor grado de complejidad, mayor o menor tiempo de evolución de la diabetes ni por ser más o menos mayores.

Respecto a la valoración sensorial cualitativa, se observó una mejor valoración de la FED respecto a la FE (Fig. 2), aunque no se alcanzaron diferencias estadísticamente significativas ni en la percepción del olor (p = 0,986), del sabor (p = 0,755) o de la textura (p = 0,789). No se encontraron diferencias estadísticamente significativas cuando se analizaron por orden de aleatorización, sexo, grado de desnutrición, mayor o menor grado de complejidad, mayor o menor tiempo de evolución de la diabetes ni por ser más o menos mayores.

Tabla II. Resultados detallados de la VGS

Porcentaje de peso perdido	< 5 % = 6,9 % 5-10 % = 82,8 % > 10 % = 10,3 %
Cambios en la ingesta dietética	Sin cambios: 34,5 % Sólida insuficiente: 65,5 %
Síntomas gastrointestinales	Ninguno: 69,0 % Anorexia: 17,2 % Diarrea: 6,9 % Disfagia: 6,9 %
Capacidad funcional	Sin disfunción: 41,4 % Trabajo reducido: 34,5 % Ambulante sin trabajar: 24,1 %
Estrés metabólico	Sin estrés: 82,8 % Estrés bajo: 17,2 %
Pérdida de grasa	Leve: 86,2 % Moderada: 13,8 %
Pérdida de masa muscular	Leve: 75 % Moderada: 25 %

VGS: valoración global subjetiva.

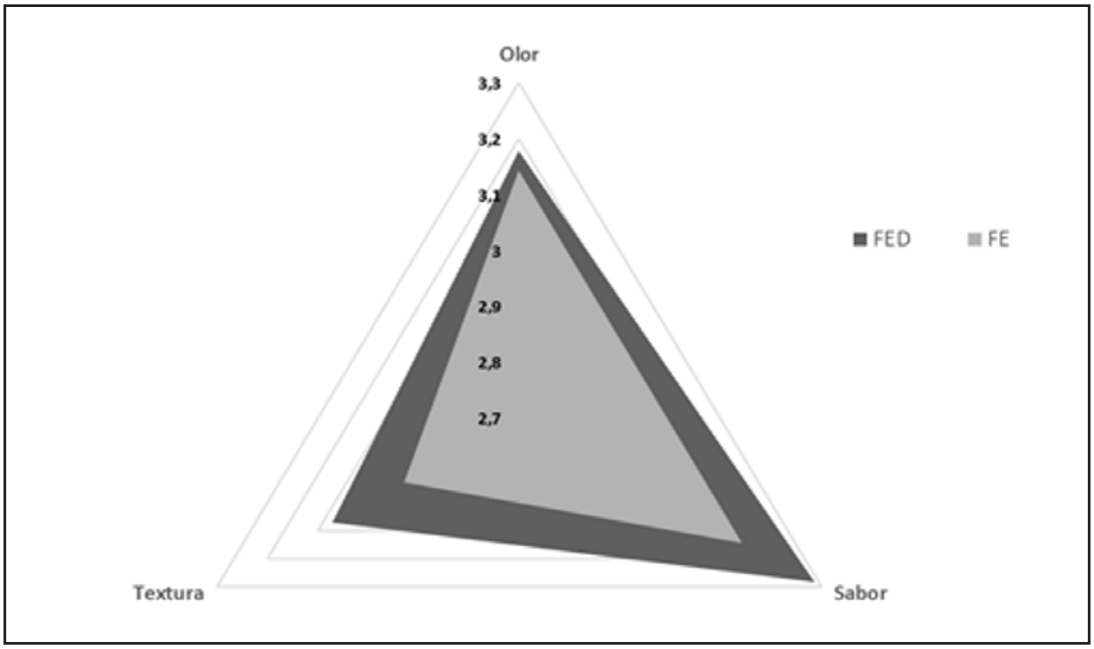

Figura 1. Valoración sensorial cuantitativa de los suplementos a estudio. FED: fórmula específica para diabetes; FE: fórmula estándar.

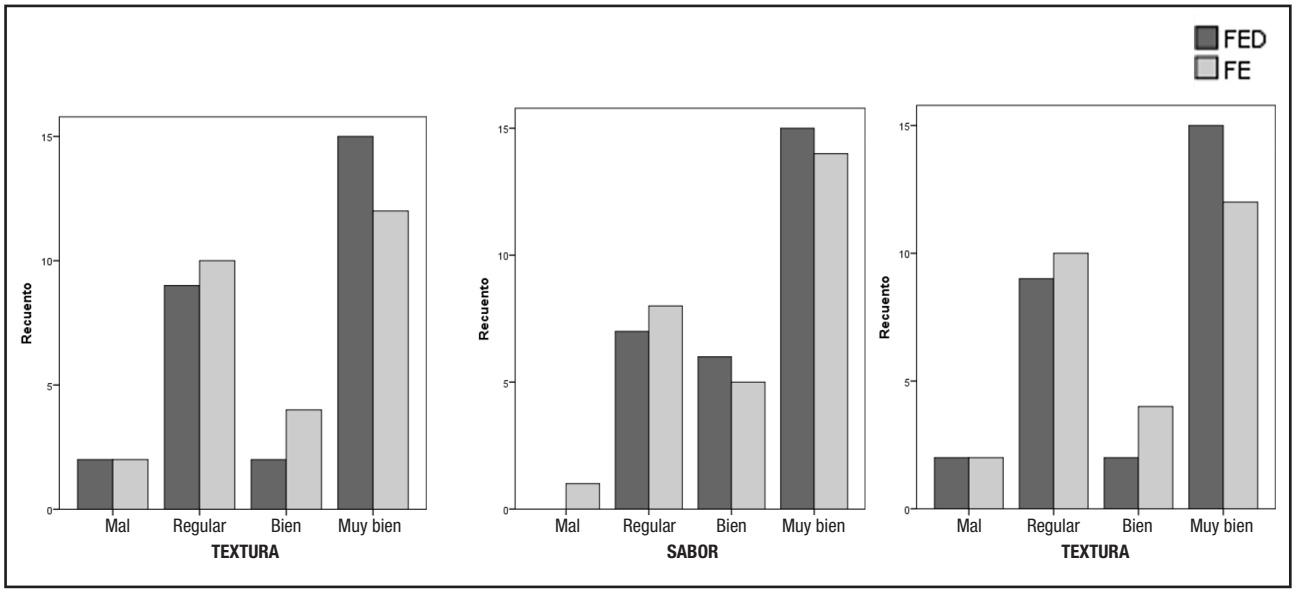

Figura 2. Valoración sensorial cualitativa de los suplementos a estudio. FED: Fórmula específica para Diabetes; FE: Fórmula estándar.

DISCUSIÓN

La fórmula específica para diabetes con aceite de oliva virgen extra, diseñada específicamente para cubrir las necesidades concretas del paciente diabético, ha demostrado que consigue una aceptación sensorial tan adecuada como una fórmula estándar.

Los pacientes del estudio presentaron una edad avanzada, un largo tiempo de evolución de la diabetes tipo 2 y un índice de comorbilidad elevado. Se conoce que, a mayor edad, los individuos requieren una mayor concentración de ingredientes para percibir los diferentes sabores, especialmente dulces y salados (17). La disminución en la capacidad gustativa es muy común en ancianos y puede condicionar su estado nutricional y su evolución clínica. La pérdida del sentido del gusto resulta una situación multifactorial en la que se incluyen cambios fisiológicos como la disfunción de los receptores celulares del gusto, un inadecuado mantenimiento de la higiene y de la salud bucal, así como una disminución de la función olfativa. Aunque no existe un consenso general sobre la idea de una alteración de la percepción quimicosensorial asociada a la edad avanzada *per* se, está comúnmente aceptado que son los diferentes eventos asociados a la edad, un mal estado general de salud, la polimedicación y la pluripatología los que pueden condicionar esta disminución en la percepción del gusto (18).

A su vez, se ha demostrado que la diabetes *mellitus* tipo 2 puede disminuir la percepción de los sabores. En el estudio de Catamo et al., en el que realizaron una comparación en la percepción de los diferentes sabores entre individuos sanos y diabéticos, determinaron que los diabéticos presentaron una menor sensibilidad debido al impacto de los episodios de hiperglucemia (19). Esta disminución en la percepción del gusto puede condicionar una menor ingesta de alimentos de forma general y que requieran que los alimentos, y de forma concreta los SNO, presenten una saborización dulce más marcada.

Aunque en nuestro estudio no se hayan encontrado diferencias por el estadio de la desnutrición, se sabe que esta va a determinar el desarrollo de disgeusia y de otras formas de alteraciones en el sentido del gusto (20). Se sabe que las deficiencias nutricionales, tanto de origen primario como secundario, pueden desencadenar alteraciones en la percepción del gusto o exacerbar los efectos inducidos por el envejecimiento. En particular, el zinc desempeña un papel importante en varias vías metabólicas esenciales y es un componente de una gran variedad de metaloenzimas que intervienen en la transducción del gusto, como la anhidrasa carbónica IV. Se ha identificado la deficiencia de zinc como un factor causante de los trastornos del gusto que pueden provocar cambios en el apetito (21).

Nuestro estudio resulta el primero que plantea la aceptación sensorial de una fórmula diabética respecto a una estándar en pacientes con DM2 en riesgo de desnutrición. Existen otros estudios en los que se ha evaluado la aceptación de FED en pacientes diabéticos, pero, como en el estudio de Grau et al., se evalúa la aceptación entre varias dietas para conocer las preferencias del consumidor final (22).

Como fortalezas del estudio, cabe destacar que es el primero en el que se evalúa la aceptación sensorial de un suplemento nutricional específico para diabetes con AOVE, EPA y DHA sin azúcares añadidos. El AOVE es un alimento con marcadas características organolépticas determinadas, fundamentalmente, por sus componentes minoritarios (1-3 % del total) a partir de compuestos fenólicos como el hidroxitirosol y sus derivados (oleuropeina y tirosol), tocoferoles y otros compuestos como hidrocarburos (escualeno) o pigmentos como la provitamina A (23). Otros ingredientes de la fórmula FED que pudieron marcar la sabo-

rización del producto fueron el EPA y el DHA. Estos dos ácidos grasos provienen del aceite de pescado, cuyas características sensoriales están condicionadas con un olor y un sabor muy marcados por el componente oleoso de esta y por la elevada sensibilidad a su enranciamiento en presencia de oxígeno debida a la configuración espacial de los ácidos grasos omega-3 y a sus insaturaciones (24). Es necesario destacar que el proceso industrial de formulación y de fabricación de un SNO requiere de un trabajo de neutralización de olores y de sabores y posterior saborización y aromatización que favorezcan una adecuada aceptación por parte del paciente. Dentro de los saborizantes empleados, la sacarosa es uno de los ingredientes más habituales, ya que no solo mejora la saborización del SNO, sino que contribuye a obtener un mejor color (reacción de Maillard) y una mejor textura (25).

Respecto a las limitaciones, cabe destacar que solo se recogieron tres variables de la valoración sensorial (olor, sabor y textura). Esta decisión se tomó teniendo en cuenta el perfil del paciente al que estaba dirigida (edad avanzada y sin entrenamiento en el campo de las catas de alimentos) para que pudiese participar de forma sencilla. Respecto al tamaño muestral, de 29 pacientes, ha sido superior al realizado en otros estudios por otros autores y, además, resulta compensatorio al haberse planteado como ensayo clínico cruzado. Cabría destacar que el tiempo prolongado que ha supuesto el reclutamiento de pacientes se ha debido a la parálisis que se produjo por la pandemia COVID durante el año 2020 y primera parte del 2021 y por la falta de concienciación en la detección de desnutrición en la atención ambulatoria del paciente con diabetes tipo 2 por parte del personal sanitario.

CONCLUSIONES

El suplemento nutricional específico para el paciente con diabetes formulado con aceite de oliva virgen extra, EPA y DHA, una mezcla específica en hidratos de carbono, fibra soluble e insoluble, presentó una adecuada aceptación sensorial del paciente desnutrido con diabetes *mellitus* tipo 2.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

Glycaemic and insulinaemic impact of a diabetes-specific oral nutritional supplement with extra-virgin olive oil in patients with type 2 diabetes *mellitus* at nutritional risk: a randomized, double-blind, crossover, multicentre clinical trial (DIACARE)

Impacto glucémico e insulinémico de un suplemento nutricional oral con AOVE específico para diabetes en pacientes en riesgo nutricional y con diabetes mellitus *tipo 2: ensayo clínico, aleatorizado, doble ciego, cruzado y multicéntrico (DIACARE)*

José Manuel García Almeida[1], Isabel M.ª Vegas Aguilar[1], Alicia Calleja Fernández[2], Cristina Porca Fernández[3], Tamara Casañas Quintana[2], Cristina Tejera Pérez[3], Francisco Tinahones Madueño[1], Diego Bellido Guerrero[3]

[1]Endocrinology and Nutrition Department. Hospital Universitario Virgen de la Victoria. Málaga, Spain. [2]Medical Department. Adventia Pharma S. L. Las Palmas de Gran Canaria, Spain. [3]Endocrinology and Nutrition Department. Complexo Hospitalario Universitario de Ferrol. Ferrol. A Coruña, Spain

Abstract

Introduction: there is controversy about the usefulness of specific enteral nutrition formulas in malnourished patients with diabetes. The effects on blood glucose and other aspects of metabolic control are not fully understood in the scientific literature.

Objective: the aim of the study was to compare the glycaemic and insulinaemic response of patients with type 2 diabetes at risk of malnutrition after oral feed between a diabetes-specific formula with AOVE (DSF) and a standard one (STF).

Methods: a randomized, double-blind, crossover, multicentre clinical trial was conducted in patients with type 2 diabetes at risk of malnutrition (SGA). The patients were randomized to receive either DSF or STF, a week apart. A glycaemia and insulinaemia curve was made at times 0 minutes, 30 min, 60 min, 90 min, 120 min, and 180 min after the patients drank 200 ml of the oral nutritional supplement (ONS). The principal variables were the area under the curve (AUC0-t) of glucose and insulin.

Results: 29 patients (51 % women) were included, who were on average 68.84 (SD 11.37) years old. Regarding the degree of malnutrition, 86.2 % presented moderate malnutrition (B) and 13.8 % severe (C). When the patients received the DSF, they had a lower mean of glucose AUC0-t (-3,325.34 mg/min/dl [95 % CI: -4,3608.34 to -2,290.07]; $p = 0.016$) and also a lower mean of insulin AUC0-t (-451.14 µU/min/ml [95 % CI: -875,10 to -27.17]; $p = 0.038$). There were no differences in the degree of malnutrition.

Conclusion: compared with STF, DSF with AOVE showed a better glycaemic and insulinaemic response in patients with type 2 diabetes at risk of malnutrition.

Keywords:

Diabetes *mellitus* type 2. Disease-related malnutrition. EVOO. Postprandial glycaemia. Postprandial insulinaemia. Interstitial glucose.

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Conflict of interest: ACF and TCQ are employees of Adventia Pharma S.L. The rest of the authors declare no conflict of interest.

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Correspondence:

Alicia Calleja Fernández. Departamento Médico. Adventia Pharma. C/ Viera y Clavijo, 30, 2.º. 35002 Las Palmas de Gran Canaria, Spain
e-mail: a.calleja@adventiapharma.com

Resumen

Introducción: la utilidad de las fórmulas específicas de nutrición enteral en el paciente desnutrido con diabetes resulta controvertida. Sus efectos sobre la glucosa en sangre y otros aspectos del control metabólico no se conocen del todo en la literatura científica.

Objetivo: el objetivo del estudio fue comparar la respuesta glucémica e insulinémica de los pacientes con diabetes de tipo 2 (DM2) en riesgo de desnutrición tras la ingesta oral de una fórmula específica para diabetes (DSF) con aceite de oliva virgen extra (AOVE) y una estándar (STF).

Métodos: ensayo clínico aleatorizado, doble ciego, cruzado y multicéntrico enpacientes con DM2 en riesgo de desnutrición (SGA). Los pacientes se asignaron aleatoriamente para recibir DSF o STF con una semana de diferencia. Se realizó una curva de glucemia e insulinemia en los siguientes tiempos: 0 minutos, 30 min, 60 min, 90 min, 120 min y 180 min tras la ingesta de 200 ml del suplemento nutricional oral (SNO). Las variables principales fueron el área bajo la curva (AUC0-t) de glucosa e insulina.

Resultados: se incluyeron 29 pacientes (51 % mujeres), con una edad media de 68,84 años (DE 11,37). En cuanto al grado de desnutrición, el 86,2 % presentaba desnutrición moderada (B) y el 13,8 %, severa (C). Cuando los pacientes recibieron DSF tuvieron una media más baja de AUC0-t de glucosa (-3325,34 mg/min/dl [IC 95 %: de -4.3608,34 a -2.290,07]; $p = 0,016$) y también una media más baja de AUC0-t de insulina (-451,14 µU/min/ml [IC 95 %: de -875,10 a -27,17]; $p = 0,038$) respecto a cuando recibieron STF. No hubo diferencias por el grado de desnutrición.

Conclusión: la fórmula con AOVE específica para diabetes mostró una mejor respuesta glucémica e insulinémica en pacientes con diabetes de tipo 2 en riesgo de desnutrición respecto a una fórmula estándar.

Palabras clave:

Diabetes *mellitus* tipo 2. Desnutrición relacionada con la enfermedad. Aceite de oliva virgen extra. Glucemia posprandial. Insulinemia posprandial. Glucosa intersticial.

INTRODUCTION

Diabetes *mellitus* (DM) is a chronic disease with a prevalence of 4.0 % to 6.0 % in adults worldwide (1) The patient profile is very heterogeneous with different pharmacological and nutritional treatment needs (2) DM involves accelerated atherosclerosis, leading to organ failure due to macro- and micro-angiopathy (3-6).

Disease-related malnutrition (DRM) in DM is a complication that often goes unnoticed. The VIDA study, conducted in hospitalized elderly diabetic patients, showed that the prevalence of malnutrition is higher in diabetic patients than in non-diabetic patients, with malnutrition rates of 21.2 % in diabetic patients and a risk of malnutrition of 39.1 % (7,8). This DRM in diabetic patients leads to an increase in the risk of mortality (9).

Studying the metabolic response after intake is essential for assessing the postprandial situation. It will depend on the glycaemic response, marked mainly by carbohydrate intake, which in turn will depend not only on the type of carbohydrate but also on other nutrients, such as fat, fibre, and protein, in terms of both quantity and quality. This means that the overall composition of the intakehas an impact on the metabolic response of diabetic patients (10).

The ADA 2022 guidelines set out recommendations for a healthy diet following a so-called Mediterranean diet pattern, which is rich in monounsaturated fatty acids, mainly from olive oil, and polyunsaturated fatty acids (omega-3), besides being rich in fibre and low in sodium. Glycaemic load and glycaemic index recommendations should be made on an individual basis according to the patient's clinical situation (2). In patients at high cardiovascular risk, extra virgin olive oil, in the context of a Mediterranean diet, has shown multiple benefits in the development and progression of diabetes (11,12).

Regarding artificial nutritional support, multiple studies have been conducted to assess the impact of enteral nutrition formulas on the metabolic and glycaemic response in diabetic patients (13-19). Nevertheless, there is currently controversy in clinical practice guidelines about the benefits of formulations specifically designed for diabetic patients (20). The meta-analysis by Sanz París et al (13). investigates the benefits for metabolic control and glycaemic control of formulas with a high intake of monounsaturated fatty acids [>20 % of the total energy (TE)]. It is necessary to develop studies focused on diabetic patients with disease-related malnutrition with an adequate phenotypic and aetiological diagnosis (21).

Continuous interstitial glucose monitoring allows us to assess an individual's glycaemic response in a more comprehensive way. This technology, which is becoming increasingly widespread in our environment, allows us not only to monitor glucose continuously but also to determine periods in and out of range and to detect silent hypoglycaemia (22). This continuous monitoring has been shown to reduce complications related to the timing, frequency, and intensity of hypoglycaemic episodes (23). Regarding the monitoring of the glycaemic response of malnourished diabetic patients after the intake of nutritional support, these tools may be advantageous for assessing the impact of diet and supplementation on an ongoing basis.

In patients with diabetes and obesity, a study has been published with diabetes-specific dietary substitutes assessing the interstitial glycaemic response using FreeStyle-Libre® technology. In this study, the researchers describe the benefits of a diabetes-specific formula (DSF) as a replacement for breakfast and show that when used as an afternoon snack, it improves both glycaemic control and behavioural factors related to the dietary management of diabetes (24).

Currently, there is no study that has assessed the glycaemic impact of a specific formulation of a diabetes-specific oral nutritional supplement using continuous interstitial glucose monitoring.

The aim of the study was to compare the glycaemic and insulinaemic response of patients with type 2 diabetes at risk of malnutrition after oral feed between a diabetes-specific formula (DSF) and a standard one (STF).

METHODS

From March 2019 to April 2022, we conducted a randomized, double-blind, crossover, multicentre, controlled clinical trial. ClinicalTrials.gov Identifier: NCT05423938.

PATIENTS

Adult patients with a diagnosis of DM2 (confirmed by the use of oral hypoglycaemic agents for at least two months) at risk of malnutrition or malnourished (diagnosed with subjective global assessment [SGA]) were recruited. Patients with DM1 or DM2 on insulin therapy and patients with DM secondary to steroids were excluded. Also excluded were patients on treatment with alpha-glucosidase inhibitors, as well as those with a BMI > 35 kg/m^2, malignant neoplasia, advanced chronic kidney disease (glomerular filtration rate < 30 ml/min), severe hepatopathy and gastroparesis, or a chronic infectious disease (active tuberculosis, hepatitis B or C, HIV). Pregnant or lactating women and patients with an allergy or intolerance to any of the ingredients of the formulas could also not participate.

SAMPLE SIZE CALCULATION

Regarding the sample size calculation, the results of a study by De Luis et al. (2013) were used (19) in which a mean difference in peak plasma glucose concentration of 20 % and a standard deviation of 22.97 mg/dL were obtained. At a confidence level of 80 %, 13 patients per experimental arm would be needed. Allowing for a loss to follow-up of 10 %, 14 patients per group are then considered, making a total of 28 patients.

METHODOLOGY

At the initial visit, randomization, SGA, and anthropometric assessment (weight and height) were carried out, besides measuring the body composition with bioimpedance. A continuous interstitial glucose monitor (FreeStyle-Libre®Pro, Abbott®) was placed, and a unique unit of the first oral nutritional supplement (ONS) of 200 ml, whose identity was unknown to both the patient and the principal investigator, was taken. Patients came to the test fasting (between 8 and 12 hours), having ingested an average of 150 g of carbohydrates per day during the three previous days, without consuming alcohol or having practiced intense physical exercise during the previous 24 hours. Blood samples were drawn for glycaemia and insulinaemia determination at 0 minutes, 30 min, 60 min, 90 min, 120 min, and 180 min (± 5 min). On day 8, the intermediate visit was held, and the same procedure as in the initial visit was repeated, but the ONS taken by the patient was the second formula to be studied. On day 15, the interstitial blood glucose sensor was removed.

FORMULAS TO BE STUDIED

The description of each formula is detailed in table I:

- DSF (Bi1 DIACARE® hp/hc, Adventia Pharma): polymeric, hypercaloric, and hyperproteic, with fibre.
- STF (Bi1 CONTROL®, Adventia Pharma): polymeric, hypercaloric, and hyperproteic, without fibre.

Each oral nutritional supplement (ONS) was presented in a 200 ml blank Tetra Pak® package in exactly the same way for both types of ONS. Each package was labelled with a numerical code as the only differentiation between the two products for the patient to receive either the experimental supplement (DSF) or the control (STF).

LABORATORY TECHNIQUES

The laboratory techniques used for biochemical determinations were: hexokinase for glucosa; chemiluminescence for insulin; bromocresol green for albumin; nephelometry for prealbumin; Latex Enhanced Immunoturbidimetric Assay for Wide-Range for CRP; enzymatic CHOD-PAP method for cholesterol.

Table I. Macronutrient composition of study formulas per 100 ml

	DSF (a)	STF (b)
Energy (kcal)	150	150
Protein g / TE %, (ingredients)	7.5 g / 20 % (whey, caseinate, and plant protein)	7.5 g / 20 % (caseinate)
Carbohydrate g / TE %, (ingredients) Sugars	13 g / 42 % (dextrin, maltodextrin, and isomaltulose) 1.9 g (1.3 g isomaltulose)	34.5 g / 46 % (maltodextrin and sucrose) 6.8 g (0 g isomaltulose)
Fat g / TE % (ingredients) Saturated (TE %) MUFA (TE %) PUFA (TE %) EPA&DHA (mg)	7.0 g / 36 % (EVOO, canola, and fish oil) 7.4 % 25.4 % 9.4 % 75 mg	7.6 g / (34 %) (sunflower) 5.7 % 11.3 % 17.0 % -
Fibre Soluble Insoluble	2.3 g 1.6 g 0.7 g	-

DSF: diabetes-specific formula; EVOO: extra virgin olive oil; TE %: percentage of total energy; MUFA: monounsaturated fatty acid; PUFA: polyunsaturated fatty acid; SFT: standard formula. A: Bi1 diacare® hp-hc, Adventia Pharma S. L., Spain; B: Bi1 control hp-hc®, Adventia Pharma S. L., Spain.

RANDOMIZATION

The randomization procedure was performed by the person responsible for the statistical analysis of the study, using a numerical table. Each patient received a participant number so that he or she could start the study with one product or the other (experimental [DSF] or control [STF]) in a crossover manner.

ETHICAL ISSUES

The study was conducted in accordance with the Declaration of Helsinki. The study protocol, patient information sheet, and informed consent were approved by the Málaga Provincial Research Ethics Committee, with the code JGA-DIACARE-2018-01. All patients were informed of the conditions of participation in the study and agreed to participate after signing the informed consent.

STATISTICAL ANALYSIS

For comparison of the glycaemic variability between the two groups, the following parameters were determined: the mean blood glucose, the standard deviation of the mean blood glucose, the area under the concentration curve, the time from nutrition administration to the last measurable glucose concentration (AUC0-t), the maximum glucose concentration (Cmax), and the time to reach the maximum glucose concentration (Tmax). The same determinations were performed with insulin, except for the maximum concentration and the time to reach it. The AUC0-t was calculated by the trapezoidal method (17).

For the analysis, the Student's t-test was used for continuous variables and the chi-square test for categorical variables. Non-parametric variables were analyzed with Wilcoxon test. For continuous variables, differences between groups are summarized by the 95 % confidence interval (CI 95 %) of the mean difference and the standard deviation (SD), or median and intercuartile range (SPSS Inc. 22.0, Chicago, IL, USA) was used to analyce the data.

RESULTS

DEMOGRAPHIC AND DEVELOPMENTAL PARAMETERS OF TYPE 2 DM

Twenty-nine patients were included in the study (Fig. 1), 51 % female. The mean age was 68.84 (11.37) years. The Charlson complexity index was 4.14 (1.57). The participants had a time course of type 2 diabetes *mellitus* of 8.66 years (6.89) and an HbA1c of 6.29 % (1.12); the treatment received was mostly metformin (93.1 %), combined, in some cases, with GLP1 analogues and IDPP-IV.

NUTRITIONAL STATUS

Of all the patients, 86.2 % were at nutritional risk (SGA = B), and 13.8 % were severely malnourished (SGA = C). The percentage of weight lost was 8.66 % (5.76), and the patients had a BMI of 24.88 kg/m^2 (4.52), a fat mass (FM) of 24.52 % (8.53), and a fat free mass (FFM) of 75.48 % (9.33). Regarding blood tests, an albumin level of 4.08 mg/dl (0.54), a pre-albumin level of

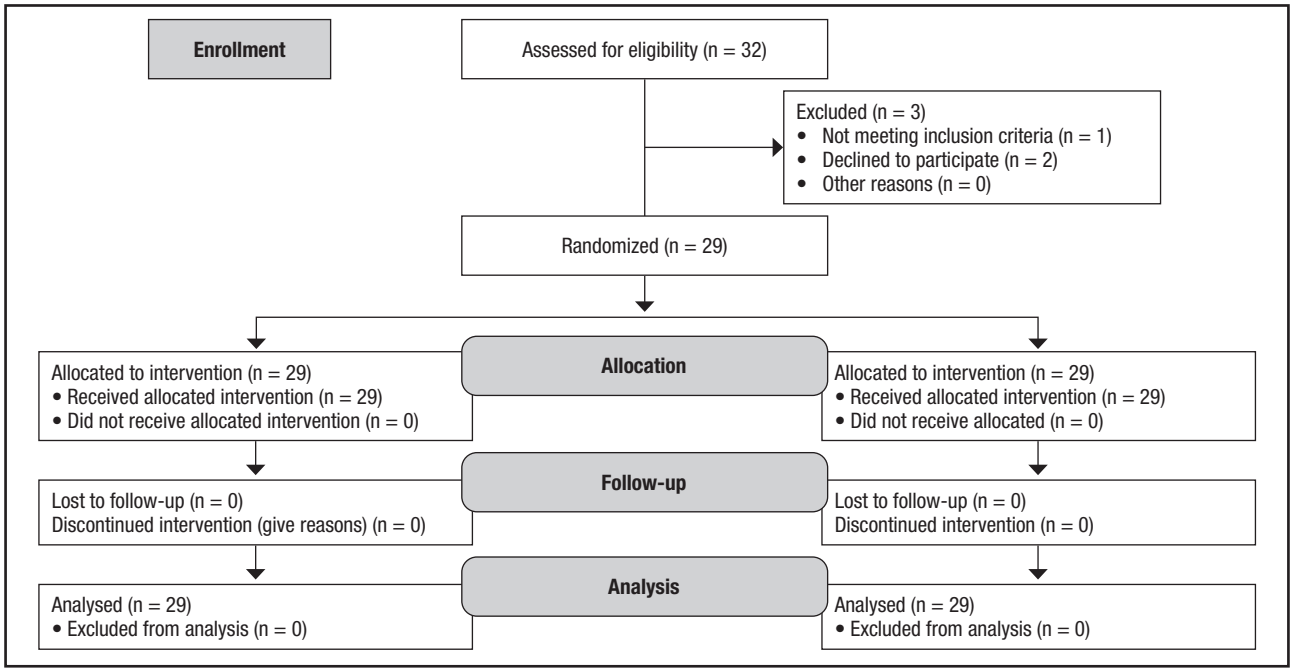


Figure 1.
Flow diagram.

27.22 mg/dl (8.66), a CRP of 3.52 (1.76), and a cholesterol level of 162.92 mg/dl (49.18) were determined.

ANALYSIS OF PLASMA GLUCOSE

Analysis of the kinetic parameters of glucose concentration depicted in table II indicates that patients treated with DSF had a significantly lower mean of AUC0-t, Cmax and plasma glucose at each measured time, than with STF (Fig. 2). In addition, no significant differences were observed in period, sequence effects, or nutritional status.

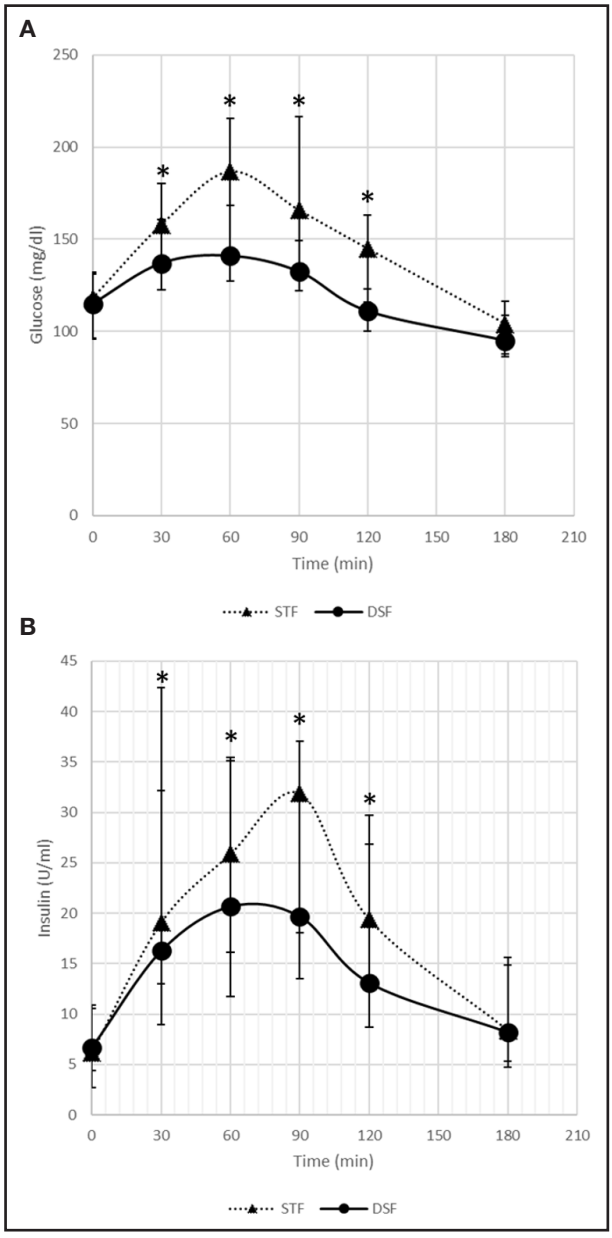


Figure 2.

Median glucose (A) and insulin (B) concentrations (intercuartile range). *Significant differences between products ($p < 0.05$); DSF: diabetes-specific formula; STF: standard formula.

ANALYSIS OF PLASMA INSULIN

The analysis of the kinetic parameters of plasma insulin concentration is presented in table II. It is observed that patients treated with DSF had a significantly lower mean AUC0-t and plasma insulin at each measured time, than patients who received STF. In addition, no significant differences were observed in period, sequence effects, or nutritional status.

DETERMINATION OF CONTINUOUS INTERSTITIAL GLUCOSE MONITORING

The results of the continuous interstitial glucose monitoring of the patients evaluated showed a mean blood glucose of 104.06 mg/dl (28.59), with an interquartile range of 35.13 mg/dl. The glucose management indicator (GMI) was 5.8 %, and the glucose variability was 27.1 %, defined as the percent target coefficient of variation (% CV) ≤ 36 %. Time in the range, high, and low values are summarized in figure 3. The different interstitial glucose profiles are depicted in figure 4.

DISCUSSION

The DSF with EVOO, designed to meet the specific needs of diabetic patients, has been shown to achieve a better glycaemic and insulinemic response in diabetic patients at risk of malnutrition.

The impact of DSF on glycaemia, compared to STF, was a lower AUC0-t value. These differences in glycaemia may be explained by the difference in carbohydrate intake, not only in quantity but also in the carbohydrate mix. In DSF, the use of isomaltulose and the mixture of dextrin and maltodextrin, with a low DE index, has been shown to be effective in the matrix of the enteral formula, improving the glycaemic response compared to the standard formula. In this case, the presence of fibre in DSF has also conditioned this better response, as has been shown in studies carried out in the same field (25). These data agree with other previously published studies evaluating the impact on glycaemia of enteral diets specifically formulated for diabetic patients. In a study by De Luis et al. (19), carried out in patients with type 2 diabetes *mellitus* without malnutrition, a difference in AUC was observed in favour of DSF compared to STF (mean difference: -4,753.26 mg min/dL [95 % CI: -7,256.69 to -2,249.82]; $p = 0.001$). This greater difference than that detected in our study can be explained by the characteristics of the standard formula used in this study, as it had a lower percentage of fat and carbohydrates than the formula used by us. In a study by Lansink et al. (2016), the researchers also observed statistically significant differences in blood glucose AUC0-t, with the measurement in the DSF group being lower than that in the STF group (167.6 mmol/L min [121.1] *vs.* 515.6 mmol/L min [181.1]; $p < 0.001$). A study by Alish et al. (2010) also shows that DSF improves the glycaemic response in diabetic patients by reducing AUC0-t compared to STF (1,690.7 mg min/dL [431.5] *vs.* 7,460.3 mg min/dL [1,074.9]; $p < 0.001$) (15).

Table II. Impact on plasma glycaemia and plasma insulinaemia

Plasma concentrations of glucose	DSF (mean SD)	STD (mean SD)	Difference (mean SD)	CI 95 %	*p*
Basal (mg/dl)	115.90 (24.40)	118.69 (27.40)	-2.79 (10.11)	-6.64 to 1.05	0.148
30 (mg/dl)	140.48 (24.95)	157.97 (31.84)	-17.48 (22.48)	-26.03 to -8.93	< 0.001
60 (mg/dl)	149.34 (38.92)	178.90 (47.02)	-29.55 (33.54)	-42.31 to -16.79	< 0.001
90 (mg/dl)	142.86 (45.79)	175.59 (53.80)	-32.72 (28.70)	-43.64 to -21.81	< 0.001
120 (mg/dl)	129.76 (48.41)	154.90 (53.76)	-25.14 (25.79)	-34.95 to -15.33	< 0.001
180 (mg/dl)	113.34 (41.45)	121.97 (46.62)	-8.62 (18.17)	-49.20 to -23.07	< 0.001
AUC0-t glucose (mg/min/dl)	22,652.07 (6,759.20)	25,977.41 (7,562.79)	-3,325.34 (2,721.68)	-4,360.62 to -2,290.07	0.016
Cmax	156.72 (44.84)	192.86 (50.50)	-36.14 (34.35)	-49.20 to -23.07	< 0.001
Tmax	63.10 (35.26)	67.24 (28.52)	-4.14 (35.61)	-17.68 to 9.41	0.537
Plasma concentrations of insulin	**DSF (mean SD)**	**STD (mean SD)**	**Difference (mean SD)**	**CI 95 %**	***p***
Basal (U/ml)	8.61 (6.03)	6.91 (5.29)	1.70 (3.42)	-0.40 to 3.01	0.123
30 min (U/ml)	22.82 (18.05)	27.24 (20.66)	-4.42 (13.90)	-9.71 to 0.86	0.098
60 min (U/ml)	27.14 (21.41)	31.51 (23.88)	-4.37 (10.92)	-8.52 to -0.21	0.040
90 min (U/ml)	22.06 (13.94)	31.53 (19.28)	-9.47 (12.54)	-14.24 to -4.70	< 0.001
120 min (U/ml)	17.51 (12.76)	22.63 (13.94)	-5.12 (12.45)	-9.85 to -0.39	0.035
180 min (U/ml)	10.64 (9.47)	9.74 (5.82)	0.91 (8.60)	-2.36 to 4.18	0.575
AUC0-t insulin U/ min/ml	2,825.90 (1,849.20)	3,277.03 (1,784.79)	-451.14 (1,114.58)	-875.10 to -27.17)	0.038

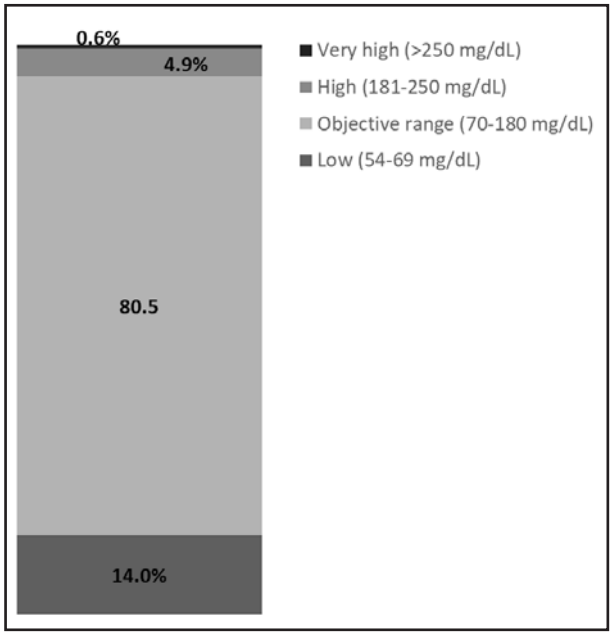
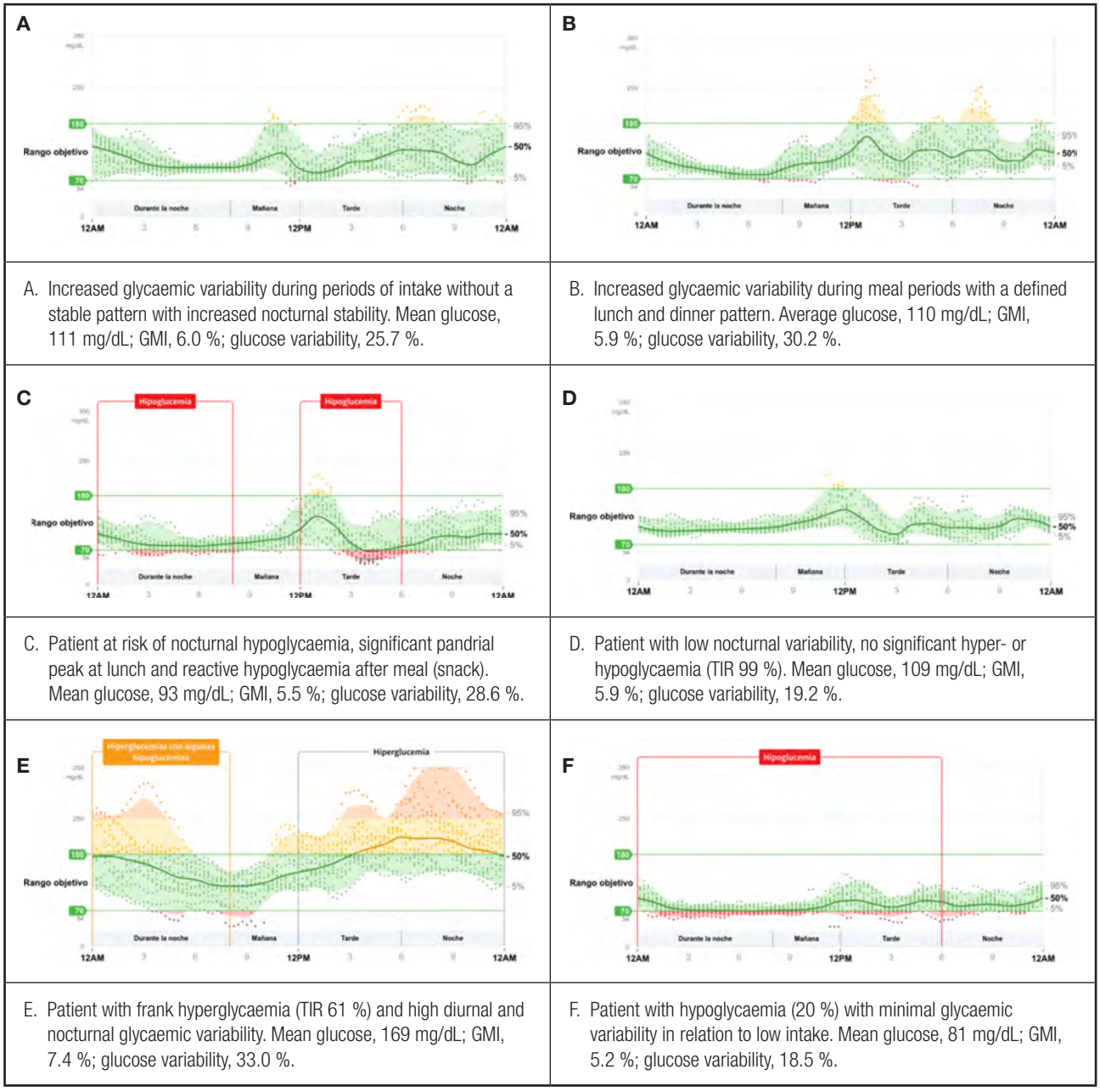


Figure 3.
Ranking of mean interstitial blood glucose in 29 patients over 14 days.

The impact of DSF with EVOO on insulinaemia, compared to STF, resulted in a lower AUC0-t value. These data agree with other previously published studies evaluating the impact on insulinaemia of enteral diets specifically formulated for diabetic patients. In a study by De Luis et al. (2013), a difference in AUC0-t in favour of DSF compared to STF was observed (mean difference: -930.27 µU/mL/min [CI 95 %: -1,696.34 to -164.2]; $p = 0.039$) (19). In a study by Lansink et al. (2016), the researchers also observed statistically significant differences in the AUC0-t of insulinaemia, with the measurement being lower in the DSF group than in the STF group (4,446.7 pmol/L min [3,021.6] *vs.* 7,336.6 pmol/L min [5,134.4]; $p < 0.001$). A study by Alish et al. (2010) also shows that DSF improves the insulinaemic response in diabetic patients by reducing the insulinaemic response (AUC0-t) of diabetic patients compared to STF (4,723.1 µU/mL/min [1,001.7] *vs.* 9,050.8 µU/mL/min [1,869.1]; $p < 0.001$).

Regarding the impact of a monounsaturated fat-rich DSF on glycaemic control and nutritional status in the medium to long term, the study by De Luis et al. 2008 evaluated the impact of two supplementation doses (2 or 3 packs/day). The authors concluded that DSF is effective in improving HbA1c and nutritional status, especially when the pattern is with three packs per day (26).



A. Increased glycaemic variability during periods of intake without a stable pattern with increased nocturnal stability. Mean glucose, 111 mg/dL; GMI, 6.0 %; glucose variability, 25.7 %.

B. Increased glycaemic variability during meal periods with a defined lunch and dinner pattern. Average glucose, 110 mg/dL; GMI, 5.9 %; glucose variability, 30.2 %.

C. Patient at risk of nocturnal hypoglycaemia, significant pandrial peak at lunch and reactive hypoglycaemia after meal (snack). Mean glucose, 93 mg/dL; GMI, 5.5 %; glucose variability, 28.6 %.

D. Patient with low nocturnal variability, no significant hyper- or hypoglycaemia (TIR 99 %). Mean glucose, 109 mg/dL; GMI, 5.9 %; glucose variability, 19.2 %.

E. Patient with frank hyperglycaemia (TIR 61 %) and high diurnal and nocturnal glycaemic variability. Mean glucose, 169 mg/dL; GMI, 7.4 %; glucose variability, 33.0 %.

F. Patient with hypoglycaemia (20 %) with minimal glycaemic variability in relation to low intake. Mean glucose, 81 mg/dL; GMI, 5.2 %; glucose variability, 18.5 %.

Figure 4.

Aggregation of 14 days of ambulatory glucose profile (AGP) in 6 patients with different clinical profiles. GMI: glucose mangement indicator; TIR: time in range.

It would be interesting to propose studies with EVOO-rich DSF to assess its metabolic impact and nutritional status in the medium to long term in chronic patients with nutritional support.

The studied DSF had a lower insulinaemic response, which is beneficial *per se*. The data collected on insulinaemia highlight the differences in the maximum peak insulinaemia at minute 60 in the DSF group, respect to STF that it was at minute 90, as well as in the AUC0-t. These elevated insulin levels in the standard diet are associated with increased cardiovascular risk, not just hyperglycaemia. We know that this insulinaemic response is conditioned by dietary fat intake (type and amount), fibre intake, protein quality, and carbohydrate intake (type and amount), as indicated in the ADA 2022 guidelines (2). Considering the type of DSF evaluated, the contribution of extra virgin olive oil, both in terms of its high content of MUFA (27) and in terms of its bioactive phenolic compounds (28), the high content in whey protein, which promotes insulin sensitivity (29), the fibre, and the specific carbohydrate mix, may account for this better insulinaemic response compared to STF.

The patients presented in this study were old, had a long history of DM2, and had a high comorbidity index. The patients evalu-

ated had good metabolic control, with an HbA1c value within the optimal control parameters, but this situation may be caused by malnutrition (30).

The assessment of the nutritional status with the SGA has been the gold standard for the diagnosis of malnutrition in recent years until the appearance of the GLIM criteria (31). In our study, among the variables assessed by the SGA, it was weight loss, decreased lean mass, and decreased fat mass, as well as decreased dietary intake, that determined the diagnosis of malnutrition, and not BMI. In this regard, we observed that malnourished diabetic patients have BMI values within the ranges of normal weight, overweight, and type 1 obesity, already identified in previous studies, such as the VIDA study (7). This implies that a nutritional diagnosis using BMI alone in type 2 diabetic patients may underestimate the prevalence of malnutrition (7).

This is the first study to analyse the interstitial glycaemic response through continuous monitoring using the FreeStyle-Libre®Pro system to assess the effect of ONS in malnourished diabetic patients. Continuous monitoring over 14 days not only measures the impact on blood glucose of the supplement under study and control, but also includes the patient's dietary intake. In this study, only aggregated data are shown, but it was observed that there was a 14 % of the time below 70 mg/dl. It could be a wake-up call that patients with malnutrition and type 2 diabetes may present episodes of hypoglycaemia, and need to be monitored properly. One of the advantages of using these devices in the monitoring of diabetic patients on enteral nutrition is to ensure adequate glycaemic control and the detection and prevention of hypoglycaemic episodes (23).

One of the strengths of the study is that it is the first study to evaluate the glycaemic and insulinaemic response of DSF with EVOO. EVOO is a food that has demonstrated multiple benefits in patients at high cardiovascular risk and, specifically, in diabetic patients (25). Also, for the first time, continuous monitoring of interstitial glucose in malnourished diabetic patients was included, which, although it was not compared with plasma measurements (because it was not the objective of the study), was used to evaluate glycaemic control, time in range, and episodes of hypoglycaemia.

Regarding limitations, the software of the FreeStyle-Libre®Pro device did not allow us to obtain specific interstitial glycaemia in the same period as plasma measurements. The sample size of 29 patients was larger than that in other studies and was compensated for by the fact that it was designed as a crossover clinical trial. It should be noted that the prolonged time involved in patient recruitment was the lack of awareness of the detection of malnutrition in the outpatient care of DM2 patients by healthcare professionals.

CONCLUSIONS

The diabetes-specific formula for diabetic patients, formulated with extra virgin olive oil, a specific mixture of carbohydrates, fibre, and rich in whey protein, not only benefits glycaemic control but also improves the insulinaemic response in patients with type 2 diabetes *mellitus* at risk of malnutrition.

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Trabajo Original

Pediatría

In vitro prebiotic activity of rhLf and galactooligosaccharides on infant intestinal microbiota

Actividad prebiótica in vitro *de lactoferrina y galactooligosácridos sobre la microbiota intestinal infantil*

Esmat Aly[1,2], Gaspar Ros-Berruezo[1], Rubén López-Nicolás[1], Aliaa Ali Darwish[2], Teresa Sánchez-Moya[1], David Planes-Muñoz[1], Carmen Frontela-Saseta[1]

[1]Food Science and Nutrition Department. Faculty of Veterinary Sciences. Regional Campus of International Excellence "Campus Mare Nostrum". Universidad de Murcia. Espinardo, Murcia. Spain. [2]Dairy Technology Research Department. Food Technology Research Institute (FTRI). Agricultural Research Center (ARC). Giza, Egypt

Abstract

Objective: human lactoferrin (Lf) and human milk oligosaccharides possess a wide range of functions. So, the present study focusses on the role of Lf and/or galactooligosaccharides (GOS) in the modulation of gut microbiota composition.

Methods: recombinant human lactoferrin (rhLf) was added to the first infant formula (0.10, 0.15, 0.20 %) alone or in combination with GOS (1 %) in vessels of a small-scale batch culture fermentation model. Short-chain fatty acids (SCFAs), microbial population groups, and pH were monitored through fermentation for 24 hours.

Results: insignificant changes were observed in pH values and acetic acid accumulated during fermentation. Propionic acid content has been insignificantly increased while butyric acid has been insignificantly decreased. Moreover, increments in all bacterial groups except for *Bacteroides* were observed through the fermentation process. *Lactobacillus* and *Bifidobacterium* showed an increase in relation to initial time over the fermentation process, demonstrating the prebiotic effect of lactoferrin and GOS. After 24 hours of fermentation, all tested ingredients showed significant similarities in *Enterococcus* for controls except for 0.20 % rhLf + 1 % GOS, which provoked a diminution of *Enterococci* growth.

Conclusion: despite the importance of the batch culture fermentation technique in uncovering the prebiotic activity of food ingredients, it is not useful for detecting the prebiotic nature of Lf due to its nature as a protein. Thus, Lf maybe shows its prebiotic activity on the gut microbiota through other mechanisms.

Keywords:

Lactoferrin.
Galactooligosaccharides.
Intestinal microbiota.
Prebiotic activity.

Resumen

Objetivo: la lactoferrina humana (Lf) y los oligosacáridos de leche materna presentan un amplio rango de funciones. El presente estudio se centra en el papel de la Lf y/o galactooligosácridos (GOS) en la modulación de la composición de la microbiota intestinal.

Métodos: se añadió lactoferrina humana recombinante (rhLf) a fórmula infantil (0,10, 0,15, 0,20 %), sola o en combinación con GOS (1 %) en botes de fermentación colónica. A lo largo de 24 horas de fermentación, se monitorizaron ácidos grasos de cadena corta, grupos de poblaciones microbianas y pH.

Resultados: se observaron pequeños cambios en valores de pH y cantidad de ácido acético durante la fermentación. El contenido de ácido propiónico aumentó ligeramente, mientras que el butírico sufrió un ligero descenso. Todos los grupos bacterianos estudiados incrementaron, excepto los *Bacteroides,* durante la fermentación. *Lactobacillus* and *Bifidobacterium* mostraron un incremento respecto al valor inicial, demostrando el efecto prebiótico de la lactoferrina y los GOS. A las 24 horas de fermentación, todos los ingredientes estudiados mostraron similitud al control en cuanto a *Enterococcus,* excepto para 0,20 % rhLf + 1 % GOS, donde disminuyó el crecimiento de los enterococos.

Conclusión: a pesar de la importancia de los estudios de fermentación *in vitro* para descubrir potenciales ingredientes prebióticos, no fue útil en el caso de lactoferrina debido a su naturaleza proteica. Por tanto, la lactoferrina podría mostrar su actividad prebiótica en la microbiota intestinal a través de otros mecanismos.

Palabras clave:

Lactoferrina.
Galactooligosacáridos.
Microbiota intestinal.
Actividad prebiótica.

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Correspondence:

Rubén López-Nicolás. Food Science and Nutrition Department. Faculty of Veterinary Sciences. Regional Campus of International Excellence "Campus Mare Nostrum". Universidad de Murcia. 30100 Espinardo, Murcia. Spain
e-mail: rubenln@um.es

INTRODUCTION

Recently, the awareness of functional food's importance is highly increasing as this food has several potential health-promoting activities. In this sense, consumers highly demand those ingredients that positively affect intestinal flora (1). Among these functional ingredients are human lactoferrin (hLf) and human milk oligosaccharides (HMOs) such as galactooligosaccharides (GOS). hLf is a 703-amino acid glycoprotein isolated from the whey fraction of human milk which exerts many biological effects such as antimicrobial, modulation of the immune system, and iron metabolism (2). Many previously published data revealed the prebiotic nature of these components of human milk, where they can improve the growth of some beneficial bacteria, i.e., *Bifidobacteria* and *Lactobacilli* (3,4). Thus, the gut microbiota of breast-fed infants is characterized by its high content of these healthy microorganism as compared to those fed infant formulas (5). Therefore, and in line with the current trend in infant formula manufacturing, several infant formulas exist in the market containing Lf and/or GOS to increase their functionality, and highly resemble human milk composition (6).

GOS, another functional ingredient, is characterized by its high resistance to digestion and reaches the colon in intact form, where they serve as fermentable substances leading to produce short-chain fatty acids (SCFAs) and decreasing colon pH. These consequences improve the growth of the beneficial bacteria and prevent the attachment of enteropathogens. However, many *in vitro*, *in vivo,* and preclinical studies are needed to discover the functionality of human milk components, especially Lf and HMOs. Thus, the main objective of the present study is to evaluate the potential prebiotic efficacy of three different concentrations of recombinant human Lf and/or GOS through using the batch culture fermentation model.

MATERIALS AND METHODS

CHEMICALS

Recombinant human lactoferrin (rhLf) was purchased from Sigma Chemical Co. (cat. no. L1294, St. Louis, MO, United States). Vivinal GOS syrup (dry matter 75 % of which GOS was 59 %, lactose 21 %, glucose 19 %, and galactose 1 %) was provided by Hero Baby Co. (Alcantarilla, Murcia, Spain).

PREPARATION OF THE FECAL INOCULUM

Fecal samples were obtained from three healthy babies (aged 2-4 months) without any known metabolic or gastrointestinal disorders and antibiotics were not taken before fecal sample donation. Fresh fecal samples were immediately placed in anaerobic jars and transported to the laboratory within two hours from collection. Fecal samples were prepared following the procedure previously described by Sánchez-Moya et al. (7).

IN VITRO BATCH CULTURE FERMENTATIONS

Three independent small-scale fecal batch cultures were carried out, each of them corresponding to samples from the three different babies. First of all, 1 % (w/v) lactose was added to the media before autoclaving because it is the main sugar in milk. The fecal slurry and autoclaved MBM were prepared on the same day and maintained overnight under conditions of anaerobiosis at 37 °C, before use. For each batch, MBM was distributed into different glass vessels (5 ml per vessel) with 5, 7.5, or 10 mg of rhLf with (or without) a mixture of 1 % GOS. In addition, 1 % GOS was used as prebiotic control (positive control) (8).

The ingredients assayed (rhLf and GOS) (at the different concentrations) were added to each vessel just before inoculation with the fecal slurry (50 µl of the fecal slurry). The different treatments were incubated at 37 °C in anaerobic conditions. Samples were removed after 0, 10, and 24 h to pH measurement, SCFAs, and bacteria quantification similarly to Beards et al. (8).

The different treatments used in this study are the following: positive control (1 % GOS), single recombinant human lactoferrin (rhLf) (0.10 % rhLf, 0.15 % rhLf, 0.20 % rhLf) and lactoferrin added to 1 % GOS (0.10 % rhLf + 1 % GOS, 0.15 % rhLf + 1 % GOS, 0.20 % rhLf + 1 % GOS).

MEASUREMENT OF pH

The pH values of batch culture samples were measured immediately after taking the aliquots. This measurement was done in triplicate directly by using the pH meter (Crison, Barcelona, Spain).

SHORT-CHAIN FATTY ACIDS ANALYSIS BY GC

SCFAs analysis in fecal cultures was determined by GC according to González-Bermúdez et al. (9). Every sample was performed in quadruplicate.

ANALYSIS OF FECAL MICROBIOTA COMPOSITION BY qPCR

Bacterial DNA from fermented samples was extracted prior to qPCR analysis by using a QIAamp® DNA Stool Minikit (Qiagen, Germany) in a similar form to González-Bermúdez et al. (9). After DNA extraction, samples were stored at -80 °C until further analysis. Quantitative real-time PCR (qPCR) was used to analyze microbiota from fermented samples using specific primers targeting different bacterial groups (total bacteria, *Bacteroides, Enterobacteriaceae, Enterococcaceae, Lactobacillus,* and *Bifidobacterium*). PCR amplification and detection were performed similarly to González-Bermúdez et al. (9) and Sánchez-Moya et al. (7) by using a 96-well CFX96™ Real-Time PCR thermocycler (Bio-Rad, Madrid, Spain).

Bacterial strains were obtained from the German Collection of Microorganism and Cell Cultures (DMSZ) and the Spanish Type Culture Collection (CECT) (Table I). Every sample was analyzed in quadruplicate and the results were expressed as the logarithm of genome equivalents per ml (Log genome Eq/ml) (10).

STATISTICAL ANALYSIS

The effect of the different samples at the same *in vitro* fermentation time, on the evolution of pH, the SCFAs production, and the microbiota growth were tested using one-way ANOVA, with the samples as a factor. To compare the effect of the *in vitro* fermentation time for each used sample, on the parameters previously commented, one-way ANOVA was used as well, with time as a factor. In both cases, when data were not parametric, the Kruskal-Wallis test was used. Subsequent Tukey's multiple comparisons or Nemenyi test multiple comparisons were used when data were parametric or not respectively. Before statistical analysis, normality and homoscedasticity were confirmed by using Shapiro-Wilk and Bartlett tests, respectively. The software R version 3.6.2 (2019-12-12) was used to perform all analyses. The package ggplot2 of the same software was used to do plots. A level of significance of $p < 0.05$ has been considered for each statistical analysis.

RESULTS

It is well-known that there is a positive correlation between gut microbiota and the diet. Thus, the current research is focusing on modulating the gut microbiota using prebiotics such as GOS, and rhLf. The prebiotic substances are several food ingredients that can pass the upper part of the gastrointestinal tract in intact form until reaching the colon, where they are fermented by the colonic beneficial bacteria, especially *Bifidobacteria* and *Lactobacilli*. The prominent event that occurs during this process is modulation of the intestinal microbiota composition leading to forming SCFAs as main metabolites, which are accompanied by pH decline.

pH EVOLUTION DURING FERMENTATION

The pH evolution during fermentation for each sample through the time (0, 10, and 24 hours) is shown in table II. As it can be seen, for each sample, pH decreased quickly and significantly ($p < 0.05$) at ten hours of incubation to the 0-hour point, being this drop bigger for the samples with GOS. At ten hours of incubation, we obtained the lowest value of pH in presence of 1 % GOS (PC), whereas 0.10 % rhLf followed by 0.20 % rhLf and 0.15 % rhLf, respectively, had the maximum values of pH, although without statistically significant differences among the studied samples into ten hours. The values of pH continued decreasing at 24 hours of fermentation as well, with statistically significant differences ($p < 0.05$) for the 0.1 % and 0.15 % rhLf cases with respect to the previously analysed time, being the lowest value of pH for 1 % GOS. The remaining samples at 24 hours had similar pH mean values and no statistically significant differences were found among the samples used at this time. It is also worthy to note that samples including GOS decrease pH to a higher degree and faster than the same samples without GOS.

SHORT-CHAIN FATTY ACIDS EVOLUTION DURING FERMENTATION

The obtained findings in this study regarding SCFAs production by the fecal bacterial population are shown in figure 1 for the total concentration of SCFA (mM) (acetic, propionic, butyric, i-butyric, i-valeric, n-valeric, i-caproic, n-caproic and heptanoic acids) and in figure 2 for the molar proportions of the main SCFA (acetic, propionic and butyric acid) as well as minor SCFA (i-butyric, i-valeric, n-valeric, i-caproic, n-caproic and heptanoic acid).

Table I. Bacterial target, primer sequences and annealing temperature used to qPCR analysis

Bacterial target	Primer sequences (5´-3´)	Annealing temperature (°C)
Total bacteria	Fwd: GTGSTGCAYGGYYGTCGTCA Rv: ACGTCRTCCMCNCCTTCCTC	60
Bacteroides-Prevotella	Fwd: GAGAGGAAGGTCCCCCAC Rv: CGKACTTGGCTGGTTCAG	60
Enterobacteriaceae	Fwd: TGCCGTAACTTCGGGAGAAGGCA Rv: TCAAGGACCAGTGTTCAGTGTC	60
Enterococcaceae	Fwd: CCCATCAGAAGGGGATAACACTT Rv: ACCGCGGGTCCATCCATC	60
Lactobacillus	Fwd: AGCAGTAGGGAATCTTCCA Rv: CATGGAGTTCCACTGTCCTC	60
Bifidobacterium	Fwd: GATTCTGGCTCAGGATGAACGC Rv: CTGATAGGACGCGACCCCAT	60

Table II. pH evolution during 24 hours of fermentation

Samples	0 hour	10 hours	24 hours
1 % GOS (PC)	8.51 ± 0.12*	5.07 ± 0.23†	4.70 ± 0.14†
0.10 % rhLf	8.51 ± 0.12*	5.36 ± 0.28†	4.79 ± 0.19‡
0.15 % rhLf	8.51 ± 0.12*	5.26 ± 0.16†	4.94 ± 0.08‡
0.20 % rhLf	8.51 ± 0.12*	5.34 ± 0.22†	4.88 ± 0.31†
0.10 % rhLf + 1 % GOS	8.51 ± 0.12*	5.15 ± 0.17†	4.89 ± 0.18†
0.15 % rhLf + 1 % GOS	8.51 ± 0.12*	5.19 ± 0.36†	4.91 ± 0.22†
0.20 % rhLf + 1 % GOS	8.51 ± 0.12*	5.24 ± 0.09†	4.93 ± 0.26†

*GOS: galactooligosaccharides; rhLf: recombinant human lactoferrin. Results are expressed as mean ± SD from triplicate. *, † and ‡ indicate statistically significant ($p < 0.05$) differences in the same row.*

As it can be seen in figure 1, the total SCFAs levels increased after 24 hours of incubation of fecal microbiota with the tested ingredients. The highest values of total SCFAs were detected after fermentation in the presence of 0.10 % rhLf + 1 % GOS followed by 0.15 % rhLf + 1 % GOS and 0.2 % rhLf + 1 % GOS as compared with the positive control group, but not significantly. The obtained findings revealed, as unexpected, that total SCFAs in the presence of 1 % GOS showed the lowest value after 24 hours as compared to other substrates, revealing the high effect of Lf in the SCFA production. Non-significant differences ($p < 0.05$) were observed between total SCFAs for all treatments at the same time. Among the various detected SCFAs, acetic acid has been the most contributor to total SCFA, followed by similar amounts of both propionic acid and butyric acid. After 24 hours of fermentation, elevated production of acetic acid was reported, and its higher value was found for 0.10 % rhLf + 1 % GOS followed by 0.20 rhLf + 1 % GOS and 0.15 % rhLf + 1 % GOS as compared with the control group. Unexpectedly, in the presence of 1 % GOS, the acetic acid production was the lowest compared with the remaining samples after 24 hours. It is worthy to note that the highest value of acetic acid after ten hours was reported in presence of 1 % GOS as compared with all treatments.

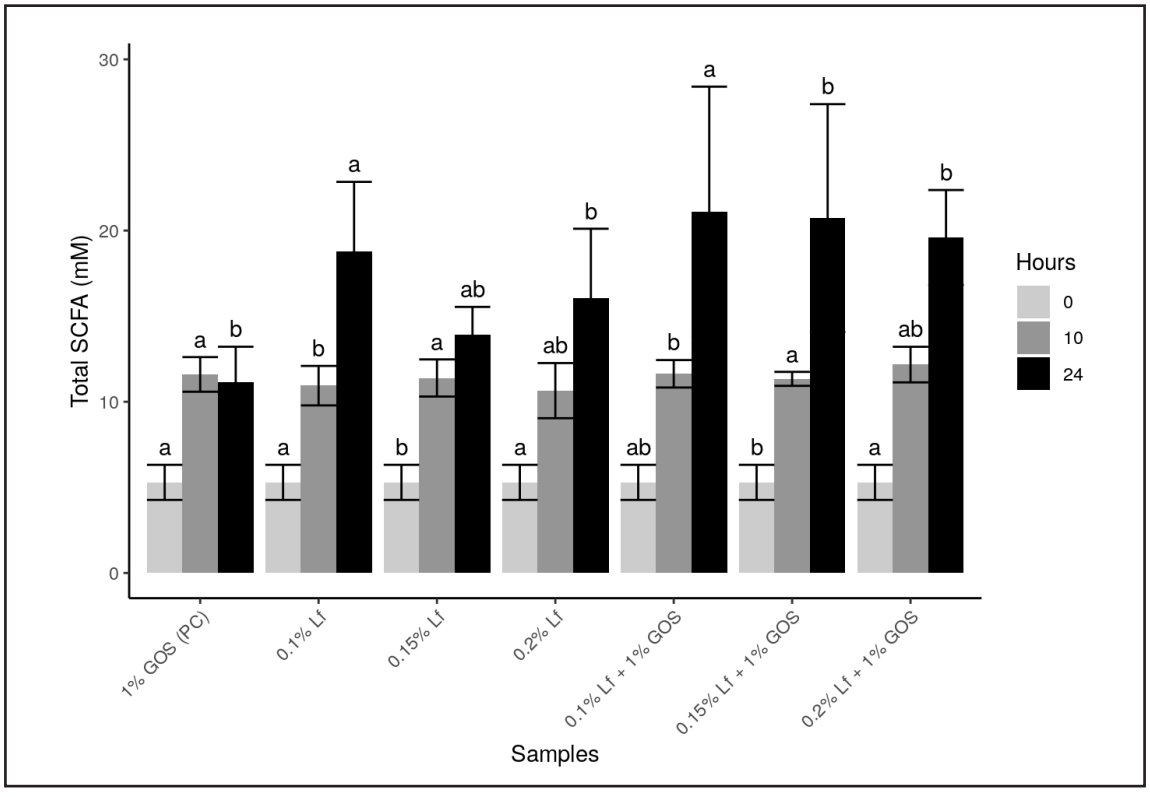

Figure 1.

Total short-chain fatty acids (SCFA) concentration produced at 0, 10, and 24 hours of incubation with rhLf and/or GOS in batch culture fermentation vessels. GOS: galactooligosaccharides; rhLf: recombinant human lactoferrin.

However, non-significant ($p < 0.05$) changes in the acetic acid production by the tested ingredients were observed at the different points of sampling and this may be a result of the differences between the predominant intestinal flora in the three fecal slurries of the three donors.

In the case of propionic acid, the findings revealed a moderate increase in its level for all the tested ingredients after 24 hours of fermentation. After ten hours of fermentation, the group of samples containing 0.20 % rhLf showed the lowest value as compared with the rest of the treatments, while after 24 hours, the highest value of propionic acid was found in the presence of 0.10 % rhLf + 1 % GOS followed by 0.15 % rhLf + 1 % GOS, and the lowest value was observed in the presence of 1 % GOS. These findings revealed that although there are non-significant ($p < 0.05$) differences between the values of propionic acid among the different treatments, it might exist a synergistic contribution between rhLf and GOS to produce SCFA. The contrary occurred for butyric acid, which decreased moderately at 24 hours of fermentation as compared to its content at zero time of incubation. The highest value of butyric acid was observed at 24 hours in the presence of 0.20 % rhLf + 1 % GOS followed by the control sample but it is not significantly ($p < 0.05$) different from the values of the different treatments. Finally, small variability between butyric content of the other groups whether at ten hours or 24 hours was observed.

Interestingly, as a consequence of the SCFAs production pattern mentioned above, the acetic acid/propionic acid ratio highly increased at ten hours of fermentation. Then, this ratio decreased moderately or highly depending on the added compound. Control group acetic/propionic ratio became the highest value at ten hours, while 0.15 % Lf was the lowest value at 24 hours (Fig. 3). Our findings reported that positive control led to a significant change ($p < 0.05$) in the acetic/propionic acid ratio. Remarkably, the highest decrease in this ratio observed in the present study was for the 0.2 % rhLf group.

Because of the obtained findings (Fig. 2), it is worth noting that there was no clear trend related to the effect of rhLf and/or GOS on the production of minor SCFAs in fecal cultures fermentation except for isobutyric acid, which was found to be increased at 24 hours in all treatments as well as in the control group (data not shown).

ANALYSIS OF MICROBIOTA DURING FERMENTATION

Changes in microbiota composition have been shown after the whole fermentation process and using different doses of rhLf and GOS as substrate (Table III). Increments in total bacterial numbers were observed in all samples through the fermentation process, being the time of fermentation ten and 24 hours approximately two Log genome Eq/mL higher with respect to the initial time (time 0 h) ($p < 0.05$). More counts of total bacteria were observed after using GOS (1 %) and different 0.1 % of rhLf added to GOS (1 %) as fermentable substrate. However, after total fermentation, the addition of different concentrations of single rhLf did not produce significant increases compared to positive control and 0.1 % of rhLf + 1 % GOS.

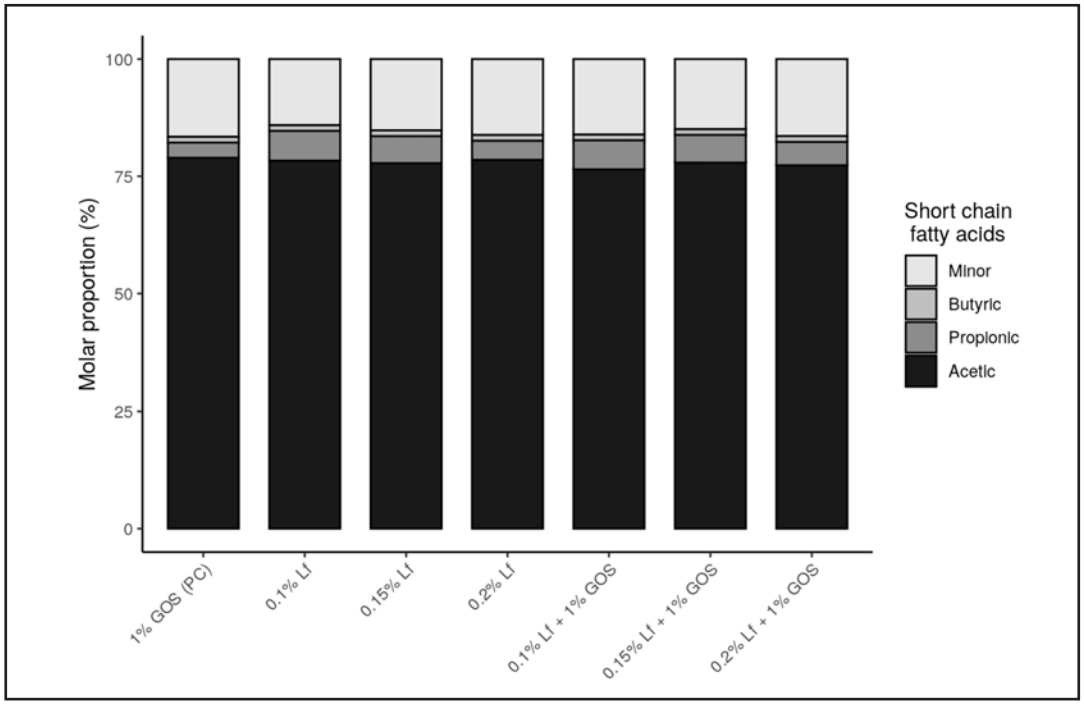

Figure 2.

Molar proportion (%) of minor and major short-chain fatty acids (SCFA) concentration produced in batch culture fermentation vessels containing rhLf and/or GOS. GOS: galactooligosaccharides; rhLf: recombinant human lactoferrin.

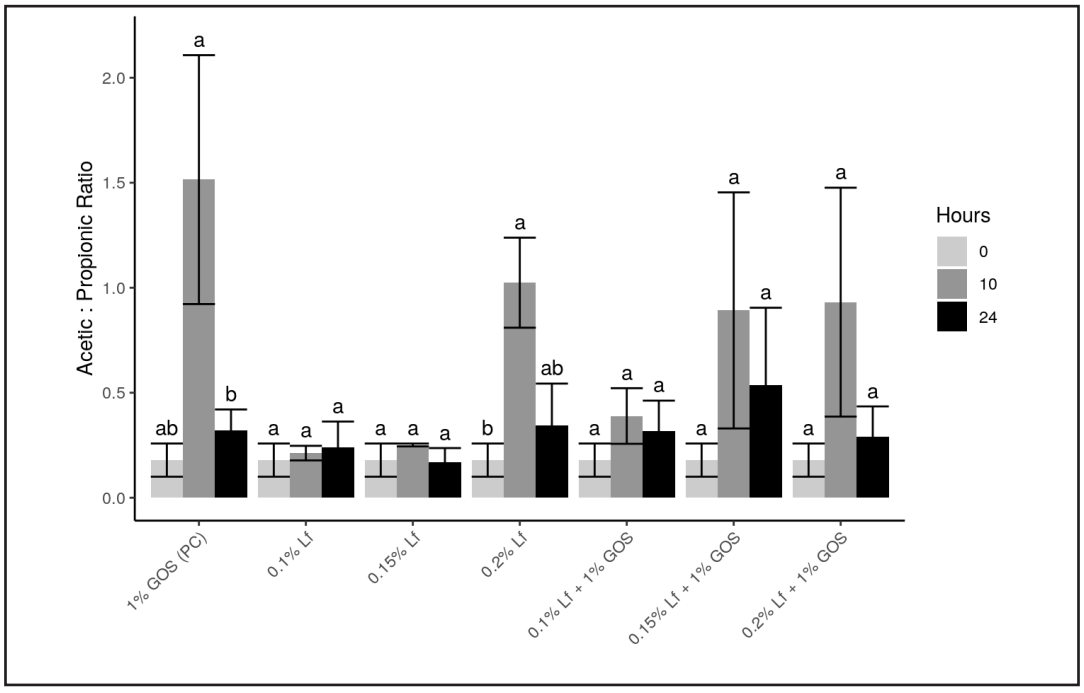

Figure 3.

Acetic: propionic ratio produced at 0, 10, and 24 hours of incubation with rhLf and/or GOS in batch culture fermentation vessels. GOS: galactooligosaccharides; rhLf: recombinant human lactoferrin.

Table III. Bacterial populations (Log gen Eq/ml) after 24 hours of incubation with rhLf and/or GOS using batch culture fermentation

	Time (h)	GOS (1 %)	0.10 % rhLf	0.15 % rhLf	0.20 % rhLf	0.10 % rhLf + 1 % GOS	0.15 % rhLf + 1 % GOS	0.20 % rhLf + 1 % GOS
Total bacteria	0 h	$5.65^{B} \pm 0.82$	$5.65^{B} \pm 0.82$	$5.65^{C} \pm 0.82$	$5.65^{C} \pm 0.82$	$5.65^{B} \pm 0.82$	$5.65^{C} \pm 0.82$	$5.65^{B} \pm 0.82$
	10 h	$7.77^{A,a} \pm 0.17$	$7.74^{A,a} \pm 0.10$	$7.64^{A,a} \pm 0.07$	$7.52^{A,b} \pm 0.07$	$7.73^{A,a,b} \pm 0.26$	$7.64^{A,a,b} \pm 0.15$	$7.48^{A,a,b} \pm 0.27$
	24 h	$7.67^{A,a} \pm 0.13$	$7.58^{A,a,b,c} \pm 0.27$	$7.29^{B,c} \pm 0.17$	$7.32^{B,b,c} \pm 0.16$	$7.70^{A,a} \pm 0.15$	$7.53^{B,a,b} \pm 0.10$	$7.48^{A,a,b,c} \pm 0.23$
Bacteroides	0 h	5.05 ± 0.58	5.05 ± 0.58	5.05 ± 0.58	5.05 ± 0.58	5.05 ± 0.58	5.05 ± 0.58	5.05 ± 0.58
	10 h	5.31 ± 0.96	5.37 ± 0.90	5.28 ± 0.77	5.13 ± 0.75	5.31 ± 0.92	5.20 ± 0.77	5.11 ± 0.78
	24 h	5.19 ± 0.81	5.29 ± 0.97	5.16 ± 0.77	5.08 ± 0.73	5.28 ± 1.01	5.15 ± 0.84	5.07 ± 0.70
Enterobacteriaceae	0 h	$4.43^{C} \pm 0.64$	$4.43^{C} \pm 0.64$	$4.43^{C} \pm 0.64$	$4.43^{C} \pm 0.64$	$4.43^{B} \pm 0.64$	$4.43^{B} \pm 0.64$	$4.43^{B} \pm 0.64$
	10 h	$6.66^{A,b,c} \pm 0.11$	$6.63^{A,a,b} \pm 0.13$	$6.52^{A,a,b,c,d} \pm 0.10$	$6.43^{A,d,e} \pm 0.03$	$6.61^{A,a,b,c,d} \pm 0.23$	$6.47^{A,c,d} \pm 0.12$	$6.30^{A,d} \pm 0.25$
	24 h	$6.46^{B,a} \pm 0.16$	$6.26^{B,a,b} \pm 0.37$	$6.07^{B,b} \pm 0.27$	$6.06^{B,b} \pm 0.15$	$6.36^{A,a,b} \pm 0.31$	$6.17^{A,a,b} \pm 0.34$	$6.22^{A,a,b} \pm 0.22$
Enterococcaceae	0 h	$2.25^{B} \pm 0.48$	$2.25^{C} \pm 0.48$	$2.25^{B} \pm 0.48$	$2.25^{C} \pm 0.48$	$2.25^{C} \pm 0.48$	$2.25^{B} \pm 0.48$	$2.25^{B} \pm 0.48$
	10 h	$4.45^{A,a,b} \pm 0.29$	$4.14^{B,a,b,c} \pm 0.47$	$3.94^{A,b,c} \pm 0.46$	$3.79^{B,c} \pm 0.38$	$4.01^{B,b,c} \pm 0.51$	$3.75^{A,b,c} \pm 0.60$	$3.70^{A,c} \pm 0.23$
	24 h	$4.83^{A,a} \pm 0.96$	$4.43^{A,a,b} \pm 0.56$	$3.95^{A,a,b} \pm 0.56$	$4.12^{A,a,b} \pm 0.21$	$4.43^{A,a,b} \pm 0.63$	$4.08^{A,a,b} \pm 0.55$	$3.87^{A,b} \pm 0.24$
Lactobacillus	0 h	$2.82^{A} \pm 0.87$	$2.82^{B} \pm 0.87$	$2.82^{B} \pm 0.87$	$2.82^{B} \pm 0.87$	$2.82^{B} \pm 0.87$	$2.82^{C} \pm 0.87$	$2.82^{B} \pm 0.87$
	10 h	$3.91^{A} \pm 1.54$	$3.52^{A,B} \pm 1.45$	$3.27^{A,B} \pm 1.63$	$3.20^{B} \pm 1.38$	$3.69^{B} \pm 1.69$	$3.53^{B} \pm 1.54$	$3.43^{B} \pm 1.35$
	24 h	$5.05^{A} \pm 2.14$	$4.89^{A} \pm 1.32$	$4.20^{A} \pm 1.30$	$4.88^{A} \pm 1.44$	$5.27^{A} \pm 1.23$	$4.91^{A} \pm 1.49$	$4.86^{A} \pm 1.60$
Bifidobacterium	0 h	$3.52^{C} \pm 0.65$	$3.52^{C} \pm 0.65$	$3.52^{C} \pm 0.65$	$3.52^{B} \pm 0.65$	$3.52^{C} \pm 0.65$	$3.52^{B} \pm 0.65$	$3.52^{C} \pm 0.65$
	10 h	$4.44^{B} \pm 0.71$	$4.51^{B} \pm 0.53$	$4.24^{B} \pm 0.60$	$3.82^{B} \pm 0.44$	$4.58^{B} \pm 0.42$	$4.15^{B} \pm 0.63$	$4.12^{B} \pm 0.21$
	24 h	$5.01^{A} \pm 0.88$	$5.65^{A} \pm 0.89$	$5.20^{A} \pm 0.73$	$5.19^{A} \pm 1.03$	$5.48^{A} \pm 0.74$	$5.28^{A} \pm 0.89$	$5.04^{A} \pm 1.06$

GOS: galactooligosaccharides; rhLf: recombinant human lactoferrin. Values are mean ± SD of four determinations from three independent experiments. Small letters denote significant differences ($p < 0.05$) among different treatments within the same time of fermentation (rows). Capital letters denote significant differences ($p < 0.05$) along fermentation within the same treatment.

Considering the same time of fermentation, significant differences were found according to the type of fermented ingredient. Specifically, total bacteria at 24 hours of fermented with 0.10 % rhLf 1 % GOS group and GOS (1 %) were higher compared to 0.15 and 0.20 % rhLf (7.70 ± 0.15 and 7.67 ± 0.13 *vs* 7.29 ± 0.17 and 7.32 ± 0.16 Log Eq gen/ml, respectively). These data results are interesting since the highest growth of total bacteria in the case of fermented 0.10 rhLf + 1 % GOS was coincident with the highest increases in total SCFA, specifically of acetic acid.

Regarding other bacterial groups, non-significant differences were found in the case of *Bacteroides,* neither within the same ingredient concerning the time of fermentation nor within the same time of fermentation and ingredient. Unlike other bacteria populations, the growth of *Bacteroides* group seemed to be decreased from ten to 24 hours of fermentation, although not significantly.

Enterobacteriaceae showed marked time-dependent increases in all samples. Concretely, GOS (1 %), as well as treatments with rhLf alone, showed great differences in the fermentation process. Nevertheless, the addition of 1 % of GOS to rhLf provoked significant increases from time 0 to time ten hours, being the growth after 24 hours of fermentation similar to previous stages. At ten hours of fermentation, the lowest values ($p < 0.05$) of *Enterobacteria* were found in the case of 0.20 % rhLf (6.43 ± 0.03) and 0.20 % rhLf + 1 % GOS (6.30 ± 0.25) with respect to the positive control (6.66 ± 0.11). However, in the case of 24 hours of fermentation, the lowest growth for *Enterobacteriaceae* was detected in the case of 0.15 and 0.20 % rhLf with respect to the control, which could suggest that the addition of rhLf alone to human feces after 24 hours of fermentation produced a positive effect by decreasing this bacterial group. The additive effect of 1 % of GOS and rhLf seemed to produce similar values but none in a significant manner to prebiotic control and a little higher than in the case of 0.15 % and 0.20 % of rhLf.

The lactic acid bacteria, *Enterococci,* comprises commensal and pathogenic bacteria. The results of the present study showed that all tested ingredients produced increases in *Enterococci* populations after 24 hours of fermentation regarding the initial inoculum, with increases of 2 Log gen Eq/ml, approximately. However, significant differences were found depending on the ingredient. At the time of ten hours of fermentation 0.10 % rhLf showed similar values than prebiotic control (4.14 ± 0.47 Log gen Eq/ml). Nevertheless, 0.20 % rhLf and 0.20 % rhLf + 1 % GOS showed lesser values with respect to the control. Differently, at the time of 24 hours of fermentation all tested ingredients showed significant similarities with respect to the control, except for 0.20 % rhLf + 1 % GOS, which provoked a diminution of *Enterococci* growth (3.87 ± 0.24 Log gen Eq/ml).

Regarding *Bifidobacterium* and *Lactobacillus* genera, our results showed that both bacteria increased markedly with respect to the initial time over the fermentation, showing a notable prebiotic effect on all tested substrates. Concretely all ingredients stimulated the growth of *Lactobacillus,* especially after 24 hours of fermentation, showing increments of 2 Log gen Eq/ml approximately with respect to initial values, although insignificant differences were found among different treatments. Similarly, *Bifidobacteria* showed increases after 24 hours of fermentation using GOS or rhLf as substrate, which could suggest the bifidogenic potential of both ingredients. However, neither of the two mentioned ingredients produced significant increases in *Bifidobacterium* by comparing different doses.

DISCUSSION

pH EVOLUTION DURING FERMENTATION

One of the most important factors in this topic is pH, which influences the growth and/or activity of intestinal microflora, particularly *Bifidobacteria* and *Lactobacilli.* González-Bermúdez et al. (9) indicated that decreasing pH means an increase in acidity due to increased production of SCFAs by the fecal microbiota, and reported a negative significant relationship between pH and acetic acid or total SCFAs in all sampling points.

The decreasing tendency in pH found in our study could be explained because antimicrobial properties of Lf have been reported, which reduce bacteria growth (11); meanwhile, GOS induced a fast fermentation, softening the Lf effect. At 24 hours of fermentation, pH values were similar in all samples, maybe because Lf has been degraded and its antibacterial properties have been erased.

Recently, the drop in pH from the ileum to the cecum due to the higher SCFA concentrations has had two beneficial effects. First, both *in vitro* and animal studies showed that lower pH values change gut microbiota composition, and secondly, it prevents overgrowth by pH-sensitive pathogenic bacteria like *Enterobacteriacae* and *Clostridia* (12). Regarding the role of GOS as a fermentable substrate, it has been demonstrated that it produced a large concentration of lactate after 24 hours of fermentation, reducing pH values (13), which could explain the considerable decline in pH values in this study.

SHORT-CHAIN FATTY ACIDS EVOLUTION DURING FERMENTATION

SCFAs are organic acids with 1-6 carbon atoms and are one of the main anions obtained by the degradation of polysaccharides, oligosaccharides, proteins, peptides, and glycoprotein precursors in the colon by gut microbiota. Currently, it is well confirmed that produced SCFAs have several health-promoting activities such as improving water transport, sodium absorption, and bicarbonate excretion (14). Furthermore, SCFAs play a pivotal role as nutrients for the colonic epithelium, modulators of colonic and intracellular pH, and other functions related to Fe transport, and regulators of proliferation, differentiation, and gene expression. The accumulated SCFAs decrease the colonic pH leading to modulation of the pattern of colonic microbiota, and also improve the Ca and Fe absorption (15). SCFAs accumulated in the colon

act as lowering factors of bioavailability of the toxic amines, thus protecting from the carcinogenic progress.

The SCFA evolution in our study was in line with the obtained findings by Miller and Wolin (16), revealing that acetic acid was the major SCFA accumulated after fermentation of glucose purified from cabbage. Also, it was reported by Velazquez et al. (17) that glucose fermentation by intestinal microbiota gave rise to more acetic acid but less propionic and butyric acid production than other fermentable substrates. In addition, acetic acid and total SCFAs were highly produced after short-term incubation of lactulose and GOS with intestinal flora. Likewise, Beards et al. (8) reported that the colonic fermentation of GOS induced the production of acetic acid, which correlated positively with the increase of *Bifidobacteria* populations, as acetate formation is consistent with *Bifidobacteria* and *Lactobacilli* metabolism. Similar results have been reported showing that the increasing production of acetic acid was directly associated with the increase in *Bifidobacteria* counts (18). Several published data revealed that prebiotics are the main responsible for the marked increase in the counts of *Bifidobacteria, Lactobacilli* and, subsequently, the higher production of acetic acid and total SCFAs (19) , and these changes may be responsible for promoting the defense functions of the host and thereby protecting the host from severe infection (20).

It was previously reported that propionate may form a soluble complex with iron, thereby maintaining the solubility of iron in the lumen of the colon, as well as facilitating the transfer across endosome membranes of the enterocytes (15). The low concentration of butyric acid found in our study after 24 hours of fermentation has been related to reductions of *Clostridium* and *Enterobacteriaceae* numbers. The main butyrate-producing bacterial groups found in human feces, as well as related to the decrease of *Faecalibacterium prausnitzii* (Fpra655) populations has been reported in a recent study (21) . However, the present findings showed increases of *Enterobacteriaceae* for 24 hours of fermentation. Furthermore, butyric acid production was not observed in these mostly acidic cultures when pH values of fecal cultures fall below 6.0 as indicated to occur by Walker et al. (22). Likewise, many studies revealed that acetic acid is produced at higher levels than propionic and butyric acids (23). Rossi et al. (24) indicated that the presence of FOS and inulin highly affected the production of SCFAs. Fermentation of FOS led to producing acetic and lactic acids as the main fermentation end products, while fermentation of inulin rose butyric acid level. Thus, because of the previously reported data, we can report that the type of dietary components, their composition, polymerization degree and intestinal microbiota pattern of infants, and the age of the infant may greatly influence on the accumulated SCFAs.

Respecting the acetic acid/propionic acid ratio, Delzenne and Kok (25) reported that its decreased could be suggested as a possible marker of the hypolipidemic effect of prebiotics (as noted by the inhibition of cholesterol and fatty acids biosynthesis in the liver, which finally results in a decrease in lipid levels in the blood).

It is well-known that the feeding pattern of the infant could influence the predominant microflora (type, composition, and activity) in the infant's gastrointestinal tract. The diet is the main factor in modulating the gut microbiota. This effect is greatly observed in the intestinal microflora pattern predominant in the infant gut, where *Bifidobacteria* and *Lactobacilli* are predominant in breast-fed infants gut (5), and breast human milk contains several components with a prebiotic nature, such as HMOs. The fermentation of this prebiotic can stimulate the selective growth of *Lactobacillus* and *Bifidobacteria* species and the subsequent production of SCFAs. Many published studies have shown that acetic acid was the main fermentation end-product in infants that received human milk while propionic and butyric acids were the predominance metabolites in the gut of bottle-fed infants. Various studies confirmed that the beneficial effect of prebiotics added to infant formulas strongly influenced SCFAs pattern providing a fecal SCFAs profile that is close to that of breast-fed infants, with a high level of acetate and lower level of propionate and butyrate (26).

In short, SCFAs (acetate, propionate, or butyrate), the main end-products resulting from microbial fermentation of these indigestible oligosaccharides, are well-known to possess beneficial effects on the host. Enhanced SCFAs production and increased delivery of these compounds in the distal colon, especially butyrate, may have a role in preventing colon cancer and other intestinal disorders (27). Furthermore, these metabolites can improve mineral absorption by their role in decreasing the pH of colon contents (15) leading to enhancement of the released iron from its complex with proteins, thereby increasing its bioavailability (15). Also, SCFAs possess beneficial effects on the intestinal level, as they may stimulate the proliferation of epithelial cells, thereby increasing the absorptive surface area in the colon. Likewise, prebiotics or their metabolites may create an environment in the colon that promotes the reduction of Fe^{3+} to Fe^{2+} (28) . It may stimulate the expression of iron regulatory genes, thereby increasing iron absorption, such as calbindin-D9K, which positively affect Ca absorption and DMT1, hemochromatosis protein (HFE), duodenal cytochrome b (Dcytb), and ferroprotein-1 which positively influenced Fe absorption (29).

ANALYSIS OF MICROBIOTA DURING FERMENTATION

Both ingredients, lactoferrin and GOS, could serve as a substrate for microbiota, giving place to prebiotic effects (8). Different concentrations of rhLf did not produce significant increases in total bacteria, what could be explained because of the effect of GOS. In this sense, Rycroft et al. (13) showed little insignificant increases in the total count after the use of GOS after five and 24 hours of batch culture fermentations. Nevertheless, other researchers showed significant increases in total bacteria after 24 hours of batch culture fermentation using GOS as substrate (8).

Regarding *Bacteroides,* an increase in this bacterial group has been related to beneficial effects on gut health, contributing to the synthesis of different vitamins and reducing gut inflammation (30). However, our results showed a decrease in this group from

10 to 24 hours of fermentation, which are in agreement with other authors that demonstrated that *Bacteroides* decreased after fermentation (7) due to the fall of pH (5.5 or lower) (31). In addition, *Bacteroides* could produce propionate using lactate as substrate, which could explain the poor production of propionic acid shown in our results (31).

As it has been previously mentioned in the case of total bacteria, it could exist a relationship between increases in *Enterobacteria,* SCFA production, and the addition of GOS to rhLf. At this point, it is important to note that this heterogeneous family of bacteria comprises a wide number of members of microorganisms, which can remain as a commensal organism or produce enteric diseases and dysbiosis (32). Therefore, the present results would indicate increases in desirable bacterial groups through fermentation of GOS and rhLf. However, the antimicrobial activity of lactoferrin has been widely proved. Concretely, bacteriostatic and bactericide functions have been attributed to lactoferrin, which has great implications for human health (2). These effects against a great number of G+ and G- bacteria could be mediated through the alteration of membrane permeability of bacteria or/and by sequestering the iron needed for bacteria nutrition. Several studies have demonstrated the inhibitory effect of lactoferrin against pathogens such as *Escherichia coli* and *Listeria monocytogenes* (33). Nevertheless, the present results suggest that single lactoferrin or GOS added to lactoferrin at different concentrations did not inhibit the growth of *Enterobacteria,* maybe because a higher amount of lactoferrin could be necessary to achieve the bacteriostatic/bactericide effect. In this sense, the oral administration of bovine lactoferrin in obese mice modestly inhibited the growth of these groups of bacteria (34). Regarding the effect of prebiotics, such as GOS, on *Enterobacteria*'s growth culture fermentation had proved that GOS stimulated the growth of *E. coli* after four hours of fermentation, although this increase did not continue over time (eight and 12 hours) (35). *In vivo* studies showed that the administration of several dosages of GOS to human volunteers did not change the levels of lactose-fermenting enterobacteria on fecal samples (36). These contradictory results could be due to differences in the experimental design, time of incubation, prebiotic dose, and the complexity of the gut environment.

Some species of *Enterococci* are recognized as pathogens although other members are related to antimicrobial activity because of the production of bacteriocins. In this sense, some members of the genus *Enterococcus,* such as *E. faecium* or *E. faecalis,* have been studied because of their probiotic potential. This probiotic effect has been demonstrated in the prevention and/or treatment of irritable bowel syndrome and chronic intestinal diseases (37). Our results could suggest that GOS and rhLf stimulated the growth of *Enterococci* over the fermentation. In line with our results, both GOS and lactoferrin have shown stimulants effects on the growth of *Enterococcaceae.* However, other researchers did not show any dose-effect when GOS was administered to human volunteers (36).

Regarding *Bifidobacterium* and *Lactobacillus* genera, our results showed an increase in both groups along fermentation. A wide number of studies have proved the prebiotic effect of both GOS and lactoferrin. Specifically, Rycroft et al. (13) found increases in the number of *Bifidobacteria* after five and 24 hours of fermentation and lesser effect in other groups of bacteria. Li et al. (38) demonstrated that GOS stimulated selectively the growth of *Bifidobacteria* after 24 hours of fermentation using fresh human feces. Similarly, other authors demonstrated the growth of *Lactobacilli* and *Bifidobacteria* after a batch culture fermentation using GOS as substrate (35). Many researches have proved the growth-promoting effect of lactoferrin on *Bifidobacteria.* The bifidogenic effect could be mediated by peptides derived from lactoferrin, bound iron, and sugar chains (4). For instance, *in vivo* studies have shown that the oral supplementation of bovine lactoferrin to obese mice increased the number of *Bifidobacterium* spp. after 12 weeks of treatment, which suggested the prebiotic potency of this protein (34). In addition, lactoferrin appears to modulate gut microbiota, favoring the growth of *Lactobacilli* and *Bifidobacteria* and decreasing the counts of pathogenic bacteria (39).

CONCLUSION

Despite the importance of the batch culture fermentation technique in uncovering the prebiotic activity of the food ingredients, it is not useful for detecting the prebiotic nature of Lf due to its nature as a protein. Thus, Lf maybe shows its prebiotic activity on the gut microbiota through other mechanisms.

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ARÁN

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Trabajo Original

Pediatría

Validity of the neck circumference for the diagnosis of obesity in school children living at high altitude

Validez de la circunferencia del cuello para el diagnóstico de obesidad en escolares que viven en altura

Ana María Aguilar Liendo[1], Leonor Sillo Mamani[2], Silvia P. Velásquez Mariscal[3], María Pilar Navia Bueno[1], Gerardo Weisstaub[4]

[1]Instituto de Investigación en Salud y Desarrollo. Facultad de Medicina. Universidad Mayor de San Andrés. La Paz, Bolivia. [2]Centro de Medicina Nuclear y Radioterapia El Alto. El Alto, Bolivia. [3]Instituto de Gastroenterología Boliviano Japonés. La Paz, Bolivia. [4]Instituto de Nutrición y Tecnología de los Alimentos (INTA). Universidad de Chile. Macul, Chile

Abstract

Background: body mass index (BMI) is commonly used to diagnose overweight and obesity, and waist circumference (WC) is used to estimate visceral fat. The measurement of WC is demanding, therefore, different studies proposed the use of neck perimeter.

Objective: exploring diagnostic validity of neck perimeter to diagnose overweight and obesity in 10-12 years old children in La Paz (Bolivia).

Methods: this is a cross-sectional study with a random sample of school children in El Alto (Bolivia). Weight, height, waist circumference and neck perimeter were measured, classifying the nutritional status with BMI-z according to the cut-off point of the World Health Organization (WHO) classification. The sample size was calculated for 95 % confidence level, an alpha level of 0.05 and 80 % power for diagnosis test design. To evaluate neck perimeter validity for diagnosing obesity, sensibility, specificity and positive and negative ratio likelihood were calculated using BMI gold standard according to age and sex.

Results: a number of 371 school children between 10-12 years old were included and 34 % of them presented malnutrition by excess. Sensibility and specificity of the neck perimeter to diagnose overweight and obesity were 87.5-100 % and 75.7-86.3 %, respectively.

Conclusion: neck perimeter in 10-12-year-old school children is a valid indicator for carrying out obesity diagnosis.

Keywords:

Obesity. Neck circumference. Waist circumference.

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Correspondence:

Gerardo Weisstaub. Instituto de Nutrición y Tecnología de los Alimentos (INTA). Universidad de Chile. 5524 El Líbano, Santiago de Chile. Chile
e-mail: gweiss@inta.uchile.cl

Resumen

Introducción: el índice de masa corporal (IMC) se usa comúnmente para diagnosticar el sobrepeso y la obesidad, y la circunferencia de la cintura (CC), para estimar la grasa visceral. La medición de la CC es exigente y, por ello, diferentes estudios propusieron el uso del perímetro del cuello.

Objetivo: explorar la validez diagnóstica del perímetro del cuello para diagnosticar sobrepeso y obesidad en niños de 10-12 años en La Paz (Bolivia).

Métodos: estudio transversal con una muestra aleatoria de escolares de El Alto (Bolivia). Se midieron peso, talla, circunferencia de la muñeca, perímetro de cuello, clasificando el estado nutricional con IMC-z según el punto de corte de la clasificación de la Organización Mundial de la Salud (OMS). El tamaño de la muestra se calculó para un nivel de confianza del 95 %, un nivel alfa de 0,05 y una potencia del 80 % para el diseño de la prueba de diagnóstico. Para evaluar la validez del perímetro del cuello para el diagnóstico de obesidad, se calcularon la sensibilidad, la especificidad y la razón de verosimilitud positiva y negativa utilizando el patrón oro del IMC según edad y sexo.

Resultados: se incluyeron 371 escolares de 10-12 años, de los cuales el 34 % presentaba malnutrición por exceso. La sensibilidad y especificidad del perímetro del cuello para diagnosticar sobrepeso y obesidad estuvo entre 87,5-100 % y 75,7-86,3 %, respectivamente.

Conclusión: el perímetro del cuello en escolares de 10-12 años es un indicador válido para realizar el diagnóstico de obesidad.

Palabras clave:

Obesidad. Circunferencia del cuello. Circunferencia de la muñeca.

INTRODUCTION

Overweight and obesity in childhood, puberty and adolescence have become a public health problem, significantly affecting the poorest sectors of society. In the last 40 years, it has increased from 11 to 124 million worldwide (1,2) for the same age group. In Bolivia, the prevalence of overweight and obesity in children under five years of age and schoolchildren aged 12 to 16 years ranges between 10 % and 27 %, respectively (3). Body mass index (BMI) (4) is the most widely used indicator to diagnose overweight and obesity; however, it does not assess the distribution of body fat (5,6), an aspect strongly associated with the risk of chronic non-communicable diseases (7).

Waist circumference has a significant association with visceral fat and cardiometabolic risk (8,9). However, its measurement has considerable variability in obese subjects (10), and it requires removing part of the clothing and, according to gender, different space measurements.

It would be beneficial to have a more specific, more reliable and less complicated measuring parameter, such as neck circumference (NC), to assess the impact of interventions treating and preventing overweight and obesity.

NC was studied for the first time in the pediatric population in 2010. Since then, several countries have proposed it as a tool to identify overweight, obesity, and metabolic syndrome (11-15).

It is a parameter with good inter and intraobserver reliability (16). In addition, it is significantly correlated with waist circumference and BMI and has high sensitivity and specificity to identify overweight and obesity in childhood and adolescence.

Despite the advantages mentioned, it is not yet used in clinical practice because of the lack of internationally recognized cut-off points for the pediatric age.

The objective of this study was to explore the diagnostic validity of NC to detect overweight and obesity in a sample of schoolchildren between 10-12 years of age in the city of El Alto, Bolivia, at an altitude of 4,150 meters.

MATERIAL AND METHODS

A cross-sectional and analytical study was carried out between September 2016 and June 2017 in El Alto (La Paz, Bolivia), located at 4,150 meters above sea level. The target population was 17,319 students from fifth to seventh grade of public, private and mixed schools (17). The study started after the approval of the National Bioethics Committee and prior to taking body measures, we obtained an informed parental consent. A randomized sample size selected 399 subjects. It was calculated for a confidence level of 95 %, a type I error of 5 % and a power of 80 % for diagnostic test designs, with a sensitivity and specificity of 50 % given the absence of data in Bolivia. We excluded subjects with malformations which made the measurements difficult. We used BMI-z for age to identify overweight or obese subjects, calculated using the WHO Anthro Plus (4) software. The cut-off points proposed by the WHO $\leq$ -2 were classified as "low weight"; between -2 and +1 as "eutrophic"; between BMI-z $\geq$ +1 and $<$ +2 as overweight; and BMI-z $\geq$ 2 as obesity. BMI was considered as the gold standard to validate neck circumference (4).

Two previously standardized researchers performed all the anthropometric measurements. An accuracy of 99 % was obtained in the standardization, as well as an average difference with the standard of 0.18 and 0.38, with an error of less than 1 % accuracy. Height and weight were assessed with a stadiometer and a previously calibrated electronic anthropometric scale (SECA 813® 0.1 kg).

The neck circumference was measured with an inextensible tape (SECA 20® 0.1 cm), below the laryngeal prominence and perpendicular to the long axis of the neck, in a standing position and with the head in the horizontal Frankfurt plane parallel to the floor (18). Waist circumference was measured standing and at the end of normal expiration, using the same tape, between the upper border of the iliac crest and the last rib, using a tape measure at just above the uppermost lateral border of the right ilium, at the end of a normal expiration. It was recorded at the nearest millimeter, as described by the National Center of Health Statistics (19).

The data was tabulated in Excel, and the statistical analysis was carried out in the STATA program version 13. Overweight and obese schoolchildren were grouped into a single category, "malnutrition by excess". The normality of the data was evaluated through the Kolmogorov-Smirnov test. Means and standard deviations or median and interquartile range were calculated according to the distribution of the variable.

To detect significant differences between the variables, Student's t-test, ANOVA, Kruskal-Wallis or Wilcoxon tests were used according to the normality of the data. In addition, comparisons were made by sex and by age groups. Spearman's correlation analysis was performed between neck and waist circumference and BMI-z. Neck circumference cut-off points were determined using ROC curves by age group and gender, and sensitivity, specificity, and positive and negative likelihood ratios were calculated. The cut-off points for the likelihood ratio considered were as follows: for the positive, > 10 as highly relevant and 5 to 10 as good; and for the negative, < 0.1 as highly relevant and 0.1 to 0.2 as good.

RESULTS

We studied 371 schoolchildren between 10 and 12 years of age. Eight children with undernutrition and 20 outside the age range were excluded. Table I shows that more than a third of schoolchildren had malnutrition by excess (24 % overweight and 10 % obesity).

Neck circumference increased with age and was higher in boys. In contrast, girls had higher height, weight, and BMI in all age groups (Table II).

Overweight and obese boys and girls had a greater perimeter than their eutrophic peers (31.1 ± 1.8 cm *vs* 27.9 ± 1.3 cm, respectively; $p < 0.0001$) (Table III).

The correlation analysis shows that NC has a high and significant correlation with waist circumference and the BMI-z in subjects of both sexes ($r > 0.8$; $p < 0.001$); furthermore, the correlation of the BMI-z with NC is similar to BMI-z with waist circumference (Table IV).

The sensitivity and specificity of the NC to diagnose overweight malnutrition ranged from 84.6 % to 92.3 % and 86.4 % to 92.0 %, respectively. In all age and sex groups, the area under the curve was greater than 0.90, and the positive likelihood ratio was > 5 (Table V).

Table VI shows the direct association between the probability of being obese and the NC value through a logistic regression model; this association is independent of the age and sex of the subject.

Finally, the area values under the ROC curve show a high discriminative capacity of the NC cut-off points to separate schoolchildren with and without excess malnutrition at all ages (Fig. 1).

Table I. Characteristics of sample in Bolivian schoolchildren aged 10-12 years (n = 371)

Variable	Average ± SD	CI 95 %
Age (years)	11.2 ± 0.7	(11.1-11.2)
Weight (kg)	38.5 ± 8.7	(37.6-39.4)
Height (cm)	140.8 ± 6.8	(140.1-141.5)
BMI (kg/m^2)	19.3 ± 3.2	(18.9-19.6)
BMI-z	0.6 ± 1.1	(0.5-0.7)
Height/age- z	0.9 ± 0.7	(0.9-1.0)
NC (cm)	29.1 ± 2.2	(28.9-29.3)
WC (cm)	68.8 ± 9.4	(67.8-69.8)
Overweight (%)	24.5	(20.4-29.1)
Obesity (%)	10.2	(7.5-13.7)

SD: standard deviation; CI: confidence interval; NC: neck circumference; WC: waist circimference; BMI-z: body mass index z; BMI-z ≥ 2: overweight; BMI-z ≥ 3: obesity.

Table II. Characteristics of the sample in Bolivian children aged 10-12 years in both genders

	Girls			Boys		
Age (years)	**10**	**11**	**12**	**10**	**11**	**12**
n	79	98	33	69	64	28
Weight (kg)	37.8 ± 8.7	39.5 ± 8.1	42.5 ± 8.7*	35.0 ± 8.6	38.3 ± 7.7	41.3 ± 9.9*
Height (cm)	139.9 ± 6.1*	142.4 ± 6.3*	145.6 ± 6.8*	136.9 ± 6.3*	139.8 ± 5.9*	144.1 ± 7.2*
NC (cm)	28.8 ± 2.2	29.0 ± 2.0	29.3 ± 2.2	28.9 ± 2.3	29.5 ± 2.0	30.0 ± 2.7
WC (cm)	68.0 ± 9.7	68.5 ± 8.6	69.9 ± 9.5	67.0 ± 9.3	70.3 ± 9.0	72.0 ± 11
BMI-z	0.6 ± 1.2	0.5 ± 0.9	0.4 ± 1.0	0.6 ± 1.2	0.8 ± 1.0	0.7 ± 1.0
Height/age-z	0.8 ± 0.5	1.0 ± 0.7	1.2 ± 0.9	0.9 ± 0.6	0.9 ± 0.8	1.2 ± 0.8
Overweight (%)	25.3	20.4	21.2	23.2	31.2	32.1
Obesity (%)	11.4	8.2	3.0	13	11	14.3

**ANOVA (Bonferroni) < p 0.05. NC: neck circumference; WC: waist circimference; BMI-z: body mass index z; BMI-z ≥ +1 to < +2: overweight; BMI-z ≥ 2: obesity.*

Table III. Neck circumference in Bolivian schoolchildren according to gender, age and nutritional status

Nutritional status	Normal	Overweight/obesity
Girls (years)		
10	27.0 ± 1.6*	31.0 ± 1.4*
11	27.2 ± 1.1*	31.2 ± 1.8*
12	28.1 ± 1.5*	31.7 ± 2.5*
Total	28.0 ± 1.5*	31.3 ± 1.7*
Boys (years)		
10	27.8 ± 1.2*	30.9 ± 2.2*
11	28.3 ± 1.2*	31.3 ± 1.5*
12	28.1 ± 1.4*	32.1 ± 2.1*
Total	28.0 ± 1.2*	31.7 ± 2.0*

**t-test $p < 0.0001$.*

Table IV. Association of neck circumference, waist circumference and BMI-z (Spearman's correlation) in Bolivian children aged 10-12 years in both genders

	NC		WC
	AC	BMI-z	BMI-z
Girls			
10	0.84*	0.84*	0.91*
11	0.81*	0.82*	0.84*
12	0.83*	0.86*	0.86*
Boys			
10	0.84*	0.83*	0.89*
11	0.87*	0.80*	0.88*
12	0.94*	0.89*	0.90*

**$p < 0.001$. NC: neck circumference; WC: waist circimference; BMI-z: body mass index z.*

Table V. Usefulness of neck circumference for the diagnosis of overweight and obesity in Bolivian schoolchildren aged 10-12 years in both genders

	n	NC (cm)	AUC	S (%)	E (%)	LR (+)	LR (-)
Girls (years)							
10	79	29.1	0.96	86.2	92.0	10.7	0.14
11	98	29.5	0.94	85.7	88.6	7.5	0.16
12	33	30.5	0.90	75.0	88.0	6.2	0.28
Boys (years)							
10	69	29.1	0.92	88.0	86.4	6.9	0.04
11	64	29.8	0.94	84.6	89.5	8.0	0.17
12	28	29.9	0.97	92.3	86.7	6.9	0.08

NC: neck circumference (cut points); AUC: area under the curve; S: sensitivity, E: specificity LR likelihood ratio positive (+) and negative (-).

Table VI. Association of neck circumference with obesity in a logistic regression model

		Obesity OR (95 % CI)
Neck circumference (cm)	Model I	2. 6 (2.0 to 3.4)*
	Model II	2.7 (2.0 to 3.6)*

*Model I: without adjustment. Model II: adjusted by age and sex. *Significant values p < 0.01. BMI: body mass index; CI: confidence interval; OR: odds ratio.*

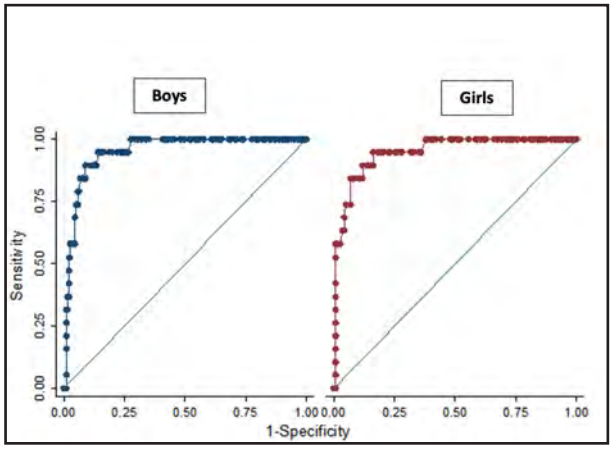

Figure 1.

Receiver operating characteristic curve of neck circumference as an indicator of obesity in Bolivian children aged 10-12 years in both genders.

DISCUSSION

This study supports the validity of NC for the identification of overweight and obesity in schoolchildren aged 10-12 years of both sexes who live at high altitudes.

The prevalence of malnutrition due to excess in our study is similar to UNICEF's in 2020, which indicated that 22 % of the school population in Bolivia was overweight and 11 % was obese (20).

Similar to other studies, we found a positive correlation (≥ 0.60) between NC, BMI and WC (21,22). A cross-sectional study conducted in India in 360 subjects (13-16 years old) found a good and significant (< 0.001) correlation between NC and WC in both men (0.72) and women (0.67) (14). Another Mexican study, which included schoolchildren aged 6-11 years of both sexes with normal weight, detected a correlation between NC and BMI (between 0.51 and 0.67) and waist circumference (between 0.59 and 0.72) (17).

In the present study, NC values for obese children ranged between 30.9 and 31.7 cm. For subjects of the same age, the study by Kym et al. presented values between 30.5 and 32.5 cm (21), and Valencia Sosa et al., between 28.5 and 30.3 cm (n = 1,800) (17). Kelishadi et al. reported a higher average NC in overweight and obese schoolchildren compared to eutrophic counterparts (n = 23,000) (23).

Our study's sensitivity (84.6-92.3 %) and specificity (86.4-92.0 %) values using NC to diagnose malnutrition due to excess were high and comparable to other studies, like that of Taheri M. et al., with a sensitivity of 75-83 and specificity of 71-85 using NC in schoolchildren to diagnose malnutrition due to excess (16). The lowest sensitivity value in our study was in 12-year-old girls, probably due to the low prevalence of obesity at that age in our study (3 %). The best sensitivity and specificity values in the different groups were obtained with NC cut-off points between 29 cm and 29.9 cm. When comparing our results with those of Castro Piñero J et al., we observed that our NC cut-off points were lower (24).

Iñarritu-Pérez M et al., with NC cut-offs of 30.0 and 29.3 cm for 12-year-olds, 31.9 and 30.4 cm for 13-year-olds, and 33.5 and 30.7 cm for 14-year-old in male and female Mexican adolescents, respectively, have the highest sensitivity and specificity. The NC cut-offs identified overweight/obesity in 80 % of males and 86 % of females, and indicated significant correlations ($p < 0.01$) in males and females with weight ($r = 0.821$ and $r = 0.840$, respectively), BMI ($r = 0.649$ and $r = 0.819$, respectively), WC ($r = 0.710$ and $r = 0.813$, respectively) and mid-upper arm circumference ($r = 0.736$ and $r = 0.815$, respectively) (25).

Our results should be analyzed considering the altitude at which the study was carried out. Different investigations show that body composition can be modified by the altitude at which the subjects live. Lowland and highland children differ in their patterns of stunting, BMI, WC and WCH index (26). Santos C et al. observed that schoolchildren who lived at higher altitudes had a lower prevalence of obesity than those who lived at sea level (6.3 % *vs* 41 %, respectively). Tibetan children living permanently above 4,000 m show a phenotypic adaptation in chest growth and a moderate reduction in linear growth. The differences could be explained by the environment, stress exposure to cold climate, and hypoxia, discarding the influence of food patterns and economic conditions. Although we did not find studies of NC done at high altitudes, the data above suggest considering altitude as a variable to consider when defining references (27).

Our study has certain limitations that must be considered when interpreting the results. As we diagnose overweight and obesity through the BMI, we cannot distinguish between the percentage of lean mass and body fat mass. Another aspect to consider is the small sample size in some of our groups.

In summary, we found that NC identified correctly a large proportion of overweight and obese schoolchildren. NC measurement is a simple technique that does not require undressing the individual, has good inter- and intra-rater reliability, and could be used to screen for excess malnutrition. Despite all these advantages, it is essential to bear in mind that there are still no established NC percentiles for each age and sex, nor do we have defined cut-off points to diagnose overweight/obesity.

This study is carried out in children living at high altitudes, where NC is used as a screening tool to identify malnutrition by

excess in school age children; we did not find other studies for the same age population living at high altitude.

We hope to encourage the development of new studies in these particular settings which include a large population and, in the future, analyze its association with metabolic syndrome and other chronic pathologies.

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Trabajo Original

Pediatría

Growth trajectories in children with cleft lip and/or palate

Trayectorias de crecimiento en niños con fisura labial y/o palatina

Rocío Gallego[1,2], Iris Iglesia-Altaba[1,3,4,5], Ignacio Moral[2,6], Iván Iso[6], Elena Delso[6], Gerardo Rodríguez[1,2,3,4,5]

[1]Aragon Institute for Health Research (IIS Aragón). Zaragoza, Spain. [2]Universidad de Zaragoza. Zaragoza, Spain. [3]Growth, Exercise, Nutrition and Development (GENUD) Research Group. Faculty of Health Sciences. Universidad de Zaragoza. Zaragoza, Spain. [4]Instituto Agroalimentario de Aragón (IA2). Zaragoza, Spain. [5]Maternal and Infant Health and Development Network (SAMID). RETICS – Instituto de Salud Carlos III. Madrid, Spain. [6]Oral and Maxillofacial Surgery Service. Hospital Universitario Miguel Servet. Zaragoza, Spain

Abstract

Introduction: the nutritional status and growth of children with cleft lip and/or palate (CL/P) can be affected due to feeding difficulties caused by their anatomy and the surgical interventions.

Objective: this retrospective longitudinal study aims to analyse the growth trajectories of a cohort of children with CL/P and compare them with a healthy representative cohort of children from Aragon (Spain).

Methods: type of cleft, surgical technique and sequelae, and weight, length/height and body mass index (BMI) (weight/height^2) at different ages (0-6 years) were recorded. Normalized age- and sex-specific anthropometric Z-scores values were calculated by World Health Organization (WHO) charts.

Results: forty-one patients (21 male, 20 female) were finally included: 9.75 % cleft lip *(n* = 4/41), 41.46 % cleft palate *(n* = 17/41) and 48.78 % cleft lip and palate *(n* = 20/41). The worst nutritional status Z-scores were achieved at the age of three months (44.44 % and 50 % had a weight and a BMI lower than -1 Z-score, respectively). Mean weight and BMI Z-scores were both significantly lower than controls at one, three and six months of age, recovering from that moment until the age of one year.

Conclusions: the highest nutritional risk in CL/P patients takes place at 3-6 months of age, but nutritional status and growth trajectories get recovered from one year of age compared to their counterparts. Nevertheless, the rate of thin subjects among CL/P patients is higher during childhood.

Keywords:

Cleft lip. Cleft palate. Growth. Nutrition.

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Correspondence:

Gerardo Rodríguez Martínez. Pediatrics Area. Faculty of Medicine. Universidad de Zaragoza. Domingo Miral, s/n. 50.009 Zaragoza, Spain
e-mail: gerard@unizar.es

Resumen

Introducción: el estado nutricional y el crecimiento de los niños con labio y/o paladar fisurado (CL/P) pueden verse afectados debido a las dificultades de alimentación provocadas por su anatomía y las intervenciones quirúrgicas.

Objetivo: este estudio longitudinal retrospectivo tiene como objetivo analizar las trayectorias de crecimiento de una cohorte de niños con CL/P y compararlos con una cohorte representativa de niños sanos de Aragón (España).

Métodos: se registraron el tipo de fisura, la técnica quirúrgica y las secuelas, el peso, la longitud/talla y el índice de masa corporal (IMC) (peso/talla2) a diferentes edades (0-6 años). Se calcularon las Z-score de los valores antropométricos según edad y sexo, mediante las tablas de la Organización Mundial de la Salud (OMS).

Resultados: se incluyeron 41 pacientes (21 hombres, 20 mujeres): 9,75 % con fisura labial *(n* = 4/41), 41,46 % con fisura palatina *(n* = 17/41) y 48,78 % con fisura labiopalatina *(n* = 20/41). Los valores Z-scores de la antropometría más bajos se alcanzaron a los tres meses de edad (el 44,44 % y el 50 % tenían un peso y un IMC inferiores a -1 Z-score, respectivamente). Los valores de peso medio y de las puntuaciones Z del IMC fueron significativamente más bajos en los pacientes con fisura que en los controles a los uno, tres y seis meses de edad, recuperándose a partir de ese momento hasta equipararse al año de edad.

Conclusiones: el mayor riesgo nutricional en pacientes con CL/P se presenta entre los tres y seis meses de edad, pero su estado nutricional y las trayectorias de crecimiento se normalizan a partir del año de edad. Sin embargo, la proporción de individuos delgados entre los pacientes con CL/P es mayor durante la infancia.

Palabras clave:

Fisura labial. Fisura palatina. Crecimiento. Nutrición.

INTRODUCTION

Cleft lip and/or palate (CL/P) are a type of congenital anomalies that affect one per 700-750 newborns and are caused by embryological defects in the formation of the upper lip and palate during the early stages of pregnancy (1). In addition to the stigmatizing aesthetic defect, CL/P associate feeding and breathing problems, ear infections and hearing loss, speech pathology, and dental and developmental problems of the jaws (2,3). Therefore, these patients require, on the one hand, a multidisciplinary approach (surgical, orthopaedic, orthodontic, otorhinolaryngological, phoniatric and psychologic) that must be done early in life and, on the other hand, a prolonged follow-up both to avoid functional impairment and to allow normal development of the child (4). There are several classifications but, overall, the cleft may affect the lip, the palate or both, and they can be unilateral or bilateral (5).

In children with CL/P, nutritional status can be affected because of feeding difficulties, mainly due to their anatomy and the surgical interventions themselves, as well as airway and middle ear infections (6,7). Consequently, these patients may have impaired growth and development during their first months of life, more or less marked depending on the type of cleft, and they may need nutritional support and aid with feeding practices (8,9). However, after two years of age, the nutritional prognosis and growth trajectories in most of them are similar to those of their peers (10,11).

The available studies on long-term growth and nutritional outcome of children with CL/P are scarce in the literature but, despite the fact that the nutritional prognosis seems to improve from two years of age (12-14), there is not enough conclusive evidence about their growth and body composition patterns during childhood (15). Furthermore, CL/P populations are from very different geographical origins and only a few of the existing studies, about long term growth prognosis of CL/P patients, have compared anthropometric measurements of CL/P children with their counterpart healthy controls (15-17). Thereby, more studies are needed to assess longitudinal growth, from birth to childhood, of those children with higher nutritional risk and the long-term consequences on their nutritional status and body composition. This article aims to analyse the growth trajectories of a cohort of Spanish children with isolated cleft lip and/or palate (without pathology or associated syndrome) who required surgical intervention and to compare them with international standards and with a healthy representative cohort of children from Aragón.

MATERIAL AND METHODS

STUDY DESIGN AND SAMPLE SIZE

This is a study with a retrospective longitudinal design in which the medical records of the patients seen in the Children's Oral and Maxillofacial Surgery consultation of a reference hospital born between 2009-2014 were reviewed. The selection criteria were: patients with a diagnosis of cleft lip, cleft palate or cleft lip and palate born in that period. In each of the selected patients, data collected were sex, date of birth, type of cleft, date and type of intervention, surgical technique and sequelae, as well as weight, length (height) and body mass index (BMI) (weight/size^2) at different ages (0-6 years). Sixty patients born between 2009 and 2014 were initially reviewed with a diagnosis of CL/P, from which 41 patients (21 male and 20 female) were finally selected because they had full longitudinal registration of anthropometric measurements in their medical records and they did not associate any pathology or syndrome.

A cohort of Spanish children participating in the Growth and Feeding during Infancy and Early Childhood in Aragon (CALINA) study (18,19), born in the same year (2009), were used as control group. CALINA is an ongoing birth cohort study whose sample is a representative cohort of our population. CALINA's study main objective was to assess growth patterns, body composition and feeding aspects in infants and children and to examine prenatal, postnatal and sociocultural factors which may influence them. The cohort was randomly drawn from births occurring from March 2009 to February 2010 in different localities in the region

of Aragon (Spain), recruited from Primary Care centres by trained paediatric staff and with compliance and attendance over 80 % of the population living in this area.

One thousand six hundred and thirty families were contacted to participate in the CALINA study and 1,602 families accepted to participate. After eliminating children with any malformation, diseases or physical disabilities and without information on sex, birth weight, length at birth, and date and place of birth, a total of 1,540 new-born infants were examined at birth and periodically re-examined at two weeks, monthly and yearly. After the six-year follow-up, 323 children no longer participated in the study (retention rate 79 %). Children with missing values in exposures, covariates or outcomes at baseline or follow-up were excluded. Asians were not included because models could not run satisfactorily due to the small size of the sample that led to unstable results. Finally, the analysis included 1,031 children (19).

Research project in CL/P patients and CALINA study were both approved by the Aragón Clinical Research Ethics Committee.

ANTHROPOMETRIC MEASUREMENTS

Anthropometric measurements in CL/P patients were obtained through the data collected in their electronic medical records. Length/height, weight and BMI were registered at the ages of one, three and six months and at one, two, four and six years old. Normalized age- and sex-specific anthropometric Z-score values were calculated in both studies (CL/P children and CALINA) by using child growth standards tables of the World Health Organization (WHO) (20,21).

STATISTICAL ANALYSIS

The data were entered into a database and analyses were conducted using the statistical software package IBM SPSS Statistics Version 26. A descriptive analysis was carried out using mean and standard deviation (SD) for continuous variables and frequencies and percentages for categorical variables. Differences in continuous and categorical anthropometric variables between CL/P and CALINA groups were compared using Student's t tests and Chi-squared analyses, respectively. The criterion for statistical significance was set at $p < 0.05$.

RESULTS

Forty-one patients were finally included, 21 male and 20 female. Different types of clefts were intervened: 9.75 % cleft lip ($n = 4/41$), 41.46 % cleft palate ($n = 17/41$) and 48.78 % cleft lip and palate ($n = 20/41$). In addition, 59.8 % ($n = 25/41$) were operated from the first surgical time, 6.9 % ($n = 3/41$) from the second surgical time, 16.1 % ($n = 6/41$) were operated on sequelae and 17.2 % ($n = 7/41$) had several interventions. The average age at the time of the first intervention was seven months (SD = 1.58) in the cleft lip and 12 months (SD = 2) in the cleft palate. In reference to sequelae, in cleft palate and cleft lip palate patients ($n = 37$), pharyngoplasty was performed due to velopharyngeal incompetence in 18.91 % ($n = 7$) at an average age of 5.9 years (SD = 1.89), and 21.62 % ($n = 8$) presented palatal fistula. In cleft lip and cleft lip palate patients ($n = 24$), 20.83 % ($n = 5$) were reoperated for labial sequelae.

Anthropometry (weight, length/height and BMI) mean Z-scores at each age and gender in CL/P patients and gender differences are shown in table I. There are no statistically significant differences between boys and girls at any age and in any of the variables. Mean anthropometric Z-scores were low in both sexes during the first year of age but all measurements seem to progressively reach normality later (Table I and Fig. 1). In fact, when trajectories of growth Z-scores parameters of CL/P infants are compared with those from the CALINA study, mean weight and BMI Z-scores are both significantly lower at one, three and six months of age but not at one year or later (Fig. 1A and C). The highest differences in terms of weight and BMI Z-scores are at the age of three months when CL/P subjects showed lower values, recovering from that moment until the age of one year. Although the length is also low during the first months, it does not show statistically significant differences compared to the control group at any time (Fig. 1B). Thus, it can be seen that length is slightly affected in infants with CL/P.

The percentage of CL/P patients with a Z-score lower than -1 for weight, length/height and BMI has been compared at each age with controls in figure 2. The proportion of CL/P patients that could be at nutritional risk is significantly higher during the first months of age based on weight (Fig. 2A) and BMI (Fig. 2C). At three months of age, when the differences are greater, 44.44 % and 50 % of CL/P patients had respectively a weight and BMI lower than -1 Z-score, compared with 15.54 % ($p < 0.001$) and 12.79 % ($p < 0.001$) in controls. Although these differences become smaller, the percentage of CL/P patients with low BMI remains higher than that of controls at 2-6 years of age (7-10 % higher) with statistical differences at six years of age ($p < 0.05$) (Fig. 2C). Regarding length, no statistically significant differences were found at any age in comparison with controls (Fig. 2B).

DISCUSSION

This study, with a retrospective longitudinal design, aims to analyse the growth trajectories of children, from birth to six years of age, with isolated CL/P (without associated pathology or syndrome) born between 2009-2014, and to compare them to their counterparts. The highest nutritional risk in CL/P patients takes place at 3-6 months of age but nutritional status and growth trajectories get recovered from one year of age compared to their counterparts. Nevertheless, the rate of thin subjects among CL/P patients is higher during childhood. The presence of these congenital orofacial malformations may influence negatively the nutritional prognosis of CL/P patients and, consequently, alter growth and development mainly during infancy (6,7).

Table I. Anthropometry at each age and gender in CL/P patients

		Total (*n* = 41) X (95 % CI)	Male (*n* = 21) X (95 % CI)	Female (*n* = 20) X (95 % CI)	*p*
Z weight	1 m	-0.707 (-0.960 - -0.454)	-0.644 (-0.974 - -0.315)	-0.777 (-1.203 - -0.350)	0.603
	3 m	-0.925 (-1.204 - -0.647)	-0.929 (-1.334 - -0.523)	-0.921 (-1.347 - -0.496)	0.980
	6 m	-0.438 (-0.765 - -0.110)	-0.493 (-0.975 - -0.010)	-0.376 (-0.870 - 0.116)	0.724
	1 y	0.025 (-0.307 - 0.358)	-0.037 (-0.522 - 0.448)	0.103 (-0.398 - 0.605)	0.677
	2 y	0.152 (-0.163 - 0.468)	0.107 (-0.401 - 0.616)	0.197 (-0.233 - 0.630)	0.777
	4 y	0.000 (-0.351 - 0.351)	-0.065 (-0.583 - 0.451)	0.070 (-0.460 - 0.600)	0.701
	6 y	0.077 (-0.370 - 0.523)	0.079 (-0.535 - 0.694)	0.073 (-0.671 - 0.820)	0.990
Z height	1 m	-0.210 (-0.488 - 0.070)	-0.137 (-0.544 - 0.270)	-0.290 (-0.712 - 0.132)	0.587
	3 m	-0.280 (-0.583 - 0.024)	-0.380 (-0.828 - 0.068)	-0.167 (-0.615 - 0.281)	0.485
	6 m	0.157 (-0.112 - 0.427)	0.185 (-0.161 - 0.533)	0.126 (-0.336 - 0.588)	0.826
	1 y	0.287 (-0.035 - 0.610)	0.210 (-0.237 - 0.655)	0.385 (-0.134 - 0.904)	0.589
	2 y	0.164 (-0.171 - 0.500)	0.151 (-0.270 - 0.573)	0.177 (-0.396 - 0.750)	0.940
	4 y	-0.067 (-0.302 - 0.167)	0.023 (-0.318 - 0.365)	-0.163 (-0.516 - 0.190)	0.429
	6 y	0.106 (-0.205 - 0.417)	0.174 (-0.271 - 0.620)	0.005 (-0.472 - 0.482)	0.594
Z BMI	1 m	-0.875 (-1.188 - -0.563)	-0.851 (-1.253 - -0.450)	-0.903 (-1.438 - -0.368)	0.871
	3 m	-1.057 (-1.360 - -0.755)	-0.995 (-1.372 - -0.620)	-1.126 (-1.653 - -0.598)	0.669
	6 m	-0.717 (-1.111 - -0.323)	-0.813 (-1.397 - -0.228)	-0.610 (-1.194 - -0.026)	0.610
	1 y	-0.192 (-0.550 - 0.163)	-0.213 (-0.700 - 0.272)	-0.167 (-0.755 - 0.421)	0.897
	2 y	0.001 (-0.378 - 0.381)	-0.113 (-0.701 - 0.475)	0.116 (-0.427 - 0.658)	0.549
	4 y	0.041 (-0.374 - 0.456)	-0.140 (-0.731 - 0.450)	0.123 (-0.402 - 0.870)	0.368
	6 y	-0.029 (-0.505 - 0.447)	-0.094 (-0.748 - 0.560)	0.066 (-0.728 - 0.860)	0.742

Z: Z-score; BMI: body mass index; CI: confidence interval; y: year; m: month. Statistical significance was set at p < 0.0.

In a recently published systematic review about long term growth patterns in CL/P patients, there were only six studies which analysed their nutritional prognosis during childhood and growth patterns from two years of age (15). The selected studies in this systematic review showed very varied results: three of them found some growth differences between cleft children and their counterparts (16,17,22) but the other three did not (13,23,24). Moreover, different groups of clefts were considered in each of these studies, diverse outcome measures were assessed and patients came from varied origins (three from Latin America, one from the United States, one from Asia and one from Europe) (15). In all of the previously reported studies about growth trajectories from two years of age in CL/P patients, anthropometric Z-scores were calculated (15); however, only in two of them and with a cross-sectional design, one in Colombia and the other one in Sweden, CL/P measurements were compared with controls (16,17). Thus, to our knowledge, ours is the second study that assesses growth trajectories in CL/P patients in Europe from two years of age, comparing them with controls, and the only one that does so worldwide in a population-based cohort study.

Our results are in agreement with what was previously published in children under two years of life (8,12,25,26). Below this age, there is a risk of malnutrition due to feeding difficulties, due to their anatomy and the surgical procedures themselves, as well as airway and middle ear infections (26-29). In our study, that happens especially during the first half year of age and the recovery, in terms of mean anthropometric trajectories, seems to be reached at one year of age. In fact, when the percentage of children with weight, length and BMI less than -1 Z-score (risk of malnutrition) has been analysed in our study, about half of children with CL/P are at risk of undernutrition at six months of age but later, from the first year of life, there are no statistical differences comparing with controls. However, the percentage of children with BMI less than -1 Z-score during childhood tends to be higher than in their peers (7-10 % higher), indicating that there are proportionally more thin children in the CL/P group than in the reference population.

On the other hand, it would seem reasonable to hypothesize that in these patients, in which growth restriction is evident during the first months of life due to early undernutrition followed by a later rapid weight gain, overweight and/or obesity risk could be increased in the long term as a compensatory response, either due to the effects of "metabolic programming" and/or by an excess of family insistence that they eat beyond their needs. However, no data supporting this hypothesis have been found in our sample (19,30,31).

In terms of growth recovery, our results after one year of age may reflect that nowadays in our healthcare environment, with

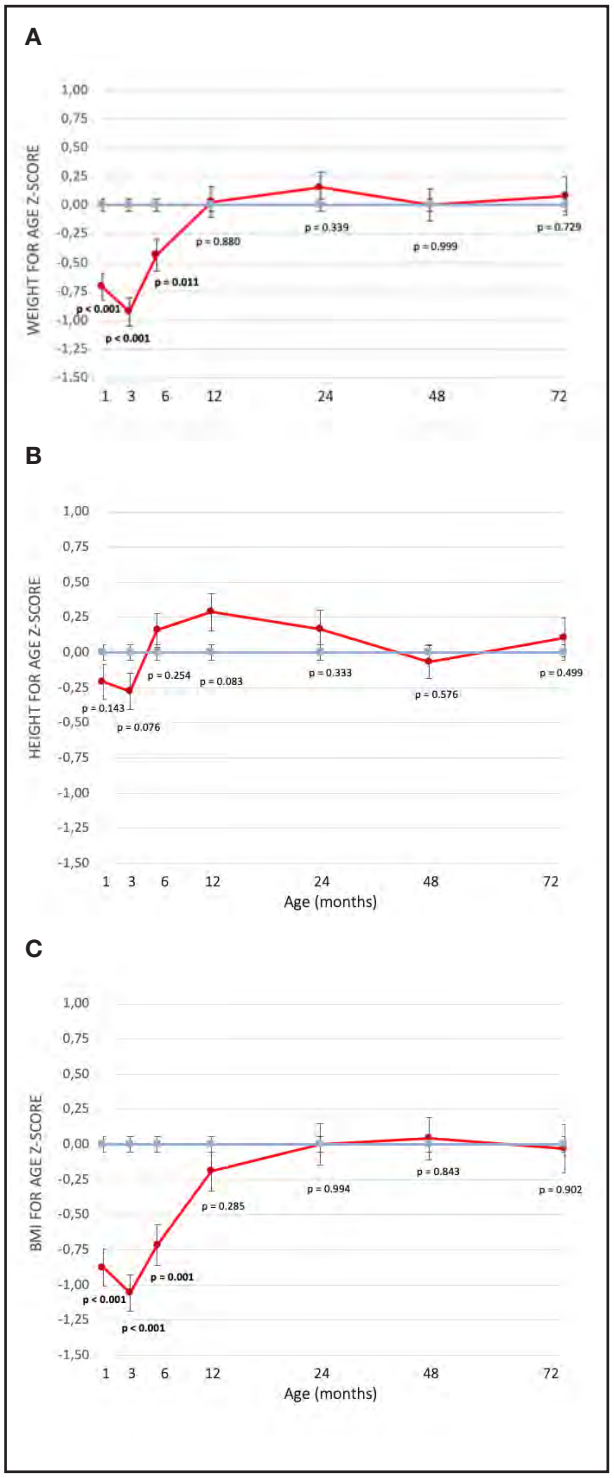

Figure 1.

Anthropometry charts for weight, height and body mass index (BMI) Z-scores of cleft lip and/or palate (CL/P) patients compared with CALINA study children. A. Anthropometry chart for weight Z-scores of CL/P patients compared with CALINA study children. Statistical significance was set at $p < 0.05$. B. Anthropometry chart for height Z-scores of CL/P patients compared with CALINA study children. Statistical significance was set at $p < 0.05$. C. Anthropometry chart for BMI Z-scores of CL/P patients compared with CALINA study children. Statistical significance was set at $p < 0.05$.

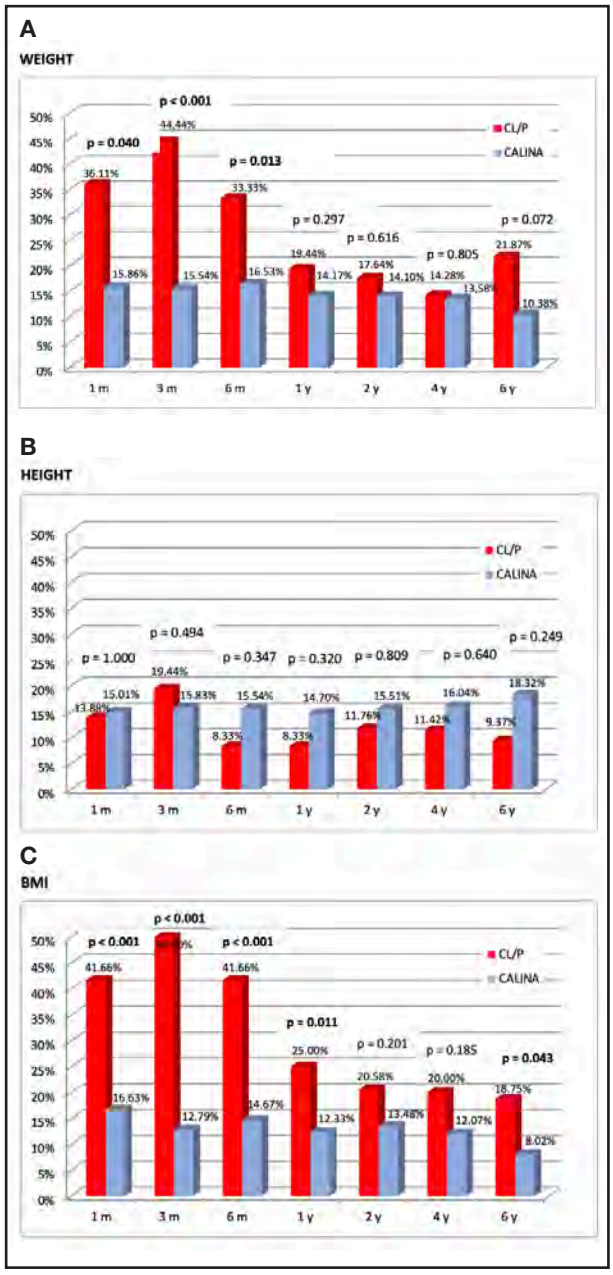

Figure 2.

Percentage of children with weight, height and BMI less than -1 Z-score in CL/P and CALINA samples. A. Percentage of children with weight less than -1 Z-score in CL/P and CALINA samples. Statistical significance was set at $p < 0.05$. B. Percentage of children with height less than -1 Z-score in CL/P and CALINA samples. Statistical significance was set at $p < 0.05$. C. Percentage of children with BMI less than -1 Z-score in CL/P and CALINA samples. Statistical significance was set at $p < 0.05$. BMI: body mass index; y: year; m: month; CL/P: cleft lip and/or palate.

the appropriate multidisciplinary management of these children, they get comparable to their healthy counterparts. This satisfactory outcome happens earlier than in other studies from Uganda or Syria (14,32,33). However, there is still much to improve in the first year of age in CL/P patients, especially during the first six months,

when feeding difficulties are more relevant and it is just the time before the first surgeries are usually done. It is in this period when our sample had the highest rate of undernutrition, indicating a poor health outcome and a disadvantage to face the surgery.

Looking into growth trajectory differences between the types of clefts, the sample was not big enough to analyse them in this study because there were only four patients with isolated cleft lip. In this regard, it has been reported that the more extensive the cleft, the more functional impairment there will be. Patients with cleft that affect only the lip should not have difficulty with breastfeeding (34). However, children with unilateral or bilateral complete cleft lips, as well as those with cleft palate, may have difficulties in feeding more frequently, mainly because the cleft lip can compromise sucking during breastfeeding while the cleft palate can cause milk to pass into the nasal cavity (6,7,27,35).

The main limitation of this study might be its sample size. However, this sample offers a current representative population of CL/P patients, followed up longitudinally in our health area, and controlled by the same specialized staff. This sample included all patients attended at the third-level reference hospital of our region for the management and treatment of patients with CL/P. The final number of patients is not so high as to perform more complex statistical analyses, but it does represent the global universe of the sample and it gives a real view of our results about this topic.

As strength of this study, it should be highlighted the fact that age- and sex-specific anthropometric Z-scores were calculated for each patient and, besides, that these data were compared with our own control sample of healthy counterparts (18). These aspects have allowed us to normalize the anthropometric measurements throughout the study period (from birth to six years old) in both sexes, to have a longitudinal view of each variable with respect to an international standard (WHO) and, at the same time, to compare them with real and current measurements of a control group.

From the results of this study, we can conclude that in Spanish children with CL/P there were no differences in growth between sexes. Their nutritional status and growth trajectories get recovered from one year of age compared to their healthy counterparts. The highest nutritional risk in these patients takes place at 3-6 months of age, when more efforts have to be done to improve feeding aspects and nutritional prognosis, in order to get the patient ready for surgery in the best conditions. During childhood, growth trajectories of CL/P patients are appropriate and similar to those of their counterparts. The rate of thin subjects among CL/P patients is higher during childhood but further larger studies are needed to confirm the long term consequences of these malformations on final growth and body composition later in life.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Nutrición en el anciano

Vitamin B12 supplementation improves cognitive function in middle aged and elderly patients with cognitive impairment

La administración de suplementos de vitamina B12 mejora la capacidad cognitiva en pacientes de mediana edad y ancianos con deterioro cognitivo

Li Zhou[1], Xue Bai[2], Jiagui Huang[1], Yongjun Tan[1], Qin Yang[1]

[1]Department of Neurology. The First Affiliated Hospital of Chongqing Medical University. Chongqing, China. [2]Department of Neurology. The First People's Hospital of Neijiang. Sichuan, China

Abstract

Objectives: to determine the effects of vitamin B12 supplementation on neuropsychological function and disease progression in middle aged and elderly patients with cognitive impairment.

Methods: this was a prospective case-control study. From May 2020 to May 2021, 307 participants clinically diagnosed with cognitive impairment in the Department of Neurology of the First Affiliated Hospital of Chongqing Medical University were enrolled. A total of 115 patients were included in this study. Meanwhile, 115 participants with cognitive impairment were randomly assigned in equal proportions to two groups: vitamin B12 treatment group ($n = 58$, vitamin B12 500 mg/d intramuscularly for seven days, followed by cobamamide 0.25 mg/d and methylcobalamin 0.50 mg/d) and the control group ($n = 57$). Demographic characteristics and blood biochemical variables were obtained from all participants. Cognitive performance was measured using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Cognitive performance was measured at baseline and after six months.

Results: the vitamin B12 supplementation treatment patients who presented with cognitive impairment showed significant improvement, especially in attention, calculation ($p < 0.01$) and visual-constructional ability ($p < 0.05$), in their neuropsychological function compared to their matched group.

Conclusion: vitamin B12 supplementation may improve frontal function in patients with cognitive decline. Vitamin B12 levels should be investigated in all patients with cognitive impairment.

Keywords:

Vitamin B12. Cobalamin. Cognitive impairment. Middle aged and elderly. Frontal function.

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Conflict of interest: the authors declare no conflict of interest.

Ethics approval: before participation in our study, all subjects signed an informed consent document according to the procedures required by the Research Ethics Committee of the Institute, which also approved the study protocol.

Data availability statement: this study complied with the guidelines for human studies and was conducted in accordance with the World Medical Association Declaration of Helsinki. The authors confirm that the data supporting the findings of this study are available within the article.

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Correspondence:

Qin Yang. Department of Neurology. The First Affiliated Hospital of Chongqing Medical University. Chongqing 400016, China
e-mail: xyqh200@126.com

Resumen

Objetivos: determinar los efectos de la suplementación con vitamina B12 en la función neuropsicológica y la progresión de la enfermedad en pacientes de mediana edad y adultos mayores con deterioro cognitivo.

Métodos: se realizó un estudio prospectivo de casos y controles; se estudiaron 307 participantes, desde mayo de 2020 a mayo de 2021, diagnosticados clínicamente con deterioro cognitivo en el Departamento de Neurología, el Primer Hospital Anexado a la Universidad Médica de Chongqing. En el estudio se incluyeron un total de 115 pacientes con deterioro cognitivo que fueron asignados aleatoriamente en proporciones iguales a dos grupos: un grupo de tratamiento con vitamina B12 ($n = 58$, vitamina B12 500 mg/d intramuscular durante 7 días, seguido de cobamamida 0,25 mg/d y metilcobalamina 0,50 mg/d) y un grupo de control ($n = 57$). Se obtuvieron las características demográficas y las variables bioquímicas sanguíneas de todos los participantes. El rendimiento cognitivo se midió mediante el miniexamen del estado mental (MMSE) y la evaluación cognitiva de Montreal (Moca) al inicio del estudio y a los 6 meses.

Resultados: los pacientes con deterioro cognitivo que recibieron tratamiento de suplementación con vitamina B12 mostraron una mejora significativa, especialmente en la atención, el cálculo ($p < 0,01$) y la capacidad visuoespacial ($p < 0,05$), en su función neuropsicológica en comparación con el grupo control.

Conclusión: la suplementación con vitamina B12 puede mejorar la función frontal en pacientes con deterioro cognitivo. Los pacientes con deterioro cognitivo deben conocer sus propios niveles de vitamina B12.

Palabras clave:

Vitamina B12. Cobalamina. Deterioro cognitivo. Mediana edad y ancianos. Función frontal.

INTRODUCTION

Cognitive impairment is defined as a progressive decline in memory, learning, spatial positioning, reasoning, judgment, and the evaluation of brain functions. It is an unstable cognitive state and early intervention can prevent progression to dementia (1). Prevalence of cognitive impairment is 10-20 % for adults aged ≥ 65 years (2,3). There is a 25 % probability that cognitive impairment will progress to dementia within one year, and 50 % within ten years (4,5). What is more, the incidence of dementia increases with increasing age and reaches 20-40 % in adults aged ≥ 85 years. Recently, the relationship between cognitive impairment and vitamin B vitamins has attracted extensive attention.

Vitamin B12, also known as cobalamin (Cbl), is the only water-soluble vitamin containing metallic element cobalt. Vitamin B12 is only synthesized by microorganisms, and dietary vitamin B12 is provided mainly from animal foods, such as meat, dairy, eggs, fish and B12 supplements (6). Therefore, insufficiency of intake (vegetarians, intestinal diseases, etc.), absorption defects (pernicious anemia, Imerslund Grasbeck syndrome), transport disorders (transcobalamin defects), and cell processing defects (Cbl A-F mutations) can lead to vitamin B12 deficiency (7). Prevalence of vitamin B12 deficiency is 5-40 % in people beyond 60 years of age, depending on the diagnostic criteria used (8-11). Vitamin B12 is very important for the hematological and nervous systems. In addition, vitamin B12 is also a vital biologically active coenzyme: methylcobalamin and adenosylcobalamin, which are the cofactors for homocysteine methyltransferase and methylmalonyl CoA mutase (7,12), are essential for maintaining homeostasis of homocystine (Hcy) and methylmalonic acid (MMA). Vitamin B12 plays an essential role in the synthesis of neurotransmitters and structural elements of neurons (13), thus, vitamin B12 deficiency is associated with cognitive impairment and other mental disorders (14-16).

Some studies have shown that early supplementation of B vitamins can effectively reduce total Hcy (tHcy) levels in the elderly with high tHcy levels, slow down the rate of brain atrophy, reduce the levels of inflammatory cytokines in human peripheral blood (17), and prevent conversion from cognitive impairment to dementia (18-20). However, other researchers found that vitamin B12 and folic acid supplements did not significantly reduce cognitive decline in people with cognitive impairment (21,22). More importantly, there are relatively few randomized controlled studies on the improvement of cognitive function by vitamin B12 supplementation alone, and the specific clinical prognosis evaluation is not conclusive.

Therefore, the aim of the present work is to determine the effect of vitamin B12 supplementation on neuropsychological function and disease progression in middle-aged and elderly Chinese patients with cognitive impairment.

MATERIAL AND METHODS

STUDY DESIGN

This was an interventional study to whether treatment with vitamin B12 slowed cognitive impairment progression in middle-aged and elderly Chinese patients. The participants were enrolled between May 2020 and May 2021. Trained graduate students and mental health clinicians performed relevant investigations. Details of the recruitment process are shown in figure 1.

SUBJECT DESCRIPTION

We prospectively collected data from participants diagnosed clinically with cognitive impairment and in stable condition from the Department of Neurology of the First Affiliated Hospital of Chongqing Medical University, Chongqing, China.

Inclusion criteria were as follow: a) age 45 years and over; b) a Mini-Mental State Examination (MMSE) score of less than 24, a Montreal Cognitive Assessment (MoCA) score of less than 26; c) willingness to participate in the study; and d) not using any nutritional supplementation known to interfere with nutrition status, folate metabolism, or cognitive function in the three months prior to recruitment.

Exclusion criteria were as follow: a) subjects diagnosed with bipolar disorder, Parkinson's disease, multiple sclerosis, motor neuron disease, a developmental disability, central nervous

system inflammation, progressive malignancy, psychotic symptoms, or a diagnosis of schizophrenia or an alcohol or drug dependency; b) subjects were also excluded if they had any medical or psychological condition that prevented them from completing assessments; and c) incomplete patient clinical data and lack of cooperation with the investigators.

NUTRITIONAL INTERVENTIONS

Patients with cognitive impairment were randomly divided to receive vitamin B12 supplementation or control without any daily treatment for six months.

Injectable vitamin B12 was administered intramuscularly at a dose of 500 mg once a day for seven days, followed by cobamamide, which was given in the dose of 0.25 mg orally, and methylcobalamin in the dose of 0.50 mg orally every day during the next days. Both groups were closely followed up and monitored for six months and then again at six months using a repeat MMSE/MoCA score.

During the follow-up, both groups were closely monitored for any neurological or cognitive worsening. Approval from the Institutional Ethics Committee was obtained prior to the start of the study.

This study was conducted in compliance with the ethical principles of the Declaration of Helsinki. All participants were informed of the study objectives, and their consent to participate in the study was obtained. The research protocol was approved by the Medical Ethics Committee of Chongqing Medical University, China.

DIAGNOSIS OF COGNITIVE IMPAIRMENT

The MMSE measures the general cognitive function. It comprises six domains: orientation, registration, attention and calcu-

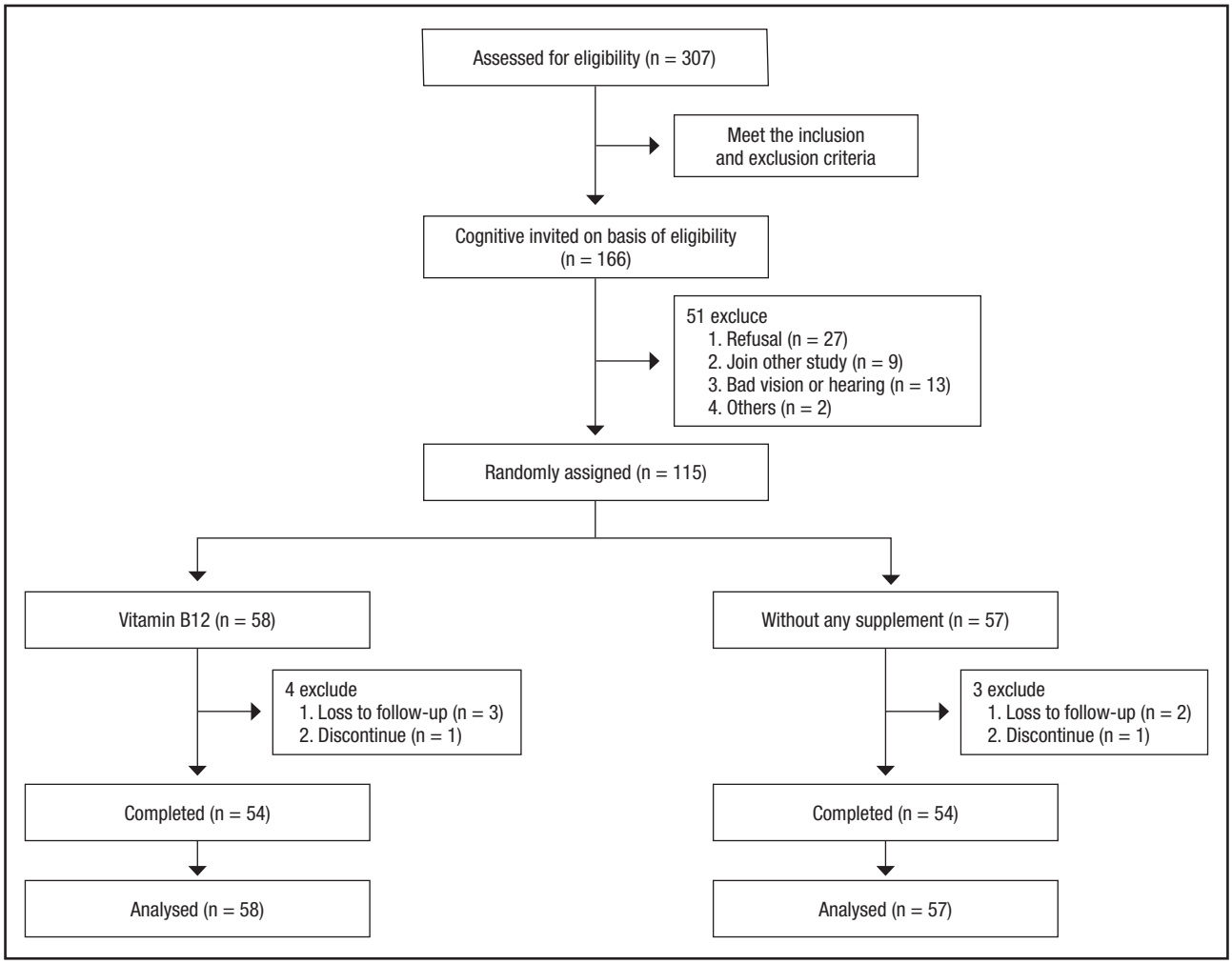

Figure 1.

Screening, randomization and follow-up of participants.

lation, recall, language, and visuospatial function. The maximum scores for various domains ranged from 1 to 10. The six domain scores resulted in a total score of 30, with a higher score indicating better general cognitive function (23,24). The sensitivity and specificity of the MMSE have been examined in individuals with cognitive impairment (25).

The MoCA-30 is a brief cognitive function test. It comprises seven domains: short-term memory, visuospatial function, executive function, attention, concentration, working memory, language, and orientation. The implementation duration was approximately ten minutes (26). The maximum scores for the various domains ranged from 1 to 6. Together, the seven domain scores totaled 30, with higher scores indicating better general cognitive function. The sensitivity and specificity of the MoCA-30 have been examined in individuals with cognitive impairment (27,28).

Table I. Baseline characteristics of participants with cognitive impairment by treatment groups

Characteristics	Vitamin B12 group n = 58	Control group n = 57	*p*
Sociodemographic characteristics			
Age, y	60.1 ± 10.0	61.7 ± 9.7	0.423
< 65	37 (63.8 %)	34 (59.6 %)	0.648
65-79	20 (34.5 %)	20 (35.1 %)	0.946
≥ 80	1 (1.7 %)	2 (3.4 %)	0.559
BMI	22.7 ± 2.9	22.5 ± 7.5	0.901
Education (y)	7.8 (6.9, 8.8)	7.0 (5.7, 8.3)	0.289
< 6	6 (10.3 %)	13 (22.8 %)	0.072
6-9	40 (69.0 %)	34 (59.6 %)	0.297
> 9	12 (20.7 %)	10 (17.5 %)	0.668
Health risk behaviors			
Current smoking	21 (20.7 %)	26 (45.6 %)	0.305
Excessive alcohol use	11 (19.0 %)	8 (14.0 %)	0.477
Medical history			
Hypertension	7 (12.1 %)	12 (21.1 %)	0.195
Heart disease	5 (8.6 %)	1 (1.8 %)	0.098
Diabetes	2 (3.4 %)	2 (3.5 %)	0.986
Stroke	2 (3.4 %)	3 (5.3 %)	0.635
Depression	0 (0.0 %)	1 (1.8 %)	0.313
Hematological findings			
Vitamin B12 levels (pg/ml)	310.3 (269.8, 350.9)	307.1 (244.5, 369.7)	0.932
Folic acid (ng/ml)	12.8 (11.3, 14.3)	11.1 (9.7, 12.4)	0.089
tHcy (μmol/l)	15.0 (10.1, 19.9)	14.7 (12.7, 16.7)	0.902
Vitamin B12 deficiency	14 (24.1 %)	17 (29.8 %)	0.492
Low folic acid	1 (1.7 %)	1 (1.8 %)	0.990
High folic acid	9 (15.5 %)	7 (12.3 %)	0.616
High tHcy	7 (12.1 %)	10 (17.5 %)	0.052
MMSE	25.9 ± 2.9	24.5 ± 4.2	0.052
MoCA	22.5 ± 3.3	22.1 ± 4.1	0.067

BMI: body mass index; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment. Variables are presented as %, median (P25, P75) or mean ± SD.

Table II. The levels of blood biomarker parameters at baseline and after sixth month of supplementation with vitamin B12 or control

Items	Groups	Cases	Groups		
			Before treatment	After 6 months	*p*
Vitamin B12 (pg/ml)	Vitamin B12	*n* = 58	310.3 (269.8, 350.9)	412.9 (376.5, 449.3)	0.000†
	Control	*n* = 57	307.1 (244.5, 369.7)	248.9 (204.1, 339.4)	0.113
	p		0.932	0.000§	
tHcy (μmol/l)	Vitamin B12	*n* = 58	15.0 (10.1, 19.9)	12.1 (10.4, 13.8)	0.509
	Control	*n* = 57	14.7 (12.7, 16.7)	15.5 (13.1, 18.3)	0.707
	p		0.902	0.624	
Folic acid (ng/ml)	Vitamin B12	*n* = 58	12.8 (11.3, 14.3)	12.2 (11.0, 13.4)	0.189
	Control	*n* = 57	11.1 (9.7, 12.4)	10.7 (9.9, 12.9)	0.063
	p		0.089	0.002§	

*Variables are presented as median (P25, P75). Compared with before treatment, *p < 0.05, †p < 0.01. Compared with control, ‡p < 0.05, §p < 0.01.*

Table III. The neurocognitive test scores at baseline and after sixth month of supplementation with vitamin B12 or control

Items	Groups	Cases	Groups		
			Before treatment	After 6 months	*p*
MMSE	Vitamin B12	*n* = 58	25.9 ± 2.9	27.5 ± 2.4	0.002†
	Control	*n* = 57	24.5 ± 4.2	24.4 ± 4.5	0.831
	p		0.052	0.000§	
MoCA	Vitamin B12	*n* = 58	22.5 ± 3.3	23.1 ± 3.3	0.328
	Control	*n* = 57	22.1 ± 4.1	20.71 ± 4.6	0.625
	p		0.067	0.004§	

*MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment. Variables are presented as mean ± SD. Compared with before treatment, *p < 0.05, †p < 0.01. Compared with control, ‡p < 0.05, §p < 0.01.*

Table IV. Changes of MMSE scores at baseline and after sixth month of supplementation with vitamin B12 or control

Items	Groups	Cases	Groups		
			Before treatment	After 6 months	*p*
Orientation	Vitamin B12	*n* = 58	9.0 ± 1.1	9.5 ± 0.9	0.009†
	Control	*n* = 57	8.5 ± 1.4	8.6 ± 1.5	0.747
	p		0.055	0.000§	
Registration	Vitamin B12	*n* = 58	3.0 ± 0.2	3.0 ± 0.1	0.563
	Control	*n* = 57	2.8 ± 0.4	2.8 ± 0.4	0.830
	p		0.015*	0.010§	
Attention and calculation	Vitamin B12	*n* = 58	3.6 ± 1.3	4.2 ± 1.0	0.007†
	Control	*n* = 57	3.5 ± 1.5	3.4 ± 1.5	0.802
	p		0.973	0.004§	

(Continues on next page)

Table IV (Cont.). Changes of MMSE scores at baseline and after sixth month of supplementation with vitamin B12 or control

Items	Groups	Cases	Groups		
			Before treatment	After 6 months	*p*
Recall	Vitamin B12	*n* = 58	1.8 ± 0.8	2.0 ± 0.8	0.098
	Control	*n* = 57	1.5 ± 0.9	1.4 ± 1.0	0.690
	p		0.189	0.001§	
Language	Vitamin B12	*n* = 58	8.0 ± 0.3	8.0 ± 0.3	0.737
	Control	*n* = 57	7.7 ± 0.8	7.7 ± 1.0	0.761
	p		0.079	0.046‡	
Visuospatial function	Vitamin B12	*n* = 58	0.6 ± 0.5	0.8 ± 0.4	0.012*
	Control	*n* = 57	0.5 ± 0.5	0.4 ± 0.5	0.353
	p		0.393	0.000§	

*MMSE: Mini-Mental State Examination. Variables are presented as mean ± SD. Compared with before treatment, *p < 0.05, †p < 0.01. Compared with control, ‡p < 0.05, §p < 0.01.*

BIOCHEMICAL ANALYSES

All patients underwent clinical history, neurologic examination, and complete blood work. Blood samples were collected at baseline and six months after venipuncture after a 10- to 12-hour overnight fast. Antecubital venous blood at 2-3 ml was collected from the patient on an empty stomach in the morning, centrifuged at 3,000 rpm for ten minutes, and analyzed by routine tests performed in the Department of Medical Laboratory of the First Affiliated Hospital of Chongqing Medical University, Chongqing, China.

According to laboratory instructions, vitamin B12 deficiency was defined as a serum B12 concentration < 180 pg/ml. Folic acid deficiency (< 3 ng/ml), high levels of folic acid (> 19.9 ng/ml), and high levels of tHcy (> 15 μmol/l) were also defined. Hemoglobin (Hb) and mean corpuscular volume (MCV) levels were analyzed according to the age-adjusted normal ranges.

STATISTICAL ANALYSES

SPSS 22.0 software package was applied to perform the statistical analysis (IBM Corporation, version 22.0, for Windows). Frequencies and percentages were calculated. Continuous variables were examined using the Shapiro-Wilk first. If the data were normally distributed, the Student's t-test was used; otherwise, the non-parametric Mann-Whitney U test was used. The Chi-squared test (χ^2 test) and Fisher's exact test were used for comparison between independent groups of categorical data. For all statistical tests, values of $p < 0.05$ (two-tailed) were considered as statistically significant.

RESULTS

A total of 307 patients were enrolled in the study from May 2020 to May 2021. A total of 192 patients were eventually excluded for the following reasons: 141 patients did not meet the inclusion and exclusion criteria, 27 patients refused to undergo cognitive testing, nine patients underwent another study, 13 patients suffered from bad vision or weak hearing, and two patients had other reasons. The recruitment, enrollment and flow of participants during the trial are shown in figure 1.

Finally, 115 patients were eligible for this study, 58 were randomly assigned to vitamin B12, and 57 to control group, respectively. Seven participants (2.3 %) were unable to complete the trial and the dropout rates were similar among all the groups ($p > 0.05$). On the basis of the number of unused capsules in the returned dispensers, the mean compliance was high, with 99 % of the capsules reportedly consumed.

Table I shows the baseline characteristics of the study population. No significant differences were observed between the two treatment groups ($p > 0.05$). The randomization procedure was successful because the groups were fairly well balanced in terms of demographic, biochemical, and cognitive data. No adverse events were reported during the trial.

The results are presented in tables II and III. At month 6, the vitamin B12 treatment group showed a significant increase in serum B12 levels ($p < 0.01$) and MMSE scores compared to those before treatment ($p < 0.01$). The vitamin B12 treatment group had an increase in MoCA score and a reduction in tHcy levels compared to those before treatment, but the difference was not significant ($p > 0.05$). Moreover, at month 6, the vitamin B12 treatment group showed a significant increase in serum active B12 ($p < 0.01$) and MMSE/MoCA scores compared to the control group ($p < 0.01$).

The changes in the six domains of MMSE scores between the two groups are compared in table IV. At six months, the B12 treatment group showed a significantly improvement in orientation, attention, and calculation compared to before treatment ($p < 0.01$). In addition, visuospatial function improved significantly

in the B12 treatment group compared to that before treatment ($p < 0.05$). Specifically, at month 6, B12 treated group improved significantly orientation, registration, attention and calculation, recall, visuospatial function ($p < 0.01$), and language ($p < 0.05$) compared to the control group.

DISCUSSION

Our results showed that vitamin B12 supplementation improved cognitive function in middle-aged and elderly individuals over a six-month period, especially in attention and calculation ($p < 0.01$) and visuospatial function ($p < 0.05$). In addition, vitamin B12 supplementation prevents the progression of cognitive impairment in patients. All of these results support vitamin B12 as a part of routine assessments for treatment candidates of cognitive impairment, which can be easily and rapidly determined at outpatient departments. For bedside practicality, we also evaluated the seven domains of MoCA-30 in each group respectively. If confirmed in larger and longer-term randomized trials, it is expected to be widely used in clinical practice.

The relationship between vitamin B12 and cognitive impairment or dementia is likely multifactorial. The mechanisms may include methylation disorders, demyelination, neurotransmitter and neurotrophic factor synthesis disorders, accumulation of toxic metabolites such as tHcy and methylmalonic acid, and immune system dysfunction (15,17,29-31).

Cognitive decline in older adults is a public health concern. To date, several studies have evaluated the effect of B vitamins as a treatment for cognitive impairment or dementia, but only the VITACOG and FACIT trials have reported the benefits of treatment (32,33). Recently, a Korean study found a clear association between low vitamin B12 levels and progressive cognitive impairment in 202 patients with cognitive decline, with an increased level of vitamin B12, which could slow the progression of cognitive decline to dementia (31). Moreover, 56 % of 202 patients had a level between 100 and 200 pg/ml, and 15.3 % had a vitamin B12 level between 50 and 100 pg/ml (31). In addition, 7.5 % of dementia patients had a vitamin B12 deficiency (vitamin B12 levels < 200 pg/dl). In our study, we found that 29.6 % of patients with cognitive impairment had vitamin B12 deficiency (vitamin B12 levels ≤ 180 pg/ml). However, it must be noted that this ratio may be much lower than the true ratio because the standard of vitamin B12 levels used in this study is 180-900 pg/ml, which may lead to some patients with metabolic vitamin B12 deficiency being ignored by us. In addition, in our study, 50.4 % of patients with cognitive impairment had metabolic vitamin B12 deficiency (vitamin B12 levels ranged from 180 to 400 pg/ml). In 2016, early treatment of metabolic vitamin B12 deficiency was suggested as an important strategy to prevent dementia (15). Thus, future studies should focus on the association between vitamin B12 levels and cognitive dysfunction.

In our study, we found that vitamin B12 supplementation improved MMSE scores in middle-aged and elderly individuals with cognitive decline, over a six-month period, especially in attention and calculation and visual-constructional ability. This suggests that vitamin B12 supplementation could improve the function of the frontal lobes of the brain, which is consistent with the results of other studies (35,36). Furthermore, studies have reported that vitamin B12 deficiency could manifest with the symptoms of frontotemporal dementia and that they are completely reversible after substitution therapy (36,37), further supporting our results. Therefore, the effects of treatment have shown that early identification and alternative treatment can significantly reverse symptoms, which is an important step toward a healthy mental state.

The strength of our study is that it explicitly controls for key confounders, such as using any nutritional supplementation, the diseases which influence cognitive score; the scores of different aspects of cognitive function were compared in detail, and the results that support our idea of improved cognition with replacement therapy. Our study had several limitations. First, as a sample of a relatively small number of patients with cognitive decline who underwent vitamin B12 testing for various clinical indications, it lacked a systematic collection of vitamin B12 data, potentially leading to selection bias. Second, our experiment was conducted in the outpatient department of an affiliated university hospital. Most participants in the study had a higher level of education, which might have led to selection bias. In addition, due to the influence of COVID-19, the number of outpatient clinics has decreased, resulting in a small number of patients being included and lost visits, which cannot reflect the real results in our region. Finally, the follow-up period was only six months, and a longer follow-up period was needed to assess the improvement in cognitive function.

CONCLUSION

In summary, in our study it was noted that with vitamin B12 supplementation, there was improvement in cognitive function scores in middle-aged and elderly individuals with cognitive decline although no definite conclusion can be made as the follow-up period was very short. Moreover, vitamin B12 treatment may improve frontal function in patients with cognitive decline. Vitamin B12 levels should be investigated in all patients with cognitive impairment. Larger and longer-term randomized trials on vitamin B12 are needed.

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ARÁN

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Trabajo Original

Nutrición en el anciano

Serum vitamin D levels and mortality in Mexicans: results from the Mexican Health and Aging Study

Niveles séricos de vitamina D y mortalidad en mexicanos: resultados del Estudio Nacional de Envejecimiento en México

Enrique Díaz de León González[1], Hugo Gutiérrez Hermosillo[2], Jorge Morales Torres[3]

[1]High Specialty Medical Unit. Centro Médico Nacional del Noreste. Hospital de Traumatología y Ortopedia No. 21. Instituto Mexicano del Seguro Social. Monterrey, Nuevo León, Mexico. [2]Geriatrics Department. Hospital Aranda de la Parra. León, Guanajuato. México. Centro Universitario del Sur. Universidad de Guadalajara. Guadalajara, Mexico. [3]Hospital Aranda de la Parra. León, Guanajuato. Mexico

Abstract

Background: the population in Latin America is aging and elders face several obstacles for good health, including an elevated frequency of vitamin D deficiency. Thus, identification of patients at high risk to develop its negative consequences should be a priority**.**

Objective: the objective of this analysis was to determine if levels of vitamin D lower than 15 ng/ml are associated with high mortality in Mexican elderly population, from the database of the Mexican Health and Aging Study (MHAS).

Methods: prospective, population study in Mexico, that included Subjects of 50 years and older who were evaluated for Serum vitamin D levels during the year 2012 (third wave of the study). Serum 25(OH)D levels were categorized into four groups, based on cutoff points used in previous studies on vitamin D and frailty: < 15, 15-< 20, 20-< 30 and ≥ 30 ng/ml. Mortality was evaluated during 2015 (fourth wave of the study). Hazard ratio was calculated (for mortality) through Cox Regression Model, adjusted for covariates.

Results: we included 1626 participants, and those with lower levels of vitamin D were older, more often women, required more aid for activities of daily living, reported higher number of chronic diseases, and lower scores on cognition. The relative risk of death was 5.421 (95 % CI 2.465-11.92, $p < 0.001$) for the participants with vitamin D levels < 15, which after adjusting for covariates, remained statistically significant.

Conclusions: levels of vitamin D lower of 15, are associated with an increase in the rate of mortality in community-dwelling senior Mexicans.

Keywords:

Vitamin D. Mortality. Mexico. Elderly.

Resumen

Introducción: la población en América Latina está envejeciendo y los adultos mayores enfrentan varios obstáculos para gozar de buena salud, incluida una frecuencia elevada de deficiencia de vitamina D. Por lo tanto, la identificación de pacientes con alto riesgo de desarrollar sus consecuencias negativas debe ser una prioridad.

Objetivo: el objetivo de este análisis fue determinar si los niveles de vitamina D inferiores a 15 ng/ml están asociados con una alta mortalidad en la población adulta mayor mexicana, a partir de la base de datos del Estudio de Salud y Envejecimiento en México.

Métodos: estudio poblacional prospectivo en México, que incluyó Sujetos de 50 años y mayores que fueron evaluados para los niveles de vitamina D en suero durante el año 2012 (tercera ola del estudio). Los niveles séricos de 25(OH)D se clasificaron en cuatro grupos, según los puntos de corte utilizados en estudios previos sobre vitamina D y fragilidad: < 15, 15-< 20, 20-< 30 y ≥ 30 ng/ml. La mortalidad se evaluó durante 2015 (cuarta ola del estudio). Se calculó la razón de riesgo (para la mortalidad) a través del modelo de regresión de Cox, ajustado por covariables.

Resultados: incluimos 1626 participantes, y aquellos con niveles más bajos de vitamina D eran mayores, más a menudo mujeres, requerían más ayuda para las actividades de la vida diaria, informaron un mayor número de enfermedades crónicas y puntuaciones más bajas en cognición. El riesgo relativo de muerte fue de 5,421 (IC 95 % 2,465-11,92, $p < 0,001$) para los participantes con niveles de vitamina D < 15, que después de ajustar por covariables, se mantuvo estadísticamente significativo.

Conclusiones: niveles de vitamina D inferiores a 15, se asocian con un aumento en la tasa de mortalidad en adultos mayores mexicanos residentes en la comunidad.

Palabras clave:

Vitamina D. Mortalidad. México. Ancianos.

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Correspondence:

Enrique Díaz de León González. Internal Medicine Department. High Specialty Medical Unit. Hospital de Traumatología y Ortopedia No. 21. Instituto Mexicano del Seguro Social. Monterrey, Nuevo León, México
e-mail: edleon20@hotmail.com

INTRODUCTION

Vitamin D status has been studied in all continents and most countries over the world, and there is a global high prevalence of deficiency (1), ranging from 30 to 70 %, constituting a public health problem (2). The aging population in Latin America is characterized by an elevated poverty rate, a high burden of comorbidity, and sub-optimal social conditions contributing to a poor health status, where social and health services are limited (3), which may also contribute to increase the prevalence of vitamin D deficiency (4). Mexico is living the demographic and epidemiological transitions associated with the increase in life expectancy, and a growing number of elders (5), and a high prevalence of vitamin D deficiency (6,7), despite being a country with adequate exposure to sun and ultraviolet B rays (UVB) during the year (8).

Low levels of vitamin D are frequently found in the elderly as a result of changes associated with aging on vitamin D and calcium and metabolism such as decreased calcium absorption, intestinal resistance of calcium absorption to circulating $1,25(OH)_2D$, decreased vitamin D receptor, decreased renal production of $1,25(OH)_2D$ by the aging kidney, decreased skin production of vitamin D, and substrate deficiency of vitamin D (9).

Low vitamin D levels are associated with several geriatric syndromes, including frailty (10-12), sarcopenia (13), falls, fractures, cognitive impairment, depression, cardiovascular disease, colorectal cancer, diabetes (14), and mortality in general (15-20), and in distinct clinical scenarios, such as institutionalized elderly people (21). Although, the evidence shows that low serum levels of vitamin D are associated with mortality, currently there is no consensus on optimal 25(OH)D concentrations (14,22,23). While there are many recommendations regarding optimal levels of vitamin D (24), a putative threshold in which of vitamin D is associated with higher mortality in Mexican population has not been defined. Our hypothesis is that vitamin D levels below 15 are associated with a higher mortality in Mexican population. Therefore, the objective of this analysis was to determine the association between low levels of vitamin D and mortality in Mexican population, from the database of the Mexican Health and Aging Study (MHAS) (25), a prospective study in Mexicans, as well as their couples, who through a survey on the processes of aging and the burden of disease that occur in this group and recording data in 2001, 2003, 2012, and 2015 (with measurement of mortality).

MATERIAL AND METHODS

To carry out the present work we used the MHAS database (25). The methodology was conducted by the Center for Population Studies at the University of Pennsylvania, Center for Research on Population at the University of Maryland and the Center for Demography and Ecology, University of Wisconsin, while the National Institute of Statistics, Geography and Informatics (INEGI) of Mexico performed fieldwork. Information related to various aspects, such as dynamics of health, family structure and intergenerational transfers, migratory behaviors and socioeconomic differences by income and property ownership was collected. The sample is representative of the non-institutionalized population component aged 50 years in 2000. Collecting data from the first round was conducted from May to October 2001 and a second round took place from June to September 2003 in which participants were re-interviewed in 2001, and a third and fourth round in the years 2012 and 2015 respectively. For the present analysis all subjects 50 years or older evaluated during the 2012 wave, with serum levels of vitamin D, who underwent a follow-up in 2015 and determined whether they were still living or not were selected. We excluded participants in who we could not determine the status of the studied variables (missing values). The MHAS is partly sponsored by the National Institutes of Health/ National Institute on Aging (grant number NIH R01AG018016) and the INEGI in Mexico. Data files and documentation are public use and available at www.MHASweb.org (25).

CATEGORIZATION OF VITAMIN D

Methodological parameters for determining levels of vitamin D can be found in the web page of the MHAS (25) and were described previously by Carrillo Vega et al. (6). Briefly, Biomarkers and vitamin D were obtained between October and November 2012, with trained personnel, who performed the peripheral venipuncture. After the venipuncture, the sample was centrifuged during 15 minutes to separate the serum, and stored in two 2-mL tubes. Serum vitamin D levels was measured with a chemiluminescent microparticle immunoassay (CMIA-Architect Abbott Laboratories. Abbott Park, IL, USA). The measurement interval of this CMIA ranged from 8 to 160 ng/mL, and the intra- and inter-assay coefficients of variation were < 10 %. Serum 25(OH) D levels were categorized into four groups, based on cut-points used in previous studies on vitamin D and frailty: < 15, 15-< 20, 20-< 30 and ≥ 30 ng/ml (10,11).

ANALYZED COVARIATES

We analyzed the following variables: gender, age, self-reported comorbidities such as hypertension or high blood pressure, diabetes or high sugar level in blood, cancer, lung disease, heart disease (heart attack), brain disease (stroke, stroke or transient ischemic attack), arthritis or rheumatism, kidney and/or liver infection, Pneumonia, Herpes Zoster, and Tuberculosis. For these comorbidities, we created the variable number of comorbidities, representing the sum of the latter, and have values ranging from 0 to 12. We also included: quality of vision, and hearing, frequency of smoking, and drinking. Cognitive status was evaluated through the cross-cultural cognitive examination, which has a sensitivity of 100 % and a specificity of 83 % for patients with dementia (26). Depressive symptoms were measured with a validated nine-item questionnaire (27). Functional assessment was obtained by the number of basic or BADL (bathing, dressing,

toileting, moving, eating and being continent, score 0-6) and instrumental activities of daily living or IADL (preparing hot food, buy food, taking medications and managing their money, score 0-4) for which require assistance. Mortality was reported in the fourth round of the survey in 2015. Missing values were considered in the case of respondents did not answer or replied, "do not know" on each of the variables analyzed. All subjects who participated in the study gave their informed consent at the time of interview.

STATISTICAL ANALYSIS

The analysis was performed by the method of complete cases (only those subjects without missing values in the variables analyzed) (28). Participants were characterized by using descriptive statistics, and included median, and interquartile range for quantitative variables, and absolute frequencies, and percentages in the case of qualitative variables. Chi square tests were used to determine differences between qualitative variables, and Kruskal Wallis test to demonstrate the difference between quantitative variables. *p* values lower than 0.05 were considered statistically significant. The variable survival time was calculated from the time in weeks between the date of the clinical evaluation of the third (2012) and the fourth wave (2015) evaluation or by the date of death. The degree of association of variables was measured with hazard ratio through Cox regression model. A minimum of 121 participants in each group was estimated to identify statistically significant difference in proportions between 0.15 and 0.025 through Chi square two-tailed test, power of 0.9 and alpha of 0.05 for mortality variable. All statistical analyses were performed using Stata/SE, version 12 (Stata Corporation, College Station, TX, USA).

RESULTS

GENERAL CHARACTERISTICS OF THE PARTICIPANTS IN THE YEAR 2012

Baseline clinical and demographic characteristics of 1626 selected participants were grouped and analyzed according to vitamin D levels (Table I and Fig. 1). The groups of vitamin D levels < 15, 15-< 20, 20-29, and 30 or more, included 174 (9.3 %), 339 (20.8 %), 772 (47.4 %), and 341 (20.9 %) respectively. With regard to their general characteristics, those with lower levels of vitamin D were older, more often women, required more aid for activities of daily living, reported higher number of chronic diseases, and lower scores on cognition.

Table I. Demographic and health variables of respondents in the Mexican Health and Aging Study, according to serum vitamin D levels in ng/mL

	Less than 15	15 to < 20	20 to < 30	30 or more	
Variable	**n = 174**	**n = 339**	**n = 772**	**n = 341**	***p***
Age (years)	66 (58-73)	63 (56-70)	61 (55-68)	59 (54-66)	0.043
Grouped age					
50 to 59 years	49 (28.2 %)	125 (36.9 %)	351 (45.5 %)	174 (51 %)	
60 to 69 years	58 (33.3 %)	129 (38.1 %)	253 (32.8 %)	112 (32.8 %)	
70 to 79 years	41 (23.6 %)	62 (18.3 %)	123 (15.9 %)	40 (11.7 %)	< 0.001
80 to 89 years	23 (13.2 %)	21 (6.2 %)	40 (5.2 %)	14 (4.1 %)	
90 to 99 years	3 (1.7 %)	2 (0.6 %)	4 (0.5 %)	1 (0.3 %)	
100 years or more	0 (0 %)	0 (0 %)	1 (0.1 %)	0 (0 %)	
Gender					
Man	47 (27 %)	116 (34.2 %)	336 (43.5 %)	182 (53.4 %)	< 0.001
Woman	127 (73 %)	223 (65.8 %)	436 (56.5 %)	159 (46.6 %)	
Global self-reported quality of health					
Excellent	2 (1.1 %)	5 (1.5 %)	20 (2.6 %)	7 (2.1 %)	
Very good	6 (3.4 %)	13 (3.8 %)	27 (3.5 %)	18 (5.3 %)	0.265
Good	59 (33.9 %)	113 (33.3 %)	204 (26.4 %)	96 (28.2 %)	

(Continues on next page)

Table I (Cont.). Demographic and health variables of respondents in the Mexican Health and Aging Study, according to serum vitamin D levels in ng/mL

	Less than 15	15 to < 20	20 to < 30	30 or more	
Variable	**n = 174**	**n = 339**	**n = 772**	**n = 341**	***p***
Fair	89 (51.1 %)	169 (49.9 %)	449 (58.2 %)	188 (55.1 %)	0.068
Poor	18 (10.3 %)	39 (11.5 %)	72 (9.3 %)	32 (9.4 %)	
Use of glases	109 (62.6 %)	200 (59 %)	411 (53.2 %)	179 (52.5 %)	
Quality of vision with glasses					
Excellent	6 (3.4 %)	11 (3.2 %)	29 (3.8 %)	8 (2.3 %)	0.928
Very good	10 (5.7 %)	32 (9.4 %)	68 (8.8 %)	25 (7.3 %)	
Good	78 (44.8 %)	164 (48.4 %)	348 (45.1 %)	168 (49.3 %)	
Fair	70 (40.2 %)	106 (31.3 %)	268 (34.7 %)	119 (34.9 %)	
Poor	8 (4.6 %)	19 (5.6 %)	41 (5.3 %)	14 (4.1 %)	
Legally blind	0 (0 %)	0 (0 %)	1 (0.1 %)	0 (0 %)	
Use of hearing aid	4 (2.3 %)	2 (0.6 %)	12 (1.6 %)	5 (1.5 %)	0.367
Ever smoked	68 (39.1 %)	129 (38.1 %)	305 (39.5 %)	143 (41.9 %)	0.769
Currently drinks alcohol	38 (21.8 %)	86 (25.4 %)	211 (27.3 %)	96 (28.2 %)	0.295
Hypertension	82 (47.1 %)	145 (42.8 %)	344 (44.6 %)	117 (34.3 %)	0.007
Diabetes *mellitus*	50 (28.7 %)	98 (28.9 %)	156 (20.2 %)	42 (12.3 %)	< 0.001
Cancer	5 (2.9 %)	8 (2.4 %)	19 (2.5 %)	4 (1.2 %)	0.511
Pulmonary disease	17 (9.8 %)	18 (5.3 %)	54 (7 %)	16 (4.7 %)	0.11
Myocardial infarction	6 (3.4 %)	12 (3.5 %)	24 (3.1 %)	9 (2.6 %)	0.915
Cerebrovascular disease	3 (1.7 %)	4 (1.2 %)	12 (1.6 %)	5 (1.5 %)	0.958
Rheumatism	29 (16.7 %)	54 (15.9 %)	106 (13.7 %)	38 (11.1 %)	0.218
Kidney infection	5 (2.9 %)	2 (0.6 %)	15 (1.9 %)	4 (1.2 %)	0.174
Liver infection	19 (10.9 %)	22 (6.5 %)	79 (10.2 %)	31 (9.1 %)	0.209
Tuberculosis	1 (0.6 %)	0 (0 %)	4 (0.5 %)	1 (0.3 %)	0.577
Pneumonia	6 (3.4 %)	2 (0.6 %)	8 (1 %)	1 (0.3 %)	0.007
Herpes zoster	7 (4 %)	6 (1.8 %)	22 (2.8 %)	3 (0.9 %)	0.082
At least one fall	66 (37.9 %)	138 (40.7 %)	301 (39 %)	123 (36.1 %)	0.648
Cross-cultural cognitive	44 (33-60.6)	45.33 (33.33-59.67)	45.67 (34-58)	45.33 (33-58)	0.733
Number of chronic diseases	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-1)	< 0.001
Number of depressive symptoms	3 (1-6)	3 (1-5)	3 (1-6)	3 (1-5)	0.932
Help in at least one BADL	41 (23.6 %)	46 (13.6 %)	106 (13.7 %)	33 (9.7 %)	0.002
Help in at least one IADL	43 (24.7 %)	45 (13.3 %)	107 (13.9 %)	60 (17.6 %)	< 0.001
Body mass index	29.27 (25.8-32.7)	29 (25.83-31.81)	28.69 (25.67-32.12)	27.27 (24.27-30.32)	0.001

The data represent absolute frequencies and percentages or medians (interquartile range). Data were compared with chi squared or Kruskal Wallis. The number of chronic diseases is the sum of hypertension, diabetes, cancer, respiratory disease, acute myocardial infarction, cerebrovascular disease, rheumatism, kidney infection, liver infection, tuberculosis, pneumonia and herpes zoster.

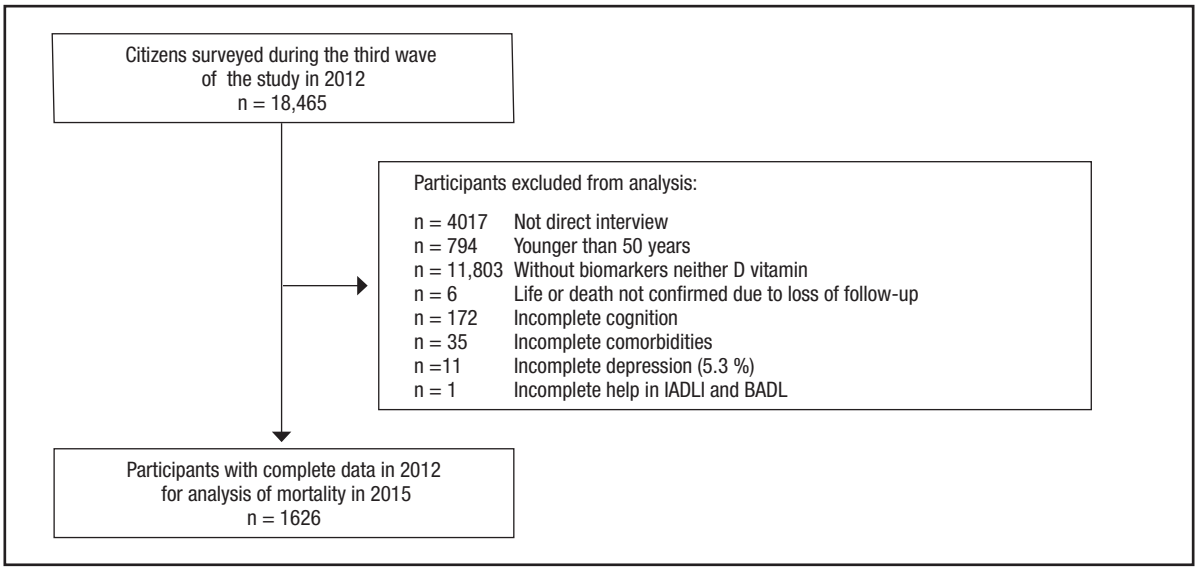

Figure 1.
Flowgram of the study.

VITAMIN D LEVELS AND THEIR ASSOCIATION WITH MORTALITY AT THE YEAR 2015

After a mean follow up of 162.1 weeks (95 % CI 161.3-162.9), the number of deaths among participants was 22 (12.6 %), 10 (2.9 %), 24 (3.1 %), and 8 (2.3 %) in those with vitamin D levels <15, 15-<20, 20-29, and 30 or more, respectively ($p<0.001$). The unadjusted relative risk was 5.421 (95 % CI 2.465-11.92, $p<0.001$) and 1.257 (95 % CI 0.5024-3.147 $p=0.8021$) and 1.325 (95 % CI 0.6015-2.919 $p=0.4829$) for the participants with vitamin D levels <15, 15-<20, 20-29, respectively, which after adjusting for covariates, levels of vitamin D lower of 15 remained statistically significant (Table II).

DISCUSSION

The objective of this analysis was to determine the association between low levels of vitamin D and mortality in Mexican population, from the database of the Mexican Health and Aging Study (MHAS).

When reviewing the clinical characteristics of the members of the groups, it was found that levels of vitamin D lower than 15 were associated with older age, female sex, lower scores on cognition, required more aid in BADL, and more chronic diseases, which agrees with the findings of Dobnig et al.(15), and Schottker et al. (17), in German population, as well as by Pilz, and colleagues (16), in Netherland. Consistency was clear in age and comorbidities such as diabetes, but in those studies, neither cognition nor functionality were measured.

We found a striking association of mortality with levels of vitamin D below 15 ng/ml. This association remained even after adjusting for confounding variables such as age, sex, number of chronic diseases, cognition score, and number of basic and instrumental activities of daily living for requiring support, and depression scale score. These results are consistent with findings from other studies that used the similar cut point used

Table II. Vitamin D serum levels (ng/ml) in participants from the Mexican Health and Aging Study, and its association with mortality

	***n* = 1625**	
Variable	***p***	**HR (CI 95.0 %)***
< 15	0.006	3.276 (1.401-7.66)
15 to 20	0.87	0.923 (0.357-2.393)
20 to < 30	0.972	1.015 (0.447-2.302)
30 or more		1

*HR: hazard ratio. *Adjusted for age, sex, number of depressive symptoms, number of chronic diseases, cognitive score and help in at least one BADL.*

in the present study (15-17,29). In the report by Vogt et al. (29), the result is partially explained by frailty status, while in that performed by Dobnig et al. (15), mortality was associated with the groups of participants with median levels of 6 and 13 ng/ml. Mean level of vitamin D was 12 ng/ml in the group of participants with higher mortality in the study of Pilz et al. (16), and below 12 ng/ml in the study of Schottker et al. (17).

Possible explanation for this association, is that the vulnerability could be a marker of another underlying disorder, and is associated with social or environmental factors that may increase the risk of mortality (30). In this case, one possible explanation is frailty syndrome. It has been associated with vitamin D levels below 15 ng/ml found by Ensrud et al. (10) and Pabst et al. (11), while Gutierrez Robledo et al. (12), report it at levels below 12 ng/ml. Frailty is associated with higher mortality (31,32), which could explain the association of the number of deaths found at vitamin D levels below 15.

Both, frailty syndrome and hypovitaminosis D are very common among older persons in Latin America (4,33). Their association has been well established (10-12,29). Although evidence is still limited, several authors have proposed to supplement enough vitamin D (800 to 2000 IU daily) to reach a serum level of 30 ng/ml to help in the prevention and control of frailty (34). A growing number of voices propose to create strategies to improve the status of vitamin D in older adults and the general population to decrease the burden of disease (35) as well as mortality (36,37).

The present study has some limitations. First, the medical conditions of the study population and the activities of daily living are self-reports on the state of health, although several studies have found consistency in self-reports and direct measurements (38). Second, the loss of subjects during follow-up, and analysis of complete cases may have influenced the study results, and produced selection bias (39). It is well known that subjects who do not complete the performance measures in population studies (probably like those not included in the present analysis) are expected to be less healthy, and more likely to die (40), increasing the possibility of survival bias. Despite these limitations, this study has many strengths, including its large sample size of men and women living in the community (which makes it generalizable), its prospective design, the ability to evaluate multiple medical conditions and factors that have been reported previously with an association with adverse outcomes.

CONCLUSION

Vitamin D levels below 15 constitute a marker of risk, of a higher mortality in community-dwelling Mexican population aged 50 years and older.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Obesidad y síndrome metabólico

Dietary inflammatory index and its association with leptin and adiponectin in Uygur overweight/obese adults

Índice de inflamación de la dieta y su relación con la leptina y la adiponectina en adultos de Uygur con sobrepeso/obesidad

Kaibinuer Zaibibuli, Dina Muheyati, Mei-Xia Lv, Guliqiekeran Aisike, Muhairemu Jielili, Jing Zhao, Ayinuer Aihemaiti, Jia Han

Department of Nutrition and Food Hygiene. College of Public Health. Xinjiang Medical University. Urumqi, Xinjiang. People's Republic of China

Abstract

Introduction: chronic inflammation contributes to a wide range of metabolic disorders through the influence of diet. The dietary inflammatory index (DII) was developed to measure the inflammation potential of diet.

Objectives: Uygur adults have a high prevalence of obesity, but the causes of this condition remain unclear. In this study we investigated the association between DII and adipocytokines among overweight and obese Uygur adults.

Methods: a total of 283 obese and overweight Uygur adults were included. Sociodemographic characteristics, anthropometric measurements, dietary surveys and biochemical indicators were collected by standardized protocols. The DII score was calculated using a valid and reliable 93-item food frequency questionnaire (FFQ). Linear regression was used to estimate the relationship between DII and adipocytokines.

Results: the DII score was 1.35 ± 1.08, ranging from -2.14 to +3.11. There was a significant inverse correlation between DII and high-density lipoprotein cholesterol (HDL-C) in the unadjusted model (β = -0.12, $p = 0.02$), and this remained after adjustment for age, gender, body mass index (BMI). DII was negatively associated with adiponectin (ADPN) (β = -203.15, $p = 0.04$) and positively associated with leptin (LEP) concentration (β = 1.64, $p = 0.002$) after adjustment for age, gender and BMI.

Conclusion: a pro-inflammatory diet, as indicated by a higher DII score, is associated with adipose tissue inflammation in Uygur adults and supports the hypothesis that diet may play a role in the development of obesity through inflammatory modulation mechanisms. A healthy anti-inflammatory diet is feasible for obesity intervention in the future.

Keywords:

Dietary inflammatory index. Obesity. Leptin. Adiponectin.

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Conflicts of interest: the authors declare no conflicts of interest.

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Correspondence:

Jia Han. Department of Nutrition and Food Hygiene. College of Public Health. Xinjiang Medical University. Shang De North Road, 567. Urumqi, Xinjiang. 830000 People's Republic of China
e-mail: yuerel.bat@163.com

Resumen

Introducción: la inflamación crónica causa múltiples trastornos metabólicos a través de la influencia de la dieta. El índice de inflamación dietética (DII) se estableció para medir el potencial inflamatorio de la dieta.

Objetivo: los adultos de Uygur presentan una alta prevalencia de obesidad, pero las causas de esta condición aún no están claras. En el presente estudio se investigó la relación entre DII y adipocitocinas en adultos uigur con sobrepeso y obesidad.

Métodos: se incluyeron 283 adultos de Uygur obesos y con sobrepeso. Las características sociodemográficas, antropométricas, dietéticas y bioquímicas se recogieron mediante un protocolo estandarizado. El índice DII se calculó utilizando un cuestionario de frecuencia alimentaria (FFQ) válido y fiable de 93 elementos. Se realizó una regresión lineal para estimar la relación entre DII y adipocitocinas.

Resultados: la puntuación DII fue de 1,35 ± 1,08 y osciló entre -2,14 y +3,11. En el modelo no ajustado hubo una correlación negativa significativa entre DII y colesterol lipoproteínico de alta densidad (HDL-C) (β = -0,12, p = 0,02) que permaneció después de ajustar la edad, el sexo y el índice de masa corporal (IMC). Después de ajustar la edad, el sexo y el IMC, el DII se correlacionó negativamente con la concentración de adiponectina (β = - 203,15, p = 0,04) y positivamente con la concentración de leptina (β = 1,64, p = 0002).

Conclusión: las puntuaciones más altas de DII sugieren que la dieta proinflamatoria está relacionada con la inflamación del tejido adiposo en los adultos de Uygur, y apoyan la hipótesis de que la dieta puede desempeñar un papel en el desarrollo de la obesidad a través del mecanismo de regulación de la inflamación. La dieta antiinflamatoria saludable es factible para futuras intervenciones de obesidad.

Palabras clave:

Índice de inflamación dietética. Obesidad. Leptina. Adiponectina.

INTRODUCTION

Obesity is a major public health issue around the world. The World Health Organization (WHO) reports that since 1975, obesity has nearly tripled (1). Overweight and obesity, linked primarily to overconsumption of dietary energy, are strongly associated with an increased prevalence of diabetes, hypertension, and cardiovascular disease, as well as increased mortality from related non-communicable diseases (NCDs) (2).

It is now recognized that low-grade, chronic systemic inflammation is associated with most NCDs, including diabetes, obesity, cardiovascular disease, etc. (3). For a long time people have believed that adipose tissue's main function is to store energy; however, it is now known that adipose tissue also functions as a major endocrine organ that secretes adipokines, cytokines, and chemokines (4). Adipocyte hypertrophy in obesity is accompanied by disturbances in lipid metabolism and alterations in adipokine secretion, with a shift towards a pro-inflammatory phenotype (5). Adipokines like leptin and adiponectin are an indispensable part of the cascade of various metabolic and physiological signals, such as in the process of insulin signaling, glucose absorption, fatty acid oxidation, and other energy metabolism (6). Leptin is one of the main adipokines, and it influences multiple endocrine functions; it binds to specific receptors in the hypothalamic arcuate nucleus and suppresses appetite, thus playing an important role in body weight regulation (7). However, excessively increased circulating leptin makes the brain less sensitive to leptin leading to failure to respond, thus reducing leptin's ability to suppress appetite or increase energy expenditure, increasing food intake, and ultimately leading to overweight and obesity (8). In obese individuals, the overproduction of circulating leptin also greatly promotes a low-grade inflammatory state (9). Adiponectin, as adipokines, binds to receptors to promote glucose intake and prevent gluconeogenesis and fatty acid accumulation by activating AMPK, PPARα and other signaling molecules, thereby preventing insulin resistance and excessive accumulation of liver fat, and exerting anti-inflammatory effects (10). The adiponectin/leptin ratio has been proposed as a biomarker of adipose tissue dysfunction, showing a negative correlation with body mass index (BMI) and systemic inflammation (11,12). Cytokines such as interleukins (IL), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) also have important physiological functions and are involved in the generation, coordination, and cessation of immune or inflammatory responses (13). Persistent inflammation, whether due to prolonged exposure to stimuli or an inappropriate response to self-molecules, can lead to a chronic phase (14) characterized by sustained elevation of inflammatory cytokines.

Diet plays a significant role in modulating chronic inflammation (15). Dietary patterns can affect systemic inflammation, either directly or indirectly. Western diet is rich in red meat, high-fat dairy products, and refined grains, and is associated with high levels of inflammatory markers CRP and IL-6 (16). Conversely, a Mediterranean diet low in red meat and butter, and high in whole grains, fruits and vegetables, is associated with inflammation reduction (16,17).

The Dietary Inflammatory Index (DII) was developed to provide a quantitative means for assessing the role of diet in relation to health outcomes ranging from blood concentrations of inflammatory cytokines to chronic diseases (18,19). A negative DII score means the diet is anti-inflammatory. On the contrary, a positive score indicates that the diet is pro-inflammatory. Since its development the DII has been widely studied in various disease contexts to test the hypothesis that dietary inflammation is a determinant of NCD risk and mortality (3). A proinflammatory diet was significantly associated with a higher annual weight gain and a higher risk of developing new-onset overweight or obesity (20), while an anti-inflammatory diet, a healthy diet, and the consumption of healthy plant-based foods were all associated with a lower risk of developing obesity (21). In the cross-sectional Spanish PREDIMED (*Prevención con Dieta Mediterránea*) study, Ruiz-Canela et al. reported that the DII score was associated with higher average BMI, waist circumference and waist:height ratio in Spanish people (22). An intervention with an anti-inflammatory diet resulted in a significant reduction in body weight and visceral adipose tissue, and caused improvements in the participants' cardiometabolic and inflammatory status (23). Therefore, it is necessary to study diet inflammation level in different obese populations from the perspective of prevention. A cross-sectional

study showed that the prevalence of obesity was higher in the Uygur and Kazakh populations (24). Our previous study revealed that adiponectin and adiponectin/leptin ratio were inversely associated with metabolic syndrome (25), and that waist-hip ratio and leptin were negatively correlated with obesity in Uygur residents (26). It is unclear the relationship between DII and intermediate biomarkers in obese Uygur residents. Therefore, the aim of this study was to explore the association between a DII reflecting a more pro-inflammatory diet and adipocytokines among overweight and obese Uygur adults using a linear regression model.

MATERIALS AND METHODS

The current study included 283 obese and overweight Uygur adults according to inclusion and exclusion criteria. The data from a previous survey on dietary intake and obesity of local people in Hotan County during August 2018, Xinjiang. The inclusion criteria: body mass index (BMI) ≥ 24 kg/m^2; 25 to 65-year-old Uygur residents who had lived in this area for at least 5 years, and agreement to participate in this study. All participants signed an informed consent. The exclusion criteria: pregnancy and lactation; inability to give their informed consent. The study was approved by the Ethics Cometittee of First Affiliated Hospital of Xinjiang Medical University [20170214-150].

Overweight/Obesity can be known by body mass index (BMI), which is calculated by dividing weight by the square of height. Overweight: 24 kg/m^2 ≤ BMI < 28 kg/m^2; obesity: BMI ≥ 28 kg/m^2 (according to *The health industry standard of the people's Republic of China - Determination of adult weight [2013 Edition]*).

The general information (including age, gender, education, marital status, smoking and alcohol consumption habits, monthly income and self-reported physical activity) was obtained through face-to-face interviews.

Anthropometric indices were measured according to standard protocols, comprising height (accurate to 0.1 cm) and weight (accurate to 0.1 kg) under fasting conditions with light clothing and without shoes. All anthropometric measurements were done by trained personnel using calibrated instruments. In order to avoid the error of the results as much as possible, the same machine and standard were adopted by trained personnel in the measurement.

Dietary intake was collected using a validated and reliable 93-item food frequency questionnaire (FFQ), which was designed according to the local dietary characteristics and related references (27). The dietary intake data were collected by trained investigators and participants in face-to-face interviews.

Dietary inflammatory index (DII) is a literature-based tool that assesses the inflammatory properties of diet by reviewing 1,943 peer-reviewed articles that analysed 45 food variables and measured their associations with inflammation (18). The calculation of the dietary inflammation index can be divided into four steps: 1. Dietary intake data of participants were obtained through the FFQ. According to the 2016 Edition of the Chinese Food Composition Table, the dietary intake data were converted into the food composition content contained in the DII scale. 2. Dietary intake data of participants were compared with the global standard dietary intake database, which provide a reliable estimation of the mean and standard deviation, and the Z-score of each nutrient or food was calculated, i.e.: Z = (actual dietary intake amount - standard global mean) / standard deviation. Subsequently, to minimize the effect of "right-skewing", the Z-value was converted into percentiles, while each percentile was multiplied by 2 and finally subtracted by 1. 3. Then the resulting value was multiplied by the corresponding food parameter effect score to obtain the food parameter-specific DII score for an individual (18). 4. Finally, all dietary parameter-specific DII scores were added together to calculate the overall DII score. The higher the DII score, the stronger the proinflammatory effect.

In the present study, a total of 22 food parameters were obtained by the FFQ, and used to compute DII (namely:energy, protein, total fat, carbohydrate, cholesterol, dietary fiber, vitamin A, thiamine, riboflavin, niacin, vitamin C, vitamin D, vitamin E, folic acid, vitamin B_6, magnesium, iron, zinc, selenium, garlic, onion and pepper). The DII was divided into three tertiles, with first (< 1.15), second (≥ 1.15 and < 1.95), and third (≥ 1.95) being the most anti-inflammatory, neutral, and pro-inflammatory tertile, respectively.

The biochemical analyses were conducted on venous blood samples that had been collected after a 12-hour fast. The serum levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), and fasting insulin (FIN) were detected using an BS-460 and BS-800M automatic biochemical analyzer (Shenzhen Mindray company); leptin (LEP), adiponectin (ADPN), tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and C-reactive protein (CRP) were measured by the enzyme-linked immunosorbent assay (ELISA) method with an appropriate kit (Elabscience Biotechnology Co.,Ltd). The ADPN/LEP ratio was calculated as the ratio between serum concentrations of adiponectin and leptin. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the formula: [(fasting glucose (mmol/L)) × (fasting insulin(ml/U))] / 22.5).

All analyses were performed using the SPSS software (version 25). The normality of quantitative variables was assessed using Q-Q plots and the Kolmogorov-Smirnov test. Normal quantitative variables were presented as the mean ± standard deviation (SD), skewed and categorical variables as frequency and percentage, and continuous variables as median and P_{25}, P_{75}. The relation between the DII score as independent variable and adipocytokine concentration as dependent variable was tested by linear regression (Model 1, unadjusted). Model 2 represents a regression analysis with adjustment for age, gender, and BMI. *p* values of < 0.05 were considered to be statistically significant.

RESULTS

Among the 283 adults, 193 women and 80 men, 103 overweight and 180 obese, mean age was 46.40 years. The mean DII was 1.35 (SD = 1.08), ranged from -2.14 (most anti-inflamma-

tory) to 3.11 (highly pro-inflammatory). The participants' characteristics are summarized in table I. Overall, those participants with high pro-inflammatory diet (third tertile) were more likely to be female, married, less educated people.

The dietary intakes are indicated in table II. Those participants with a lower DII score had higher intakes of anti-inflammatory diet components, such as dietary fiber, thiamine, riboflavin, vitamin A, B_6, C, D, E, zinc, magnesium, selenium, niacin and folic acid.

The β coefficient and standard error (SE) of correlation between DII and adipocytokines are shown in table III. The DII score is a significant reverse trend between HDL-C in the unadjusted model (β = -0.12, SE = 0.05, p = 0.02), and this remained after adjustment for age, gender, and BMI (β = -0.12, SE = 0.05, p = 0.02). Moreover, the DII score was positively associated with the LEP in the unadjusted model (β = 2.35, SE = 0.56, $p < 0.001$) and adjusted model (β = 1.64, SE = 0.53, $p = 0.002$). In addition, there was a negative relationship between ADPN and DII after controlling age, gender, BMI (β = -203.15, SE = 96.48, p = 0.04). The adiponectin/leptin ratio was negatively correlated with DII in the unadjusted model (β = -62.16, SE = 24.29, p = 0.01), but this relationship was not observed after controlling for age, gender, and BMI. And no statistical association was observed between DII and other biochemical indices in both the unadjusted and adjusted models.

Table I. Characteristics of participants according to the tertiles of DII [n (%)]

Variables	T1 (n = 94)	T2 (n = 95)	T3 (n = 94)	χ^2	*p*
Age (years)				2.74	0.26
25~	35 (37.20)	43 (45.30)	46 (48.90)		
45~65	59 (62.80)	52(54.70)	48 (51.10)		
Gender				6.09	0.04
Male	36 (38.30)	33 (34.70)	21 (22.30)		
Female	58 (61.70)	62 (65.30)	73 (77.70)		
Education				21.87	< 0.001
Primary and below	63 (67.00)	49 (51.60)	43 (45.70)		
Middle and high school	28 (29.80)	22 (23.10)	28 (29.80)		
University or higher	3 (3.20)	24 (25.30)	23 (24.50)		
Marital status				34.13	< 0.001
Single	3 (3.20)	21 (22.10)	30 (31.90)		
Married	82 (87.20)	67 (70.50)	48 (51.10)		
Divorced / Widowed	9 (9.60)	7 (7.40)	16 (17.00)		
Monthly income (¥)				5.89	0.21
< 1000	46 (48.90)	41 (43.20)	46 (48.90)		
1000~3000	25 (26.60)	22 (23.20)	14 (14.90)		
≥ 3000	23 (24.50)	32 (33.70)	34 (36.20)		
Smoking status				5.63	0.06
Yes	19 (20.20)	9 (9.50)	10 (10.60)		
No	75 (79.80)	86 (90.50)	84 (89.40)		
Drinking status				3.79	0.15
Yes	14 (14.90)	9 (9.50)	6 (6.40)		
No	80 (85.10)	86 (90.50)	88 (93.60)		
Physical activity				1.77	0.41
Yes	30 (31.90)	28 (29.50)	36 (38.30)		
No	64 (68.10)	67 (70.50)	58 (61.70)		
BMI (kg/m^2)				1.24	0.54
24~28	38 (40.40)	31 (32.60)	34 (36.20)		
≥ 28	56 (59.60)	64 (67.40)	60 (63.80)		

BMI: body mass index; Overweight: 24 kg/m^2 ≤ BMI < 28 kg/m^2; Obesity: BMI ≥ 28 kg/m^2. T1: < 1.15, 1.15 ≤ T2 < 1.95, T3 ≥ 1.95.

Table II. Comparison of dietary intake of participants according to the tertiles of DII (M [P_{25}, P_{75}])

Food parameter	T1 (n = 94)	T2 (n = 95)	T3 (n = 94)	*p*
Energy (kcal)	2654.00 (2207.50, 2988.00)	2011.00 (1719.00, 2202.54)	1651.00 (1403.75, 1916.00)	< 0.001
Protein (g)	89.65 (73.10, 106.85)	65.20 (52.80, 71.46)	55.65 (43.18, 64.15)	< 0.001
Total fat (g)	73.95 (58.13, 93.80)	61.40 (46.20, 68.21)	50.55 (39.58, 61.03)	< 0.001
Carbohydrate (g)	380.65 (324.10, 448.33)	295.80 (244.10, 331.00)	239.40 (196.48, 294.28)	< 0.001
Cholesterol (mg)	380.00 (213.5, 550.75)	212.00 (126.00, 309.18)	217.00 (107.25, 378.50)	< 0.001
Fiber (g)	17.30 (14.90, 20.92)	12.30 (8.90, 13.60)	7.40 (5.60, 10.23)	< 0.001
Vitamin A (μg RAE)	934.00 (578.25, 2428.00)	605.00 (403.00, 1036.05)	367.50 (276.50, 484.50)	< 0.001
Thiamine (mg)	1.42 (1.22, 1.65)	1.03 (0.77, 1.17)	0.72 (0.58, 0.88)	< 0.001
Riboflavin (mg)	1.19 (0.96, 1.46)	0.77 (0.63, 0.91)	0.59 (0.50, 0.72)	< 0.001
Vitamin B6 (mg)	0.52 (0.42, 0.57)	0.44 (0.34, 0.47)	0.33 (0.27, 0.40)	< 0.001
Niacin (mg)	20.40 (16.34, 24.99)	15.48 (12.07, 16.63)	11.84 (9.86, 14.73)	< 0.001
Folic acid (μg)	104.10 (87.70, 128.78)	81.29 (60.00, 93.10)	73.43 (48.95, 92.65)	< 0.001
Vitamin C (mg)	106.00 (89.88, 126.15)	93.90 (76.20, 100.50)	67.15 (56.95, 80.08)	< 0.001
Vitamin D (μg)	6.20 (1.30, 12.68)	0.80 (0.20, 4.00)	0.80 (0.10, 1.23)	< 0.001
Vitamin E (mg)	34.14 (24.15, 44.12)	22.22 (16.88, 29.99)	19.39 (14.93, 27.30)	< 0.001
Mg (mg)	380.00 (333.50, 448.00)	276.00 (236.00, 305.15)	205.50 (182.00, 250.00)	< 0.001
Fe (mg)	28.25 (24.45, 36.20)	19.80 (16.30, 22.45)	14.85 (12.88, 17.60)	< 0.001
Zn (mg)	14.68 (12.40, 17.44)	10.42 (8.52, 11.59)	7.96 (6.80, 9.36)	< 0.001
Se (μg)	64.39 (46.04, 79.78)	46.20 (35.33, 51.54)	42.32 (33.44, 51.47)	< 0.001
Garlic (g)	5.00 (5.00, 7.00)	5.00 (4.73, 5.00)	5.00 (0.00, 5.00)	< 0.001
Onion (g)	10.00 (7.00, 10.00)	10.00 (7.00, 13.70)	10.00 (7.00, 25.25)	0.007
Pepper (g)	30.00 (25.00, 30.00)	30.00 (28.00, 30.24)	30.00 (20.00, 35.00)	0.024

Data were reported as median (interquartile range) and analyzed using the Kruskal-Wallis H-test.

Table III. Standardized regression coefficients (β) and their standard error (SE), and p-value of the association of DII score with BMI and biochemical measurements

Variables	Model 1			Model 2		
	β (95 % CI)	SE	*p*	β (95 % CI)	SE	*p*
BMI (kg/m^2)	0.30 (-0.054, 0.658)	0.18	0.09	0.22 (-0.14, 0.59)	0.18	0.22*
TC (mmol/L)	0.03 (-0.08, 0.14)	0.06	0.55	0.08 (-0.03, 0.19)	0.06	0.15
TG (mmol/L)	0.04 (-0.14, 0.20)	0.09	0.70	0.07 (-0.10, 0.25)	0.09	0.40
LDL-C (mmol/L)	0.02 (-0.08, 0.12)	0.05	0.67	0.02 (-0.08, 0.13)	0.05	0.64
HDL-C (mmol/L)	-0.12 (-0.22, -0.02)	0.05	0.02	-0.12 (-0.22, -0.02)	0.05	0.02
FBG (mmol/L)	0.01 (-0.17, 0.18)	0.09	0.97	0.01 (-0.17, 0.19)	0.09	0.88
FIN (pmol/L)	0.04 (-0.31, 0.38)	0.18	0.84	-0.02 (-0.37, 0.33)	0.18	0.90
HOMA-IR	0.01 (-0.10, 0.13)	0.06	0.85	0.002 (-0.12, 0.12)	0.06	0.97
LEP (ng/mL)	2.35 (1.25, 3.45)	0.56	< 0.001	1.64 (0.59, 2.69)	0.53	0.002
ADPN (ng/mL)	-193.27 (-387.72, 1.18)	98.79	0.05	-203.15 (-393.07, -13.22)	96.48	0.04
CRP (mg/L)	-0.17 (-0.40, 0.08)	0.12	0.18	-0.15 (-0.39, 0.09)	0.12	0.21
IL-6 (pg/mL)	-0.88 (-2.00, 0.26)	0.58	0.13	-0.91 (-2.00, 0.19)	0.56	0.10
TNF-α (pg/mL)	-1.25 (-2.81, 0.31)	0.79	0.12	-1.12 (-2.63, 0.39)	0.77	0.15
ADPN/LEP-ratio	-62.16 (-109.97, -14.34)	24.29	0.01	-44.45 (-92.13, 3.22)	24.22	0.06

Model 1, linear regression analysis without adjustment; Model 2, linear regression analysis with adjustment for age, gender, and BMI or without BMI.*

DISCUSSION

Chronic inflammation can lead to various metabolic diseases including obesity through the influence of diet, and DII is a new method to evaluate the characteristics of dietary inflammation. Our findings showed that DII score was positively correlated with the concentration of leptin and negatively correlated with adiponectin in this studied obese Uygur adults. In addition, the DII score was inversely related to high-density lipoprotein. We did not find CRP, IL-6, and TNF-α to be correlated with DII score.

DII plays a very practical role in assessing the inflammation potential of diet. In our study, the positive association between DII score and leptin concentration suggests a role for the inflammatory properties of the diet in regulating adipose tissue inflammation. Considering nutrients, as with other studies (28,29), in this study DII was significantly inversely related to intake of dietary fiber and various specific nutrients (thiamine, riboflavin, vitamin A, B_6, C, D, E, zinc, magnesium, selenium, niacin and folic acid). All these associations matched the DII's expected direction. However, it should be noted that T3 (with a highly pro-inflammatory diet) had relatively low intakes of energy, protein, total fat, carbohydrates, cholesterol and iron. Maryam et al. (30) reported that there were significant decreasing trends in the proportion of energy intake from carbohydrates, proteins and iron across categories of the DII score (from quartile 1 to quartile 4). Asadi et al. (31) also reported that participants in the third group of DII had a lower energy intake. These results are consistent with the results of this study. This may take into account the demographic characteristics of the participants as well as their dietary habits, such as according to the group of DII, it can be seen that there are more obese people in the T3 group. Obese people may have the intention to control their dietary intake to achieve weight loss.

Obesity and obesity-related diseases are closely connected to the serum levels of leptin and adiponectin (32). The majority of obese individuals show leptin resistance, characterized by abnormally increasing serum leptin but diminished effects of leptin on inhibiting appetite and enhancing energy expenditure, which causes an increased food intake (8,33). Leptin also stimulates the production of proinflammatory cytokines IL-6 and TNF-α, and promotes inflammation (9). In this study, the DII score was shown to be positively associated with leptin concentration after adjusting for age, gender, and BMI. The same was observed in other studies in which there was a significant correlation between plasma leptin concentration and DII score ($\beta = 0.096$, $p = 0.020$) (34).

Adiponectin has insulin-sensitizing, anti-atherogenic, and anti-inflammatory effects, and, in certain settings also decreases body weight (9,35). In our study there was a negative correlation between DII score and adiponectin concentration in the adjusted model. These results indicated that an anti-inflammatory diet is associated with a lower risk of developing obesity in Uygur adults. In other studies, Frühbeck et al. reported that the adiponectin/leptin ratio is a good indicator of a dysfunctional adipose tissue that may be a useful estimator of obesity- and MS-associated cardiometabolic risk, allowing the identification of a higher number of subjects at risk (10,11). In our study, we did not observe any relationship between DII and adiponectin/leptin ratio after controlling for age, gender, and BMI. More studies are needed to confirm these observations in the future. In our study, we also did not observe DII as related to other inflammatory indices (CRP, IL-6, TNF-α) as other studies did (36,37). A study has reported that the dietary pattern has an important role in affecting circulating inflammatory markers in adults (38), but influencing factors involve all aspects, not just one. Staying up late, sedentary behavior and other lifestyle play a key role in regulating inflammation and health (39).

Obesity is also linked to dyslipidemia, caused primarily by insulin resistance and pro-inflammatory adipokines (40). In this study, we found that the concentration of HDL-C was negatively correlated with DII score after adjustment for age, gender and BMI in a linear regression model. The result was consistent with that by Neufcourt et al. (41), who demonstrated that higher DII scores were associated with higher TG and lower HDL-C. Abdollahzad et al. (42) also confirmed a correlation between DII score and lipid profile.

Our study has several strengths and limitations. To our knowledge, this is the first study to examine the relationship between DII and adipocyte-related factors in rural Uygurs. A pro-inflammatory diet, as indicated by a higher DII score, is associated with adipose tissue inflammation in Uygur adults and supports the hypothesis that diet may have a role in the development of obesity through inflammatory modulation mechanisms. As a cross-sectional study it also has some limitations. First, there were only 22 food parameters that were used to calculate DII in this study. A few food parameters were not available for calculating DII scores. For instance, coffee, thyme/oregano, rosemary, green/black tea, etc., are very scarcely or not at all consumed by this population. Second, the small sample size may have an impact on the interpretation of the results, so it is necessary to increase the sample size in different regions and populations to verify the usefulness of DII. To be sure, diet can modulate inflammation, but this does not mean that it is the only influencing factor. Finally, there are many other factors that will have certain effects — especially sedentary behavior and physical activity play a key role in regulating inflammation and health (39). In this study, participants with a high pro-inflammatory diet (third tertile) were more likely to be female, married, and less educated. The majority of overweight/obese people were female (68.20 %) because in the season when the study began, some young and middle-aged men went out to work, while some women stayed at home. Besides, we observed according to the tertiles of DII that higher educated people prefer to choose an anti-inflammatory diet, which is possibly related to their health literacy. Therefore, these results must be taken into account when explaining them. It is suggested that we should pay attention to these problems in our next research work.

CONCLUSIONS

In summary, our study showed that the DII score was negatively associated with HDL-C and ADPN, and positively associated with LEP concentration. These results support that diet has a certain influence on adipose tissue inflammation, and an anti-inflammatory diet is associated with a lower risk of develop-

ing obesity in Uygur adults. A healthy lifestyle (including choosing an anti-inflammatory diet) may help guide local people, and may also open up new areas of research.

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Trabajo Original

Obesidad y síndrome metabólico

Protective effect of manganese treatment on insulin resistance in HepG2 hepatocytes

Efecto protector del tratamiento con manganeso sobre la resistencia a la insulina en hepatocitos HepG2

Qingwen Zhang[1,2], Shili Song[3], Ruyue Jiang[4], Jingyi Zhang[2,5], Lixin Na[2]

[1]College of Medical Technology, [2]Collaborative Innovation Center and [5]College of Public Health. Shanghai University of Medicine and Health Sciences. Shanghai, P. R. China. [3]Linping District Center for Disease Control and Prevention. Hangzhou, Zhejiang. P. R. China. [4]Publich Health College. Harbin Medical University. Haerbin, Heilongjiang. P. R. China

Abstract

Objectives: manganese (Mn) is closely related to type 2 diabetes *mellitus* and insulin resistance (IR), but the exact mechanism is unclear. This study aimed to explore the regulatory effects and mechanism of Mn on IR using hepatocyte IR model induced by high palmitate (PA), high glucose (HG) or insulin.

Methods: HepG2 cells were exposed to PA (200 μM), HG (25 mM) or insulin (100 nM) respectively, alone or with 5 μM Mn for 24 hours. The expression of key proteins in insulin signaling pathway, intracellular glycogen content and glucose accumulation, reactive oxygen species (ROS) level and Mn superoxide dismutase (MnSOD) activity were detected.

Results: compared with control group, the expression of phosphorylated protein kinase B (Akt), glycogen synthase kinase-3β (GSK-3β) and forkhead box O1 (FOXO1) in the three IR groups was declined, and this decrease was reversed by Mn. The reduction of intracellular glycogen content and increase in glucose accumulation in IR groups were also inhibited by Mn. Additionally, the production of ROS was increased in IR models, compared with normal control group, while Mn reduced the excessive production of ROS induced by PA, HG or insulin. However, Mn did not alter the activity of MnSOD in the three IR models.

Conclusion: this study demonstrated that Mn treatment can improve IR in hepatocytes. The mechanism is probably by reducing the level of intracellular oxidative stress, enhancing the activity of Akt/GSK-3β/FOXO1 signal pathway, promoting glycogen synthesis, and inhibiting gluconeogenesis.

Keywords:

Insulin resistance. Type 2 diabetes. Manganese.

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Author contributions: Lixin Na conceived and designed the study. Qingwen Zhang, Shili Song and Ruyue Jiang performed the experiments, Jingyi Zhang and Fe Xu participated in the data collection and analysis. Qingwen Zhang and Shili Song interpreted the data and wrote the manuscript. All authors read and approved the final manuscript. Qingwen Zhang and Shili Song have contributed equally to this work.

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Correspondence:

Lixin Na. College of Public Health. Shanghai University of Medicine and Health Sciences. Shanghai, P. R. China
e-mail: nalixin2003@163.com

Resumen

Objetivos: el manganeso (Mn) está estrechamente relacionado con la diabetes *mellitus* tipo 2 y la resistencia a la insulina (RI), pero el mecanismo exacto aún no está claro. Este estudio tuvo como objetivo explorar los efectos reguladores y el mecanismo del Mn sobre la RI utilizando un modelo de RI en hepatocitos inducido por palmitato alto (PA), glucosa alta (HG) o insulina.

Métodos: las células HepG2 se expusieron a PA (200 μM), HG (25 mM) o insulina (100 nM), solas o junto con 5 μM de Mn durante 24 horas. Se evaluó la expresión de proteínas clave en la vía de señalización de la insulina, el contenido intracelular de glucógeno y la acumulación de glucosa, el nivel de especies reactivas de oxígeno (ROS) y la actividad superóxido dismutasa del manganeso (MnSOD).

Resultados: en comparación con el grupo de control, la expresión de proteína quinasa B fosforilada (Akt), la glucógeno sintasa quinasa-3β (GSK-3β) y la proteína *forkhead box* O1 (FOXO1) en los tres grupos de RI se redujo, y esta disminución fue revertida por el Mn. La reducción del contenido de glucógeno intracelular y el aumento de la acumulación de glucosa en los grupos de RI también fueron inhibidos por el Mn. Además, la producción de ROS aumentó en los modelos de RI en comparación con el grupo de control normal. Mientras que el Mn redujo la producción excesiva de ROS inducida por PA, HG o insulina. Sin embargo, el Mn no alteró la actividad de la MnSOD en los tres modelos de RI.

Conclusión: este estudio demostró que el tratamiento con Mn puede mejorar la RI en hepatocitos. El mecanismo probablemente sea mediante la reducción del nivel de estrés oxidativo intracelular, mejorando la actividad de la vía de señalización Akt/GSK-3β/FOXO1, promoviendo la síntesis de glucógeno e inhibiendo la gluconeogénesis.

Palabras clave:

Resistencia a la insulina. Diabetes tipo 2. Manganeso.

INTRODUCTION

Insulin resistance (IR) is associated with the impairment of the biological response to insulin stimulation of key target tissues, especially liver, muscle, and adipose tissue, which is the major factor to the pathogenesis of type 2 diabetes *mellitus* (1). The environmental lifestyle-related factors such as high-free fatty acid (FFAs) diet, over-nutrition, nutritional imbalance etc., have been well recognized as the risk factors leading to a sharp increase of IR (2-4). Exploring the connection between dietary factors and IR has become a research hotspot in the field of diabetes.

Manganese (Mn) is one of the essential micronutrients in the human body, which exists mainly in the form of Mn metalloenzymes, such as Mn superoxide dismutase (MnSOD) (5-7). Mn is widely distributed in the liver and is involved in multiple biological functions of cells, including serving as a cofactor for many enzyme systems, participating in the metabolism of glucose and lipids, improving the immune function, etc. (5-7). Two recent prospective cohort studies (8) demonstrated that an appropriate increase in dietary Mn intake could reduce the risk of type 2 diabetes *mellitus.* The researchers speculated that the mechanism probably be that dietary Mn can increase the activity of MnSOD and reduce the oxidative stress. The *in vivo* studies showed that rats with dietary Mn-deficient had reduced insulin secretion and impaired glucose tolerance (9), while dietary treatment with Mn increase the MnSOD activity in diabetic fatty Rats (10) and high-fat diet-induced mice (11), improve glucose tolerance and enhance insulin secretion (11). According to the current researches, Mn indeed has the protective function against type 2 diabetes *mellitus* and improves IR. However, the specific mechanism of Mn on IR is still unclear, and there are few related studies.

Liver, as the target organ of insulin, is the main site where the body regulates glycogen synthesis and gluconeogenesis, maintaining the stability of blood glucose (12). When in the condition of high glucose (13), FFAs (14,15) and high insulin (16), or certain cytokines such as tumor necrosis factor-α (TNF-α) (17), the hepatocyte can be induced to develop IR. Oxidative stress is considered to be the pivotal common soil mechanism for various factors leading to IR (18-20). The increased production of reactive oxygen species (ROS) during various harmful stimuli triggers the activation of stress-sensitive serine/threonine kinase signaling pathways, leading to impaired activation of phosphatidylinositol 3 kinase (PI3K)/protein kinase B (Akt) signaling pathway, accompanied by decreased downstream glycogen synthesis and increased gluconeogenesis in the liver (14,20,21).

In the present study, HepG2 cells were induced by high concentration of palmitic acid or glucose or insulin to establish hepatocyte IR model. The expression of key enzymes for insulin signal regulation, glucose metabolism related molecules, intracellular ROS and MnSOD enzyme activity was analyzed to explore the role and specific mechanism of Mn in improving IR and glucose metabolism, expecting to provide new ideas for the nutritional prevention of IR.

MATERIALS AND METHODS

CHEMICALS AND REAGENTS

$MnCl_2 \bullet 4H_2O$ and palmitic acid were purchased from Sigma-Aldrich Company (St Louis, MO, USA). D-glucose and recombinant human insulin were purchased from Solarbio (Beijing, China). Glycogen Content Assay Kit was purchased from Solarbio (Beijing, China). Glucose oxidase assay kit was purchased from Applygen (Beijing, China). 2-(*N*-(7-nitrobenz-2-oxa-1, 3-diazol-4-yl) amino)-2-deoxy-D-glucose (2-NBDG) was purchased from Invitrogen (Carlsbad, CA, USA). Reactive Oxygen Species Assay Kit was purchased from Beyotime Biotechnology (Shanghai, China). SOD Assay kit was purchased from Cayman Chemicals (Ann Arbor, MI, USA). The antibodies against Akt and *p*-Akt (Ser473), GSK-3β and *p*-GSK-3β (Ser9), FOXO1 and *p*-FOXO1 (Thr24) were obtained from Cell Signaling Technology, Inc. (Danvers, MA, USA). The anti-β-actin antibody was purchased from ABclonal (MA, USA).

CELLS CULTURE AND TREATMENT

Human hepatoma cell line HepG2 cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) (Hyclone, USA) and 10 % (v/v) fetal bovine serum (FBS) (Genial, USA) in 5 % (v/v)

CO_2 at 37 °C humidified atmosphere. HepG2 cells were seeded in six-well plates at a density of 5×10^5 cells/well and grown at 37 °C overnight, then exposed to palmitate (PA, 200 μM), high glucose (HG, 25 mM) or insulin (Insulin, 100 nM) respectively alone for IR model induction (15, 22) or with Mn (5 μM, MnCl2) for 24 hours. Then, cells were stimulated with 100 nM insulin for ten minutes and then harvested for further analysis.

WESTERN BLOT

The total cell lysates were obtained using RIPA lysis buffer (Beyotime, China). Then the protein was denatured and separated by SDS-PAGE, and further transferred onto PVDF membrane (Merck Millipore, USA). After blocking with TBST (0.5 % Tween-20) containing 5 % (w/v) non-fat milk, the membranes were then incubated with specific primary antibodies: anti-Akt/*p*-Akt (1:1000), anti-GSK-3β/*p*-GSK-3β (1:1000), anti-FOXO1/*p*-FOXO1 (1:1000) and anti-β-actin (1:50000) at 4 °C overnight in blocking solution. Following three times of washed with TBST, the membranes were incubated with HRP-conjugated secondary antibodies (1:7500) (Promega, USA) at room temperature for one hour. Images were acquired and quantified using Alpha chemiluminescence gel imaging system FluorChem™ E (Protein Simple, Inc., USA).

DETERMINATION OF GLYCOGEN CONTENT

Glycogen content was measured by glycogen content assay kit according to the instruction manual provided with the kit. Glycogen content was calculated and normalized with cellular protein content.

DETERMINATION OF INTRACELLULAR GLUCOSE LEVEL

The intracellular glucose was measured according to the instruction manual provided with the glucose oxidase assay kit. The glucose concentration was normalized with cellular protein concentration.

ROS DETECTION

HepG2 cells were incubated with DCFH-DA (2,000 μM) in serum-free medium at 37 °C for 20 minutes. Then cells were transferred into the centrifuge tube and centrifuged at 1,000 rpm for three minutes. The cell pellets were resuspended twice with PBS and filtered in a flow tube. The intracellular fluorescence intensity was measured by flow cytometry.

MnSOD ACTIVITY ASSAY

The activity of MnSOD was determined according to the instruction manual provided with the kit. The absorbance value was measured at the 450 nm wavelength. MnSOD activity was normalized with cellular protein concentration.

STATISTICAL ANALYSIS

Statistical analyses were performed using the SPSS 21.0 soft package. One-way ANOVA followed by Turkey's test was used to determine differences between groups, data were given as the means ± standard deviations (SD), p-values < 0.05 and < 0.01 were considered as significant.

RESULTS

Mn REGULATES THE INSULIN SIGNALING PATHWAY BY INCREASING THE ACTIVATION OF Akt

Akt is a key kinase in the PI3K/Akt pathway of the insulin signaling pathway (23). The phosphorylation and activation of Akt is critical for the activity of downstream glucose-metabolizing enzymes. As shown in figure 1, the expression of *p*-Akt in all three IR model groups was more significantly inhibited, compared with the normal control group, suggesting that the IR models were successfully established. Moreover, Mn treatment obviously enhanced the phosphorylation of Akt, and reversed the inhibitory effect of high concentrations of PA, glucose or insulin on Akt phosphorylation (Fig. 1).

Mn TREATMENT IMPROVES GLUCOSE METABOLISM DISORDER IN IR HepG2 CELLS

Mn treatment improves glycogen synthesis ability of IR hepatocytes

Glycogen synthase kinase-3β (GSK-3β) is a kinase downstream of Akt that is responsible for glycogen synthesis (24). As shown in figure 2, the expression of *p*-GSK-3β in all three IR models was more significantly decreased, compared with the normal control group. While Mn treatment obviously increased the expression of *p*-GSK-3β, it reversed the inhibition of GSK-3β phosphorylation induced by PA, HG or insulin (Fig. 2A-C). To further identify the role of Mn on glycogen synthesis, intracellular glycogen content was investigated. The similar results were obtained that three IR models all clearly reduced intracellular glycogen content, and Mn treatment significantly increased intracellular glycogen content, compared with three IR model groups (Fig. 2D-F).

Mn treatment reduces gluconeogenesis ability of IR hepatocytes

Forkhead box O1 (FOXO1) is a transcription factor involved in the regulation of hepatic gluconeogenesis and is also regulated

by Akt phosphorylation (24). The results indicated that *p*-FOXO1 protein expression levels were all significantly decreased in three IR models, compared with the normal control group (Fig. 3). While Mn treatment upregulated the phosphorylation of FOXO1, it reversed the inhibition effect of FOXO1 phosphorylation induced by PA, HG or insulin.

Mn treatment reduces intracellular glucose accumulation of IR hepatocytes

To further verify the positive effect of Mn on glucose metabolism in hepatocytes, intracellular glucose net content was detected. Results showed that the intracellular glucose contents were all remarkably increased in three IR model groups, compared with normal control group, and Mn treatment decreased the intracellular glucose content of three IR model groups (Fig. 4). However, this positive effect of manganese on glucose accumulation in hepatocytes was not observed in the cells supplemented with manganese alone.

Mn TREATMENT CAN REDUCE INTRACELLULAR ROS LEVELS

Due to the fact that the increase of ROS production can activate a variety of stress-sensitive signaling pathways and impair the normal function of insulin signals (20,21), the intracellular ROS levels were measured by flow cytometry to observe the effects of Mn treatment on oxidative stress. Figure 5 shows that intracellular ROS levels were significantly increased in three IR model groups compared with the control group. As expected, Mn treatment remarkably prevented the production of ROS induced by high concentration of PA, glucose or insulin.

THE ACTIVITY OF MnSOD IN Mn TREATMENT CELLS WAS UNCHANGED

To further explore how Mn treatment affects intracellular ROS, the antioxidant enzyme activity of MnSOD was detected. However, as shown in figure 6, there were no differences in MnSOD enzyme activity in the three IR model groups, compared with the normal control group. Moreover, Mn treatment did not affect the activity of MnSOD enzyme, compared with model groups.

DISCUSSION

This study demonstrated that Mn treatment could ameliorate hepatocyte IR and glycometabolic disorder, with the molecular mechanism of inhibiting the ROS production and activating the Akt/GSK3β/FOXO1 signaling pathway. This is the first demonstration that Mn treatment improves the hepatic HepG2 IR and glucose metabolism disorder induced by high PA, HG, or high insulin.

There are several high-risk factors that contribute to the development of IR, including increased circulating fuels, glucose and FFAs. Researches also showed that the *in vitro* IR model can be induced by high glucose, high FFAs, and high insulin to simulate the diabetic conditions of the body (14,22,25). In the present study, we established IR models with PA or glucose or insulin respectively in HepG2 cells. Results showed that the expression of *p*-Akt was significantly downregulated when HepG2 cells exposed with high concentration of PA, glucose or insulin, indicating that three different hepatocyte IR models were successfully established. Meanwhile, detection of the net content of intracellular glucose were all increased in three IR models, which further supported the successful establishment of hepatocyte IR model. While inducing IR, Mn was added to observe the preventive effect on IR.

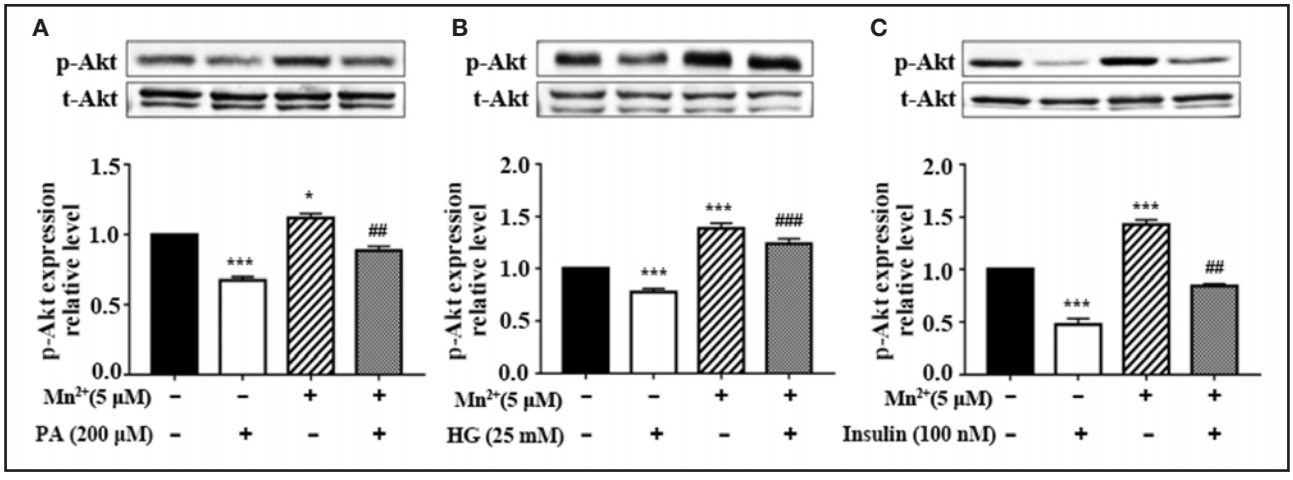

Figure 1.

Effects of Mn treatment on insulin signaling transmit in hepatocytes. A. Protein expression of *p*-Akt in PA-induced HepG2 cells. B. Protein expression of *p*-Akt in HG-induced HepG2 cells. C. Protein expression of *p*-Akt in insulin-induced HepG2 cells. $^{*}p < 0.05$ and $^{***}p < 0.001$ *vs* normal control group; $^{\#\#}p < 0.01$ and $^{\#\#\#}p < 0.001$ *vs* model group.

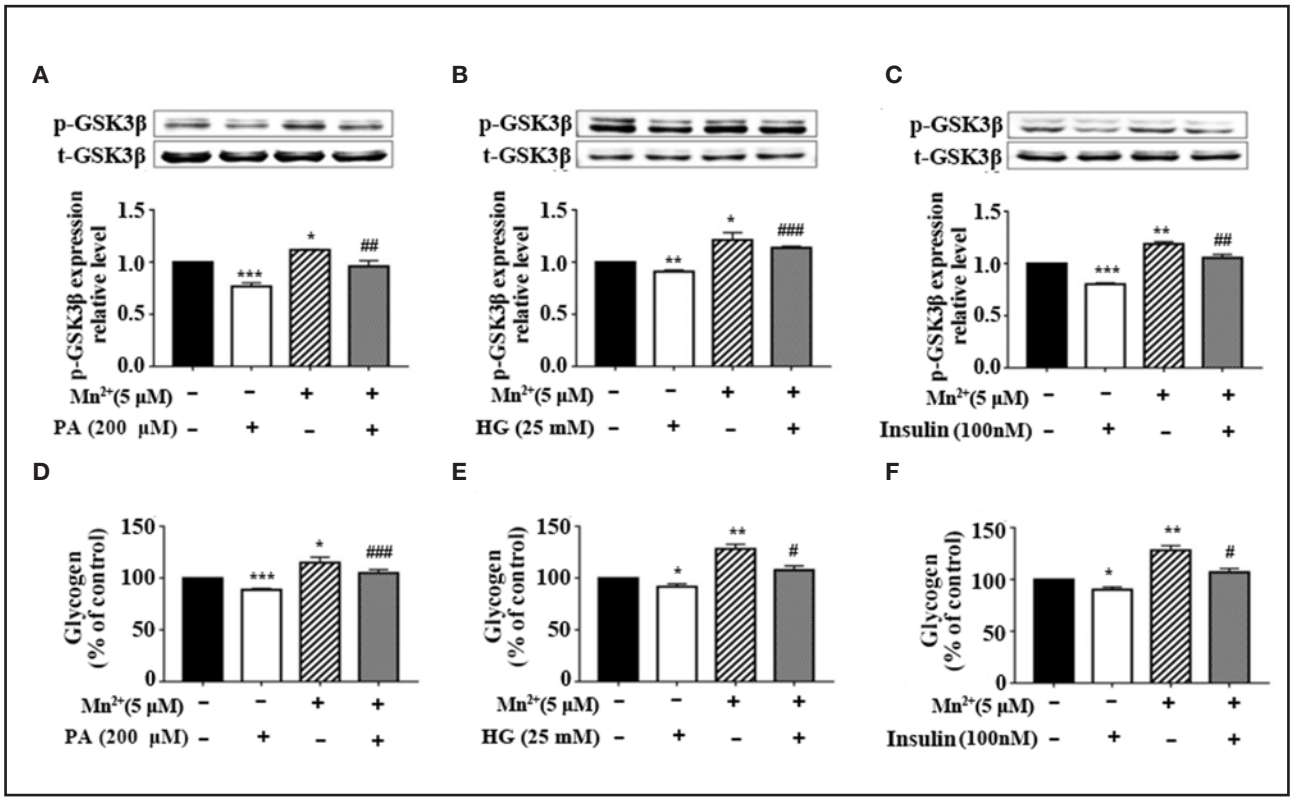

Figure 2.

Effects of Mn treatment on glycogen synthesis in hepatocytes. A-C. Protein expression levels of *p*-GSK3β in HepG2 IR models. D-F. The intracellular glycogen content in HepG2 IR models. $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ *vs* normal control group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ and $^{\#\#\#}p < 0.001$ *vs* model group.

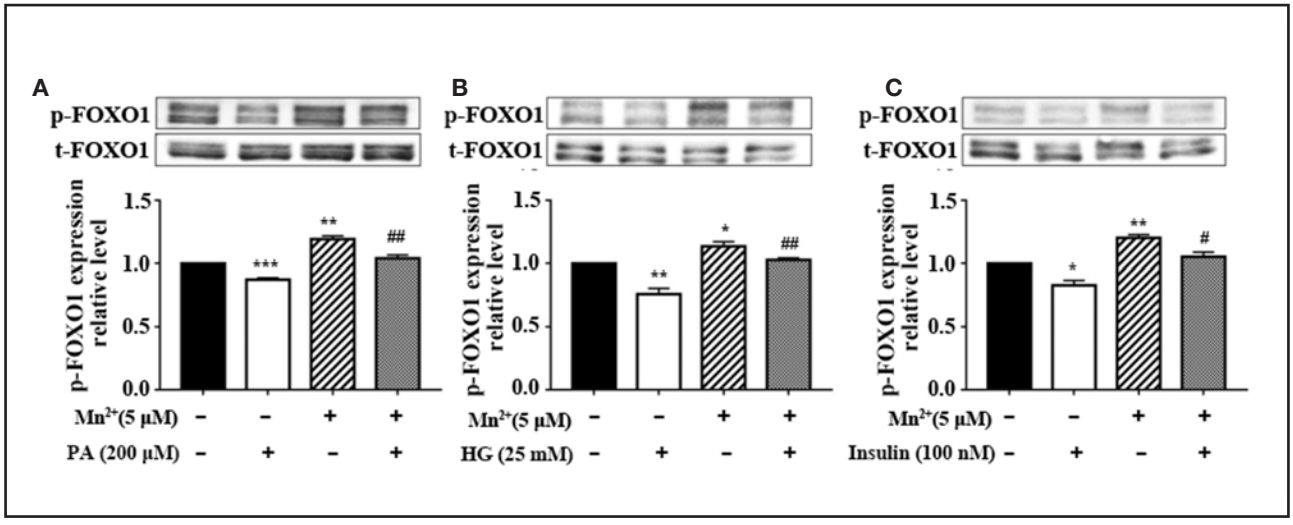

Figure 3.

Effects of Mn treatment on gluconeogenesis in hepatocytes. A. Protein expression levels of *p*-FOXO1 in PA-induced HepG2 cells. B. Protein expression levels of *p*-FOXO1 in HG-induced. C. Protein expression levels of *p*-FOXO1 in insulin-induced HepG2 cells. $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ *vs* normal control group; $^{\#}p < 0.05$ and $^{\#\#}p < 0.01$ *vs* model group.

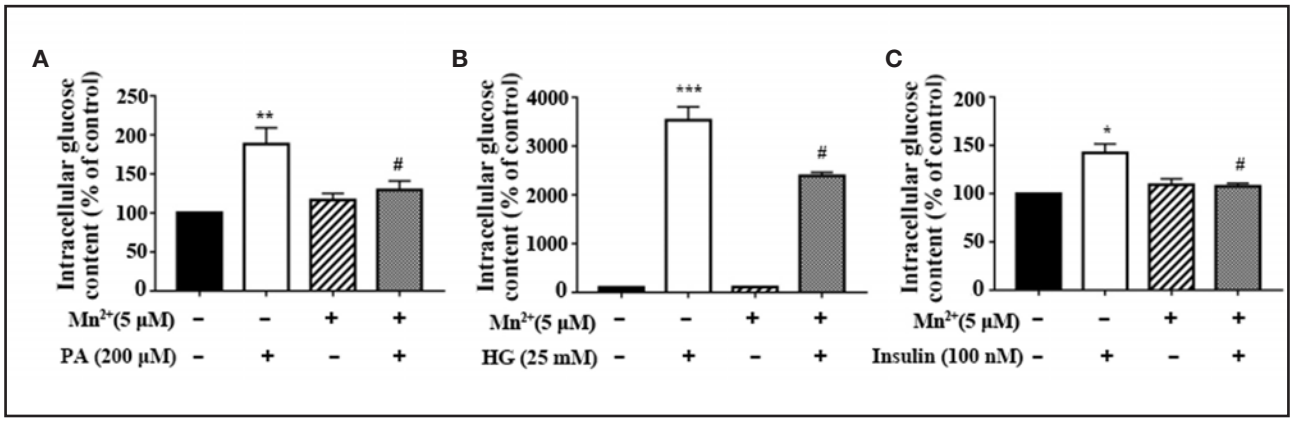

Figure 4.

Effects of Mn treatment on the net glucose net in hepatocytes. A. Relative levels of intracellular glucose content in PA-induced HepG2 cells. B. Relative levels of intracellular glucose content in HG-induced HepG2 cells. C. Relative levels of intracellular glucose content in insulin-induced HepG2 cells. $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ *vs* normal control group; $^{\#}p < 0.05$ *vs* model group.

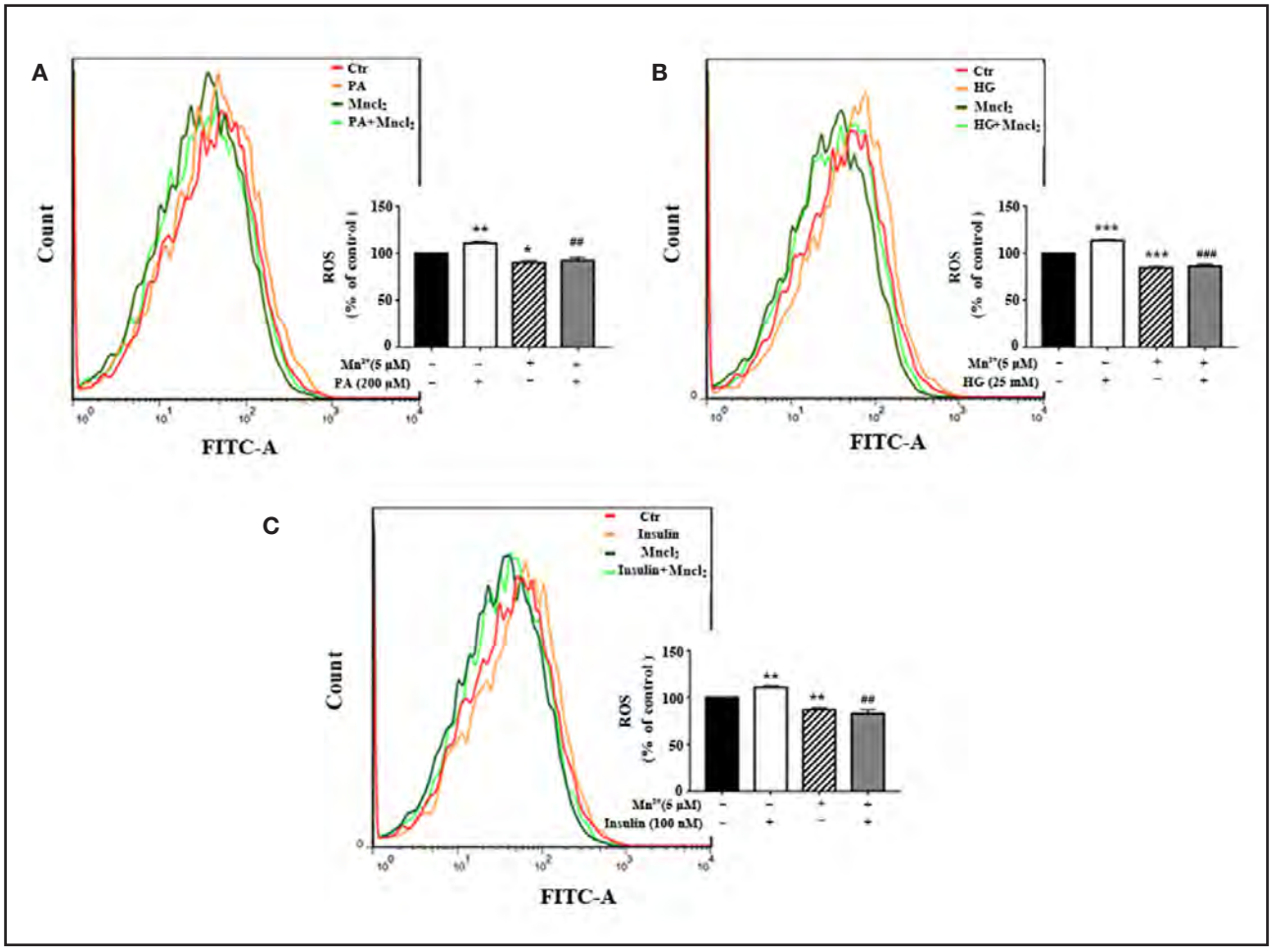

Figure 5.

Effects of Mn treatment on ROS levels in hepatocytes. A. Relative levels of ROS in PA-induced HepG2 cells. B. Relative levels of ROS in HG-induced HepG2 cells. C. Relative levels of ROS in insulin-induced HepG2 cells. $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ *vs* normal control group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ and $^{\#\#\#}p < 0.001$ *vs* model group.

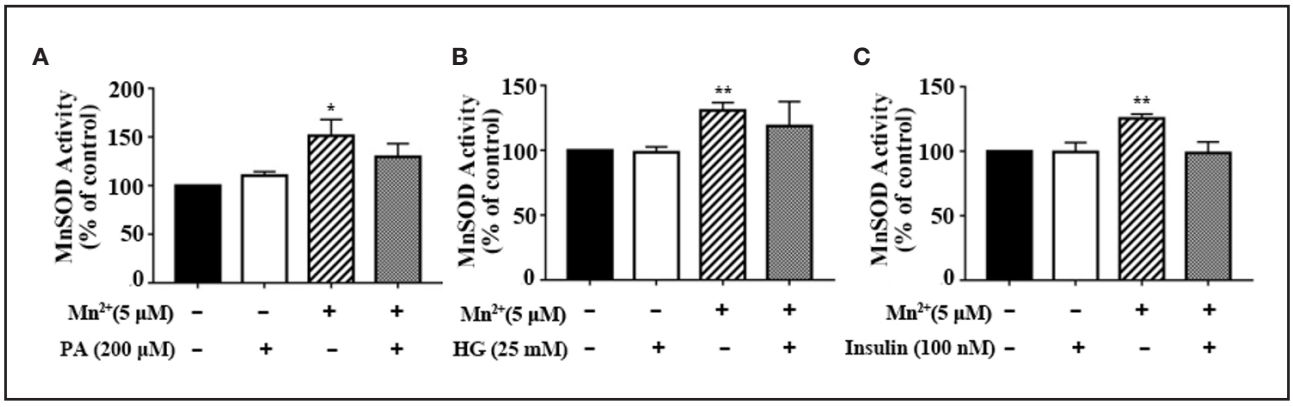

Figure 6.

Effects of Mn treatment on the activity of MnSOD in hepatocytes. A. Relative levels of MnSOD activity in PA-induced HepG2 cells. B. Relative levels of MnSOD activity in HG-induced HepG2 cells. C. Relative levels of MnSOD activity in insulin-induced HepG2 cells. $^{*}p < 0.05$ and $^{**}p < 0.01$ *vs* normal control group.

The simultaneous addition of Mn and inducer simulates the antagonistic and preventive effects of Mn when the dietary Mn intake is high in real life. Currently, many studies on the prevention of IR by nutritional factors have been designed in this way (26,27). When Mn and inducer are added at the same time, there may be a direct interaction between them. Of course, this direct interaction is probably either a part of the mechanism of Mn to prevent IR, or will produce bias, which needs to be further explored in our follow-up work.

Dysfunction of insulin signal transduction pathway directly contributing to hepatic IR and glucose metabolism disorder, the PI3K/Akt signal is a key component of insulin signal transduction pathway (23). During IR, the expression of *p*-Akt is decreased and the insulin signal cannot be transmitted, leading to an incapacitation for the regulation of downstream glucose metabolism. Some studies have shown that certain nutrients, such as the phytochemicals like quercetin, and mulberry anthocyanin extract, can significantly improve high glucose- or high FFAs-induced IR by increasing the phosphorylation of Akt (15,28,29). Micronutrients like zinc can also improve the inhibition of Akt phosphorylation induced by high FFAs (27). Consistently, this study showed that Mn treatment could upregulate the expression levels of *p*-Akt induced by PA, HG or insulin, suggesting that Mn treatment can improve the insulin signal transmission disorder in hepatic IR via promoting the activation of PI3K/Akt signaling.

GSK-3β and FOXO1 are both the downstream of PI3K/Akt signaling pathway, and play important roles in regulating glucose metabolism disorder (24). By increasing glycogen synthesis and inhibiting hepatic glucose output, the liver contributes to the disposal of enteral glucose loads, thus helping to maintain normal glucose tolerance (30). GSK-3β is a serine/threonine kinase that regulates the activity of glycogen synthase in the liver (31). When the insulin signaling pathway is activated, GSK-3β will be phosphorylated and inactivated to activate glycogen synthase and increase glycogen content in the liver (32). The present study showed that the phosphorylation of GSK-3β were all decreased in three IR models, while Mn treatment reversed the inhibitory effect of GSK-3β phosphorylation in all IR models (Fig. 2A-C). Furthermore, Mn treatment increased the intracellular glycogen content of three model groups (Fig. 2D-E). These results indicated that Mn treatment improved the IR hepatocytes glycogen synthesis and increased the intracellular glycogen content. On the other hand, during fasting, the liver provides glucose through gluconeogenesis pathway to maintain normal blood glucose and ensure the normal function of cells (30). FOXO1 is a nuclear transcription factor that induces the transcriptional expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, two key rate-limiting enzymes in the gluconeogenesis pathway, which can increase blood glucose (33). Once being phosphorylated, FOXO1 will translocate from nucleus to cytoplasm, thus inhibiting its transcriptional activity and translational expression, causing the decrease of gluconeogenesis (34). The results in the present study indicated that the phosphorylation of FOXO1 were all decreased in three different IR models (Fig. 3). While Mn treatment upregulated the FOXO1 phosphorylation, it reversed the inhibitory effect of FOXO1 phosphorylation in three IR models (Fig. 3). These data demonstrated that Mn treatment inhibited the gluconeogenesis of IR hepatocytes. This work thus far suggested that Mn treatment could effectively improve the abnormal glycogen synthesis and gluconeogenesis in IR hepatocytes through Akt/GSK3β/FOXO1 signaling pathway.

Oxidative stress plays an important role in contributing to the development of IR and type 2 diabetes (20). Loh et al. showed that physiological ROS can promote the sensitivity of host to insulin (35), but long-term stimulation of high-glucose, high-FFAs or hyperinsulinemia could cause the excessive production of ROS through mitochondrial pathway, ultimately leading to IR (36,37). Studies have demonstrated that the excessive production of ROS could activate oxidative stress-sensitive pathways, resulting in decreased IRS-1/2 tyrosine phosphorylation, which in turn causes decreased phosphorylation of Akt and its downstream signaling (such as GSK3β and FOXO1), and eventually inducing

impaired glycogen synthesis and aggravated gluconeogenesis in liver (14, 38). In the present study, the production of ROS was increased in IR HepG2 cells. As expected, Mn treatment reduced the high-level of ROS in three IR models. Based on the results obtained, we speculated that the mechanism of Mn in improving the IR hepatocyte glucose metabolism disorder probably partly through the inhibition of ROS production.

MnSOD is one of the typical Mn-dependent metalloenzymes, which is an important antioxidant enzyme in mitochondria. MnSOD has the activity of eliminating excessive ROS and reducing oxidative stress (16). However, the present study showed that Mn treatment did not affect the MnSOD activity in all three IR HepG2 cells, suggesting that the regulatory effects of Mn on ROS involved other mechanisms independent of MnSOD. Similar to our data, previous studies have shown that Mn treatment decreased the production of ROS in the liver and ameliorated endothelial cell dysfunction mediated by adiponectin, independent of MnSOD (10,11). Consequently, further studies are needed to determinate the specific mechanisms of Mn alleviating oxidative stress, improving hepatocyte IR and glucose metabolism. Certain studies have shown that miRNAs are involved in oxidative stress, IR regulation, and regulating insulin metabolic activities, including AKT, GSK-3β, etc. (39,40). Zheng et al. demonstrated that miR-195 was upregulated in the H2O2-induced oxidative stress cell model or hepatic tissue and retina tissue of STZ-induced diabetic rats and silencing of miR-195 significantly reduced ROS level in the heart of diabetic mice (41). Moreover, miR-1 (42) and miR-200c (43) have also been proved to be involved in regulating oxidative stress. Therefore, the miRNA regulation mechanism provides us with a new research perspective, which probably the specific regulation mechanism of Mn supplementation on glucose metabolism and oxidative stress.

Taken together, our work demonstrated for the first time that Mn treatment can improve IR induced by PA, HG or insulin in HepG2 hepatocytes, and revealed that the potential mechanisms are associated with the inhibition of ROS production and activation of Akt/GSK3β/FoxO1 signaling. These data suggested that proper supplement of dietary Mn may be an effective way to prevent IR, which provides new ideas and certain research basis for the research and treatment of type 2 diabetes *mellitus.*

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Obesidad y síndrome metabólico

Effect of MetioNac® in patients with metabolic syndrome who are at risk of metabolic dysfunction associated fatty liver disease: a randomized controlled trial

Efecto de MetioNac® en pacientes con síndrome metabólico que están en riesgo de padecer enfermedad de hígado graso asociado a disfunción metabólica: un estudio controlado aleatorizado

Elena Garicano Vilar[1], Sara Sanz Rojo[1], Sara López Oliva[1], Silvia Martínez[2], Ana Terrén Lora[1], Ismael San Mauro Martín[1]

[1]Research Centers in Nutrition and Health (CINUSA Group). Madrid. [2]Margan Biotech. Ajalvir, Madrid

Abstract

Introduction: metabolic syndrome comprises a combination of diabetes, high blood pressure, and obesity, and metabolic associated fatty liver disease (MAFLD) is associated with it.

Objective: to evaluate the effect of supplementation with *S*-adenosyl-L-methionine + *N*-acetylcysteine + thioctic acid + vitamin B6 (MetioNac®) for 3 months on lipidic and biochemical parameters in subjects with metabolic syndrome and at risk of MAFLD. The reduction in body weight and the oxidative stress markers malondialdehyde (MDA) and superoxide dismutase (SOD) were also evaluated.

Methods: patients with metabolic syndrome, at risk of MAFLD (FIB-4 < 1.30), and with an indication for weight reduction were recruited ($n = 15$). Control group followed a semipersonalized Mediterranean diet (MD) for weight reduction, according to the recommendations of the Spanish Society for the Study of Obesity (SEEDO). Experimental group, in addition to the MD, took three capsules of MetioNac® supplement per day.

Results: compared with the control group, subjects taking MetioNac® showed significant ($p < 0.05$) reductions in the levels of TG and VLDL-c, as well as in total cholesterol, LDL-c, and glucose levels. They also showed increased levels of HDL-c. Levels of AST and ALT decreased after the intervention with MetioNac®, but this decrease did not reach statistical significance. Weight loss was observed in both groups.

Conclusion: supplementation with MetioNac® may be protective against hyperlipidemia, insulin resistance, and overweight among metabolic syndrome patients. Further studies on this issue are needed in a larger population.

Keywords:

Metabolic syndrome. Metabolic associated fatty liver disease. *S*-adenosyl-L-methionine. *N*-acetylcysteine. Thioctic acid. Vitamin B6.

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Correspondence:

Ismael San Mauro Martín. Research Centre in Nutrition and Health (CINUSA Group). Paseo de la Habana, 43. 28036 Madrid, Spain
e-mail: info@grupocinusa.es

Resumen

Introducción: el síndrome metabólico se define como una combinación de diabetes, hipertensión arterial y obesidad, que se asocia con la enfermedad del hígado graso asociada a disfunción metabólica.

Objetivo: evaluar el efecto de la suplementación con *S*-adenosil-L-metionina + *N*-acetilcisteína + ácido tióctico + vitamina B6 (MetioNac®) durante 3 meses sobre parámetros lipídicos y bioquímicos en sujetos con síndrome metabólico y en riesgo de enfermedad del hígado graso asociada a disfunción metabólica. También se evaluaron la reducción del peso corporal y los marcadores de estrés oxidativo malondialdehído (MDA) y superóxido dismutasa (SOD).

Métodos: se reclutaron pacientes con síndrome metabólico, riesgo de enfermedad del hígado graso asociada a disfunción metabólica (FIB-4 < 1,30) y con indicación de reducción de peso ($n = 15$). El grupo control siguió una dieta mediterránea (DM) semipersonalizada para la reducción de peso, de acuerdo con las recomendaciones de la Sociedad Española para el Estudio de la Obesidad (SEEDO). El grupo intervención, además de la DM, tomó tres cápsulas diarias de MetioNac®.

Resultados: en comparación con el grupo de control, los sujetos que tomaron MetioNac® mostraron reducciones significativas ($p < 0.05$) en los niveles de TG y VLDL-c, así como en los niveles de colesterol total, LDL-c y glucosa. También mostraron niveles elevados de HDL-c. Los niveles de AST y ALT disminuyeron después de la intervención con MetioNac®, pero esta disminución no fue estadísticamente significativa. También se observó una pérdida de peso en ambos grupos.

Conclusión: la suplementación con MetioNac® puede proteger contra la hiperlipidemia, la insulinorresistencia y el sobrepeso en pacientes con síndrome metabólico. Sin embargo, es necesario realizar más estudios y seleccionar un mayor número de participantes.

Palabras clave:

Síndrome metabólico. Enfermedad del hígado graso asociada a disfunción metabólica. *S*-adenosil-L-metionina. *N*-acetilcisteína. Ácido tióctico. Vitamina B6.

INTRODUCTION

Metabolic syndrome is the name for a group of risk factors that raises the risk for heart disease and other health problems (1). Metabolic syndrome may be diagnosed if a subject meets three or more of the following criteria: a) being overweight or having excess fat around the waist; b) high triglyceride levels and low levels of high-density lipoprotein cholesterol (HDL-c); c) high blood pressure (consistently 140/90 mmHg or higher); and d) inability to control blood sugar levels (insulin resistance) (2). The incidence of metabolic syndrome often parallels the incidence of obesity and type 2 diabetes, so the global prevalence of metabolic syndrome can be estimated to be about one-quarter of the world population (2).

Metabolic associated fatty liver disease (MAFLD), before named as Non-alcoholic fatty liver disease (NAFLD) is a liver disease associated with metabolic syndrome and all its risk factors, obesity, insulin resistance, type 2 diabetes *mellitus*, hypertension, and hyperlipidemia (3).

Heart-healthy lifestyle changes, including dietary changes, weight control, management of stress, physical activity, and quitting smoking, are the first line of treatment for metabolic syndrome. Statins, aspirin, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers prescribed in evidence-based doses may be helpful as adjuncts to lifestyle changes in the treatment of metabolic syndrome, but they do not represent alternatives (4). Moreover, although agents are being tested in clinical trials for their ability to reverse the effects of fatty liver, the only proven treatments are weight loss and increased physical activity, which are hard to sustain (5). Among the dietary intervention measures and lifestyle changes contemplated by the latest consensus document for the management of this disease is the Mediterranean diet (MD) (evidence B1) (6).

S-adenosyl-L-methionine, *N*-acetylcysteine, thioctic acid, and pyridoxine (vitamin B6) are four powerful antioxidants. *S*-adenosyl-L-methionine donates methyl groups in essential protein, lipid, and nucleic acid methylation reactions (7). *N*-acetylcysteine has an antioxidant and protective action. It is a precursor of cysteine in the hepatic transsulfuration pathway, and it donates reducing groups and acts against oxidized free radicals (8). Thioctic acid is a short chain fatty acid that stimulates the glutamate-cysteine ligase enzyme that synthesizes glutathione from cysteine (9). Thioctic acid mediates the recovery of reduced glutathione from oxidized glutathione and, thanks to its thiol group, neutralizes radicals and recovers glutathione and other antioxidants, such as Q-10 and vitamins C and E (10). Pyridoxine is a water-soluble vitamin that must be replaced with the diet daily. It is a cofactor that induces the hepatic transsulfuration pathway by activating the cystathionine-β-synthase and cystathionine γ-lyase enzymes. This prevents the increase in methionine and contributes to the normal metabolism of homocysteine (11).

The main aim of this study was to evaluate the effect of supplementation with *S*-adenosyl-L-methionine + *N*-acetylcysteine + thioctic acid + vitamin B6 (MetioNac®) for 3 months on lipidic [total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), very low density lipoprotein cholesterol (VLDL-c)] and biochemical [glucose, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and γ-glutamyl transpeptidase (GGT)] parameters in subjects with metabolic syndrome and at risk of MAFLD. The reduction in body weight and the oxidative stress markers malondialdehyde (MDA) and superoxide dismutase (SOD) were also evaluated.

METHODOLOGY

DESIGN

This was a randomized pilot clinical trial carried out by the Nutrition and Digestive System Units of Hospital Ruber Internacional Paseo de la Habana (Grupo Quirón), with approval, on February 17, 2020, from the Research Ethics Committee with medicinal products of Grupo Hospitalario QuirónSalud-Catalunya. It complies with the guidelines indicated by Good Clinical Research Practices, the Biomedical Research Law 14/2007, and the Declaration of Helsinki and its subsequent revisions (Fortaleza, Brazil, 2013). The confiden-

tiality of patient data was respected in accordance with the Organic Law 3/2018, of December 5, on the Protection of Personal Data and Guarantee of Digital Rights. Informed written consent was obtained from all participants, before the study procedures.

SUBJECTS

Men and women between the ages of 45 and 65 years, with metabolic syndrome, at risk of MAFLD (FIB-4 < 1.30), and with an indication for weight reduction were recruited. Metabolic syndrome was considered present when abdominal circumference was ≥ 94 cm in men and ≥ 80 cm in women and when two or more of the following criteria were also met: triglycerides ≥ 150 mg/dl or 1.7 mmol/l, HDL-c < 40 mg/dl in men and < 50 mg/dl in women, systolic pressure ≥ 130 and/or diastolic pressure ≥ 85 mmHg, and fasting glycemia ≥ 100 mg/l (5.6 mmol/l) or type II diabetes.

Patients with an indication for bariatric surgery, hepatitis C or B virus infection, uncontrolled type I or type II diabetes (>127 mg/dl or 6.5 % HbAc1), fibrosis stage F2 or higher, or diagnosis of a chronic disease other than type 2 diabetes, hypertriglyceridemia, or hypertension were excluded. Also excluded were (a) patients who received chronic pharmacological treatment or had any other pathology requiring medical intervention during the duration of the study, except for the purposes of glycemic control or reduction of triglyceride levels or blood pressure; (b) patients who were receiving drug treatment for fibrosis; and (c) patients who failed to express an intention to abstain from alcohol or to adhere to the dietary and exercise recommendations. Pregnant and lactating patients could not participate.

After assessment at the baseline visit, patients meeting all the inclusion and exclusion criteria were randomly divided into two groups. Group A (control) followed a semipersonalized MD for weight reduction, according to the recommendations of the Spanish Society for the Study of Obesity (SEEDO). Group B, in addition to following the MD, took three capsules of MetioNac® supplement per day, two in the morning and one in the evening. Patients returned to the clinic for a follow-up visit at week 4 and at the end of the study. The intervention lasted for 3 months.

SAMPLE SIZE CALCULATIONS

The basal glucose levels (with a reference range of 75-106 mg/dl with a variance of 31 mg/dl) was expected to improve by 22-25 mg/dl. A dropout rate of 5 % was expected. The calculated sample size per group needed to be 19, which was rounded up to ≥ 20, to achieve a power of ≥ 75 % with $\alpha = 0.05$ and a confidence interval of 95 %. Randomization was carried out using a random number table and an assignment group table.

FOOD SUPPLEMENT

MetioNac® is a food supplement that combines *S*-adenosyl-L-methionine (200 mg), *N*-acetylcysteine (100 mg), thioctic acid (75 mg), and vitamin B6 (0.65 mg). MetioNac® was formulated to help the synthesis of glutathione from intermediate metabolites that intervene in the metabolic pathways of hepatic methylation and transsulfuration. MetioNac® was dispensed in tablets formulated with LUBRITAB®, a patented extended-release excipient for direct compression formulas.

DIET

In addition to the administration of MetioNac®, participants were given a semipersonalized MD. This diet was adjusted to the intolerances and allergies of each person. Energy expenditure was calculated using the Harris-Benedict equation (12) to determine the caloric intake. As recommended by the Spanish Society for the Study of Obesity (SEEDO), diets with a reduction of 500–1000 kcal/day were provided for weight loss (13). Four diets were designed, one for each week, and different interchangeable options were given in each diet.

DATA COLLECTION

Liver profile biomarkers, including AST, ALT, alkaline phosphatase, GGT, and albumin, were measured. Metabolic response was monitored by abdominal circumference, HDL-c, LDL-c, and VLDL-c levels, triglycerides, blood pressure, and fasting glucose. Oxidative stress markers such as MDA and SOD were measured. The NAFLD fibrosis score (NFS) was also recorded. The NFS (14) is a noninvasive scoring system based on several laboratory tests that help to estimate the amount of scarring in the liver. The NFS is based on the following formula: $-1.675 + 0.037 \times$ age (years) $+ 0.094 \times$ BMI (kg/m^2) $+ 1.13 \times$ impaired fasting glucose/diabetes (yes = 1, no = 0) $+ 0.99 \times$ AST/ALT ratio $- 0.013 \times$ platelet ($\times 10^9$/l) $- 0.66 \times$ albumin (g/dl). The NFS results are classified as follows: NFS < -1.455 = F0-F2 (no, mild, or moderate fibrosis); NFS -1.455 to 0.675 = indeterminate score; and NFS > 0.675 = F3-F4 (severe fibrosis or cirrhosis). Weight and body composition were measured by bioimpedance with a Tanita BP601 in accordance with standardized recommendations. The differences between the aforementioned biomarkers and indices were measured at the beginning and at the end of the intervention.

DATA ANALYSIS

SPSS 27.0 software was used to analyze the results. All data acquired, including age, sex, anthropometric measurements, and clinical markers, were descriptively analyzed. Means and standard deviations were calculated for quantitative variables and frequencies for qualitative variables. The existence of statistically significant differences ($p < 0.05$) between the qualitative variables was established after the completion of the chi-square test and/or ANOVA.

RESULTS

DESCRIPTION OF THE STUDY POPULATION

Between March 2021 and June 2021, 27 patients with metabolic syndrome and at risk of NAFLD were randomly assigned to receive either just a semipersonalized MD (control group) or MetioNac® in addition to a semipersonalized MD (MetioNac® group). In the control arm, five patients completed the study, with nine lost to follow-up. In the MetioNac® arm, ten patients completed the study, with three dropping out (Fig. 1).

Seventy-three percent of the study population were women. The two groups, control and MetioNac®, had similar baseline characteristics ($p > 0.05$) (Table I).

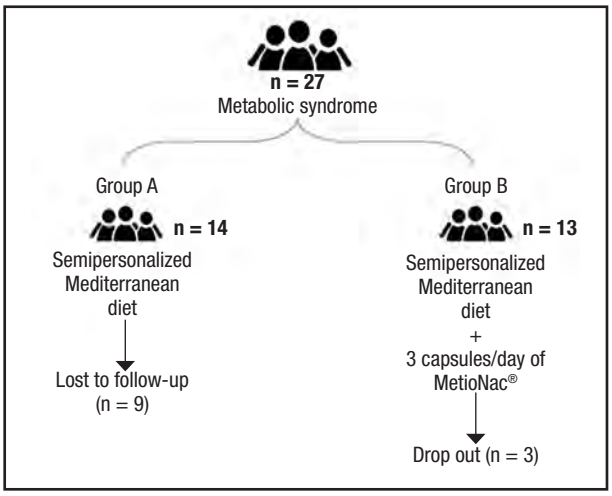

Figure 1.
Study design.

EFFECT OF METIONAC® ON BODY WEIGHT AND THE LIPIDIC PROFILE

In this study, weight loss was programmed through an MD. The control group displayed a significant reduction ($p = 0.026$) in weight (-4.1 ± 2.7 kg) after following the MD diet; the MetioNac® group also succeeded in achieving weight loss (-2.9 ± 6.569 kg) but the reduction did not reach significance ($p > 0.05$) (Table II).

Regarding lipidic profile, patients who were taking the MetioNac® supplement showed reductions in total cholesterol (TC) and LDL-c levels from 206.6 ± 37.3 to 192.4 ± 35.2 mg/dl and from 127.0 ± 26.3 to 119.0 ± 35.2 mg/dl, respectively (Fig. 2). In contrast, control subjects displayed increased TC and LDL-c levels (Table II). Moreover, patients taking MetioNac® had a significant reduction ($p = 0.048$) in VLDL-c (Table II; Fig. 2) and TG levels ($p = 0.043$) (Fig. 2). In addition, in MetioNac® group levels of HDL-c increased by 1.7 ± 9.6 mg/dl after treatment.

EFFECT OF METIONAC® ON SERUM GLUCOSE, AST, ALT, AND GGT LEVELS

Secondary outcome measures were changes in serum glucose, albumin, AST, ALT, and GGT levels. In the present study, supplementation with MetioNac® helped reduce the serum glucose levels, while in the control group, glucose levels continued to rise (Table II; Fig. 2).

We also observed decreased levels of AST and ALT after the intervention with MetioNac®, although the reductions were higher in the control group (Table II). Regarding GGT levels, only the control group benefited from a decrease (71.4 ± 84.9 to 52.2 ± 50.5 U/l) (Table II).

Table I. Baseline demographic, anthropometric, and physiological characteristics and exercise in the control and MetioNac® groups

	Control (n = 5)		MetioNac® (n = 10)		
	Mean	**SD**	**Mean**	**SD**	***p* value**
Demographics					
Age (years)	49.8	4.494	52.4	7.531	0.494
Female patients (%)	80		70		
Anthropometrics					
Height (cm)	168.2	8.643	164.6	10.167	0.511
Weight (kg)	87.1	14.734	85.1	17.184	0.825
Total fat (%)	40.3	8.703	34.1	14.287	0.397
Visceral fat (%)	10.8	2.588	10.6	4.904	0.934
Muscle mass (%)	49.5	9.113	46.8	19.845	0.773
Bone mass (kg)	2.6	0.460	2.5	1.035	0.796
Waist circumference (cm)	103.4	8.142	95.0	35.528	0.617

(Continues on next page)

Table I (Cont). Baseline demographic, anthropometric, and physiological characteristics and exercise in the control and MetioNac® groups

	Control (n = 5)		MetioNac® (n = 10)		
	Mean	**SD**	**Mean**	**SD**	***p* value**
Physiological parameters					
Systolic pressure (mmHg)	130.4	18.393	120.0	44.487	0.629
Diastolic pressure (mmHg)	79.8	5.167	75.7	27.657	0.752
Exercise					
Exercise (days/week)	3.0	3.317	2.7	3.057	0.864
Exercise time (min/day)	36.0	32.863	39.0	44.833	0.897

SD: standard deviation.

Table II. Baseline and final biochemical characteristics and NAFLD fibrosis score (NFS) and their paired differences after treatment

	Control group			MetioNac® group			
	Baseline (B)	**Final (F)**		**Baseline (B)**	**Final (F)**		
	Mean (SD)	**Mean (SD)**	**P value**	**Mean (SD)**	**Mean (SD)**	***p* value**	***p* value**
NFS	-5.6 (0.5)	-5.2 (0.7)	0.197	-5.3 (1.1)	-5.2 (1.0)	0.897	
Difference (B-F)	-0.4 (0.5)			-0.1 (0.8)			0.464
Weight (kg)	87.1 (14.7)	83.0 (12.7)	0.026*	85.1 (17.2)	82.2 (14.7)	0.200	
Difference (B-F)	4.1 (2.7)			2.9 (6.6)			0.689
Total cholesterol (mg/dl)	185.8 (31.4)	189.2 (30.4)	0.520	206.6 (37.3)	192.4 (35.2)	0.266	
Difference (B-F)	-3.4 (10.8)			14.2 (37.9)			0.199
Triglycerides (mg/dl)	122.2 (19.7)	111.6 (26.1)	0.359	140.5 (62.6)	100.8 (46.0)	0.043*	
Difference (B-F)	10.6 (22.9)			39.7 (53.2)			0.269
HDL cholesterol (mg/dl)	52.2 (13.8)	50.2 (15.7)	0.178	51.5 (9.2)	53.2 (7.3)	0.588	
Difference (B-F)	2.0 (2.7)			-1.7 (9.6)			0.420
LDL cholesterol (mg/dl)	109.2 (28.5)	116.6 (21.3)	0.180	127.0 (26.3)	119.0 (35.2)	0.646	
Difference (B-F)	-7.4 (10.2)			8.0 (37.8)			0.253
VLDL cholesterol (mg/dl)	24.4 (4.0)	22.4 (5.0)	0.399	28.1 (12.7)	20.2 (9.0)	0.048*	
Difference (B-F)	2.0 (4.7)			7.9 (11.0)			0.276
Glucose (mg/dl)	95.8 (10.1)	100.8 (11.0)	0.026*	101.4 (14.7)	97.5 (9.0)	0.405	
Difference (B-F)	-5.0 (3.2)			3.9 (14.1)			0.194
Albumin (g/dl)	4.5 (0.3)	4.6 (0.2)	0.634	4.5 (0.2)	4.6 (0.3)	0.057	
Difference (B-F)	-0.1 (0.3)			-0.1 (0.189)			0.560
AST (U/l)	24.4 (14.1)	19.6 (3.1)	0.404	28.8 (14.4)	25.8 (7.2)	0.722	
Difference (B-F)	4.8 (11.5)			3.0 (12.9)			0.800
ALT (U/l)	30.4 (26.1)	22.2 (9.4)	0.380	37.9 (19.8)	32.4 (13.3)	0.414	
Difference (B-F)	8.2 (18.6)			5.4 (18.9)			0.797
Alkaline phosphatase (U/l)	97.4 (36.4)	91.4 (19.7)	0.484	83.3 (31.5)	86.0 (29.6)	0.576	
Difference (B-F)	6.0 (17.4)			-2.7 (13.7)			0.323
GGT (U/l)	71.4 (84.9)	52.2 (50.5)	0.290	56.7 (48.9)	60.4 (81.6)	0.646	
Difference (B-F)	19.2 (35.2)			-3.7 (43.1)			0.325
MDA (mcmol/l)	0.7 (0.2)	1.1 (0.3)	0.016*	0.8 (0.6)	0.9 (0.5)	0.463	
Difference (B-F)	-0.4 (0.2)			-0.1 (0.4)			0.198
SOD (U/g Hb)	1431.0 (268.7)	1474.6 (191.6)	0.768	1336.6 (415.6)	1365.5 (298.6)	0.851	
Difference (B-F)	-43.6 (309.0)			-28.9 (473.2)			0.951

*AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT; γ-glutamyl transpeptidase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low density lipoprotein; NAFLD: nonalcoholic fatty liver disease; MDA: malondialdehyde; SOD: superoxide dismutase. *Statistically significant ($p < 0.05$).*

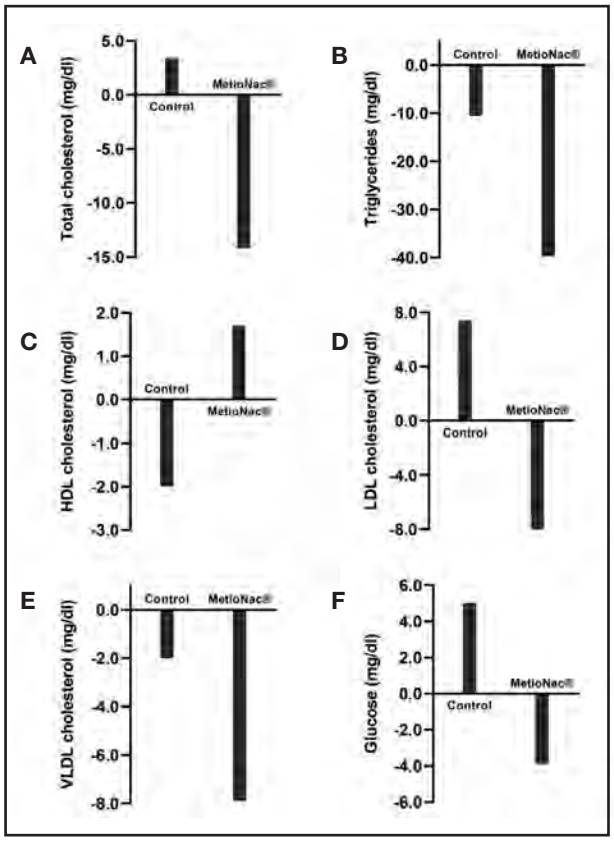

Figure 2.

Improvement in lipidic parameters (TC, TG, HCL-c, LDL-c, and VLDL-c) and glucose level after the intake of MetioNac®.

EFFECT OF METIONAC® ON MDA AND SOD LEVELS

The oxidative stress markers were also evaluated. We did not observe that either supplementation with MetioNac® or the MD lowered the levels of MDA or SOD (Table II).

EFFECT OF METIONAC® ON THE NAFLD FIBROSIS SCORE (NFS)

Changes in the NFS (Table II) were also recorded. At the end of the follow-up, we classified the patients into three subgroups according to the pattern of progression of liver fibrosis by comparing the NFS at baseline to the NFS at the end of the follow-up period. Most patients were in the progressive fibrosis (60 %) group, while 33.3 % were in the regressive fibrosis group and 6.7 % remained stable.

DISCUSSION

The first-line approach to control metabolic syndrome is weight control and exercise. The MD with components such as fish, nuts, fruits, olive oil, whole grains, and vegetables was declared by the United Nations Educational, Scientific and Cultural Organization (UNESCO) to be a diet with the ability to preserve the state of health and improve longevity (15). The MD pattern have been found to be inversely related to the body mass index (16). The MD has also been proposed as an effective diet to lower the fat around the mid-section (17). In this study, in which weight loss was programmed through an MD, the control group displayed a significant reduction in weight (-4.1 ± 2.7 kg) whereas the MetioNac® group, although also succeeded in achieving weight loss (-2.9 ± 6.569 kg), did not reach significance.

Metabolic syndrome is characterized by elevated triglycerides and reduced HDL-c (2), and although individuals with the metabolic syndrome often have average levels of LDL-c, they may have qualitative abnormalities, such as small dense LDL particles (18). Since NAFLD is a hepatic manifestation of metabolic syndrome, excessive cholesterol deposition in the liver is presumed to be a risk factor for disease progression (19). The lifestyle changes recommended by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) for control of dyslipidemia (i.e., elevated levels of triglycerides and decreased levels of HDL-C) in patients with metabolic syndrome include (a) reduced intake of saturated fats and dietary cholesterol, (b) intake of dietary options to enhance lowering of LDL-c, (c) weight control, and (d) increased physical activity (20). A study by Babio et al. (17) suggested that the MD may reverse metabolic syndrome, improve the conglomeration of markers that includes high cholesterol, triglycerides, and blood pressure, and reduce insulin resistance. In our study, patients who were taking the MetioNac® supplement showed reductions in total cholesterol (TC) and LDL-c levels from 206.6 ± 37.3 to 192.4 ± 35.2 mg/dl and from 127.0 ± 26.3 to 119.0 ± 35.2 mg/dl, respectively. In contrast, control subjects displayed increased TC and LDL-c levels. Moreover, patients taking MetioNac® had a significant reduction in VLDL-c levels. Excess TG accumulation in the arteries increases the risk of stroke, heart attack, and heart disease (21), while TG accumulation in the liver is a hallmark of MAFLD (22). Since TG is a potential source of oxidative stress, it has been considered to be a "bad fat" (22). We found that MetioNac® was able to reduce TG levels significantly, meaning it may represent a good option to tackle the latter issue. Summaries of the lipid profile in metabolic syndrome also show depleted plasma HDL-c (23). This was also observed in our MetioNac® group, in which levels of HDL-c increased by 1.7 ± 9.6 mg/dl after treatment. In this context, Tortosa et al. (24) previously concluded that HDL-c levels were higher among participants with metabolic syndrome who better adhered to the Mediterranean food pattern. Nevertheless, lipid profile after treatment has to be verified simultaneously because the association between lipid profile and treatment efficacy has not yet been determined.

On the other hand, there are several clinical determinants of progression of fibrosis in MAFLD. The presence of insulin resistance is one of the major predictors of fibrosis progression (25) as well as being an indicator for metabolic syndrome (2). Systemic insulin resistance is characterized by the inability of

insulin to reduce blood glucose levels appropriately (26). As the production rates of glucose are highly aberrant in hepatocytes in the presence of a high insulin level, this is characterized as a sign of hepatic insulin resistance (27). The results of the present study showed that supplementation with MetioNac® helped reduce the serum glucose levels, while in the control group, glucose levels continued to rise. Greater adherence to the MD was associated with a lower degree of insulin resistance (28), which may explain the reductions in glucose levels in our study. In a randomized, cross-over intervention trial, Ryan et al. (29) showed that, compared with a low-fat high-carbohydrate diet, MD improved insulin sensitivity and hepatic steatosis in patients with biopsy-proven MAFLD in the absence of weight loss.

Other clinical determinants of MAFLD diagnosis and fibrosis progression rate are ALT, AST, and GGT levels above the upper limits of normal (30). We observed higher reduction of AST and ALT levels in the control group and, regarding GGT levels, only the control group benefited from a decrease (71.4 ± 84.9 to 52.2 ± 50.5 U/l). In a study by Mansour-Ghanaei et al. (31), the mean values of ALT, AST, and GGT in the NAFLD group were higher than those in the non-MAFLD group. The authors also observed that, when they compared the changes in biochemical parameters with different degrees of MAFLD, there was a relationship between GGT ($p = 0.004$), ALT ($p = 0.007$), and AST ($p < 0.001$) and the severity of fatty liver.

During the process of lipid peroxidation, a wide range of pre-inflammatory products are produced that result in progression of the disease. One of these by-products is MDA, which is a common marker for oxidative stress (32). In a study by Moreto et al. (33), subjects with higher plasma MDA showed a higher prevalence of MetS and higher values of waist circumference, glucose, triglycerides, and γ-glutamyl transferase. An increase in serum oxidative markers (e.g., MDA) paralleled by a decrease in the activity of antioxidants has also been observed in patients with MAFLD (34). Varma et al. (35) demonstrated plasma MDA levels to be significantly increased in diabetic or obese MAFLD patients as compared with healthy controls. Interestingly, Kumar et al. (36) also demonstrated how patients with MAFLD have significantly higher levels of MDA and other oxidative markers in comparison to chronic viral hepatitis patients. According to Kani et al. (37), dietary intervention followed by weight reduction leads to a reduction in serum MDA. Specifically, the Dietary Approaches to Stop Hypertension (DASH) diet, which is abundant in antioxidants and is designed to be rich in fruits, vegetables, and whole grains, led to a reduction in the serum levels of inflammatory markers, including MDA (38). However, we did not observe that either supplementation with MetioNac® or the MD, which is similar in concept to the DASH diet, lowered the levels of MDA. SOD, another plasma oxidative stress-related parameter, followed the same trend. When other dietary compounds such as vitamins E and C were tested by Zelber-Sagi et al. (39) in the search for an association between these and MDA levels, the authors found an inverse association between dietary vitamin E intake and serum MDA level.

Finally, at the end of the follow-up, we classified the patients into three subgroups according to the pattern of progression of liver fibrosis. Most patients were in the progressive fibrosis (60 %) group, while 33.3 % were in the regressive fibrosis group and 6.7 % remained stable. Treeprasertsuk et al. (39) classified MAFLD patients similarly and observed that most patients were in the stable fibrosis (60 %) and progressive fibrosis (37 %) groups, with only 3 % in the regressive fibrosis group, after the use of statins and metformin during the follow-up period. The NFS uses two diagnostic cutoffs, a low cutoff score (-1.455) to exclude advanced fibrosis (negative predictive value 88 %-93 %) and a high cutoff score (0.676) to diagnose advanced fibrosis (positive predictive value 82 %-90 %) (14), leaving one-third of patients in a "gray zone" where liver biopsy is still required. In our study, all patients remained below the low cutoff score. However, it is worth mentioning that the MD has shown an inverse relationship with MAFLD prevalence (40), that it reduces liver steatosis (29), and that patients in the present study could have benefited from it.

CONCLUSIONS

Early recognition and proper management of metabolic syndrome and MAFLD are of major importance. Various indicators such as lipid profile, AST, ALT, GGT, plasma glucose, and fasting insulin level play a significant role in metabolic syndrome and MAFLD. These indicators assist in understanding the severity and prognosis of the diseases, and can offer a basis for early intervention. However, none of the currently available biomarkers have sufficient accuracy to enable diagnosis, which is why predictive scores play an important role in providing a cutoff capable of distinguishing between absence of fibrosis and presence of advanced fibrosis in the context of MAFLD.

Given the complex physiopathology of metabolic syndrome and MAFLD, it is unlikely that one drug by itself will deliver significant clinical outcomes. On the other hand, combinations of components like MetioNac® (*S*-adenosyl-L-methionine, *N*-acetylcysteine, thioctic acid, and vitamin B6) with different targets could perhaps aid in improving metabolic syndrome and, in consequence, risk of MAFLD. The ultimate goal of this approach should be to establish an opportune treatment that decreases or halts disease progression and improves prognosis.

LIMITATIONS

The promoter and CRO are aware of the pilot and exploratory nature of the study. The reason for the high dropout rate was the COVID-19 pandemic as the study was conducted in parallel with the 3 months lockdown followed by intermittent mobility restrictions for 1 year. Other relevant limitations were the sample size, the lack of measurement of an abdominal ultrasound or FibroScan to confirm the presence of liver fibrosis and assess the potential improvement of treatment, instead of measuring and evaluating MAFLD risk biomarkers.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Mini nutritional assessment-short form test: criterion and predictive validity in older adults from a long-term care unity

Versión corta del test de valoración nutricional: validez de criterio y predictiva en adultos mayores de una unidad de cuidados de larga duración

Ana Meneses[1], Cláudia Silva[2], Cíntia Pinho-Reis[3], Rita Soares Guerra[4]

[1]Faculdade de Ciências da Saúde. Universidade Fernando Pessoa. Porto, Portugal. [2]Instituto de Investigação, Inovação e Desenvolvimento Fernando Pessoa (FP-I3ID). Biomedical and Health Sciences (FP-BHS). Faculdade Ciências da Saúde. Universidade Fernando Pessoa. Porto, Portugal. [3]Instituto de Investigação, Inovação e Desenvolvimento Fernando Pessoa (FP-I3ID). Unidade de Cuidados Continuados - Fundação Fernando Pessoa. Hospital-Escola da Universidade Fernando Pessoa. São Cosme, Portugal. [4]Instituto de Investigação, Inovação e Desenvolvimento Fernando Pessoa (FP-I3ID). Faculdade Ciências da Saúde. Universidade Fernando Pessoa. Laboratório Associado em Energia, Transportes e Aeroespacial. Instituto de Ciência e Inovação em Engenharia Mecânica e Engenharia Industrial (LAETA, INEGI). Campus da FEUP. Porto, Portugal

Abstract

Introduction: the Mini Nutritional Assessment Short-Form test (MNA-SF) is valid for malnutrition screening and diagnosis of older adults, but few studies evaluated if it predicts hospital length of stay (LOS) and were conducted in long-term care units.

Objective: this study aims to evaluate the criterion and predictive validity of MNA-SF.

Methods: a prospective observational study was conducted in older adults from a long-term care unity. MNA Long Form test (MNA-LF) and MNA-SF were applied, at admission and at discharge. Percentage of agreement, kappa and intra-class correlation coefficients (ICC) were determined. Sensitivity and specificity of MNA-SF were calculated. The independent association of MNA-SF with LOS (adjustment for Charlson index, sex, age, education) was assessed by Cox regression analysis [results presented as hazard ratio (HR) and 95 % confidence intervals (CI)].

Results: this sample is composed of 109 older adults (62.4 % women), aged 66-102 years. According to MNA-SF at admission, 7.3 % of participants presented normal nutrition status, 55.1 % were at risk of malnutrition and 37.6 % were malnourished. Agreement, kappa and ICC were 83.5 %, 0.692 and 0.768 at admission, and 80.9 %, 0.649 and 0.752 at discharge. MNA-SF sensitivities were 96.7 % at admission and 92.9 % at discharge; specificities were 88.9 % and 89.5 %, at admission and at discharge. According to MNA-SF at discharge, being at risk of malnutrition (HR = 0.170, 95 % CI: 0.055-0.528) or malnourished (HR = 0.059, 95 % CI: 0.016-0.223) lowered the odds of being discharged to home or to usual residence.

Conclusions: a high agreement was found between MNA-LF and MNA-SF. MNA-SF revealed high sensitivities and specificities. An independent association was found between risk of malnutrition or malnutrition by MNA-SF and LOS. The use of MNA-SF instead of MNA-LF should be considered in long-term care units given its criterion and predictive validity.

Keywords:

Malnutrition. Risk of malnutrition. Hospital length of stay. Survival analysis.

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Correspondence:

Rita Soares Guerra. Faculdade de Ciências da Saúde. Universidade Fernando Pessoa. Rua Carlos da Maia, 296. 4200-150 Porto, Portugal
e-mail: ritaguerra@ufp.edu.pt

Resumen

Introducción: la versión corta del test de valoración nutricional (MNA-SF) es válida para la evaluación del riesgo nutricional y de la desnutrición de los adultos mayores, pero pocos estudios han evaluado si predice la duración de la estancia hospitalaria (LOS) y se realizaron en unidades de cuidados de larga duración.

Objetivo: evaluar la validez predictiva y de criterio del MNA-SF.

Métodos: se realizó un estudio observacional prospectivo en adultos mayores de una unidad de cuidados de larga duración. Se aplicaron el formulario largo del MNA (MNA-LF) y el MNA-SF al ingreso y al alta. Se determinó el porcentaje de concordancia, kappa y coeficientes de correlación interclase (CCI). Se calcularon la sensibilidad y la especificidad del MNA-SF. Se evaluó la asociación independiente del MNA-SF con la LOS (ajustada por: índice de Charlson, sexo, edad y educación) mediante análisis de regresión de Cox (resultados: *hazard ratio* [HR] e intervalos de confianza [IC] del 95 %).

Resultados: esta muestra está compuesta por 109 adultos mayores (62,4 % mujeres), con edades de 66-102 años. Según el MNA-SF al ingreso, el 7,3 % de los participantes estaban bien nutridos, el 55,1 % estaban en riesgo nutricional y el 37,6 % estaban desnutridos. La concordancia, kappa y CCI fueron del 83,5 %, del 0,692 y del 0,768 al ingreso y del 80,9 %, del 0,649 y del 0,752 al alta. Las sensibilidades del MNASF fueron de 96,7 % al ingreso y de 92,9 % al alta; las especificidades fueron de 88,9 % y de 89,5 %, al ingreso y al alta. Según el MNA-SF al alta, estar en riesgo nutricional (HR = 0,170, IC 95 %: 0,055-0,528) o desnutrido (HR = 0,059, IC 95 %: 0,016-0,223) redujo las probabilidades de ser dado de alta al domicilio o la residencia habitual.

Conclusiones: se encontró una gran concordancia entre el MNA-LF y el MNA-SF el MNA-SF reveló grandes sensibilidad y especificidad. Se encontró una asociación independiente entre la desnutrición o el riesgo nutricional por MNA-SF y la LOS. El uso de MNA-SF en lugar de MNA-LF debe considerarse en unidades de cuidados de larga duración dada su validez predictiva y de criterio.

Palabras clave:

Desnutrición. Riesgo nutricional. Duración de la estancia hospitalaria. Análisis de supervivencia.

INTRODUCTION

Malnutrition is a clinical situation characterised by an "inadequate supply of energy, protein or other nutrients necessary for the maintenance and repair of tissues. Usually, this condition occurs due to inadequate food intake and / or increased energy and / or nutritional needs". Malnutrition can lead to an altered body composition, specifically regarding weight and muscle mass loss, but also to a decrease in motor and cognitive functions (1). Risk of malnutrition, which often results from a combination of weight loss, reduced food intake and disease activity, is itself a condition that should be assessed and documented in clinical care (2).

Malnutrition and also risk of malnutrition are prevalent among older adults. A review study in a sample of 4507 older adults from 12 different countries, showed that the prevalence of malnutrition or its risk was 38 % in the community, 86 % at the hospital and 92 % in rehabilitation units (3). More recent data from hospitalised patients shows that malnutrition frequency in older adults varies from 9.4 % to 17.3 % and the frequency of malnutrition risk varies from 55.1 % to 56.4 % (4,5).

Data from 2015 by the National Network of Continuing Care in Portugal indicates that between 8 % to 20 % of admissions in different types of Continuing Care Units were due to malnutrition (6). This condition results into an increased likelihood of mortality: malnourished patients have a mortality rate of 12 %, whereas the mortality rate of patients without malnutrition is 1 % (7).

In fact, it has been consistently demonstrated that malnutrition and malnutrition risk predispose the older population to an increased risk of mortality but also to an increased risk of morbidity, infection, longer hospital length of stay (LOS), and a decreased functional capacity (8,9), being consequently associated to a worse quality of life (10). Taking into consideration all these negative effects, together with the high frequencies described in this population, the early identification of malnutrition or its risk is extremely important.

The validity of malnutrition diagnostic and screening tools is essential for clinical practice since it refers to the ability of the tool to correctly identify a patient who does or does not have malnutrition or risk of malnutrition (11). Moreover, validity must be kept in mind when assessing the performance of a tool in the population for which it is intended to be used (12,13). This can be done by assessing both the criterion and the predictive validity (13). Criterion validity comprehends the comparison of the tool's assessment of nutrition status with that obtained using a gold standard technique. The ability of the tool to forecast clinical events is referred to as predictive validity (12,13).

The Mini Nutritional Assessment is a well validated tool that allows malnutrition screening, as well as its diagnosis in older adults, aged 65 years or over (14). This tool exists in two forms: Mini Nutritional Assessment-Long Form test (MNA-LF) (15) and Mini Nutritional Assessment-Short Form test (MNA-SF) (16). As the name implies, the application of MNA-SF is faster and easier and despite being less complete when compared to MNA-LF, many healthcare professionals prefer to use it to assess the nutritional status of older adults in clinical practice and in the hospital setting (17). According to its authors, the MNA-SF maintains the validity and accuracy of the original questionnaire (17).

The criterion validity of MNA-SF was extensively demonstrated in several settings such as community, hospital, and rehabilitation. Particularly among hospitalised patients, a substantial agreement was reported between MNA-LF and MNA-SF by kappa statistics (kappa = 0.7) (18), whereas sensitivity values of MNA-SF, based on their classification by MNA-LF, were reported to vary between 89.0 and 95.6 %, and specificities between 79.1 and 82.0 % (17). Also, in a previous study conducted among hospitalised older adults, MNA-SF was able to predict very long LOS (19).

Nevertheless, few studies evaluated the ability of MNA-SF in predicting clinical outcomes associated with malnutrition, such as LOS or mortality. Moreover, despite the vastness of criterion validation studies in the hospital setting, there is scarcity of studies conducted specifically in long-term care units. The long-term care unit is a hospitalization unit with duration greater than

90 days. It is aimed for patients with chronic illness with different levels of dependency and different degrees of complexity who do not meet the criteria to be cared at home or in another type of hospital service. The long-term care unit provides social support and maintenance of health care status to prevent and delay the worsening of the dependency process, favouring comfort and quality of life. It also ensures: maintenance of functional rehabilitation, cognitive stimulation activities, permanent nursing care, regular medical care, prescription and administration of medication, food and nutrition support, psychological support, periodic physiatrist control, physiotherapy and occupational therapy; sociocultural animation; and hygiene. The long-term care unit can provide hospitalization for temporary situations, resulting from difficulties of family support, lack of social support and the caregiver need for rest up to 90 days a year (20).

The present study aims to evaluate the criterion and predictive validity of MNA-SF through its independent association with LOS in a sample of older adults hospitalised in a long-term care unit.

METHODS

A retrospective observational study was conducted in a long-term care unity of a university hospital between January 2017 and March 2021.

Eligibility criteria for this study were admission to a long-term unit of a university hospital between January 2017 and March 2021 but whose expected discharge was March 2021, age ≥ 65 years old, and complete information regarding MNA-LF and MNA-SF at admission. Patients younger than 65 years old and with missing data for MNA-SF and for MNA-LF were excluded from the study.

The study protocol was approved by the Ethics Committee of a University Hospital: Hospital-Escola da Fundação Fernando Pessoa (Opinion No. 49).

Information that allowed for this study completion was retrieved from patients' clinical file. The data collected included socio-demographic information: age, sex, education; clinical information: clinical diagnoses according to the International Statistical Classification of Diseases and Related Health Problems (IC-11) (21); LOS in days; discharge destination: home or usual residence, death, transfer, discharge against medical advice, other destination; anthropometry: weight (kg) and height (cm); nutritional therapy: diet, oral nutritional supplements, enteral nutrition, or no nutritional therapy implemented; and the scores obtained in the MNA-LF and MNA-SF at the time of admission and of clinical discharge.

The MNA-LF is the original version, it consists of 18 questions (15) and patients can score a maximum of 30 points. According to this score, they are classified as presenting normal nutritional status (24-30 points), as being at risk of malnutrition (17-23.5 points) or malnourished (0-17 points). The MNA-SF corresponds to the initial "screening" part of the MNA-LF (16). The maximum score obtained is 14 points and subjects are classified as presenting normal nutritional status (12-14 points), as being at risk of malnutrition (8-11 points) or malnourished (0-7 points). In this study, participants' nutritional status was scored and categorized using MNA-LF and MNA-SF, at two moments (hospital admission and discharge). For MNA completion, BMI was determined. Height (cm) was measured with a tape measure from Seca 201(r), scale 0-205 cm and 1 mm graduation (22). Whenever patients were unable to assume the anthropometric position, height (cm) was estimated using demispan or knee height (23). Weight was measured with a digital dynamometer (model CR-200 and capacity 200 kg) and with a transfer crane for patients from Invacare(r) with capacity of 200 kg, according to ISO10535:2006.

The clinical diagnoses allowed the determination of the Charlson index (24,25). This index considers the number of diseases and their seriousness, since each disease is scored from 0 to 6 and therefore each patient receives a score of 0 or higher. Charlson index is therefore widely used for scoring the level of comorbidities.

In what regards statistical analysis, education was categorised into three categories: 0-6 years, > 6 years and due to high number of missing data, the category "unknown" was considered. Discharge destination was categorised into three categories: home or usual residence, death, and transfer or other destination (no patients were discharged against medical advice). Charlson index was dichotomised by its median value (< 3 e ≥ 3) as so was LOS (< 104 e ≥ 104 days).

The distribution of the variables was performed using the KolmogorovSmirnov test. Categorical variables were compared using the chisquare test and continuous variables using the Kruskal-Wallis test or ANOVA test, according to data distribution.

Criterion validity was assessed by determining the agreement between the MNA-LF and MNA-SF tools using the percentage of agreement, kappa statistics and intra-class correlation coefficients (ICC). Also, receiver operating characteristic (ROC) curves were constructed to evaluate the performance of MNA-SF for correctly screening malnourished patients based on their classification by MNA-LF. Sensitivity and specificity were calculated for a range of MNA-SF score cut-off values. The areas under the curves (AUCs) for the ROC curves and their 95 % confidence interval (CI) were also calculated. To construct ROC curves, subjects presenting normal nutrition status and at risk of malnutrition were grouped in a single category.

Predictive validity of MNA-SF was assessed by determining its association with LOS by Cox regression analysis. Hazard ratio (HR) and the respective 95 % CI were calculated. The category "normal nutrition status" was used as reference, "discharge to home or to usual residence" was used as the event and the following variables were included in the adjusted model: Charlson index (continuous), sex (dichotomous, women used as reference), age (continuous) and education (categorical, > 6 years used as reference). LOS was censored at 1000 days. Although this cut-off is arbitrary only 7.9 % of the study sample presented LOS > 1000 days.

The results were considered statistically significant for $p < 0.05$. Statistical analysis was performed using SPSS - Statistical Package for the Social Sciences, version 25.0, IBM, 2017.

RESULTS

This study sample is composed of 109 older adults, 68 women (62.4 %) and 41 men (37.6 %), aged between 66 and 102 years old, with a median age and interquartile range (IQR) equal to 78 (12) years.

According to MNA-LF at admission, 2 participants (1.8 %) presented normal nutrition status, 58 (53.2 %) were at risk of malnutrition and 49 (45.0 %) were malnourished. Regarding MNA-SF at admission, 8 (7.3 %) presented normal nutrition status, 60 (55.1 %) and 41 (37.6 %) participants were, respectively, at risk of malnutrition and malnourished (Table I). Nutritional status at discharge was evaluated for 94 older adults. According to MNA-LF, 3 (3.2 %) participants presented normal nutrition status, 53 (56.4 %) were at risk of malnutrition and 38 (40.4 %) were malnourished. For the MNA-SF these figures were respectively equal to 10 (10.6 %), 53 (56.4 %) and 31 (33.0 %) (Table I).

Agreement (%), kappa and ICC between MNA-LF and MNA-SF at admission and at discharge are presented in table I. Agreement, kappa and ICC were slightly higher at admission (83.5 %; 0.692; 0.768) compared to discharge (80.9 %; 0.649; 0.752).

Within this sample, LOS varied between 10 and 2285 days, with a median (IQR) value of 104 (261) days. Charlson index varied between 0 and 15, with a median (IQR) value equal to 3 (3) (Table II). There was no information on the clinical file regarding weight and height for 9 participants. For the remaining 100 participants,

Table I. Agreement between Mini Nutritional Assessment-Long Form (MNA-LF) and Mini Nutritional Assessment-Short Form (MNA-SF) at admission and at discharge in a sample of older adults admitted in a long-term care unity

Admission (*n* = 109)				***p****	**% of agreement**	**kappa**	**ICC†**
MNA-SF	**MNA-LF**						
	Normal nutrition status	**At risk of malnutrition**	**Malnourished**				
Normal nutrition status	2 (100.0)	6 (10.3)	0	< 0.001	83.5	0.692	0.768
At risk of malnutrition	0	50 (86.2)	10 (20.4)				
Malnourished	0	2 (3.4)	39 (79.6)				
Discharge (*n* = 94)				***p****	**% of agreement**	**kappa**	**ICC†**
MNA-SF	**MNA-LF**						
	Normal nutrition status	**At risk of malnutrition**	**Malnourished**				
Normal nutrition status	3 (100.0)	7 (13.2)	0	< 0.001	80.9 %	0.649	0.752
At risk of malnutrition	0	44 (83.0)	9 (23.7)				
Malnourished	0	2 (3.8)	29 (76.3)				

**p for χ^2 test; †Intra-class correlation coefficients.*

Table II. Comorbidity level according to Charlson index score for 109 older adults admitted in a long-term care unity

Charlson index score	***n* (%)**
0	5 (4.6)
1	10 (9.2)
2	18 (16.5)
3	27 (24.8)
4	19 (17.4)
5	12 (11.0)
6	3 (2.8)
7	3 (2.8)
8	3 (2.8)
9	3 (2.8)
10	2 (1.8)
12	2 (1.8)
15	2 (1.8)

weight varied between 31.0 and 97.0 kg with mean (SD) equal to 57.8 kg (14.2), whereas height varied between 145.0 and 188.0 cm, with mean (SD) of 162.3 cm (8.2). BMI varied between 12.5 and 45.7 kg/m^2 and its mean (SD) was equal to 22.0 (5.4) kg/m^2. There was no information regarding nutritional treatment for 1 participant. An individual nutritional therapy was prescribed to 108 participants, whereas 17 of those also received oral nutritional supplements.

Sample characterization according to nutritional status is presented in table III. A higher proportion of malnourished participants according to MNA-LF and to MNA-SF presented lower educational achievement and lower BMI, and died during hospital stay.

ROC curves and MNA-SF cut-off values at which most individuals are correctly classified, and a minimum of individuals are incorrectly classified, the calculated sensitivity, specificity, AUCs and 95 % CI for malnutrition evaluated by MNA-LF are presented in figure 1 and table IV. Sensitivity for MNA-SF was higher at admission, compared to discharge, whereas specificity was higher at discharge (Table IV). Nevertheless, the sensitivity and specificity values obtained at both moments were high.

In univariable Cox regression analysis, being malnourished according to MNA-SF at discharge was associated with lower odds of being discharged to home or to usual residence. No association was found for at risk of malnutrition and LOS at discharge, nor between risk of malnutrition and malnutrition by MNA-SF and

Table III. Socio-demographic, clinical and nutritional characteristics of 109 older adults admitted in a long-term care unit, according to Mini Nutritional Assessment Long Form (MNA-LF) and Mini Nutritional Assessment Short-Form (MNA-SF)

	MNA-LF				MNA-SF			
	Normal nutrition status	**At risk of malnutrition**	**Malnourished**	***p***	**Normal nutrition status**	**At risk of malnutrition**	**Malnourished**	***p***
Sex, n (%)				0.128				0.693
Women	0	39 (67.2)	29 (59.2)		4 (50.0)	39 (65.0)	25 (61.0)	
Men	2 (100)	19 (32.8)	20 (40.8)		4 (50.0)	21 (35.0)	16 (39.0)	
Age, years, median (IQR)	67 (-)	79 (13)	78 (11)	0.107	79 (13)	78 (13)	81 (11)	0.866
Education, years, n (%)				*0.048*				*0.034*
0-6	1 (50.0)	28 (48.3)	19 (38.8)		4 (50.0)	28 (46.7)	16 (39.0)	
> 6	1 (50.0)	3 (5.2)	2 (4.1)		2 (25.0)	4 (6.7)	0	
Unknown	0	27 (46.6)	28 (57.1)		2 (25.0)	28 (46.7)	25 (61.0)	
Discharge destination, n (%)				*0.002*				*0.033*
Home or usual residence	0	33 (56.9)	15 (30.6)		3 (37.5)	34 (56.7)	11 (26.8)	
Death	0	14 (24.1)	24 (49.0)		2 (25.0)	16 (26.7)	20 (48.8)	
Transfer / other destination	2 (100)	11 (19.0)	10 (20.4)		3 (37.5)	10 (16.7)	10 (24.4)	
LOS, days, median (IQR)	651 (-)	91 (289)	103 (161)	0.180	365 (1143)	90 (213)	124 (182)	0.355
LOS, days, n (%)				0.261				0.262
< 104	0	33 (56.9)	25 (51.0)		3 (37.5)	36 (60.0)	19 (46.3)	
≥ 104	2 (100)	25 (43.1)	24 (49.0)		5 (62.5)	24 (40.0)	22 (53.7)	
Charlson index, median (IQR)	3.5 (-)	3 (3)	3.5 (3)	0.750	4.5 (8)	3 (3)	3 (3)	0.056
Charlson index, n (%)				0.495				0.121
≤ 3	1 (50)	35 (60.3)	24 (49.0)		2 (25.0)	37 (61.7)	21 (55.0)	
> 3	1 (50)	23 (39.7)	25 (51.0)		6 (75.0)	23 (38.3)	20 (45.0)	
Weight*, kg	72.5 (4.9)	62.3 (13.9)	51.3 (12.2)	*< 0.001*	73.3 (16.1)	60.7 (13.2)	50.5 (11.1)	*< 0.001*
Height*, cm	181.5 (2.1)	161.6 (8.1)	162.2 (7.6)	*0.003*	169.1 (9.1)	161.7 (8.0)	161.7 (7.9)	*0.048*
BMI*, kg/m^2	22.0 (1.0)	24.0 (5.6)	19.5 (4.3)	*< 0.001*	25.6 (6.0)	23.3 (5.5)	19.4 (4.1)	*< 0.001*
Nutritional treatment†, n (%)				0.648				0.443
Diet	2 (100)	50 (86.2)	39 (81.3)		8 (100)	50 (83.3)	33 (82.5)	
Diet and supplements	0	8 (13.8)	9 (18.8)		0	10 (16.7)	7 (17.5)	

*IQR: interquartile range; LOS: hospital length of stay; *Missing for weight, height and BMI (n = 9); †Missing for Nutritional treatment (n = 1); there were no registration of patients receiving enteral nutrition or who were not receiving nutritional therapy.*

LOS at admission. After adjusting for Charlson index, sex, age, and education, being at risk of malnutrition or malnourished by MNA-SF at discharge was associated with lower odds of being discharged to home or to usual residence. Again, no association between nutritional status by MNA-SF at admission with LOS was found (Table V).

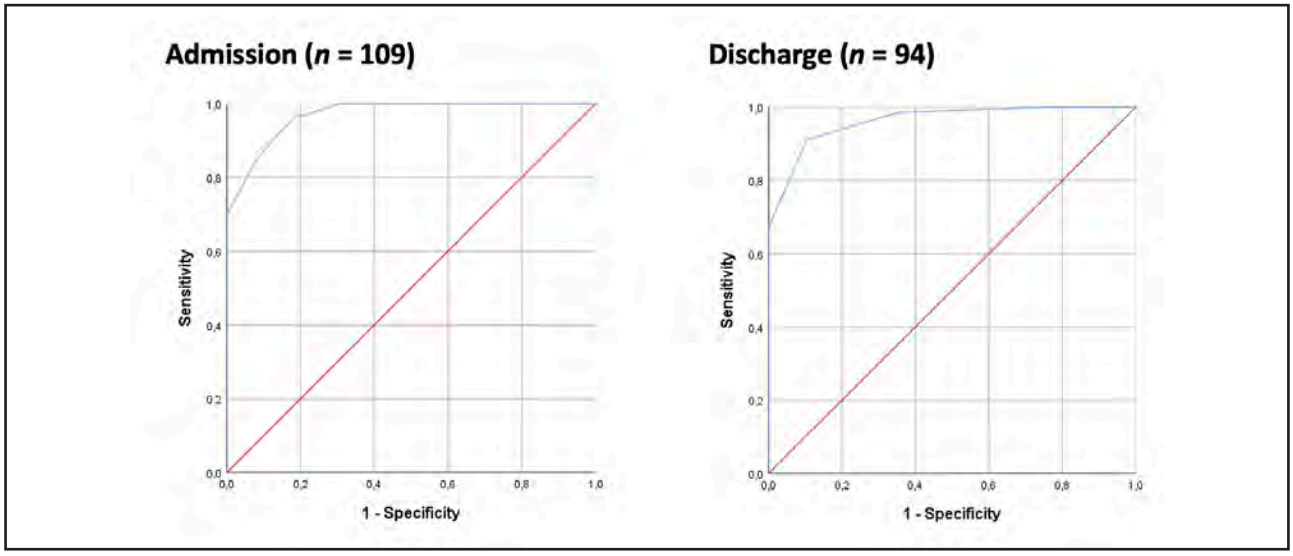

Figure 1.

Receiver operating characteristic (ROC) curves of Mini Nutritional Assessment-Short Form (MNA-SF) for malnutrition screening, based on Mini Nutritional Assessment-Long Form classification (MNA-LF) in a sample of older adults admitted in a long-term care unity. *Normal nutrition status and at risk of malnutrition versus malnourished.

Table IV. Mini Nutritional Assessment Short-Form (MNA-SF) cut-offs and diagnostic values for malnutrition screening based on malnutrition status classification by Mini Nutritional Assessment-Long Form (MNA-LF) in a sample of older adults admitted in a long-term care unity

	Sensitivity (%)	Specificity (%)	AUC	95 % CI	Cut-off
Admission (*n* = 109)	96.7	88.9	0.970	0.945-0.995	8
Discharge (*n* = 94)	92.9	89.5	0.970	0.942-0.998	9

AUC: area under the curve; CI: confidence interval.

Table V. Hazard ratios for being discharged to home or to usual residence associated with risk of malnutrition and malnutrition identified with Mini Nutritional Assessment-Short Form (MNA-SF) in a sample of older adults admitted in a long-term care unity

	Model 1		Model 2	
Admission (*n* = 109)	**Crude HR**	**95 % CI**	**Adjusted* HR**	**95 % CI**
Normal nutrition status	1		1	
At risk of malnutrition	1.973	0.603-6.449	2.101	0.530-8.329
Malnourished	0.823	0.228-2.966	0.867	0.197-3.814
	Model 3		**Model 4**	
Discharge (*n* = 94)	**Crude HR**	**95 % CI**	**Adjusted* HR**	**95 % CI**
Normal nutrition status	1		1	
At risk of malnutrition	0.605	0.268-1.368	*0.170*	*0.055-0.528*
Malnourished	0.185	0.060-0.566	0.059	0.016-0.223

**Adjusted for Charlson index (continuous), sex (dichotomous, women used as reference), age (continuous) and education (categorical, > 6 years used as reference).*

DISCUSSION

The criterion and predictive validity of MNA-SF through its independent association with LOS in a sample of older adults hospitalised in a long-term care unit was shown in the present study.

Regarding criterion validity, an agreement ≥ 81 % between MNA-SF and MNA-LF was found. In fact, a high agreement between MNA-SF and MNA-LF for the categories "malnourished" and "at risk of malnutrition" was reached, although those percentages are less than 100 %, the agreement found for "normal nutrition status" category. Considering kappa statistics and according to more conservative interpretations, the agreement between the MNA-SF and the MNA-LF was moderate (kappa ≥ 0.65). Taking into consideration the ICCs (≥ 0.75), a good agreement between the two tools was found. If the "cut-off points for rating validation results of malnutrition screening tools" proposed by Power and colleagues (13) are used, a good agreement between MNA-SF and MNA-LF in this sample of older adults from a long-term care unit can be established, regardless of the interpretation using kappa statistics or ICC. These results contribute to the criterion validity of MNA-SF in older adults hospitalised in long-term care units.

In a study conducted in 201 older patients (≥65 years) who were hospitalised in geriatric wards, the MNA-SF and the MNA-LF categorised 93.4 % and 91.1 % of the participants as being at risk of malnutrition or malnourished, frequencies slightly higher than the ones from the present study. The kappa value between MNA-SF and MNA-LF was 0.70, and similar to the values found in the present study (26). According to the results of Schrader *et al.*, in a sample of 190 participants in a daytime geriatric hospital, the kappa value between the same tools was 0.53, demonstrating a moderate and lower agreement than the one found in the present study (8). It is worth mentioning the lower proportions of subjects at risk of malnutrition and malnourished in the aforementioned study, respectively of 44.7 % and 5.8 % according to MNA-LF and of 36.3 % and 8.9 % according to MNA-SF. The different setting (daytime geriatric hospital *vs.* long-term care unit) may explain the lower magnitude of malnutrition and its risk and the lower agreement between the tools.

In another study that included 657 older adults (≥ 65 years) from community, nursing home and rehabilitation settings, agreement between the MNA-LF and MNA-SF was between 81.4 % and 84.6 % and therefore similar to the agreement found in the present study, whereas kappa values for the entire sample varied between 0.76 and 0.79 and therefore higher than the values obtained in the present study. Again, the different settings and the implied different characteristics of the participants may explain these differences, as in the aforementioned study the best agreement of classification was found in the community setting (90.4-90.8 %) and the highest kappa for nursing homes (0.71-0.78) (27).

Although it was not a purpose of the study, the high percentage of participants who were malnourished and at risk of malnutrition reinforces the need to screen, diagnose and treat malnutrition, as well as to place the appropriate resources to better treat this condition in older adults admitted in long-term care units.

According to ROC analysis, the cut-offs for MNA-SF scores for which best diagnostic values were obtained are 8 and 9, for nutritional status evaluation at admission and discharge, respectively. The sensitivity (≥ 93 %), specificity (≥ 89 %) and AUC (0.970) values obtained for MNA-SF were very high and highly satisfactory (13) demonstrating the criterion validity of MNA-SF for older adults from a long-term care unit. In ROC analysis, participants presenting normal nutrition status and risk of malnutrition were grouped in the same category due to the small number of participants in the normal nutrition status category, and although this is probably due to the poor nutritional status of older adults that seek long-term care, this procedure was previously done in a study conducted among 1744 community-dwelling older subjects and 859 older subjects from nursing homes. The authors of this previous study determined sensitivity and specificity by merging at risk/malnourished participants into one category and by merging normal nutrition status/at risk of malnutrition in one category. MNA-SF diagnostic values for screening undernutrition based on MNA-LF were between 74.1-100 % and 89.9-97.3 %, for sensitivity and specificity, respectively (28). In the present study, specificities were generally lower, but sensitivities were within this range. It is also worth noticing that sensitivity and specificity values found in the present study are higher than those described in an MNA-SF validation study conducted in 2032 geriatric patients (mean age 82.3 years): sensitivity: 85-89 % and specificity: 82-84 % (16). Sensitivities described in the present study are also similar to those reported in another validation study among 881 participants (73.8 % were community dwelling; mean age was equal to 76.4 years): 97.9 %, although specificities are lower: 100 % (29).

In a prospective cohort study conducted among 134 medical inpatients (mean age = 80 years, SD: 8 years), MNA-SF sensitivity and specificity based on MNA-LF were respectively equal to 95.6 % and 79.1 %. Comparing to those results, sensitivities from the present study were similar and specificities were higher (27).

According to our knowledge, only two studies had evaluated the association of MNA-SF with LOS. However, Nishioka and colleagues (30) included adult patients aged ≥ 20 years from the rehabilitation setting, differently from the present study where only participants aged ≥ 65 years old were included. In this previous study, MNA-SF did not predict discharge to home or to long-term care facilities by a Cox proportional hazard model: HR for malnutrition was ≥ 1.0 (p ≥ 0.96) and HR for risk of malnutrition was ≥0.90 (p ≥ 0.89). In the other study, 169 inpatients aged ≥ 65 years old from a university general hospital were included. MNA-SF performance in predicting very long LOS was analysed using ROC curves and AUC was equal to 0.6626 (19). Different statistical tests prevent direct comparisons with present study results.

Some limitations should be recognised. School achievement was unknown for 55 of the 109 participants. Moreover, MNA evaluation at discharge was available for only 94 participants. This can be due to death or unplanned transfer. It should also be recognised the possible impact of the small number of participants who presented normal nutrition status, evaluated with both MNA-LF and MNA-SF, on the statistical analysis. Therefore, the agreement, diagnostic values and association of the MNA-SF with LOS should be evaluated in

larger samples, possibly allowing for a higher number of participants presenting normal nutrition status. The possibility of occurrence of type II errors cannot be discarded due to the small sample size.

Although arbitrary, LOS was censored at 1000 days. A large follow-up was used since it may provide more information on the association between MNA-SF and LOS than if a shorter period had been used. Because LOS was longer than 1000 days for only 9 participants, 7.9 % of the study sample, a longer follow-up period probably would not have affected the present study findings.

This is believed to be the first study conducted in a sample of older adults from a long-term unit that has shown that being malnourished or at risk of malnutrition according to MNA-SF is independently associated with lower odds of being discharged to home or to usual residence. Although this study was conducted in hospitalised patients, it is important to notice that all are chronic patients and therefore different from patients admitted to different chronic, acute or surgical wards. The use of survival analysis to study the association between MNA-SF with LOS can also be regarded as a study strength, since this type of analysis allows to treat LOS as a continuous variable and allows to censor patients that experienced events different from discharge to home or to usual residence at the time of occurrence of those events. This is believed to better reflect the reality of a long-term care unit. The age range of the participants (66102 years old) can be regarded as a strength of the study and also the diversity in what regards comorbidity level of the included patients.

A high agreement was found between MNA-LF and MNA-SF. Also, MNA-SF revealed high diagnostic values in terms of sensitivity, specificity, and AUC. Moreover, an independent association was found between malnutrition or risk of malnutrition by MNA-SF and LOS. The use of MNA-SF instead of MNA-LF should be considered in long-term care units given its criterion and predictive validity.

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ARÁN

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Trabajo Original

Valoración nutricional

Assessment of the validity of a sedentary behavior questionnaire among university students from low-income regions

Evaluación de la validez de un cuestionario de comportamiento sedentario en estudiantes universitarios de regiones de escasos recursos

Luiz Fernando de Oliveira[1], Evanilson Alves dos Santos[1], Alaiana Marinho Franco[1,2], Kliver Antonio Marin[1], Marcus Vinícius Nascimento-Ferreira[1,3]

[1]Health, Physical Activity and Behavior Research (HEALTHY-BRA) Group. Universidade Federal do Tocantins. Miracema do Tocantins, TO. Brazil. [2]Instituto de Ensino Superior do Sul do Maranhão (IESMA/UNISULMA). Imperatriz, MA. Brazil. [3]Youth/Child Cardiovascular Risk and Environmental (YCARE) Research Group. Faculdade de Medicina. Universidade de São Paulo. São Paulo, SP. Brazil

Abstract

Introduction: to reduce the prevalence of overweight and obesity, lifestyle interventions, particularly in nutritional education programs, should be prioritized among university students. Monitoring sedentary behavior is an important step toward preventing and controlling obesity. Therefore, we assessed the reliability and validity of an online questionnaire on sedentary behavior among university students from low-income regions.

Methods: this cross-sectional methodological feasibility study evaluated the psychometric properties of the South American Youth/Child Cardiovascular and Environmental (SAYCARE) questionnaire. We administered this questionnaire in an online format to 195 and 117 university students (aged between 17 and 53 years) to assess its validity and reliability, respectively. The questionnaire measures the daily time spent watching TV, playing electronic games, using a computer, studying and passive commuting on weekdays and weekends. The questionnaire involved two stages (Q1 and Q2) separated by an interval of 2 weeks. Reliability was assessed using Spearman's correlation analysis. The structural validity of the construct was evaluated by exploratory factor analysis.

Results: all variables showed acceptable reliability (Spearman's rho > 0.30 and $p < 0.05$). Regarding construct structural validity, the exploratory factor analysis identified 4 factors (variance explained: 71.4 %) and did not exclude any items.

Conclusion: the online SAYCARE questionnaire exhibited acceptable reliability and structural validity for assessing sedentary behavior among university students from low-income regions.

Keywords:

Sedentary behavior. Reproducibility. Structural validity. Adults.

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Correspondence:

Kliver Antonio Marin. Health, Physical Activity and Behavior Research (HEALTHY-BRA) Group. Universidade Federal do Tocantins, Campus Universitário de Miracema. Avenida Lourdes Solino s/n, Setor Universitário. Miracema do Tocantins, Tocantins. Brazil
e-mail: klivermarin@mail.uft.edu.br

Resumen

Introducción: para reducir la prevalencia del sobrepeso y la obesidad, las intervenciones en el estilo de vida, particularmente en los programas de educación nutricional, deben priorizarse entre los estudiantes universitarios. Por lo tanto, monitorear el comportamiento sedentario es un paso importante para prevenir y controlar la obesidad. Nuestro objetivo fue investigar la confiabilidad y validez de un cuestionario *online* sobre comportamiento sedentario entre estudiantes universitarios de regiones de escasos recursos.

Métodos: este estudio transversal de factibilidad metodológica evaluó las propiedades psicométricas del cuestionario *South American Youth/ Child Cardiovascular and Environmental* (SAYCARE). Administramos este cuestionario en formato online a 195 y 117 estudiantes universitarios (de entre 17 y 53 años) para evaluar su validez y confiabilidad, respectivamente. El cuestionario midió el tiempo diario del estudiante viendo televisión, jugando a juegos electrónicos, usando una computadora, estudiando y viajando pasivamente entre semana y fines de semana. El cuestionario fue respondido en dos etapas (Q1 y Q2), con un intervalo de 2 semanas. La fiabilidad se evaluó mediante el coeficiente de correlación de Spearman. La validez estructural del constructo se evaluó mediante análisis factorial exploratorio.

Resultados: todas las variables mostraron una confiabilidad aceptable (rho de Spearman > 0,30 y p < 0,05). En la validez estructural del constructo, el análisis factorial exploratorio encontró 4 factores (varianza explicada del 71,4 %) y ningún ítem fue excluido.

Conclusión: el cuestionario SAYCARE, en formato online, exhibió una confiabilidad y validez estructural aceptables para evaluar el comportamiento sedentario entre estudiantes universitarios de regiones de escasos recursos.

Palabras clave:

Comportamiento sedentario. Reproducibilidad. Validez estructural. Adultos.

INTRODUCTION

Sedentary behavior, unlike physical inactivity, can be characterized by the performance of small movements when sitting or reclining that require an energy expenditure ≤ 1.5 metabolic equivalents (1). Epidemiological evidence supports the associations of sedentary behavior with metabolic behavior (2-4), mortality (2), and other outcomes (4) in adults. Reducing sedentary behavior could help prevent an increase in body mass index in adulthood and thereby reduce the prevalence of obesity (5), especially in college students (6).

Thus, monitoring sedentary behavior is an important step toward preventing and controlling obesity. Self-reported data (mainly collected via questionnaire) are the most frequent economically and logistically viable method of evaluating sedentary behavior in epidemiological studies (1). The COVID-19 pandemic and subsequent implementation of public health measures, such as social distancing, increased remote research (7), as studies migrated from a face-to-face format to a virtual environment. However, despite the practicality of online tools, some issues may arise regarding the quality of the collected data (8), such as differences in literacy and access to the internet, especially in low- and middle-income countries (7).

Although the use of online tools can expand and increase the flexibility of questionnaire application in epidemiological studies (9,10), including health behaviors (8), an evaluation of the psychometric properties of online sedentary behavior questionnaires, especially in low- and middle-income populations, is lacking. Thus, the objective of the present study was to evaluate the reliability and validity of an online questionnaire assessing sedentary behavior in university students from low-income regions.

MATERIAL AND METHODS

STUDY DESIGN

The present cross-sectional methodological feasibility study (11) is part of a longitudinal multicenter observational study, the 24-hour Movement Behavior and Metabolic Syndrome (24 h-MESYN) study (12), and was structured according to the concepts of the scientific method (13). During the 2021 academic year, the online questionnaire was administered to participants twice to test the temporal stability of responses (reliability) and construct structural validity. Detailed information about the 24 h-MESYN study can be found elsewhere (12).

ETHICAL ASPECTS

This study complied with the Declaration of Helsinki (2008 revision, Seoul, South Korea) and Resolution 466/2012 of the Brazilian Ministry of Health regarding the ethical principles of research involving humans. The study procedure was approved by the Ethics Committee of the *Centro Universitário do Maranhão* (UNICEUMA, no. 4055604). After the educational institution provided written consent, subjects received a formal invitation to participate in the study in a virtual environment. Subjects were also informed of the risks and discomfort of the study, in accordance with the protocols of the institution, and signed an informed consent form (ICF).

SAMPLE CHARACTERIZATION

We invited university students from a higher education institution in the municipality of Imperatriz, Maranhão, Brazil to participate in the study. In 2020, this institution had 2,225 students and offered nine majors (Nursing, Physical Therapy, Nutrition, Physical Education, Aesthetics and Cosmetics, Psychology, Social Work, Administration, and Law). To calculate the necessary sample size, we used an α of 0.05, a β of 0.10 (90 % power) and a correlation coefficient of 0.28 (14); we determined that 98 subjects were needed (15). To compensate for participant drop out (50.0 %), refusal to participate (50.0 %) and missing data (50.0 %), 342 students were invited to participate in the study. We selected students by stratified random sampling, considering distributions (60 %/40 %) based on previous studies by i) biological sex (female and male) and ii) nature of the majors (health sciences and other areas) (16,17).

ELIGIBILITY CRITERIA

We included undergraduate students ≥ 17 years of age who signed the informed consent form. We excluded students who were pregnant or had a physical disability. In the validity study, we excluded students who returned incomplete questionnaires, and in the reliability study, we excluded students who did not complete the first questionnaire. The exclusions occurred only at the time of data analysis.

STUDY VARIABLES

The operational variables of the study were (13) participant biological sex, age, major, shift of coursework, and duration of sedentary behavior.

INSTRUMENTS

We collected data through the online questionnaire, available at https://forms.gle/L92wXsVaxxfPNgpE8. The sedentary behavior questionnaire was from the South American Youth/Child Cardiovascular and Environmental (SAYCARE) study, which was developed and validated in South American children and adolescents (18). The SAYCARE questionnaire has 10 items regarding time spent watching television, using a computer and/or cell phone, studying, playing electronic games and passive commuting on weekdays and weekends (18). The responses were reported in hours per day according to a preset scale (e.g., 1, 2, 3, 4, or 5 hours per day). After administering the questionnaire, we calculated the weighted daily duration of sedentary behavior via the equation:

$$\text{sedentary behavior} = \frac{([(\text{duration on weekdays} \times 5) + (\text{duration on weekends} \times 2)])}{7}$$

Additionally, we retrieved information on biological sex (male/female), chronological age (17 to 99 years), major (Nursing, Physical Therapy, Nutrition, Physical Education, Aesthetics and Cosmetics, Psychology, Social Work, Administration, or Law) and shift of coursework (morning, afternoon, evening, or full).

Procedures

To standardize the research procedures, the multidisciplinary team of researchers underwent 20 hours of training (12). During the training period, we reviewed the online questionnaire to correct typos (and issues with semantics) and address problems with the access link. Next, we conducted data collection in three stages. The first stage consisted of a direct (face-to-face) approach, in which we explained the project and sent the *link* to the informed consent form and questionnaire via WhatsApp. If the electronic questionnaire was not completed, we sent up to three reminders. In the second and third stages, the online questionnaire was administered twice (Q1 and Q2), separated by an interval of two weeks (12). The Q2 questionnaire was sent only to those who completed the Q1 questionnaire. In the latter two steps, our contact was restricted to messaging via WhatsApp.

DATA ANALYSIS

All statistical analyses were performed using Stata software, version 15.0 (Stata Corporation, College Station, TX, USA). We used the Shapiro-Wilk test to assess the normality of data distribution. The significance level adopted was 95 % ($p \leq 0.05$). To evaluate sensitivity, we used the chi-square goodness-of-fit test compare the distributions of the samples between Q1 and Q2 (19). To evaluate reliability, we used the Spearman correlation coefficient (a non-parametric analysis) with a cutoff point of ≥ 0.30 (20). To evaluate structural validity, we performed an exploratory factor analysis with varimax rotation, excluding items with loadings < 0.3 (19). We extracted the factors based on the Kaiser rule, retaining factors with an eigenvalue > 1 (19). Previously, we conducted a preliminary analysis to determine whether an exploratory factor analysis was feasible given the data, using the Kaiser-Meyer-Olkin test (considered feasible when KMO > 0.50) to assess sample adequacy and the Bartlett test (considered statistically significant when $p < 0.05$) to assess data sphericity (19).

RESULTS

Of the 342 students contacted, 43.0 % did not complete the Q1 questionnaire and 40.0 % did not complete the Q2 questionnaire. Thus, we identified a 57.0 % response rate (students contacted who completed the Q1 questionnaire) at Q1 and a 60.0 % response rate at Q2 (students who completed the Q1 questionnaire as well as the Q2 questionnaire). Detailed information regarding the sample is shown in table I. Most participants were women aged 21 to 25 years who majored in Physical Education and attended the night shift at both Q1 and Q2. We did not identify significant differences in participant characteristics at the two time points in the sensitivity analysis (Table I).

Table II shows the characteristics of sedentary behavior according to self-report data. We observed that during a typical weekday, computer use accounted for the highest median duration, followed by studying and watching TV; during a typical weekend day, watching TV and using a computer were the most common behaviors. The mean total daily sedentary duration in our sample was 9.53 (± 4.22) hours/day (data not shown). Furthermore, we identified acceptable reliability in all variables of the SAYCARE questionnaire, with Spearman's correlation coefficients ranging from 0.72 (watching TV on a weekday) to 0.31 (passive commuting on a weekday).

Regarding structural validity (Table III), our data were appropriate for exploratory factor analysis (KMO = 0.572; Bartlett's test, $p < 0.001$). We identified the following four factors: "studying and using a computer during the week" (Factor 1), "watching TV, using a computer and studying during the week" (Factor 2), "electronic games" (Factor 3) and "passive commuting" (Factor 4); together, these factors explained 71.4 % of the variance in the data. Based on the factor loading and analysis of commonality, no items were excluded.

Table I. Sensitivity analysis based on sociodemographic and academic characteristics

Variables	Q1 (n = 195)	Q2 (n = 117)	p-value*
	%	%	
Biological sex			
Male	31.3	27.4	0.36
Female	68.7	72.6	
Chronological age (years)			
≤ 20	23.6	26.7	0.63
21 to 25	44.6	45.7	
26 to 30	18.5	14.7	
31 to 35	7.2	5.2	
≥ 36	6.2	7.8	
Major			
Nutrition	8.8	6.0	0.17
Physical Education	22.3	24.8	
Nursing	11.1	12.0	
Aesthetics and Cosmetics	7.6	1.7	
Physical Therapy	16.1	18.8	
Law	14.1	11.1	
Psychology	15.0	21.4	
Social Work	3.2	1.7	
Administration	1.8	0.9	
Shift of coursework			
Morning	20.1	20.5	0.92
Afternoon	0.5	0.9	
Evening	61.3	62.4	
Full	18.0	16.2	

*Q1: questionnaire first application; Q2: questionnaire second application. *Chi-squared goodness-of-fit test.*

Table II. Reliability analysis of the American Youth/Child Cardiovascular and Environmental (SAYCARE) sedentary behavior questionnaire

Daily time spent (hour/day)		Q1	Q2	rho
Watching TV	Weekdays	2.0 (0.0-3.0)	1.0 (0.0-3.0)	*0.72*
	Weekends	2.0 (1.0-4.0)	2.0 (1.0-3.0)	*0.68*
Playing electronic games	Weekdays	0.0 (0.0-1.0)	0.0 (0.0-2.0)	*0.55*
	Weekends	0.0 (0.0-2.0)	0.0 (0.0-2.0)	*0.56*

(Continues on next page)

Table II (Cont.). Reliability analysis of the American Youth/Child Cardiovascular and Environmental (SAYCARE) sedentary behavior questionnaire

Daily time spent (hour/day)		Q1	Q2	rho
Using a computer	Weekdays	3.0 (1.0-5.0)	4.0 (2.0-6.0)	*0.52*
	Weekends	2.0 (0.0-3.0)	2.0 (0.0-3.0)	*0.70*
Studying	Weekdays	3.0 (2.0-4.0)	2.0 (1.0-4.0)	*0.50*
	Weekends	2.0 (1.0-3.0)	1.0 (1.0-3.0)	*0.60*
Passive commuting	Weekdays	1.0 (0.0-2.0)	0.0 (0.0-1.0)	*0.31*
	Weekends	0.0 (0.0-1.0)	0.0 (0.0-1.0)	*0.52*

Values are median (25th-75th percentile). Q1: questionnaire first application; Q2: questionnaire second application; rho: Spearman's correlation coefficient. Significant values are in italics *($p < 0.05$).*

Table III. Validity analysis (exploratory factor analysis) of the American Youth/Child Cardiovascular and Environmental (SAYCARE) sedentary behavior questionnaire

Item	Factor 1	Factor 2	Factor 3	Factor 4	Uniqueness	Communality (1-uniqueness) %
Watching TV on weekdays		0.847			0.264	73.6
Watching TV on weekends		0.827			0.280	72.0
Playing electronic games on weekdays			0.857		0.207	79.3
Playing electronic games on weekends			0.905		0.161	83.9
Using a computer on weekdays	0.689				0.467	53.3
Using a computer on weekends	0.725	-0.352			0.329	67.1
Studying on weekdays	0.668	0.338			0.401	59.9
Studying on weekends	0.796				0.339	66.1
Passive commuting on weekdays				0.860	0.207	79.3
Passive commuting on weekends				0.871	0.206	79.4
Eigenvalue (proportion of variance)	2.12 (0.21)	1.78 (0.18)	1.69 (0.17)	1.55 (0.15)		
Explained variance*	0.714 or 71.4 %					

*A factor loading < 0.30 was not shown. *Proportion and explained variance for the first 4 factors (factor 1, factor 2, factor 3, and factor 4) identified by using the eigenvalue greater than one rule (Kaiser's rule).*

DISCUSSION

This study is the first to evaluate the psychometric properties of the SAYCARE questionnaire for assessing sedentary behavior among university students as well as the first to evaluate the feasibility of administering such a questionnaire in an online format in a low-income region. We found that the online SAYCARE questionnaire had acceptable temporal stability (reliability) and structural validity. Even though this questionnaire was developed for a face-to-face context, its psychometric properties were similar in a remote context (i.e., during social distancing, in an online format) as a viable alternative for collecting data in a pandemic context in a low-income region.

Although our sample varied in terms of age, sex and major, young women majoring in health sciences comprised the majority of respondents. These findings are in line with previous Brazilian epidemiological studies with university students (21,22), including those in low-income regions (17). In Brazil, young women account for the majority of enrolled in undergraduate health programs (23) who complete higher education degrees (24), which could potentially explain the demographic and academic distribution in our sample.

Our study indicates that the 10-item online SAYCARE questionnaire has acceptable reliability for measuring sedentary behavior among university students from low-income regions. These findings are in line with previous systematic reviews regarding the

psychometric properties of subjective measures among youth (25) and adults (26). Although no previous study has assessed the reliability (and validity) of the SAYCARE questionnaire in adults (to our knowledge), this tool was reliable in young people in South America (18). Consistent with this finding, a systematic review and meta-analysis reported that questionnaires assessing sedentary behavior in epidemiological studies show moderate-to-good reliability; in addition, multiple-item questionnaires have slightly better reliability than single-item questionnaires (pooled correlation coefficient: 1-item = 0.34, 2-to-9-item = 0.35; ≥ 10-item = 0.37) (26). This pattern of reliability can be explained by the stable nature of the behaviors evaluated (e.g., computer use), since sedentary behaviors tend to be more stable than active behaviors (27). Additionally, we speculate that the sedentary behaviors studied are related to the university routine, which could reinforce this behavior pattern and consequently increase the precision of data.

Moreover, we found acceptable structural validity of the SAYCARE questionnaire among the university students studied. The structural validity of this questionnaire has not been studied to date, but studies on similar questionnaires have reported satisfactory criterion (25,28), concurrent (26,28), and structural (29,30) validity. The structural validity of the SAYCARE questionnaire can be explained by its construction (18), which included the following factors: i) construction by experts in behaviors related to energy expenditure; ii) inclusion of a range of typical behaviors (e.g., watching TV, using a computer or passive commuting), which seem sufficiently diverse and complementary in their domains; iii) questionnaire covering a longer recall period (e.g., weekday, weekend) and iv) validation against an objective instrument. Alternatively, the structural validity be attributed to the number of items in the SAYCARE questionnaire. A recent systematic review noted that questionnaires with fewer items (measured behaviors) have greater psychometric robustness, possibly because the participants may struggle with multiple-item questionnaires, making it difficult to replicate patterns and domains of sedentary behavior (26).

The present study has some limitations that should be noted, such as potential biases (including social desirability) and the lack of epidemiological representativeness of the sample (11). Regarding the latter, the current study was not designed to be representative of a specific population[11]; but, to reproduce with sufficient power at a given error level the psychometric properties of the SAYCARE questionnaire under planned population distribution (e.g., age range, biological sex and major) (11). Thus, the results should not be extrapolated beyond the psychometric findings. Although we observed a high rate of refusal to participate (57.0 % at Q1 and 34.2 % at Q2), post hoc analysis revealed that the power of the sample (lowest correlation observed = 0.31; n = 117) remained significant (β = 0.14; power = 0.86). Indeed, the included sample (n = 117) was larger than the planned amount (n = 98), partially attributable to the higher prediction (up to 50.0 %) of drop outs/missing data/refusal to participate incorporated in the study design grounded in our experience in questionnaire validity in the South American population (18). The research site was also selected by convenience, although the sample was randomly selected. These choices were based on the sociodemographic and academic diversity of the institution, which may provide a good idea of the characteristics of students from low-income regions, since representative methodological studies are not feasible (31) or ethical (14). We successfully recruited a sample with similar demographic and academic characteristics in the university context from low-income regions of Brazil (17,22). Finally, the questionnaire of interest should be evaluated in terms of external validation, preferably against objective data (e.g., using an accelerometer), to confirm its ability to measure the duration of sedentary behavior in this population (32). The strengths of this study were its methodology, involving epidemiological feasibility assumptions for assessing the psychometric properties of the (online) SAYCARE questionnaire; a robust sample, in terms of size and diversity, of Brazilian university students; and its adapted protocol to collect data during social distancing measures in low-income regions.

CONCLUSION

The SAYCARE questionnaire, in online format, exhibited acceptable reliability and validity for assessing sedentary behavior in university students from low-income regions. In this online format, the questionnaire represents a low-cost alternative to face-to-face administration (useful for conditions of restricted social contact).

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Epidemiología y dietética

Gender network analysis of the Eating Disorder Examination-Questionnaire (EDE-Q7) in Peruvian adults

Análisis de red de género del Eating Disorder Examination-Questionnaire (EDE-Q7) en adultos peruanos

Cristian Ramos-Vera[1], Yaquelin E. Calizaya-Milla[2], Jacksaint Saintila[2]

[1]Research Area. Facultad de Cincias de la Salud. Universidad César Vallejo. Lima, Perú. [2]Escuela de Nutrición Humana. Universidad Peruana Unión. Lima, Perú

Abstract

Background: network assessment of eating disorder (ED)-related symptomatology from a gender perspective is an important topic of study; however, there is limited research in the Latin American context.

Objective: this study aimed to explore the patterns of association of the components of the Eating Disorder Examination-Questionnaire (EDE-Q7) according to gender, using two simultaneous network models in 890 Peruvian adults (63.51 % were women; mean age: 26.40).

Methods: two graphs considering the gender factor were made using the R package qgrap and the merged LASSO graph.

Results: higher network centrality measures were obtained for items related to body image dissatisfaction and overvaluation in women; while in the men's network, the items of food restriction and overestimation of weight were the most central symptoms.

Conclusion: both network models were invariant and showed no significant differences in both structure and connections.

Keywords:

Body dissatisfaction. Body weight. Eating disorders. Latin America. Peru.

Resumen

Introducción: la evaluación de redes de la sintomatología relacionada con los trastornos alimentarios (TA) desde el punto de vista del género es un tema importante de estudio; sin embargo, existen pocas investigaciones en el contexto latinoamericano.

Objetivo: el objetivo de este estudio fue explorar los patrones de asociación de los componentes del *Eating Disorder Examination-Questionnaire* (EDE-Q7) según el sexo mediante dos modelos de red simultánea en 890 adultos peruanos (63,51 % de mujeres; edad promedio: 26,40 años).

Métodos: se realizaron dos gráficos considerando el factor género utilizando el paquete R qgrap y el gráfico LASSO fusionado.

Resultados: se obtuvieron medidas de centralidad de red más altas para los ítems relacionados con la insatisfacción y la sobrevaloración de la imagen corporal en las mujeres; mientras que, en la red de los hombres, los ítems de restricción alimentaria y sobrevaloración del peso eran los síntomas más centrales.

Conclusión: ambos modelos de red resultaron invariables y no mostraron diferencias significativas a nivel de estructura y conexiones.

Palabras clave:

Insatisfacción corporal. Peso corporal. Trastornos alimentarios. América Latina. Perú.

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Correspondence:

Jacksaint Saintila. Escuela de Nutrición Humana. Universidad Peruana Unión. Carretera Central, km. 19, Ñaña. Lima 15, Perú
e-mail: jacksaintsaintila@gmail.com

INTRODUCTION

Eating disorders (ED) are one of the most important public health problems (1), representing a burden not only for patients but also for their families and society, due to their associated high economic and health care costs (2,3). EDs often become chronic disorders and can persist for long periods of time (4), being responsible for high morbidity and higher mortality among all psychiatric disorders (5). These disorders are characteristic of behavioral syndromes related to physiological and physical alterations (3), and are due to various factors, such as genetic, psychological, and sociocultural factors (6). Gender is a very important factor in the occurrence of ED; women are more likely to suffer from ED when compared to men; in fact, approximately 80 to 95 % of those affected are women (7-9). Despite this widespread perception that eating disorders predominantly affect women, there is growing evidence that the incidence and prevalence rate among men is increasing (10). During the last two decades, a dramatic growth in the prevalence of ED among men has been observed (11).

In several studies, the self-reported Eating Disorder Examination Questionnaire (EDE-Q) has been used to assess eating disorder symptoms. This instrument is used to assess attitudinal (weight concerns) and behavioral (binge eating) symptoms (12). In addition, it has been used in clinical and nonclinical populations (13). There are several versions of the EDE-Q; among them, the 7-item EDE-Q, which is composed of three scales that include 1) dietary restriction; 2) overestimation of shape/weight; and 3) body dissatisfaction (12). This version allows for a reduction in administration time and could provide a measure with sound psychometric properties for use in clinical and community samples in both men and women (14).

Network models offer an alternative perspective in the evaluation of psychological measures without necessarily considering a common latent variable. This approach represents the associations (edges; total or partial correlations) by using a Gaussian graph, whose thicknesses are proportional to the intensity of the correlation between the elements of the instrument nodes (15,16). In addition, it includes centrality indices that quantify the strength of the components within the network (17).

Network analysis in the research of psychological disorders is receiving increasing attention in all fields of study (16). Its use in the evaluation of the EDE-Q is denoted as an emerging system, given the interaction of the indicators with each other, which together form the construct. Such indicators are not simply caused by a common latent variable as in factor models, but direct interactions between item responses form the dynamic structure of eating disorder development. Specifically, it is possible that there is no causal variable for the occurrence of dietary restraint, body overvaluation, or body dissatisfaction (18). It is more likely that the development of ED arises as a result of interactions between these factors or their respective items (16).

It is important to evaluate these psychopathological aspects considering the gender factor, given the differences between body ideals and body image concerns (13,16). This allows us to explain which measures reinforce such sex differences in EDE-Q7, considering that there is evidence of a steady increase in the prevalence of ED in men recently (10,11). However, there are controversies in the differential characteristics in the manifestation of eating disorders between men and women; while some studies report a tentative increase in the incidence and prevalence rate of ED in men (19,20), other studies report higher levels of dietary pathologies in women (21,22). These divergent results may be related to greater emotional problems such as depression (23), which favors an increase in scores related to body dissatisfaction.

The exploration of simultaneous EDE-Q7 network structures is particularly important to evidence how higher-risk psychopathological symptoms interact with the emergence of ED in males and females, given that to date no ED-related network studies have yet been reported in South American populations. Therefore, the aim of the study was to explore the patterns of association of the components of the EDE-Q7 according to gender using two simultaneous network models in Peruvian adults.

MATERIALS AND METHODS

PARTICIPANTS AND STUDY DESIGN

A cross-sectional quantitative study was carried out using a Gaussian graphical model (partial correlation coefficient network). To evaluate the dynamic relationships of the EDE-Q7, a group of 890 Peruvian adults (63.51 % were women; mean age: 26.40) was considered using non-probabilistic convenience sampling. Approximately 70 % were university students, 25 % were high school level, 5 % were elementary school level. Additionally, 70 % lived in Lima, while 17.7 %, 6.3 %, and 6 % were from Trujillo, Arequipa, and Huancayo, respectively. Google Forms was used to share the questionnaire publicly through email and social networks such as WhatsApp and Facebook Messenger. Data were collected between May and August 2021. Foreigners and those under 18 years of age were excluded. Informed consent was obtained from those who voluntarily decided to participate in this study. To carry out this study, the ethical standards stipulated in the Declaration of Helsinki were considered. In addition, the study was reviewed and approved by the research ethics committee of Universidad César Vallejo.

EATING DISORDER EXAMINATION-QUESTIONNAIRE

The Eating Disorder Examination-Questionnaire was used considering the 7-item Spanish version (24) (Table I) because it has stronger evidence of reliability and validity than the original measure (14). This measure predicts a series of basic behavioral characteristics of eating disorders, being a Likert-type scaling measure with seven options. Reliability was obtained by the general Cronbach's alpha measure of 0.83.

Table I. The Eating Disorder Examination-Questionnaire

Items of EDE-Q7
1. Have you been consciously trying to limit the amount of food you eat to influence your weight?
2. Have you tried to avoid eating any foods you like to influence your shape or weight?
3. Have you tried to follow definite rules regarding your diet to influence your shape or weight; for example, a calorie limit, a certain amount of food, or rules about what or when you should eat?
4. Has your figure influenced the way you consider (judge) yourself as a person?
5. Has your weight influenced the way you see (judge) yourself as a person?
6. How dissatisfied have you been with your weight?
7. How dissatisfied have you felt with your figure?

Note: Spanish version of the EDE-Q7 according to Grilo et al. (24).

STATISTICAL ANALYSIS

Two Gaussian graphic models (networks of partial correlation coefficients) were calculated for men and women from the seven items of the instrument using the R qgrap package and the LASSO fused graph (25), which allows us to graphically explore the patterns of the interactive system of symptoms of the EDE-Q7 according to gender. This network approach is more reliable than bivariate analysis because it eliminates illegitimate relationships and fixes independent relationships beyond the other connections (26), considering the 5000-sample bootstrap method to reinforce the stability of the network results. To determine the level of network connections, the interpretation of effect size values (≤ 0.1 = small; > 0.1 to < 0.5 = moderate; ≥ 0.5 = large) was considered. In addition, the strength centrality index was reported as a measure that quantifies the importance of network association magnitudes (26).

Finally, the R package Network Comparison Test (NCT) was used to assess differences in network structure (assess that the structure of both networks is equal), overall strength and borders (equality in overall connectivity and between the borders of both networks) in men and women.

RESULTS

More moderate-sized connections (13) were found in the women's network (Fig. 1A). In this group, a higher measure of strength (1.27) is reported for item EQ7 (dissatisfaction with body image), which presents a greater interaction with item EQ4 (overvaluation of weight), integrating the two factors of relative closeness and superior connectivity compared to the diet restriction dimension. These items are more reinforced in the EDE-Q7 network of women, for example, the dynamic link "EQ4-EQ6" of body image overvaluation and weight dissatisfaction is more reinforced in this group compared to men. In addition, the relationship of "EQ1-EQ2" (partial r = 0.33) stands out, which, together with the other connections mentioned above, drives a better dynamic that activates the operation of the other components of this network. Likewise, the relationship between dietary restriction in the male network model was noteworthy (partial r = 0.38).

A difference of interest is visualized in the male network (Fig. 1B) in the "EQ1-EQ5" relationship (partial r = 0.27) between the dimension's weight overvaluation and diet restriction, where both items present a higher strength index (1.34 and 0.81) in males compared to females (Fig. 2). In other words, there is a higher prevalence of dietary restriction in men, while in women the measure of dissatisfaction with body image stands out. Assessment of networks for men and women using the NCT showed no differences in network structure ($p = 0.07$) or overall strength ($p = 0.06$). Because the network structure was found to be invariant, the strengths of individual connections were not tested.

DISCUSSION

The EDE-Q7 is one of the instruments most used to evaluate measures of higher risk to develop an eating disorder (14). This study was conducted in response to concerns about the non-utilization of the eating disorders network in the Latin Amer-

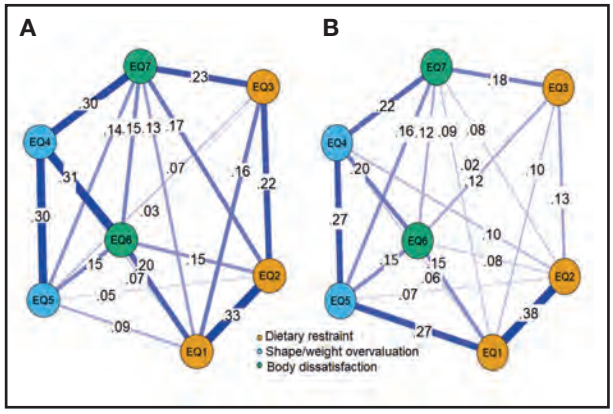

Figure 1.

A. Analysis of women's network. B. Analysis of men's network.

ican context. To our knowledge, this is the first study that evaluates through the network approach the EDE-Q7 measure that presents components such as dietary restriction, overvaluation, and dissatisfaction about weight and body image in males and females.

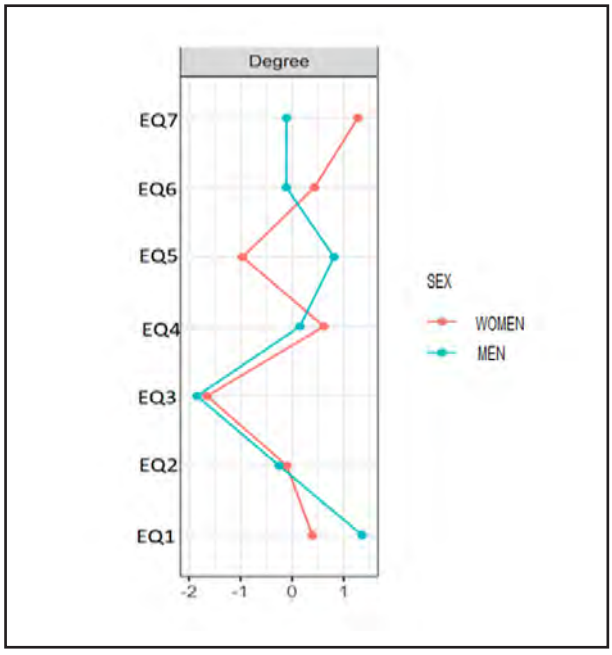

Figure 2.
Measure of force centrality.

According to the NCT measure, the dynamic network evaluation suggests that the DTS-Q7 systems for women and men shared most borders and network characteristics; however, some descriptive differences were found; for example, based on the strongest connection in both networks, EQ1-EQ2 can be considered as one of the multiple possible routes for connecting the other network elements. One of the possible connectivity routes that involve those measures of greater centrality in the network of women indicates 5 elements (EQ1-EQ2-EQ4-EQ6) that represent the three domains of the EDE-Q7, unlike men (EQ1- EQ2-EQ4-EQ5) that identify only two subscales: diet restriction and body overestimation.

Such findings suggest variations in the weight dissatisfaction dimension (more prevalent in women) and the body image dissatisfaction dimension (EQ7), which are the most central in the female network. Both items are part of the body dissatisfaction subscale. This could explain the fact that there is a greater psychological vulnerability in ED development in women compared to men. These results are supported by recent research findings that included the EDE-Q7 measures, where women reported a lower level of caporal appreciation compared to men (21). However, these results are contrasted by a study that reported higher score differences on the EDE-Q subscale in favor of women (22). On the other hand, Wang and colleagues assessed binge eating disorder in males and females through the network approach, finding a greater central importance in the two body dissatisfaction items (27). Another recent network study in the South American context demonstrated a higher measure of strength in weight dissatisfaction (ED6) in men and women, but this measure was more prevalent with higher levels of psychological distress and stress by COVID-19 (28). However, another network study conducted in men found a higher centrality of the body image devaluation symptom, however, weight devaluation was not influential in this network (16), which is contrary to the findings reported in the current study. Therefore, the implementation of ED prevention and health promotion programs in males is necessary.

The network results obtained from the current study show simultaneous statistical interactions after partializing the effects of the other network relationships. In this sense, this dynamic model applicable to instruments related to health and behavioral sciences is novel. It is also possible to integrate the results of self-report measurements or other clinical measurements, such as physiological, biochemical, anthropometric, psychiatric, and others (15,29), for the integral evaluation of the functioning and interaction of various aspects linked to different health conditions, such as arterial hypertension (30), pathology considered as one of the risk factors in mental health (31,32).

Moreover, it is possible to identify and group the variables with the highest probability of connection, these measures present an underlying latent characteristic in the structure of the network, considering the example of an exploratory graphical model reported by Ramos-Vera (33) where the relationships of depressive symptomatology in patients with arterial hypertension were grouped into two dimensions of emotional and somatic nature based on network clustering algorithms and factor analysis.

The burgeoning methodology of network analysis of statistical relationships has had some questioning about its statistical replication in binary models (37), which has been contested by (34). Regarding its use in polytomous variables, it has presented greater replicability by previous authors, but like any new methodology, it usually presents some points to discuss. It is also a method under development, which currently has statistical replication techniques (35) for the robustness of health and behavioral science research that allows evaluating new clinical hypotheses in eating disorders (36). It is also possible to evaluate the Bayes factor to weigh the evidential strength of the statistical relationships of the network (37,38) or to estimate the degree of evidence of the comparative hypotheses according to sex or other conditions of interest (39).

The results of this article from the network approach have a favorable clinical implication to direct intervention and treatment of eating disorders (40); in addition, it can be oriented to complement instrumental and correlational investigations to reinforce the inferential property of such more comprehensive conclusions for decision-making in clinical studies that may affect people's health.

LIMITATIONS

The current study has several limitations. First, the data were collected by non-probability convenience sampling (mostly female participants). In addition, the results were self-reported, which obviously limits the generalizability of the findings to other populations. Furthermore, it is important to consider that this is a cross-sectional design and therefore direct causality cannot be inferred. Finally, the data were collected during the health crisis caused by COVID-19, which could affect our results, being that COVID-19 could behave as a confounding variable affecting eating disorders.

CONCLUSION

This study that evaluated two simultaneous network models of EDE-Q7 by sex in Peruvian adults presented evidence of invariance in both structure and connection magnitudes using the network model. However, descriptive differences were found in the central network measures. In fact, in women, it was evident that the dimension of dissatisfaction with body image presented a greater network centrality. However, in the case of males, a higher central prevalence of network in the dietary restriction dimension was highlighted. Such findings allow us to explain the possible variations in the activation of factors of greater risk in the development of ED according to the gender of greater psychological vulnerability in Peruvian adults.

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ARÁN

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Trabajo Original

Epidemiología y dietética

Depression symptoms and sweet foods consumption in Mexican college men: the role of emotional eating

Síntomas de depresión y consumo de alimentos dulces en un grupo de varones universitarios mexicanos: el papel de la alimentación emocional

Irina Lazarevich, María Esther Irigoyen-Camacho, Marco Antonio Zepeda-Zepeda, María Consuelo Velázquez-Alva, Leonor Sánchez-Pérez

Health Care Department. Universidad Autónoma Metropolitana-Xochimilco. Coyoacan, Mexico

Abstract

Objective: to evaluate the association between depression symptoms and frequency of unhealthy food consumption, and to explore the mediation effect of emotional eating in this relationship in college men.

Method: a cross-sectional study was performed on 764 men at a public university in Mexico City. To assess emotional eating (EE), a validated Spanish-language version of the Eating and Appraisal Due to Emotions and Stress Questionnaire (EADES) was applied. Depression symptoms were evaluated using the scale elaborated by the Center for Epidemiologic Studies (CES-D) and a Questionnaire of Frequency of Food Consumption was used to measure frequency of food consumption. Path and mediation analysis were applied.

Results: one-fifth (20.42 %) of college men reported depression symptoms (CES-D ≥ 16). Students with depression symptoms had a higher mean EE score ($p < 0.001$), a higher frequency of fried food ($p = 0.049$), sweetened beverages ($p = 0.050$), and sweet foods consumption ($p = 0.005$) than students with low CES-D score. According to the mediation analysis, the effect of depression symptoms on the frequency of sweet foods consumption was partially mediated by EE (23.11 % of the total effect).

Conclusion: the prevalence of depression symptoms was high. EE is an important mediator in the relationship between depression symptoms and the consumption of sweet foods. Understanding the manifestation of eating behaviors in men and their relationship with depression symptoms may help clinicians and health authorities develop treatment and prevention programs aimed to decrease the risk of obesity and eating disorders.

Keywords:

Emotional eating. Depression. College students.

Resumen

Objetivo: evaluar la asociación entre los síntomas de depresión y la frecuencia de consumo de alimentos no saludables y explorar el efecto de la alimentación emocional como variable mediadora en esta relación en hombres universitarios.

Método: se realizó un estudio transversal en 764 hombres de una universidad pública en la Ciudad de México. Se aplicó la versión validada en español del *Eating and Appraisal Due to Emotions and Stress Questionnaire* (EADES) para evaluar la alimentación emocional (AE). Los síntomas de depresión fueron evaluados mediante la escala elaborada por el Centro de Estudios Epidemiológicos (CES-D) y el consumo de alimentos se evaluó con el Cuestionario de Frecuencia de Consumo de Alimentos. Se llevó a cabo un análisis de senderos y de mediación.

Resultados: una quinta parte (20,42 %) de los hombres universitarios reportaron síntomas de depresión (CES-D ≥ 16). Los estudiantes con síntomas de depresión tuvieron una puntuación media de AE más alta ($p < 0,001$), mayor frecuencia de consumo de frituras ($p = 0,049$), de bebidas azucaradas ($p = 0,050$) y de alimentos dulces ($p = 0,005$) que aquellos con baja puntuación en la escala de CES-D. De acuerdo con el análisis de mediación, el efecto de los síntomas de depresión sobre la frecuencia de consumo de alimentos dulces fue mediado parcialmente por la AE (23,11 % del efecto total).

Conclusión: la prevalencia de síntomas de depresión fue alta. La alimentación emocional es un mediador importante en la relación entre síntomas de depresión y consumo de alimentos dulces. Conocer la conducta alimentaria en los hombres y su relación con los síntomas de depresión puede ayudar a los médicos y autoridades de salud a desarrollar tratamientos y programas preventivos destinados a disminuir el riesgo de obesidad y trastornos alimentarios.

Palabras clave:

Alimentación emocional. Depresión. Estudiantes universitarios.

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Correspondence:

María Esther Irigoyen-Camacho. Health Care Department. Universidad Autónoma Metropolitana-Xochimilco. 1100 Calzada del Hueso, Col. Villa Quietud. Coyoacan, Mexico
e-mail: meirigo@correo.xoc.uam.mx

INTRODUCTION

In the last two decades, more attention has been focused on eating behaviors in men; however, research is still scarce, and men are systematically overlooked in this area. Research in men does not have the same proportion as in women, and men continue to be excluded from many studies (1).

Emotional eating (EE) represents a maladaptive eating behavior (2), which refers to an increased food intake in response to emotions, especially negative mood states, such as anxiety, frustration, sadness, and anger, among others. Emotional eating could be considered as eating with emotion-focused coping, which attempts to minimize, regulate, and prevent emotional tension, often related to difficulty in controlling the quality (food choice) and quantity of food intake (3,4). According to affective theory (5) and the five-way model proposed by Macht (6) about the bidirectional relationship between emotions and eating behavior, some individuals cannot recognize their hunger and satiety cues and confuse emotional needs and biological hunger.

Previous studies reported that women had higher scores of emotional eating than men and this behavior was associated with weight fluctuations, difficulties with weight loss or weight maintenance, binge eating, and depression symptoms (7,8). In the study by Van Strien et al. (4) it has been found that emotional eating acted as a mediator between depression and weight gain in women; however, no such mediation effect was found for men.

Studies have suggested that depression symptoms are related to eating behaviors, especially in women (4,9); nevertheless, there are contradictory findings with respect to their role in men (10,11). A study performed among United States college students by Turel et al. (12) reported no differences in depression scores between men at risk and not at risk of eating disorders.

Regarding depression symptoms and eating behaviors, according to the American Psychiatric Association (13) depression is frequently accompanied by appetite changes: decreased or increased appetite (atypical depression). Cognitive mechanisms that explain overeating in mood disorders may be a desire to achieve an instant reward and reduction of affective self-control (impulsive food choice, particularly for "comfort foods", high in fat and sugar) (14,15). In previous studies, a mediation effect of emotional eating between depression and weight gain has been found (4,16).

The biological theoretical framework on eating behavior has been focused on neurobiological processes referred to dopamine systems: food represents a natural reward and gratification related to dopamine production that influences food selection towards high-energy foods (17). Furthermore, sugar consumption is associated with reduction of stress-induced cortisol and hippocampus activation, which is typically inhibited during acute stress (18). In studies on food cravings focused on carbohydrate consumption, it has also been found that this behavior was related to serotonin deficit; therefore, some people tend to overeat sweet food to improve mildly dysphoric mood (19-21).

Konttinen et al. (22) examined the association of emotional eating and depression symptoms with food choices in Finnish men and women, aged between 25 and 64. In men, emotional eating and depression symptoms were related to a higher body mass index, and emotional eating was associated to a higher consumption of sweet foods (frequency/week), as well as with the consumption of non-sweet energy-dense foods. In France, Camilleri et al. (23) studied associations among emotional eating, depression, and the consumption of energy-dense snack food in 7,378 men over 18 years old. However, there were no relationship between emotional eating and sweet foods intake (chocolate and cakes/biscuits/pastries) in men with depression symptoms. In a systematic review of 45 studies (24) on relationship between emotional eating, consumption of hyperpalatable energy-dense foods and nutritional status, it has been indicated that emotional eating had an association with greater consumption of energy-dense snacks, particularly sweet and high-fat foods, especially with relation to negative emotions. Additionally, a mediator effect of emotional eating between depression and weight gain has been reported (4,16); however, the studies have been mostly focused on women' populations, and there is no information about mediating effect of emotional eating between depression and foods consumption.

In Mexico in recent decades, an "obesogenic environment" characterized by greater availability of high-energy foods and physical inactivity, factors related to weight gain, has been experienced widely. According to the National Survey of Health and Nutrition (NSHN) (25), the increasing prevalence of overweight/obesity in all age groups of the Mexican population has been linked to the consumption of sugary drinks, fried food, and fast food on a daily basis, as well as to a large proportion of high-energy food consumed away from home and decreased physical activity. It is worth considering that poor eating patterns acquired at a young age may persist into adulthood and lead to weight gain or other chronic diseases. The results of the Mexican NHNS reported that the prevalence of overweight or obesity ($\geq$ 25 kg/m^2) were quite high, 35.7 % in adolescent men and 73 % in those over 20 years of age; therefore, the identification of risk factors that contribute to unhealthy eating behavior is of great significance (25).

The current study aims to assess the associations among emotional eating, depression symptoms, and frequency of unhealthy food consumption in first-year Mexican college men. We hypothesized that depression symptoms are associated with high frequency of unhealthy food consumption and that this relationship is mediated by EE.

MATERIAL AND METHODS

STUDY POPULATION

A cross-sectional study was performed in a public university in Mexico City with first-year college men (n = 775, which represents 48.14 % from a total population of 1,610 men and women enrolled at the university) who participated in the 2017-year health survey that included anthropometry and online questionnaires. These questionnaires were applied for freshman students

during the first week of trimester in the computer classrooms. Students who did not complete the questionnaires were excluded from the study ($n = 11$); therefore, 764 men were included for analysis. The response rate was 98.58 %.

ETHICS

This study was part of the institutional project "Healthy University: disordered eating behaviors related to mental health in young adults". The questionnaire was completed anonymously, and the participants were assured of data confidentiality. The students participated on a voluntary basis, and they acknowledged informed consent on-line. This study has been carried out in accordance with the Code of Ethics of the World Medical Association, Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects. The University Review Board of Biological and Health Science approved the project and ethical aspects were revised (project approval date: session 1/17 February 2, 2017; project number 3450336).

INSTRUMENTS

Eating and Appraisal Due to Emotions and Stress Questionnaire (EADES)

To assess EE, the subscale Self-Efficacy in Emotion- and Stress-Related Eating (26), the Spanish-language version of the EADES was applied (Cronbach's alpha = 0.87) (27). In the present study, Cronbach's alpha was 0.91. The subscale consists of 12 items related to emotional and stress-related eating (e.g., I use food to cope with my emotions, I eat when I am upset with myself, I comfort myself with food, I eat when I am sad, I overeat when I am stressed, I feel out of control when I eat, it is hard for me to stop eating even though I feel full, among others). Participants responded to the questionnaire in accordance with their level of agreement on a scale from 1 to 5 from strongly disagree to strongly agree (the higher the score the more involvement in EE).

Center for Epidemiologic Studies Depression Scale (CES-D)

To identify depression symptoms, a Spanish-language version of the 20-item depression scale elaborated by the Center for Epidemiologic Studies (CES-D) was used, which was validated in non-clinical Mexican populations (28), with Cronbach's alpha = 0.83 in the student population (29). In the present study, Cronbach's alpha was 0.84. Likert-type items assessed the frequency of depressive symptomatology in the previous week, including depressed mood, feelings of guilt and worthlessness, psychomotor retardation and sleeping difficulties. A cut-off point of 16 was used to identify clinically significant depression symptoms (28). Prior psychological treatment was reported with a yes or no answer.

Food Frequency Questionnaire

The assessment of frequency of food consumption was based on the Food Frequency Questionnaire (30) and on dietary items from the NSHN (25). For the present study, foods classified as "not recommended for daily consumption" were analyzed (25). The carbohydrate-rich and/or energy-rich foods were categorized into four groups following the Mexican Center for Research in Nutrition and Health recommendations (30): fried food (e.g., potato chips, corn chips and tortilla chips, French fries, flour chicharron, and fried bananas, among others), sweet foods (cakes, cookies, pastries, sweets, chocolate, biscuits, sweet bread, among others), sweetened beverages (e.g., soft drinks, soda, sweetened ice-tea, natural and industrial juices), as well as fast food (hamburgers, fried chicken, pizza or sausages, hot dogs, white-bread sandwiches, among others). Frequency of food consumption was analyzed and measured in the number of days a week with the corresponding answers: less than once a week or once a week, two, three times a week, four or more times a week.

Anthropometry

Using the recommended techniques and procedures, a certified dietitian took body weight and height measurements (International Certification in Kinanthropometry, Isak Level 1).

A senior researcher supervised the anthropometric evaluation. Body weight and height were measured using a portable, electronic digital scale, equipped with a built-in stadiometer (SECA scale, model 813 and SECA stadiometer, model 213) with a precision of 0.1 kg and 0.1 cm, respectively.

Body mass index (BMI weight/height^2) was calculated. Based on the World Health Organization (WHO) criteria, the cut-off point for being overweight was BMI $\geq$ 25 kg/m^2, for being obese $\geq$ 30 kg/m^2 and for being underweight $<$ 18.5 kg/m^2.

DATA ANALYSIS

The analysis for categorical variables was performed using Chi-squared test. A bivariate analysis (ANOVA and linear regression) was performed between EE and the following variables: depressive symptoms, psychological treatment, BMI, and frequency of food consumption. The Bonferroni post-hoc test was used for multiple comparisons. Statistical significance was set at $p < 0.05$.

A mediation analysis was conducted using EE as a mediator between depression symptoms and frequency of sweet food consumption. This analysis was performed using the Karlson, Holm and Breen (KHB) method for comparing estimated coefficients of two nested nonlinear probability models. Additionally, to determine the significance of each mediation path, the indirect effects were examined over one thousand bootstrap replications; a 95 % confidence interval (95 % CI) was reported. The statistical analysis was performed using the Stata V17.0 (Stata Corp, College Station Tx, USA, 2021) statistical package.

RESULTS

A total of 764 college men were evaluated, the mean age of 21.12 years (SD, 2.85), ranging from 18 to 30 years old. Table I presents the descriptive characteristics of the participants. The mean BMI was 24.04 (SD: 3.23); 34.56 % of college men were overweight or obese.

About one-fifth of them reported depression symptoms (20.42 %) and a similar proportion received psychological treatment (20.55 %). Regarding food consumption, the results revealed that the most common frequency of fried food consumption was twice a week (39.14 %) and of sweetened beverages three times a week (37.96 %). About half of the students (49.74 %) consumed fast food twice a week and 38.48 % of them sweet food three times a week. Consumption of sweetened beverages and sweet foods almost daily (≥ 4 times a week) was observed in 15.44 % and 10.86 %, respectively, of the participants.

The mean EE score was 23.98 (SD: 9.13). Students with depression symptoms (CES-D ≥ 16) presented a higher mean EE score, (27.63; SD: 9.13) than students with CES-D score < 16 (23.05; SD: 8.90; $p < 0.001$). Similar results were observed when comparing students with (mean EE score = 27.08; SD: 8.79) and without (mean EE score = 23.99; SD: 9.80) psychological treatment ($p < 0.001$). However, mean BMI was not associated with EE score ($p = 0.396$).

Table II presents the percentage of the students with depression symptoms by frequency of fried food, sweetened beverages, and sweet food consumption. Students with depression symptoms had a higher frequency (≥ 4 times a week) of fried food ($p = 0.049$); sweetened beverages ($p = 0.050$) and sweet food consumption ($p = 0.005$).

Regarding EE and frequency of food consumption (Table III), higher mean EE scores were found in students with a higher frequency of fast food ($p = 0.050$) and sweet foods consumption ($p = 0.001$). Particularly, students with frequency ≥ 4 times a week of sweet foods consumption had a score 20.51 (SD: 8.17), while their counterparts with frequency ≤ 1 time a week had a mean EE score 17.26 (SD: 6.54). Figure 1 presents students' responses to three items of EE questionnaire, where a greater percentage difference by sweet foods consumption frequency was observed. Students with a higher consumption frequency had a greater agreement of eating when they felt sad or stressed, or unable to control how much they ate.

Based on path analysis results, EE did not have a significant effect in the relationship between depression symptoms and frequency of fat, fried food, or sweetened beverages consumption. However, a significant effect of EE was observed between depression symptoms and frequency of sweet foods consumption; figure 2 depicts the path analysis results. Depression symptoms had a positive effect on EE ($\beta_1 = 3.54$, CI: 2.28-4.79, $p < 0.001$) and, in turn, EE had a positive effect on sweet foods consumption ($\beta_2 = 0.04$, CI: 0.01-0.07, $p = 0.015$).

Table IV presents the results of the mediation analysis. The total effect of depression symptoms on frequency of sweet food

Table I. Distribution of college men according to the study variables ($n = 764$)

Variables		
Age (years) (mean ± SD)	21.12	± 2.85
	n	**%**
Living with their family		
Yes	601	78.66
No	163	21.34
Having children of their own		
Yes	19	2.49
No	745	97.51
BMI (kg/m^2) (BMI, mean ± SD)	24.04	± 3.23
	n	**%**
BMI categories		
Underweight	19	2.49
Normal weight	481	62.96
Overweight	227	29.71
Obesity	37	4.84
*Depression symptoms**		
Yes (CES-D ≥ 16)	156	20.42
No (CES-D < 16)	608	79.58
Psychological treatment		
Yes	157	20.55
No	607	79.45
Frequency of food consumption		
Fried food		
≤ 1 time a week	229	29.97
2 times a week	299	39.14
3 times a week	200	26.18
≥ 4 times a week	36	4.71
Sweetened beverages		
≤ 1 time a week	148	19.37
2 times a week	208	27.23
3 times a week	290	37.96
4 times a week	118	15.44
Fast food		
1 time a week	188	24.61
2 times a week	380	49.74
3 times a week	172	22.51
≥ 4 times a week	24	3.14
Sweet foods		
≤ 1 time a week	140	18.33
2 times a week	247	32.33
3 times a week	293	38.48
≥ 4 times a week	84	10.86

*BMI: body mass index. *Center for Epidemiologic Studies-Depression Scale (CES-D).*

consumption was significant and positive (0.71, $p = 0.005$). The direct (0.55, $p = 0.035$) and indirect (0.17, $p = 0.011$) effects were also significant and positive. According to this analysis, the indirect effect of EE represented 23.11 % of the total effect of depression symptoms on frequency of sweet food consumption.

Table II. Depressive symptoms and frequency of fried food, sweetened beverages, fast food, and sweet foods consumption in college men

	Fried food*			Sweetened beverages*			Fast food*			Sweet foods*		
	Yes *n* (%)‡	No *n* (%)‡	*p*	Yes *n* (%)‡	No *n* (%)‡	*p*	Yes *n* (%)‡	No *n* (%)‡	*p*	Yes *n* (%)‡	No *n* (%)‡	*p*
Depressive symptoms†												
Yes	12 (33.33)	144 (19.78)	0.049	32 (27.12)	124 (19.20)	0.050	8 (33.33)	148 (20.00)	0.111	26 (31.33)	130 (19.09)	0.005
No	24 (66.67)	584 (80.22)		86 (72.88)	522 (80.0)		16 (66.67)	592 (80.00)		57 (68.67)	551 (80.91)	
Total	36	728		118	646		24	740		84	680	

**Cut-off value: four or more times per week. †Depressive symptoms CES-D ≥ 16. ‡Column percentage.*

Table III. Emotional eating and frequency of food consumption in college men

Food frequency consumption	Emotional eating mean (SD)	*p**
Fried food		
≤ 1 time a week	23.61 (8.82)	0.655
2 times a week	24.03 (9.39)	
3 times a week	24.06 (9.61)	
≥ 4 times a week	25.67 (9.61)	
Sweetened beverages		
≤ 1 time a week	24.24 (9.16)	0.297
2 times a week	22.96 (9.01)	
3 times a week	24.39 (8.70)	
≥ 4 times a week	24.49 (10.28)	
Fast food		
≤ 1 time a week	22.76 (8.72)	0.050
2 times a week	24.00 (8.71)	
3 times a week	24.89 (9.71)	
≥ 4 times a week	27.04 (13.07)	
Sweet foods		
≤ 1 time a week	17.26 (6.54)	0.001
2 times a week	17.53 (6.75)	
3 times a week	18.83 (7.57)	
≥ 4 times a week	20.51 (8.17)	

**ANOVA p-value.*

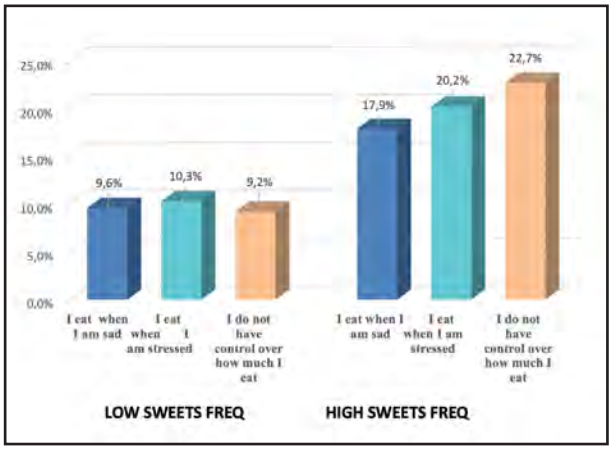

Figure 1.

Percentage of participants who indicated agreement with three questions of the emotional eating scale by frequency of sweet food consumption (low and high).

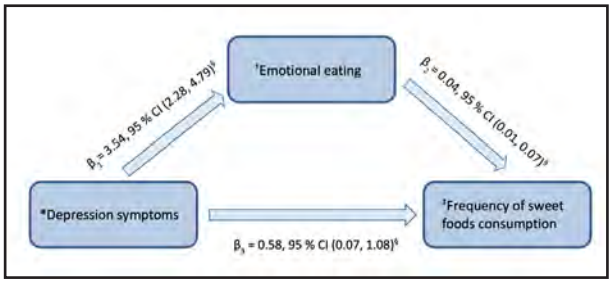

Figure 2.

Graphical representation of the path analysis. *Depression symptoms assessed with the Center for Epidemiologic Studies Depression Scale (CES-D), cut-off value CES-D ≥ 16. †Emotional eating (continuous variable) assessed with the Eating and Appraisal Due to Emotions and Stress Questionnaire (EADES). ‡Sweet foods consumption frequency cut-off value ≥ 4 times per week. §Coefficients, 95 % confidence interval (CI), unstandardized coefficients.

Table IV. Mediation analysis results and decomposition of effects of depression on sweet food consumption using emotional eating as mediator variable

	Effects	(95 % CI)*	*p*
Total effect (direct effect + indirect effect)	0.714	(0.213-1.213)	0.005
Direct effect (depression symptoms → sweet food consumption)	0.549	(0.039-1.058)	0.035
Indirect effect (depression symptoms → emotional eating → sweet food consumption)	0.165	(0.038-0.292)	0.011

**Bootstrap 95 % confidence interval (95 % CI), 1,000 replications.*

DISCUSSION

The results of the present study support our hypothesis that depression symptoms are associated with high frequency of unhealthy food consumption and that this relationship is mediated by EE. Students with depression symptoms had a higher frequency of fried food, sweetened beverages, and sweet food consumption. Additionally, greater mean EE scores were observed among students with higher frequency of fast food and sweet foods consumption.

The results of our study indicated that the relationship between depression symptoms and frequency of sweet foods consumption was partially mediated by EE (23.11 % of the total effect). This suggests that EE plays a significant role in the relationship between depression symptoms (atypical depression with increased appetite) and frequency of sweet foods consumption, together with other mechanisms that intervene in this relationship (17,18), such as food selection and eating habits, parenting styles, personality, physical activity, and type of depression. Individuals with atypical depression are frequently prone to develop abnormal eating behavior, such as overeating in response to negative emotions, which may be considered as a coping mechanism to improve altered emotional state. It is common for these individuals to have difficulty in recognizing and managing their moods. Additionally, they confuse hunger and satiety with physiological distress and turn to food consumption as a means of coping with negative emotions. In this case, emotional eating may mediate the relationship between depressive symptoms and food choices (overconsumption of "comfort food"), which can consequently lead to weight gain or eating disorders among other health problems (4,16,31).

Our findings are in accordance with Ling et al. (32), who have reported that in the United States college men and women, between 18 and 25 years old, EE was positively related to sweet foods consumption. Regarding exclusively college men, in a qualitative study performed in the United States (33), it was found that boredom and anxiety were triggers for overeating sweet foods. Similarly, in a study of Finnish men, Konttinen et al. (22) have identified that emotional eating was associated with higher consumption of sweet foods, as well as non-sweet energy dense foods (pizza, hamburgers, French fries, sausages, and chips).

The results of the present study revealed that about a fifth of the study group reported depression symptoms (20.42 %). This finding proposes areas of future research to recognize how negative emotions may affect eating behavior in men, as well to identify young men at risk of developing eating disorders, weight gain in adulthood, and/or other unhealthy behaviors related to depression.

The association between depressive symptoms and EE reported herein is consistent with previous studies performed in college men. Sze et al. (34) have identified that EE was not uncommon among Chinese college men and mild depression was significantly associated with EE. However, in the United States, Turel et al. (12) have indicated that depression symptoms were not associated with risky eating behaviors in college men, in contrast to women. In the study by Mikolajczyk et al. (10), conducted in three countries (Germany, Poland, and Bulgaria) among first-year college students, there was no positive association between food consumption (i.e., fast-food, cakes, snacks, sweets) and stress and/or depressive symptoms among male students. These contradictory results, especially for men, may be explained by cultural and social factors. According to the Mexican National Health and Nutrition Survey (25), sugar consumption is very high, and this eating habit is determined to a large extent by social and environmental factors (35). Mexico is one of the highest sugar-consuming nations in the world (36). Excessive sugar intake is a risk factor for metabolic and cardiovascular diseases and has an adverse effect on the gut microbial ecosystem. The Western diet, characterized by excessive consumption of saturated fats and added sugars, can affect the composition and balance of the gut microbiota, leading to chronic inflammation and gut dysbiosis (37). Brain-gut axis function is affected by the microbiota of the gastrointestinal tract, which, in turn, is influenced by food consumption. It has been established that depression is closely linked to this axis. It is crucial to improve intestinal dysbiosis because depression, food consumption, and intestinal function are related in a complex way (38).

The sex difference in the prevalence of mood or anxiety disorders (39), and the fact that men and women express their emotional problems according to traditional gender stereotypes (40), may affect the way in which EE mediates the relationship between depressive symptoms and the frequency of sweet food consumption. In the present study, BMI was not associated with emotional eating score and depression symptoms in first-year college men. This may be explained by the young age of the participants (most of them had 18-19 years old) and their physical activity, which is common in college men.

Among the limitations of the study was its cross-sectional design, which does not allow causal interpretation of the associations identified by the statistical models. Additionally, we applied self-reported questionnaires, an assessment method which is susceptible to response bias. However, the questionnaire was completed anonymously, and the participants were assured of data confidentiality.

The questionnaires applied in the sample for evaluating EE and depression only identified tendencies to risky behaviors, as well as symptoms of depression. These questionnaires do not diagnose any clinical condition; nevertheless, the instruments applied have been previously validated in different population groups including young Mexican adults and have been frequently used to identify unhealthy behaviors.

Further research is required to assess the role of EE in the relationship between depression symptoms and food consumption in men, as well as to identify the underlying factors of "obesogenic" environment, which may help develop targeted and coordinated prevention programs in depression and eating disorders.

CONCLUSIONS

A significant number of college men reported depression symptoms that represent a challenge for clinical practitioners and the public health sector considering the increased incidence, particularly in young population groups. The relationship between depression symptoms and frequency of sweet foods consumption was partially mediated by EE. Therefore, it is important to understand how men experience and perceive their eating behaviors, which could be useful in enhancing awareness and self-regulation in these situations. In addition, it can help develop effective targeted programs in prevention or treatment of obesity and eating disorders in this population.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Epidemiología y dietética

¿Influyen los determinantes socioeconómicos en la oferta de los menús escolares?

Do socioeconomic determinants influence school menus?

Pilar Ramos[1], Marta Font[2], Olga Juárez[1], Francesca Sánchez-Martínez[1], Maria Manera[3], Maria Blanquer[3]

[1]Agència de Salut Pública de Barcelona. Barcelona. [2]Serveis Dietètics. Barcelona. [3]Agencia de Salut Pública de Catalunya. Barcelona

Resumen

Introducción: la oferta de menús escolares es un área relevante en las estrategias de salud.

Objetivos: analizar las diferencias en el cumplimiento de las frecuencias recomendadas de alimentos y otras características del comedor escolar en los centros educativos según su titularidad y la renta del barrio.

Métodos: se ofreció la revisión trienal a los centros escolares de la ciudad de Barcelona que disponían de servicio de comedor. En los tres cursos académicos, participaron 341 centros: 175 públicos y 165 de titularidad privada. Para observar si existían diferencias, se utilizó la prueba de Pearson Chi-cuadrado o el test exacto de Fisher según el caso. Los análisis se realizaron con el programa estadístico STATA SE/15.

Resultados: no se encontraron diferencias significativas según el nivel socioeconómico del barrio del centro educativo. Los centros educativos privados y concertados presentaban un menor cumplimiento en la pasta (11,1 %), las carnes rojas y procesadas (24,7 %), la carne total (7,4 %) y la fruta fresca (12,1 %), así como un menor uso del aceite recomendado para cocinar (13,1 %). Por el contrario, en los centros educativos públicos se observaba un menor cumplimiento en la recomendación del tipo de aceite para freír (16,9 %).

Conclusiones: en los centros privados y concertados es necesario recomendar mejoras en la adecuación de las raciones. Se debería indagar en las causas que pueden explicar esta menor adecuación en varios aspectos como en el cumplimiento de las adecuaciones en estos centros.

Palabras clave:

Centros educativos. Titularidad. Menús escolares. Alimentación saludable. Comedores.

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Correspondencia:

Pilar Ramos Vaquero. Servei de Salut Comunitària. Direcció de Promoció de la Salut. Agència de Salut Pública de Barcelona. Plaça Lesseps, 1. 08023 Barcelona
e-mail: pramos@aspb.cat

Abstract

Introduction: the components of school menus is an important area in health strategies.

Objectives: the aim of this study was to analyse differences in adherence to recommended food frequencies and other characteristics of school meals in educational centres according to the type of school and neighbourhood income.

Method: schools in the city of Barcelona with a lunch service were offered a three-year review. In the three academic years, 341 schools participated: 175 were public and 165 were private. To identify any differences, the Pearson Chi-squared test or Fisher exact test were used, as appropriate. Statistical analyses were performed with the STATA SE/15 programme.

Results: no statistically significant differences were found by the socioeconomic level of the school neighbourhood. Private and subsidised schools showed lower adherence to recommendations on pasta (11.1 %), red and processed meat (24.7 %), total meat (7.4 %) and fresh fruit (12.1 %), and lower use of the recommended cooking oil (13.1 %). In contrast, public schools showed lower adherence to the recommended type of frying oil (16.9 %).

Conclusions: in private and subsidised schools, improvements should be recommended on the frequency of intake of certain foods. Future studies should examine the causes of lower adherence to certain recommendations in these centres.

Keywords:

Schools. Type of school. School meals. Healthy eating. Canteens.

INTRODUCCIÓN

Actualmente, la prevención de la obesidad es una de las áreas más relevantes en el campo de intervención de la salud pública, tanto por el incremento de la prevalencia de la obesidad como por las repercusiones que ocasiona en la salud de la población general (1). Existen evidencias de que la obesidad en la infancia se asocia con un riesgo relativo significativamente mayor de desarrollar esta enfermedad en la edad adulta, como también de desarrollar hipertensión arterial, resistencia a la insulina, disfunción endotelial y otras enfermedades cardiovasculares (2). En 2020, 158 millones de niños, niñas y adolescentes sufrían obesidad en el mundo. Sin embargo, se espera que en 2030 esta cifra aumente hasta los 254 millones (3). La prevalencia de obesidad y sobrepeso infantil en España es de un 41 % en niños y niñas de siete años (4), y en Cataluña, de un 40,4 % (5). En el caso de Barcelona, la prevalencia de obesidad infantil alcanza el 7 % en población infantil de 3-4 años, el 12,7 % de 8-9 años y el 16,5 % de adolescentes (6).

Los determinantes socioeconómicos poblacionales desfavorables están asociados a un aumento de dificultades para conseguir ingestas suficientes de alimentos y un aumento en los hábitos alimentarios poco saludables, ocasionando problemas como la obesidad (7). Al mismo tiempo, la población con un mayor nivel de estudios y con más riqueza tiende a seguir patrones alimentarios más saludables; en cambio, las dietas de peor calidad suelen ser consumidas por personas con un nivel de estudios inferior y con menos recursos económicos (8). Los ingresos y la educación más altos se asocian de forma independiente con una mayor adherencia a los patrones de alimentación similares a la dieta mediterránea y una menor prevalencia de la obesidad (9).

Por otro lado, la evidencia demuestra que los centros educativos que se encuentran en áreas socioeconómicamente desfavorables tienen una alta disponibilidad de tiendas con comida poco saludable en sus inmediaciones (10).

La comida que se ofrece en el comedor escolar es la principal comida del día, y de ahí la importancia de hacer un seguimiento y propuestas de mejora desde los ámbitos de educación y sanidad de los entes públicos (11,12). El estudio ALADINO reportó la posible protección frente a la obesidad por el hecho de comer en el colegio y podría ser explicada porque, para una parte del alumnado, el comedor escolar es una garantía de al menos una comida equilibrada y saludable al día (4), actuando así los servicios públicos como garantes de una salud universal al disminuir el gradiente de desigualdades en poblaciones vulnerables.

En Cataluña, en 2006 se inició el Plan integral de promoción de la salud a través de la actividad física y la alimentación saludable (PAAS), en el que se enmarca autonómicamente el Programa de Revisión de Menús Escolares (PReME) (13). En el año 2021, Barcelona ha sido Capital Mundial de la Alimentación Sostenible, y los comedores escolares han sido un área estratégica en el impulso y la promoción de nuevos menús y hábitos alimentarios saludables y sostenibles.

Actualmente, los comedores escolares ejercen una doble función, asistencial y educativa, y en la ciudad de Barcelona son utilizados por el 70 % de la población en edad infantil (14). El comedor escolar desempeña una importante función en relación con la salud alimentaria en cuanto al suministro de alimentos y la composición de los menús ofertados, ayudando a satisfacer las necesidades nutricionales del alumnado usuario. Cabe destacar también la función educativa (monitores/as de comedor, docentes, personal de cocina, etc.), lo cual contribuye a la construcción de hábitos alimentarios saludables a largo plazo que pueden favorecer el desarrollo individual y la promoción de la salud (15).

El objetivo de este estudio fue analizar las diferencias entre el cumplimiento de las frecuencias recomendadas de alimentos según titularidad del centro escolar (público *vs.* privado y concertado) y el nivel socioeconómico del barrio en los centros escolares del Área Metropolitana de Barcelona.

MÉTODOS

Se trata de un estudio transversal realizado durante el periodo 2017-2020 que se enmarca en un proyecto de mejora de la calidad de los menús escolares promovido por las instituciones municipales. La ciudad de Barcelona cuenta con 439 centros educativos públicos, privados y concertados de Educación Especial, Infantil, Primaria y Secundaria, de los cuales 378 disponían de servicio de comedor y fueron contactados para participar en el PReME.

El PReME en la ciudad de Barcelona ofrece anualmente de manera gratuita la revisión de programaciones de los menús es-

colares a 147 de los centros educativos (un tercio cada curso académico) y con carácter de participación voluntaria. Este periodo puede reducirse de manera excepcional en determinadas situaciones, como cuando se produce un cambio en los servicios de restauración del comedor.

El programa se iniciaba con la captación de los centros escolares, aprovechando la visita programada de inspección de la Dirección de Seguridad Alimentaria de la Agència de Salut Pública de Barcelona (ASPB) a los comedores escolares, con el fin de realizar control sanitario, para ofrecer la posibilidad de revisar los menús ofertados. En las visitas de inspección de seguridad alimentaria se realizaba una entrevista presencial al personal de referencia del comedor escolar. La fuente de información era mayoritariamente la entrevista y las personas que respondían a la entrevista eran la persona responsable de cocina o la dirección del centro educativo. Durante la entrevista, en primer lugar, se cumplimentaba una encuesta con preguntas cerradas que reunía datos sobre: a) características del centro y del espacio destinado al comedor; b) tipología y gestión del servicio de restauración; c) tiempo disponible para comer; d) accesibilidad de las máquinas expendedoras y los productos que estas ofrecían; y e) tipología de menús especiales ofertados.

En los casos en los que no era posible rellenar la encuesta, se ofrecía como estrategia alternativa la posibilidad de remitirla con posterioridad por correo electrónico. Aquellos centros que no tenían programada una inspección sanitaria en ese periodo eran contactados por el Servicio de Salud Comunitaria de la ASPB y se realizaba la recogida de los menús mediante correo electrónico.

También se recogía la programación de menús de otoño-invierno, preferentemente de octubre o noviembre, de 20 días en bloques de cinco días, a partir de la cual se recopilaban datos sobre la oferta de menús para así poder valorar su adecuación a las recomendaciones alimentarias de referencia (16).

El equipo formado por dietistas y técnicas de salud pública evaluaba el cumplimiento de las frecuencias recomendadas de los distintos grupos de alimentos y las técnicas culinarias empleadas y se elaboraba un informe individualizado que se entregaba a cada centro escolar por correo electrónico con recomendaciones personalizadas sobre aspectos a mejorar. Dichas medidas y recomendaciones de frecuencia de alimentos y técnicas culinarias en la programación de los menús escolares, especificadas en la tabla I, se basaban en los criterios establecidos por la Agencia de Salud Pública de Catalunya (13,17), autoridad competente en el área, y a su vez, estaban consensuados dentro de la estrategia Nutrición, Actividad Física y Prevención de la Obesidad (NAOS) (18).

El índice utilizado para la categorización del nivel socioeconómico fue el nivel de renta familiar disponible del barrio donde

Tabla I. Frecuencias de alimentos y de técnicas culinarias recomendadas en la programación de los menús del comedor escolar (24)

Composición de los menús	Alimentos	Raciones recomendadas por semana (5 días)
Primer plato	Arroz	1
	Pasta	1
	Legumbres	1-2
	Verduras y hortalizas	1-2
Segundo plato	Proteicos vegetales (legumbres y derivados)	0-5
	Carnes totales (carnes blancas, rojas y procesadas)	1-3
	Carne blanca (aves y conejo)	1-3
	Carne roja o procesada (ternera, cerdo, salchichas, hamburguesas, etc.)	0-1
	Pescado (blanco, azul, sepia, calamares)	1-3
	Huevos (tortilla, duro, al horno)	1-2
Tipo de plato	Precocinados (canelones, croquetas, pizzas, etc.)	0-3 al mes
	Fritos (rebozados, croquetas, enharinados, etc.)	0-2
Guarnición	Ensalada (verdura fresca cruda)	3-4
	Otros (patatas, salsas, setas, hortalizas, legumbres, pastas, arroz, etc.)	1-2
	Fritos (patatas, patatas chip, rebozados, etc.)	0-1
Postres	Fruta fresca	4-5
	Lácteos (yogur, queso fresco, cuajada)	0-1
	Fruta no fresca (seca, desecada, al horno, etc.)	0-1
	Dulces (flan, natillas, helados, fruta en almíbar, etc.)	0-1 al mes
Aceites	Aceite de girasol alto oleico o de oliva para cocinar	
	Aceite de girasol alto oleico o de oliva para freír	
	Aceite de oliva virgen extra para aliñar	

se encontraba ubicado el centro educativo. Dicho índice se obtiene de la suma del total de rentas obtenidas por cada uno de los miembros de cada hogar (RDL); estas incluyen, además de las de los miembros activos, los ingresos no directamente provenientes del trabajo, como pensiones, alquileres, becas, etc. El RDL per cápita de Barcelona en los años de estudio fue de 21.484 € (valor de referencia 100). Para nuestro estudio agrupamos en tres categorías los barrios: baja (< 90), media (90-110) y alta (> 110) (19).

La titularidad de los centros educativos se agrupó en dos categorías: a) privados y concertados; y b) públicos.

Para observar si existían diferencias en el cumplimiento de las frecuencias recomendadas de consumo de alimentos y otros aspectos (tiempo para comer, espacio comedor, gestión del comedor, tipo de restauración, menús especiales, etc.), se utilizaron la prueba de Pearson Chi-cuadrado o el test exacto de Fisher, según el caso. Los análisis se realizaron con el programa estadístico STATA SE/15.

RESULTADOS

En estos tres cursos académicos se obtuvo una cobertura del 90,2 % y un total de 341 centros educativos participantes que abarcaban a 104.033 comensales. En cuanto al perfil de los comedores escolares evaluados, en la tabla II se exponen los resultados descriptivos de la muestra.

Según el nivel de renta, 144 centros estaban situados en barrios de renta baja; 80, en barrios de renta media; y 117, de renta alta.

Tabla II. Descripción de la muestra

	Públicos	Privados y concertados	Total revisados
Centros escolares según titularidad (n)	176	165	341
Nivel de estudios (%)			
Educación Infantil	44,1 %	27,2 %	33,8 %
Educación Primaria	44,1 %	27,5 %	34 %
Educación Secundaria	5,3 %	24,6 %	17,1 %
Bachillerato	4,2 %	15,8 %	11,2 %
Ciclos formativos	0,8 %	3,3 %	2,3 %
Educación especial	1,4 %	1,6 %	1,5 %
Espacio exclusivo de comedor % (n)			
Sí	95,5 (168)	95,2 (157)	95,3 (325)
No	4,5 (8)	4,8 (8)	4,7 (16)
Tiempo para comer % (n)			
> 60 minutos	13,6 (24)	12,7 (21)	13,2 (45)
46-60 minutos	36,9 (65)	27,3 (45)	32,2 (110)
31-45 minutos	34,7 (61)	46,7 (77)	40,5 (138)
≤ 30 minutos	5,7 (10)	6 (10)	5,9 (20)
No contestan	9,2 (16)	7,3 (12)	8,2 (20)
Gestión del comedor % (n)			
Dirección del centro	62,2 (106)	78,2 (129)	68,9 (235)
Asociación de familias	33 (58)	1,8 (3)	17,9 (61)
Otros	4,5 (8)	17,6 (29)	10,8 (37)
No contestan	2,3 (4)	2,4 (4)	2,3 (8)
Servicio de restauración % (n)			
Empresa externa que cocina en la escuela	59,7 (105)	58,2 (96)	58,9 (201)
Cocina central que distribuye	7,4 (13)	15,8 (26)	11,4 (39)
Cocina y personal propio	30,7 (54)	24,8 (41)	27,9 (95)
Otros	1,1 (2)	0,6 (1)	0,9 (3)
No contestan	1,1 (2)	0,6 (1)	0,9 (3)

(Continúa en página siguiente)

Tabla II (Cont.). Descripción de la muestra

	Públicos	Privados y concertados	Total revisados
Menús especiales % (n)			
Sí	98,3 (173)	96,4 (159)	97,4 (332)
No	1,7 (3)	3,6 (6)	2,6 (9)
Menús más ofertados: % (n)			
Menús para intolerancias alimentarias			
– Sin lactosa	84,9 (148)	82,4 (136)	83,3 (284)
– Sin gluten	81,2 (143)	81,8 (135)	81,5 (278)
– Sin huevos	80,1 (141)	74,5 (123)	77,4 (264)
Menús especiales			
– Sin cerdo§	86,4 (152)	72,7 (120)	79,8 (272)
– Sin carne§	69,9 (123)	47,9 (79)	59,2 (202)
– Vegetariano§	43,7 (77)	27,3 (45)	35,8 (122)
Máquinas expendedoras de alimentos % (n)§			
Sí	2,3 (4)	12,1 (20)	7 (24)
No	97,7 (172)	87,9 (145)	93 (317)
Fiambrera% (n)*			
Sí	8,5 (15)	15,2 (25)	11,7 (40)
No	91,5 (161)	84,8 (140)	88,3(301)
Bar cafetería % (n)†			
Sí	4 (7)	12,1 (20)	7,9 (27)
No	96 (169)	87,9 (145)	92,1 (314)

*Valores de Pearson Chi-cuadrado o test de Fisher según caso: *p < 0,05; †p < 0,01; ‡p < 0,005; §p < 0,001.*

En el caso de la titularidad del centro, 175 eran públicos y 165 eran de titularidad privada y concertada. En la muestra existe mayor número de centros educativos privados y concertados en los barrios de renta alta y mayor número de centros públicos en los barrios de renta baja.

Según el nivel de renta donde se ubicaba el centro educativo, no se han encontrado diferencias significativas en la oferta de menús especiales. Tampoco hay diferencias en el tiempo disponible para comer (disponen mayoritariamente de turnos superiores a 30 minutos), la gestión del comedor, la empresa de restauración, la oferta de menús especiales, la presencia de máquinas expendedoras de alimentos, cantinas y posibilidad de llevar fiambrera, o la adecuación del menú a las recomendaciones, observándose cumplimientos similares.

El 95,3 % de los centros educativos disponía de espacio exclusivo de comedor. El 72,7 % disponía del tiempo recomendado de más de 30 minutos y menos de una hora. La dirección del centro mayoritariamente era quién gestionaba el comedor (68,9 %), seguido de la asociación de familias (17,9 %). El tipo de restauración más habitual era la empresa externa que cocina en la escuela (58,9 %), seguido de la cocina y el personal propios (27,9 %).

Los menús para intolerancias alimentarias predominantes fueron sin lactosa (83,3 %), sin gluten (81,5 %) y sin huevos (77,4 %), y para los menús especiales fueron sin cerdo (79,8 %), sin carne (59,2 %) y vegetarianos (35,8 %). Un 7 % ofrecía máquinas expendedoras de alimentos accesibles a alumnado de Educación Secundaria, un 11,7 % tenía la opción de fiambrera y un 7,9 % disponía de bar cafetería. Por otro lado, los centros educativos privados y concertados presentaban una mayor opción de llevar fiambrera y presencia de máquinas expendedoras de alimentos y bebidas y disponían de más cantinas, comparado con los públicos.

En cuanto a la gestión del comedor, en los centros educativos públicos la asociación de familias fue la segunda encargada de la gestión del comedor, mientras que en los centros educativos privados y concertados no hay participación apenas de la asociación de familias, siendo otros gestores la segunda categoría más mayoritaria.

No hay diferencias en el servicio de restauración. En la categoría de titularidad del centro educativo, la empresa externa que cocina en la escuela es el principal servicio que se ofrecía, mientras que el segundo servicio más ofrecido era el de cocina y personal propios. Podemos observar que los centros educativos públicos ofrecían más menús sin cerdo, sin carne y vegetarianos.

Se observan diferencias significativas en el grado de cumplimiento de las frecuencias recomendadas de alimentos que se tenían en cuenta a la hora de valorar la composición del menú escolar (Tabla I) si comparamos teniendo en cuenta la titularidad de los centros educativos.

En la tabla III se muestra el grado de cumplimiento de los diferentes parámetros.

Los centros educativos privados y concertados presentaban un menor cumplimiento en las recomendaciones de pasta, carnes rojas y procesadas y carne total (carnes blancas, rojas y procesadas), que eran consumidas en exceso. Asimismo, hay un menor cumplimiento en cuanto a la fruta fresca (que era consumida en defecto) y el aceite recomendado para cocinar. Por el contrario, en los centros educativos públicos se observaba un menor cumplimiento en la recomendación del tipo de aceite para freír.

En el cumplimiento del arroz, legumbres, verduras, pescado, huevos, ensalada, precocinados, fritos y aceite para aliñar no se observan diferencias significativas según la titularidad del centro educativo.

Tabla III. Porcentaje de cumplimiento de las frecuencias recomendadas de alimentos y de los tipos de aceites servidos según titularidad del centro educativo

	Público	Privados y concertados	Total
Primeros platos			
Arroz	89,8 (158)	92,1 (152)	90,9 (310)
Pasta*	42,6 (75)	31,5 (52)	37,2 (127)
Legumbres	89,8 (158)	91,5 (151)	90,6 (309)
Verduras	100	100	100
Segundos platos			
Pescado	61,4 (108)	63,6 (105)	62,5 (213)
Carnes totales (carnes blancas, rojas y procesadas)§	98,9 (174)	91,5 (151)	95,3 (325)
Carnes rojas y procesadas§	65,3 (115)	40,6 (67)	53,6 (182)
Huevos	80,1 (141)	74,5 (123)	77,4 (264)
Guarnición			
Ensalada	63,1 (111)	66,1 (109)	64,5 (220)
Postres			
Fruta fresca‡	90,9 (160)	78,8 (130)	85,1 (290)
Tipos de preparaciones			
Precocinados	76,1 (134)	66,7 (110)	71,5 (244)
Fritos (segundos platos)	96,1 (169)	97 (160)	96,5 (329)
Fritos (guarniciones)	99,4 (175)	99,4 (164)	99,4 (339)
En el menú mensual			
Verduras crudas o fruta fresca diaria	100	100	100
Hortalizas y verduras diarias	100 (176)	97 (160)	98,5 (336)
Aceites			
Aceite de oliva virgen, de oliva o de girasol alto oleico para cocinar†	76,7 (135)	63,6 (105)	70,4 (240)
Aceite de oliva virgen, de oliva o de girasol alto oleico para freír*	35,8 (63)	52,7 (87)	44 (150)
Aceite de oliva virgen para aliñar	94,3 (166)	87,9 (145)	91,2 (311)

*Valores de Pearson Chi-cuadrado o test de Fisher según caso: *p < 0,05; †p < 0,01; ‡p < 0,005; §p < 0,001.*

DISCUSIÓN

En el presente estudio se ha observado cómo los comedores escolares participantes en el PReME de la ciudad de Barcelona ofrecen, en los cursos escolares 2017-2020, unos menús saludables (11) con un elevado cumplimiento de las frecuencias recomendadas de consumo, mostrando los centros privados y concertados un menor cumplimiento respecto a algunas de las recomendaciones. Dichos resultados coinciden con un único estudio encontrado del ámbito internacional (20).

La constatación de la presencia de menús con un mayor cumplimiento en las frecuencias recomendadas en los centros públicos es una de las principales aportaciones del artículo, ya que facilitaría la prevención de factores de riesgo en una población infantil más vulnerable. Gracias a la oferta de menús saludables en todos los barrios, sin diferencias en el nivel de renta, se garantiza una ingesta adecuada y saludable en los entornos con mayor vulnerabilidad socioeconómica. El mayor cumplimiento de las recomendaciones por los centros públicos puede deberse a que en estos centros no tienen en cuenta el lucro económico y

no gestionan posibles conflictos de intereses en la gestión de la partida económica y la elección de alimentos frescos o de proximidad.

Sería interesante indagar en la causa de la mayor oferta de servicios, aparte del comedor escolar, de que disponen los centros privados y concertados, como son la opción de llevar fiambrera. El hecho de tener una cartera de servicios más completa puede ser un factor atrayente para las posibles familias usuarias. La mayor presencia de máquinas expendedoras de alimentos en los centros de Educación Secundaria y del servicio de bar y cafetería podría tener una explicación relacionada con motivos económicos, al ser una fuente de ingresos para el centro educativo. Cabe resaltar que este tipo de máquinas da fácil acceso al alumnado a alimentos y bebidas con un alto contenido calórico, de azúcar y grasas.

Se deberían investigar, en estudios futuros, las causas que pueden explicar una menor adecuación de los centros educativos privados y concertados en el cumplimiento de las recomendaciones de pasta, carne roja y procesadas, carne total y fruta fresca y el menor uso del aceite recomendado para cocinar. En este sentido, en estos centros es importante aconsejar una mayor adecuación de sus raciones y tipo de aceite.

El 72,7 % disponía del tiempo recomendado de más de 30 minutos y menos de una hora. Es importante disponer de tiempos superiores a 30 minutos, pero sin llegar a dejar más de una hora para comer, y contar con un espacio exclusivo destinado a comedor escolar puesto que estos dos factores se relacionan de manera beneficiosa con una correcta alimentación infantil (21). Sin duda alguna, dar a los escolares suficiente tiempo para comer no solo es beneficioso para su desarrollo, sino también para su bienestar, tal y como señalan distintos estudios en los que se concluye que los infantes con más tiempo para comer en el comedor escolar se alimentan mejor (21,22). Sin embargo, no pueden dedicar *más de una hora* a comer por razones higiénicas-sanitarias, ya que el plato no debe permanecer tiempo prolongado a temperatura ambiente, para garantizar tiempo libre para jugar después de comer, etc. (16).

Los menús sin lactosa, sin gluten y sin huevos son cada vez más frecuentes en los centros educativos, tanto públicos como privados y concertados, por ser las intolerancias, alergias y otros trastornos más diagnosticados y comunicados por las familias. La oferta de menús especiales sin cerdo, sin carne y vegetarianos fue superior en los centros educativos *públicos. Este hecho puede* deberse a la inclusión que fomenta la escuela pública, con más diversidad y representación de diferentes etnias y religiones.

Una limitación del estudio ha sido no poder analizar los centros educativos privados y concertados por separado, incluidos en una misma categoría, dado que no se registra información al respecto en la fase inicial. No obstante, esta limitación queda minimizada por el hecho de que el número de centros escolares privados en la ciudad es reducido. Asimismo, no se ha podido valorar el tamaño ni el consumo real de las raciones, pues los cálculos se basan en la información de la planificación mensual teórica que se presenta a las familias. Por otro lado, hay otros aspectos relevantes del entorno alimentario (por ejemplo, contenido de grasa y sodio de almuerzos) que no pudieron evaluarse a través de la encuesta, como tampoco se consideraron las posibles sustituciones de alimentos ni se analizaron los menús destinados a alumnos con necesidades especiales (diversidad funcional). También puede haber un sesgo de selección, siendo los centros que ofrecen comida más saludable los que más respondan a la encuesta.

Respecto a las fortalezas del estudio, cabe destacar que dispone de una muestra suficiente representativa de los centros educativos de la ciudad de Barcelona. Esto significa que los resultados pueden generalizarse a nivel de ciudad debido a la existencia de registros y a la monitorización realizada por parte de la Administración de salud pública local, desde la cual los comedores escolares han sido ámbito de intervención prioritario como entorno promotor de salud.

Desde los entes públicos se deberían impulsar y promover múltiples estrategias conjuntas que sigan mejorando la oferta alimentaria de los comedores escolares, como son acordar modelos de gestión, tipo de supervisión, criterios de sostenibilidad y consumo de proximidad, cumplimiento de funciones educativas y de equidad social y provisión de soporte en la concreción práctica de las normativas (12,23).

Este trabajo evidencia diferencias en la oferta de menús según la titularidad del centro y debería trabajarse para minimizarlas. Se debe valorar y garantizar la aportación de la revisión de menús en los centros públicos como herramienta de transformación de los comedores escolares reductora de desigualdades.

CONCLUSIONES

Los centros educativos privados y concertados ofrecían programaciones de menús escolares menos adecuadas a las frecuencias recomendadas respecto a la pasta, la carne roja y procesada, la carne total, la fruta fresca y el tipo de aceite de oliva para cocinar y freír.

Los centros públicos ofrecían más menús especiales sin cerdo, sin carne y vegetarianos. Los centros educativos privados y concertados presentaban una mayor opción de llevar fiambrera y mayor presencia de máquinas expendedoras de alimentos y bebidas, y disponían de más cantinas.

Podemos concluir que el nivel socioeconómico del barrio o distrito donde se ubica el centro educativo no muestra diferencias significativas ni en las características del comedor ni en el cumplimiento de las frecuencias recomendadas del consumo de alimentos.

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Trabajo Original

Epidemiología y dietética

Design and validity of the Spanish version of two questionnaires related to adverse reactions to foodstuffs

Diseño y validación de la versión española de dos cuestionarios relacionados con reacciones adversas a alimentos

Lisset Pantoja-Arévalo[1], Eva Gesteiro[1], Sergio Calonge-Pascual[1,5], Margarita Pérez-Ruiz[1], Rafael Urrialde[2,3,4], Marcela González-Gross[1,6]

[1]ImFINE Research Group. Health and Human Performance Department. Faculty of Physical Activity and Sport Sciences. Universidad Politécnica de Madrid. Madrid, Spain. [2]Genetics, Physiology and Microbiology Department. Faculty of Biological Sciences. Universidad Complutense de Madrid. Madrid, Spain. [3]Pharmaceutical and Health Sciences Department. Faculty of Pharmacy. Universidad CEU San Pablo. Madrid, Spain. [4]Nutrition Department. Faculty of Nursing. Universidad de Valladolid. Valladolid, Spain. [5]REDAFLED Research Group. Didactics of Musical, Plastic and Corporal Expression Department. Universidad de Valladolid. Soria, Spain. [6]Biomedical Research Center of Pathophysiology of Obesity and Nutrition-CIBERobn. Carlos III Health Institute. Madrid, Spain

Abstract

Introduction: there is an emerging current necessity of valid questionnaires, encompassing most of food, beverages, diseases, signs and symptoms currently related to the pathogenesis of adverse reactions to foodstuffs (ARFS) in the Spanish population.

Objectives: this study aimed to design and validate two questionnaires to assess ARFS in the Spanish population, Food and Beverages Frequency Consumption Questionnaire to Identify Adverse Reactions to Foodstuffs (FBFC-ARFSQ-18); and Pathologies and Symptomatology Questionnaire associated with Adverse Reactions to Foodstuffs (PSIMP-ARFSQ-10).

Methods: both questionnaires were designed adapting questionnaires from the literature; and validated, using the expert judgment method, in five phases: questionnaires development, pilot test and reliability, content validity, face validity, and ethical considerations. Questionnaires were developed using the REDCap™ tool hosted at the Universidad Politécnica de Madrid. A total of 20 Spanish experts evaluated the questionnaires. Cronbach's alpha reliability coefficients were calculated using SPSS version 25.0 (IBM Corp., Armonk, NY-USA) and Aiken's V coefficient values were calculated using ICaiken.exe (Visual Basic 6.0, Lima-Perú).

Results: a final construct of questions was designed, ensuring no overlap, for FBFC-ARFSQ-18 and PSIMP-ARFSQ-10. Cronbach's alpha reliability coefficients were 0.93 and 0.94; and Aiken's V coefficient values were 0.90 (0.78-0.96 CI) and 0.93 (0.81-0.98 CI) for FBFC-ARFSQ-18 and PSIMP-ARFSQ-10, respectively.

Conclusions: both validated questionnaires could be used to analyze the association between certain food and beverages consumption with ARFS, such as food allergies and food intolerances; also, to investigate the link between some specific diseases, signs and symptoms with ARFS.

Keywords:

Adverse effects. Disease management. Food and beverages. Reliability and validity. Surveys and questionnaires. Symptom assessment. Validation study.

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Correspondence:

Lisset Pantoja-Arévalo. ImFINE Research Group. Health and Human Performance Department. Faculty of Physical Activity and Sport Sciences (INEF). Universidad Politécnica de Madrid. C/ Martín Fierro, 7, 6.o, hall D. 28040 Madrid, Spain
e-mail: l.pantoja@upm.es

Resumen

Introducción: actualmente, existe una necesidad emergente de cuestionarios validados que abarquen la mayor parte de los alimentos, bebidas, enfermedades, signos y síntomas relacionados con la patogénesis de las reacciones adversas a los alimentos (RAA).

Objetivos: diseñar y validar dos cuestionarios para evaluar las RAA en población española, el Cuestionario de Frecuencia de Consumo de Alimentos y Bebidas para Identificar Reacciones Adversas de Origen Alimentario (CFCAB-RAA-18); y el Cuestionario de Patologías y Sintomatología Asociadas a Reacciones Adversas a Alimentos (PSIMP-RAA-10).

Métodos: ambos cuestionarios se diseñaron adaptando cuestionarios de la literatura y se validaron, utilizando el método de juicio de expertos, en cinco fases: desarrollo de cuestionarios, prueba piloto y confiabilidad, validez de contenido, validez aparente y consideraciones éticas. Los cuestionarios se desarrollaron utilizando la herramienta REDCap™. Un total de 20 expertos evaluaron los cuestionarios. Se calcularon coeficientes de confiabilidad alfa de Cronbach con SPSS versión 25.0 (IBM Corp., Armonk, NY-Estados Unidos) y valores del coeficiente V de Aiken con ICaiken.exe (Visual Basic 6.0, Lima-Perú).

Resultados: se diseñó una construcción final de preguntas, evitando solapamiento entre ambas herramientas. Los coeficientes de confiabilidad alfa de Cronbach fueron 0,93 y 0,94, y los valores del coeficiente V de Aiken fueron 0,90 (IC: 0,78-0,96) y 0,93 (IC: 0,81-0,98) (CFCAB-RAA-18 y PSIMP-RAA-10, respectivamente).

Conclusiones: ambos cuestionarios fueron validados y podrían utilizarse para analizar la asociación entre el consumo de determinados alimentos y bebidas con las RAA, como alergias e intolerancias alimentarias, así como para investigar el vínculo entre algunas enfermedades, signos y síntomas específicos con las RAA.

Palabras clave:

Alimentos y bebidas. Cuestionarios. Fiabilidad. Reacciones adversas. Síntomas y signos. Validez.

INTRODUCTION

The global prevalence of adverse reactions to foodstuffs (ARFS), including components of food and beverages allergy (CFBA) and components of food and beverages intolerance (CFBI), in developed countries is around 30 %, with a female dominance in adults of 60 %, representing an emerging public health concern (1,2). CFBA and CFBI can start at any age; in fact, there is an increased reported incidence of new-onset CFBA in adults (one adult for every four children) (1-3). A detailed record of the consumption of any substance that is used as food and beverages or to make food and beverages (foodstuffs) and a clinical history are essential keys for the diagnosis, management, analysis and the study of ARFS (2,4). The consumption of specific foodstuffs can induce a wide range of adverse reactions ranging from abdominal swelling to life-threatening anaphylaxis (5). The relationship of foodstuffs intake, that may cause ARFS, and the analogous diseases and symptomatology make it challenging for researchers and physicians to establish a proper analysis of ARFS.

Several approaches of tools have been launched to identify food and beverages frequency consumption in the adult population with ARFS, focusing on CFBA and celiac disease (CD): Gluten Food Frequency Questionnaire (G-FFQ) (6), the Global Allergy and Asthma European Network (GA2LEN) FFQ (7) and the Pregnancy FFQ (8). Similarly, various tools have been designed to screen a CFBA such as the CFBA Screening Questionnaire (9), the Food Allergy Questionnaire (FAQ) (10), the Allergy Questionnaire for Athletes (AQUA©) (11), the Lahey Health Allergy Questionnaire (12) and the Weill Cornell Medicine Adult Allergy Questionnaire (13). There are also separate tools available to identify specific groups of symptoms by system, such as the Gastrointestinal Symptom Rating Scale (GSRS), the self-reported Skin Complaints Questionnaire (14), the Sensitive Skin Questionnaire (15) or the UCLA Dizziness Questionnaire (UCLA-DQ) (16).

Health professionals can frequently confuse non-adverse reactions to food and beverages with ARFS, especially when using only one of the tools available without considering a group of appropriate questionnaires, or their adaptation, for the population or patient of interest (17). The diagnosis of CFBA can be confirmed with a physical exploration, clinical history, oral food challenge (OFC) or by evidence of sensitization to the culprit using, for example, skin prick test (SPT) or serologic testing measuring food-specific immunoglobulin E (IgE) by a physician. However, it has been highly suggested by previous studies (18,19), specially by the European Academy of Allergy and Clinical Immunology (EAACI) (20), to support any of the clinical tests using adequate questionnaires, to report both, foodstuffs consumption and symptomatology, as the strongest predictors of a probable CFBA (20). Nowadays, food behavior, the expansion and management of diseases and the relationship between them is evolving in developing countries (21,22). There are extensive new foodstuffs consumed in the Mediterranean Spanish area besides those belonging to the Mediterranean diet (MD); diets are becoming highly processed and several fad diets are appearing (22,23). In addition, various pathologies and diseases are currently being investigated for their potential to have a direct or indirect relationship to ARFS: atopic dermatitis (24), irritable bowel syndrome (IBS) (25), and other diseases (26,27). In this sense, to identify all the main food consumption, pathologies and symptomatology that influence ARFS, focusing on CFBA and CFBI characteristics, designing and validating a specific tool should be a priority for an efficient diagnosis, analysis and study of ARFS.

However, there is no consensus or validated questionnaire to measure, in the Spanish population, up-to-date food and beverages consumption, including current available food groups, diets, new foodstuffs and all types of possible diseases, symptoms and signs that may have a current, potential and direct relation to ARFS (not only to CFBA). Therefore, as part of a broader investigation, the objectives of this study were to design and validate, through the expert judgement method, two questionnaires to assess ARFS for the Spanish population: the Food and Beverages Frequency Consumption Questionnaire to identify Adverse Reactions to Foodstuffs (FBFC-ARFSQ-18) (*Cuestionario de Frecuencia de Consumo de Alimentos y Bebidas para Identificar Reacciones Adversas de Origen Alimentario*, CFCAB-RAA-18);

and the Pathologies and Symptomatology Questionnaire Associated with Adverse Reactions to Foodstuffs (PSIMP-ARFSQ-10) (*Cuestionario de Patologías y Sintomatología Asociadas a Reacciones Adversas a Alimentos*, PSIMP-RAA-10). Both objectives, as a first step to facilitate the identification of a population with a high probability of having ARFS, are under the umbrella of the subsequent ARFS analysis initiative through a follow-up study.

MATERIALS AND METHODS

This study developed and validated the FBFC-ARFSQ-18 and the PSIMP-ARFSQ-10 questionnaires using the expert judgement method over the following phases: a) questionnaires development; b) pilot test and reliability; c) content validity; d) face validity; and e) ethical considerations (Fig. 1).

PHASE 1: QUESTIONNAIRES DEVELOPMENT

Both questionnaires were previously adapted with available tools found in the literature to the particularities of ARFS. The FBFC-ARFSQ-18 questionnaire used a basis-format of the semiquantitative Fernández-Ballart JD et al. FFQ (28) and the International Statistical Classification of Diseases and Related Health Problems (ICD-10) was followed for the PSIMP-ARFSQ-10 questionnaire (29). Tools were designed and structured according to the researchers' insights (authors of this study). Items of FBFC-ARFSQ-18 were intended as food groups and items of PSIMP-ARFSQ-10 were designed as diseases and symptomatology of a human body system. Food groups of the FBFC-ARFSQ-18 consisted in foodstuffs with possible causative food allergens proposed by Lyons et al. (20) (Annex I; https://www.nutricionhospitalaria.org/anexos/04631-01.pdf). Initially, there were 21 items for the FBFC-ARFSQ-18 tool, however, "vegetables, garden vegetables and legume" were consolidated as a single item. Similarly, olive oil was added to item 15 "other food groups", acquiring 18 items. Likewise, there were initially five items as five human body systems as a starting point for the PSIMP-ARFSQ-10 (each item was separated into two categories, "diseases or pathologies" and "symptoms and signs", acquiring ten items in accordance with the researchers' insights). The items of FBFC-ARFSQ-18 were classified into three sections (eating habits; frequency of consumption of food and beverages; and frequency of consumption of food supplements) to identify the eating patterns of interest in diets "free of" or "containing" allergens, components and/or foodstuffs related to ARFS that can possibly cause CFBA or CFBI. The items of PSIMP-ARFSQ-10 followed the ICD-10 classification (29) to stablish the human body systems

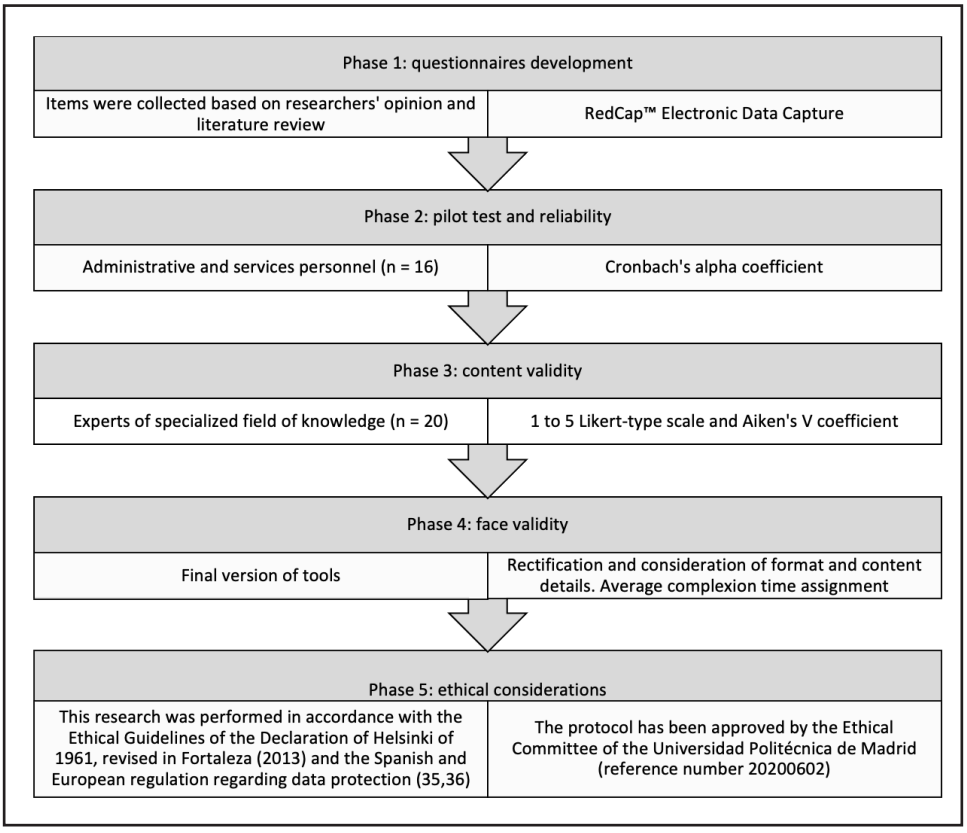

Figure 1.

Flow diagram of the phases involved in the design and validity using the expert judgement method of the FBFC-ARFSQ-18 and PSIMP-ARFSQ-10 questionnaires to assess ARFS.

and the EAACI guidelines (30) for the identification of the specific diseases, signs and symptoms related to ARFS (five sections: digestive system; skin and subcutaneous tissue; nervous system [NS]; respiratory system [RS]; and other human body systems [other diseases/pathologies, symptoms and signs, not elsewhere classified]). Both tools were hosted using RedCap™ (Research Electronic Data Capture), an electronic data capture program specifically designed for research and a secure web platform hosted at the Supercomputing and Visualization Center of Madrid (CESVIMA) of the Universidad Politécnica de Madrid (UPM). RedCap™ was also used to build and manage the online databases for both questionnaires.

Annex I.

PHASE 2: PILOT TEST AND RELIABILITY

Tools were evaluated by a pilot sample with similar characteristics to the target population to obtain qualitative assessments such as the identification of semantic errors, writing and comprehension. Inclusion criteria were: to be Spanish, living in the Region of Madrid, with age over or equal to 18 years (≥ 18 years), with non-scientific qualification (including students and retired) and presenting at least five diseases or subjective symptoms related to ARFS (Table I). Subjects with scientific background were excluded. Sampling was applied to the administrative and service personnel (ASP) of the Faculty of Physical Activity and Sport Sciences (INEF) of the UPM, to ensure evaluations by individuals who were not familiar with science. The complexion time of both questionnaires was recorded and evaluations of the approach of the items to their ARFS were calculated using the Cronbach's alpha reliability coefficient. Values greater than or equal to 0.80 (≥ 0.80) were considered as acceptable. Statistical analysis was carried out using SPSS Statistics software version 25.0 (31). At the end of the pilot test, the revised version of the tool was then reviewed by the expert judges for validation.

PHASE 3: CONTENT VALIDITY

Experts were recruited from different national research groups, hospitals, scientific institutions and universities using the contacts of the research group conducting this study (academics and practitioners of the intended field of knowledge). The inclusion criteria for being considered as an expert were: with age over or equal to 35 years old (≥ 35 years); over or equal to 15 years of career experience (≥ 15 years); academic background related to food science and/or nutrition (food science and technology professionals, dietitians, nutritionists, pharmacists, nurses and fam-

Table I. Descriptive data of the pilot sample for the adaptation of FBFC-ARFSQ-18 and PSIMP-ARFSQ-10

Evaluators	Age (years)	M/F	Country of birth	Residence	Qualification	Number of diseases, symptoms and signs related to ARFS
1	43	M	Spain	Region of Madrid	IT support	14
2	55	M	Spain	Region of Madrid	Administrative assistant	8
3	24	M	Spain	Region of Madrid	Student	16
4	24	F	Spain	Region of Madrid	Student	9
5	57	F	Spain	Region of Madrid	Administrative assistant	14
6	43	M	Spain	Region of Madrid	Audio-visual technician	7
7	44	F	Spain	Region of Madrid	Concierge	26
8	47	F	Spain	Region of Madrid	Technical assistant	7
9	55	M	Spain	Region of Madrid	Stationer	27
10	62	M	Spain	Region of Madrid	Concierge	19
11	58	F	Spain	Region of Madrid	Administrative assistant	19
12	64	F	Spain	Region of Madrid	Marketing assistant	11
13	33	M	Spain	Region of Madrid	Telecommunications technician	12
14	35	F	Spain	Region of Madrid	Security guard	6
15	64	F	Spain	Region of Madrid	Retired	8
16	66	M	Spain	Region of Madrid	Retired	13

ARFS: adverse reactions to foodstuffs; F: female; IT: information technology; M: male.

ily physicians) for the evaluation of FBFC-ARFSQ-18; and related to medicine and/or nursing (nurses and family physicians) for the evaluation of PSIMP-ARFSQ-10. A group of 33 experts were contacted, 15 experts with a wide experience in food science and/or nutrition for the FBFC-ARFSQ-18 questionnaire; and 18 experts with extensive experience in the field of medicine and/or nursing for the PSIMP-ARFSQ-10 questionnaire. After they received an e-mail invitation or on-line correspondence using a RedCap™ unique Uniform Resource Locator (URL) link, 28 experts consented to participate (15 experts for the FBFC-ARFSQ-18 and 13 experts for the PSIMP-ARFSQ-10). The final number of experts was 20 (eight experts were excluded for not accomplishing the inclusion criteria, not answering the evaluation questionnaire, or sending an incomplete evaluation).

Experts were asked to indicate below each item their opinion using an open box of comments and their degree of agreement, using a 1 to 5 Likert-type scale, where five points indicated the highest agreement and one, the lowest agreement. The standard deviations (SD) of the differences between scores have been established as a viable option for quantifying validity (32); thus, when an expert's evaluation was greater than or equal to 3 (≥ 3) SD different from the mean of the other nine experts in two or more questions (≥ 2), these values were not considered as valid because of the discordance with the rest of experts (33). The content validation coefficient for the final ten experts was calculated using Aiken's V coefficient (95 % confidence interval [CI]) and a minimum Aiken's V coefficient score of ≥ 0.75 was required for each question to be validated (33,34). Aiken's V coefficient and the lower and upper limits of confidence intervals were calculated using the software ICaiken.exe (Visual Basic 6.0, Lima, Perú) (34). Descriptive data of the experts are shown in tables III and IV.

Table II. Descriptive data of experts for the evaluation of FBFC-ARFSQ-18

Expert	Age (years)	M/F	Qualification	Highest degree	Career completion (year)	Career experience (years)
1	47	M	Human Nutrition and Dietetics	Ph.D.	2001	21
2	41	M	Pharmacy and Biochemistry	Ph.D.	2002	20
3	66	F	Nursing	MSc.	1977	45
4	65	F	Nursing	MSc.	1979	43
5	63	M	Medicine	Ph.D.	1982	40
6	71	M	Pharmacy and Nutrition	Ph.D.	1972	50
7	40	F	Human Nutrition and Dietetics, Food Science and Technology	Ph.D.	2004	18
8	49	F	Pharmacy	Ph.D.	1995	27
9	50	F	Pharmacy	Ph.D.	1999	23
10	64	M	Medicine	Ph.D.	1982	40

F: female; M: male; MSc: Master of Science; Ph.D.: Doctor of Philosophy.

Table III. Descriptive data of experts for the evaluation of PSIMP-ARFSQ-10

Expert	Age (years)	M/F	Qualification	Highest degree	Career completion (year)	Career experience (years)
1	66	F	Nursing	MSc.	1977	45
2	60	F	Medicine	Ph.D.	1992	30
3	65	F	Nursing	MSc.	1979	43
4	64	F	Nursing	MSc.	1977	45
5	65	M	Medicine	Ph.D.	1979	43
6	58	F	Medicine	Ph.D.	1985	37
7	57	F	Medicine	BSc.	1988	34
8	62	F	Medicine	Ph.D.	1983	39
9	50	M	Medicine	Ph.D.	1996	26
10	68	M	Medicine	Ph.D.	1979	43

BSc: Bachelor of Science; F: female; M: male; MSc: Master of Science; Ph.D.: Doctor of Philosophy.

Table IV. Likert-type scale values offered by the panel of experts in all FBFC-ARFSQ-18 items for validation

	FBFC-ARFSQ-18 validation									
	Expert 1	**Expert 2**	**Expert 3**	**Expert 4**	**Expert 5**	**Expert 6**	**Expert 7**	**Expert 8**	**Expert 9**	**Expert 10**
Item 1	5	5	5	2	5	5	3	5	4	5
Item 2	5	5	5	2	5	5	2	5	4	5
Item 3	5	5	5	5	5	5	4	5	5	5
Item 4	5	5	5	5	5	5	5	5	5	4
Item 5	5	5	5	5	4	5	5	5	5	5
Item 6	5	5	5	5	5	5	4	5	5	5
Item 7	5	5	5	5	5	4	4	5	5	5
Item 8	5	5	5	5	5	4	4	5	3	5
Item 9	5	5	5	4	5	5	4	5	5	5
Item 10	5	5	5	2	5	4	4	5	5	5
Item 11	5	5	5	2	5	3	5	5	3	5
Item 12	5	5	5	5	5	5	5	5	3	4
Item 13	5	5	5	3	5	4	4	5	4	5
Item 14	5	5	5	5	5	3	5	5	3	5
Item 15	5	5	5	3	5	4	5	5	5	5
Item 16	4	5	5	5	5	4	5	5	5	5
Item 17	4	5	5	5	5	4	4	5	1*	4
Item 18	5	5	5	5	5	3	4	5	2	4

*FBFC-ARFSQ-18: Food and Beverages Frequency Consumption Questionnaire to Identify Adverse Reactions to Foodstuffs. *Values ≥ 3 SD of the mean of the rest of the nine experts.*

PHASE 4: FACE VALIDITY

Open questions after each domain or section of each questionnaire were placed for experts to analyze if the categories of each questionnaire captured the intended concept; and also, to specify what experts thought the questionnaire measured, possible missing items and what they thought in general means. The percentage of experts who commented at least one section was recorded, as well as the mean complexion time of each questionnaire (data described in the Results section, Phase 4 of this document).

PHASE 5: ETHICAL CONSIDERATIONS

This research was performed in accordance with the Ethical Guidelines of the Declaration of Helsinki of 1961, revised in Fortaleza (2013) (35) and following the Spanish and European regulations on data protection (36). The protocol has been approved by the Ethics Committee of the UPM (reference number 20200602).

RESULTS

PHASE 1: QUESTIONNAIRES DEVELOPMENT

The final pool of items was categorized into three sections for the FBFC-ARFSQ-18 (eating habits, food and beverages frequency consumption and food supplement frequency consumption) and five sections for the PSIMP-ARFSQ-10 (digestive system, skin and subcutaneous tissue, nervous system, respiratory system and other human body systems [other diseases/pathologies, symptoms and signs, not elsewhere classified]). Both validated tools followed the recommendations of previous studies (9,14,20,37).

Items 1 and 2 of the FBFC-ARFSQ-18 were based on the timing of food and beverages intake, an aggregation of the number of the individual foods, main meals and food and beverages intake between meals, both to represent more closely the required food and beverages consumption patterns recommended in a previous structural validation European FFQ (37). Items 3 and 4 describe the most reported aspects of concern when it comes to ARFS: type of diet (vegan, gluten-free, fermentable oligosac-

charides, disaccharides, monosaccharides and polyols [FODMAP], biogenic amines, etc.) and type of foodstuff (processed, non-processed and type of preserved products), especially when comparing regular population and athletes (5,26,38). Items 16, 17 and 18 were added to more deeply investigate the whole food intake of the population with possible ARFS including food supplements (probiotics, vitamin D), which are not very common in a FFQ but of high significance in the pathogenesis of ARFS (25,39). Items 5 to 15 corresponded to eleven food groups designed to be answered based on the consumption of a participant or patient in the last six months with a scale describing the monthly, weekly or daily intake of each foodstuff. There is plenty of information on paediatric oral immunotherapies (OIT) and the required time interval, for an ARFS observation, after changing a specific food intake. However, some case studies with adults suggest a minimum observation of three to six months (18,40). Trying to fill in the gaps, the present study proposes the FBFC-ARFSQ-18, describing the food and beverages intake during the last six months, for the Spanish population to support the current clinical tools of diagnosis and to obtain a meaningful approach from a population with possible ARFS.

All items (from 1 to 10) of the PSIMP-ARFSQ-10 included four body categories of diseases and symptomatology (digestive, skin and subcutaneous tissue, nervous system, respiratory system) and one category of other human body systems (other diseases/pathologies, symptoms and signs, not elsewhere classified). All of these items were designed to be answered with a yes or no question with a special annotation for the questions about pathologies and diseases that if the answer is "yes", the pathology may have medical diagnosis. This annotation was made to assess the awareness of a valid relationship with ARFS. The experts agreed with the relevance of this nature of the question and considered it as a reductor of bias in self-perception of discomfort towards ARFS. Finally all pathologies and symptomatology sections have an ending question to select other diseases or symptomatology related to the same body system. There could still be some case studies approaching pathologies such as mononucleosis and CFBA (41). A final construct of questions was designed for both tools, ensuring no overlap (Annex I; https://www.nutricionhospitalaria.org/anexos/04631-01.pdf).

PHASE 2: PILOT TEST AND RELIABILITY

The pilot test was completed by 16 INEF-UPM ASP evaluators, aged 24 to 66 years (50 % women, 48.38 ± 13.96 years), during December 2021 (Table I). Three observations regarding clarity and comprehension were considered for the final version: another level for the frequency scale for food and beverages in the FBFC-ARFSQ-18 tool, "< 1 time per month", between "never" and "1 to 3 times per month"; notification of the approximate complexion time to fill each questionnaire in the instructions section of both tools; and the addition of "with medical diagnostic" after the option "yes" in the PSIMP-ARFSQ-10 tool. The average complexion time for both questionnaires, reported by ASP, was 15:05 and 6:34 minutes for the FBFC-ARFSQ-18 and PSIMP-ARFSQ-10 tools, respectively. Cronbach's alpha reliability coefficient was greater than 0.80 in both cases: 0.93 for FBFC-ARFSQ-18 and 0.94 for PSIMP-ARFSQ-10.

PHASE 3: CONTENT VALIDITY

A total of 20 Spanish experts accomplished the inclusion criteria. Five experts of the FBFC-ARFSQ-18 and three experts of the PSIMP-ARFSQ-10 were excluded; two experts did not accomplish one of the inclusion criteria and the other six, for various reasons, as not answering the evaluation questionnaire, or sending an incomplete evaluation. All experts were different and none of the experts evaluated both questionnaires (ten food science and/or nutrition professionals aged mean ± SD 55.6 ± 11.37 years evaluated the FBFC-ARFSQ-18; and ten medicine and/or nursing professionals aged mean ± SD 61.5 ± 5.38 years evaluated the PSIMP-ARFSQ-10) (Tables II and III).

Resulting values of the Likert-type scale by the ten selected experts for both questionnaires are shown in tables IV and V. Aiken's V coefficient values were greater than 0.75 in both cases: 0.90 (0.78-0.96 CI) for the FBFC-ARFSQ-18 and 0.93 (0.81-0.98 CI) for the PSIMP-ARFSQ-10 (Table VI).

PHASE 4: FACE VALIDITY

Food groups of the FBFC-ARFSQ-18 were organized in ten food groups in section 2 of the FBFC-ARFSQ-18 (Annex I https://www.nutricionhospitalaria.org/anexos/04631-01.pdf). In the FBFC-ARFSQ-18, due to the Spanish diet habits, sunflower (item 6) and olive oil (item 15) were separated, according to the recommendations of expert 7, into independent questions inside their corresponding food group. Each foodstuff represented a single question, and all their common commercial formats or types of packaging were merged in the same question. Foodstuffs that were not listed into each food group (e.g., currant, passion fruit, or any other less common food in the Mediterranean Spanish area) could be described and reported by selecting the option "Other food or beverages of this Group. Specify". Analogously, the diseases recommended by experts 1 and 3 (otitis, short bowel syndrome [SBS] and small-intestinal bacterial overgrowth [SIBO]) and the symptoms recommended by experts 1 and 6 (muscle cramps, sleep apnea, dyspnea and snoring) were included in the PSIMP-ARFSQ-10 questionnaire. Peripheral edema was relocated from item 4 ("Symptoms and signs of the skin and subcutaneous tissue") to item 10 ("Other symptoms and signs"). Nine out of ten experts commented at least one section of the FBFC-ARFSQ-18 and the PSIMP-ARFSQ-10 tool (except for experts number 9 and 5, correspondingly of each questionnaire). The average of complexion time, reported by experts, to complete both questionnaires was 14:18 and 5:52 minutes

for FBFC-ARFSQ-18 and PSIMP-ARFSQ-10 tools, respectively (Annex II and Annex III; https://www.nutricionhospitalaria.org/anexos/04631-02.pdf).

Annex II
Annex III

DISCUSSION

Both RedCap™-designed questionnaires, FBFC-ARFSQ-18 and PSIMP-ARFSQ-10, for the Spanish population with possible ARFS were validated after a previous rigorous investigation about the current causative foodstuffs of ARFS (42), as well as the associated diseases and symptomatology recently reported (30,43). To make progress on science and in response to the demands of the conclusions of the articles of Garcia-Larsen et al. (7) and Cade et al. (44), the FBFC-ARFSQ-18 tool included the evaluation of not only a single food, such as milk or egg consumption to analyze allergy, but instead, it included most of the current investigated causative foodstuffs of ARFS, such as CFBA or CFBI (42). Similarly, it contributed to the improvement of the evaluation of associated diseases and symptomatology related to ARFS; apart from following the recommendations of previous studies by Makatsori et al. (45) and Schafer et al. (46), the PSIMP-ARFSQ-10 tool not only included the assessment of a single disease and its symptoms, but instead conveniently collected the current diseases, signs and symptoms related to ARFS.

Regarding the construction and design of the FBFC-ARFSQ-18, the scientific literature provides clear evidence about the possible causative food and beverages of a CFBA or CFBI. In self-reported studies (42,47), foodstuffs such as milk, apple, tomato, egg, kiwi,

Table V. Likert-type scale values offered by the panel of experts in all PSIMP-ARFSQ-10 items for validation

	PSIMP-ARFSQ-10 validation									
	Expert 1	Expert 2	Expert 3	Expert 4	Expert 5	Expert 6	Expert 7	Expert 8	Expert 9	Expert 10
Item 1	5	5	5	5	3	4	4	5	5	5
Item 2	5	5	5	5	3	5	5	5	5	5
Item 3	5	5	5	5	2	5	4	5	5	5
Item 4	5	5	5	5	3	5	5	5	5	5
Item 5	5	5	5	5	4	5	5	5	5	5
Item 6	5	5	5	5	4	5	4	5	5	5
Item 7	5	5	5	5	2	4	4	5	5	5
Item 8	5	5	5	5	4	4	5	5	5	4
Item 9	5	5	4	5	4	4	5	5	5	5
Item 10	5	5	5	5	4	5	4	5	5	5

PSIMP-ARFSQ-10: Pathologies and Symptomatology Questionnaire Associated with Adverse Reactions to Foodstuffs.

Table VI. Number of experts pointing to each Likert-type scale value, mean score and Aiken's V coefficient for all items evaluated by experts

	FBFC-ARFSQ-18							PSIMP-ARFSQ-10						
	Likert-type scale*					Mean	Aiken's V (95 % CI) value (lower-upper limit)	Likert-type scale					Mean	Aiken's V (95 % CI) value (lower-upper limit)
	1	2	3	4	5			1	2	3	4	5		
	Number of experts							Number of experts						
Item 1	0	1	1	1	7	4.40	0.85 (0.71-0.93)	0	0	1	2	7	4.60	0.90 (0.77-0.96)
Item 2	0	2	0	1	7	4.30	0.83 (0.68-0.91)	0	0	1	0	9	4.80	0.95 (0.84-0.99)
Item 3	0	0	0	1	9	4.90	0.98 (0.87-0.99)	0	1	0	1	8	4.60	0.90 (0.77-0.96)
Item 4	0	0	0	1	9	4.90	0.98 (0.87-0.99)	0	0	1	0	9	4.80	0.95 (0.84-0.99)

(Continues on next page)

Table VI (Cont.). Number of experts pointing to each Likert-type scale value, mean score and Aiken's V coefficient for all items evaluated by experts

	FBFC-ARFSQ-18							PSIMP-ARFSQ-10						
	Likert-type scale*					Mean	Aiken's V (95 % CI) value (lower-upper limit)	Likert-type scale					Mean	Aiken's V (95 % CI) value (lower-upper limit)
	1	2	3	4	5			1	2	3	4	5		
	Number of experts							Number of experts						
Item 5	0	0	0	1	9	4.90	0.98 (0.87-0.99)	0	0	0	1	9	4.90	0.98 (0.87-0.99)
Item 6	0	0	0	1	9	4.90	0.98 (0.87-0.99)	0	0	0	2	8	4.80	0.95 (0.84-0.99)
Item 7	0	0	0	2	8	4.80	0.95 (0.84-0.99)	0	1	0	2	7	4.50	0.88 (0.74-0.95)
Item 8	0	0	1	2	7	4.60	0.90 (0.77-0.96)	0	0	0	3	7	4.70	0.93 (0.80-0.97)
Item 9	0	0	0	2	8	4.80	0.95 (0.84-0.99)	0	0	0	3	7	4.70	0.93 (0.80-0.97)
Item 10	0	1	0	2	7	4.50	0.88 (0.74-0.95)	0	0	0	2	8	4.80	0.95 (0.84-0.99)
Item 11	0	1	2	0	7	4.30	0.83 (0.68-0.91)	-	-	-	-	-	-	-
Item 12	0	0	1	1	8	4.70	0.93 (0.80-0.97)	-	-	-	-	-	-	-
Item 13	0	0	1	3	6	4.50	0.88 (0.74-0.95)	-	-	-	-	-	-	-
Item 14	0	0	2	0	8	4.60	0.90 (0.77-0.96)	-	-	-	-	-	-	-
Item 15	0	0	1	1	8	4.70	0.93 (0.80-0.97)	-	-	-	-	-	-	-
Item 16	0	0	0	2	8	4.80	0.95 (0.84-0.99)	-	-	-	-	-	-	-
Item 17	1	0	0	4	5	4.20	0.80 (0.65-0.90)	-	-	-	-	-	-	-
Item 18	0	1	1	2	6	4.30	0.83 (0.68-0.91)	-	-	-	-	-	-	-
Total Aiken's V Mean (± SD)							0.90 (± 0.06)							0.93 (± 0.03)

*CI: confidence interval; FBFC-ARFSQ-18: Food and Beverages Frequency Consumption Questionnaire to Identify Adverse Reactions to Foodstuffs; PSIMP-ARFSQ-10: Pathologies and Symptomatology Questionnaire Associated with Adverse Reactions to Foodstuffs. *Likert-type scale ranged from 1 to 5, where the minimum (1) value was based on very poor relevance and the maximum (5) on the highest degree of relevance.*

shrimp, fish, hazelnut, walnut, wheat and peanut were the most reported, although kiwi is not strictly considered as part of a strict MD. However, Telleria-Aramburu et al. (48) proposed an approach of a short FFQ for a Spanish sample of the Basque Country region, located in the north of Spain, with common Spanish food and also differencing proccessed and non-processed food, but still not very detailed regarding types of nuts, seeds, cereals, beverages, food supplements and other food groups of interest for the analysis of ARFS (48). Similarly, a European FFQ (7) has been proposed to assess the relation to allergy and asthma, not specifically CFBA; the Gluten FFQ (6), specifically focused only on cereal allergens; and the Pregnancy FFQ (8), with questions oriented to the gestation period. They are not yet available in the Spanish language and with particular characterisitics of the population of interest and/or allergy in general and not specifically ARFS, CFBA or CFBI.

EAACI and Ogulur et al. already proposed in 2017 and 2021 several diseases and symptomatology associated with CFBA (30,43). In order to improve the range of possibilities and precision of the tool (PSIMP-ARFSQ-10), specific diseases of recent investigations related to ARFS were taken into account (e.g., food protein-induced enterocolitis syndrome [FPIES], SIBO, IBS, atopic dermatitis, dizziness, etc.) (16,24-26,49). Experts who validated the questionnaire agreed with the authors of the present study about this, and other groups of diseases (SBS, hiatal hernia, pytiriasis, alopecia, panic attack) and symptomatology (xerostomia, erythema, sleep apnea, dyspnea, muscle cramps) were added from phase 1 and also following the experience and observations of 20 experts in phase 4.

This study could offer the key point to establish two validated questionnaires to analyze the main aspects of both, food consumption and diseases related to ARFS in a Spanish population under their self-perception, with the intention of being used together with a clinical diagnosis tool of the physician's choice. Furthermore, these tools could be used together with other health promotion studies and future ARFS local research projects.

This study has several strengths: the validation procedure is based on a rigorous qualitative research process, the use of a robust secure web platform for design and hosting, and the difference in the type of expertise that each professional may have towards the Spanish ARFS field, avoiding bias through multidisciplinary knowledge. The main limitation of this study is that questionnaires are designed and validated only for adults.

CONCLUSIONS

The findings of this study allow to conclude that both questionnaires designed to assess food consumption, diseases and

symptomatology in a Spanish population with possible ARFS could be used for clinical applications to analyze the association between certain food and beverages consumption with ARFS, such as, CFBA and CFBI. In addition, they could be used to investigate the link between some specific diseases, signs and symptoms with ARFS due to their optimal validity values. The FB-FC-ARFSQ-18 and the PSIMP-ARFSQ-10 questionnaires should facilitate research projects and be used together (recommended) with the clinical diagnostic tools of CFBA and CFBI.

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ARÁN

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Trabajo Original

Otros

Evaluación del efecto *in vitro* de extractos intra y extracelulares de *Lactobacillus* contra la genotoxicidad y el estrés oxidativo causado por la acrilamida

Assessment of the in vitro *effect of intra and extracellular extracts of* Lactobacillus *against genotoxicity and oxidative stress caused by acrylamide*

María Goretti Reyes López, Adriana Cavazos Garduño, Nancy Elizabeth Franco Rodríguez, Jorge Manuel Silva Jara, Julio César Serrano Niño

Centro Universitario de Ciencias Exactas e Ingenierías. Universidad de Guadalajara. Guadalajara, Jalisco. México

Resumen

Introducción: la acrilamida se forma mediante la reacción de Maillard, por lo que se encuentra en muchos productos alimenticios sometidos a procesos térmicos, generando genotoxicidad y daños al ADN. Los estudios han reportado que los lactobacilos tienen la capacidad de generar compuestos con actividad antioxidante, antigenotóxica y antimutagénica, y es por esto que el presente trabajo pretende evaluar el efecto de cepas de *Lactobacillus* y sus extractos intra y extracelulares contra la genotoxicidad y el estrés oxidativo causado por la acrilamida.

Métodos: se empleó una cepa de *Lactobacillus casei* Shirota y una cepa de *Lactobacillus reuteri* NRRL B-14171. Ambas fueron cultivadas en caldo MRS y sometidas a tratamientos mecánicos y enzimáticos para obtener los extractos extra e intracelulares. Los linfocitos fueron cultivados en medio RPMI, la peroxidación lipídica se evaluó por TBARS y la capacidad antioxidante se midió en los extractos extra e intracelulares con la técnica ABTS, empleando además una cepa de *Saccharomyces cerevisiae* RC 212 como modelo. La reducción de la peroxidación lipídica en los linfocitos se midió por TBARS y la reducción de la genotoxicidad mediante la reducción de la formación de micronúcleos en los linfocitos.

Resultados: ambas cepas evaluadas, así como sus extractos intra y extracelulares, mostraron capacidad de contrarrestar el estrés oxidativo y la genotoxicidad causada por la acrilamida.

Conclusión: los resultados encontrados, sugieren que el empleo de extractos intra y extracelulares de ambas cepas podría ser una alternativa para reducir los efectos de genotoxicidad y estrés oxidativo causados por la acrilamida sin la necesidad de requerir una estructura viable..

Palabras clave:

Acrilamida. Extractos. Lactobacilos. Antioxidante.

Abstract

Introduction: acrylamide is formed by the Maillard reaction and is found in many food products subjected to thermal processes, generating genotoxicity and DNA damage. Studies have reported that lactobacilli have the ability to generate compounds with antioxidant, antigenotoxic and antimutagenic activity, which is why the present work aims to evaluate the effect of *Lactobacillus* strains and their intra and extracellular extracts against genotoxicity and oxidative stress as caused by acrylamide.

Methods: a strain of *Lactobacillus casei* Shirota and a strain of *Lactobacillus reuteri* NRRL B-14171 were used, both were cultured in MRS broth and subjected to mechanical and enzymatic treatments to obtain extra and intracellular extracts. Lymphocytes were cultured in RPMI medium. Lipid peroxidation was evaluated by TBARS and the antioxidant capacity was measured in the extra and intracellular extracts with the ABTS technique, also using a strain of *Saccharomyces cerevisiae* RC 212 as a model. The reduction of lipid peroxidation in lymphocytes was measured by TBARS and the reduction of genotoxicity by reducing the formation of micronuclei in lymphocytes.

Results: both strains evaluated, as well as their intra and extracellular extracts, showed the ability to counteract oxidative stress and genotoxicity caused by acrylamide.

Conclusion: the results found suggest that the use of intra and extracellular extracts of both strains could be an alternative to reduce the effects of genotoxicity and oxidative stress caused by acrylamide without the need for a viable structure.

Keywords:

Acrylamide. Extracts. Lactobacillus. Antioxidant.

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Correspondencia:

Julio César Serrano Niño. Centro Universitario de Ciencias Exactas e Ingenierías. Universidad de Guadalajara. Blvd. Marcelino García Barragán, 1421, esq Calzada Olímpica. C.P. 44430 Guadalajara, Jalisco. México
e-mail: julio.serrano@academicos.udg.mx

INTRODUCCIÓN

La acrilamida es un compuesto tóxico que se forma durante el sometimiento de alimentos ricos en carbohidratos a temperaturas elevadas, mayores a 120 °C. Los productos alimenticios derivados de ingredientes vegetales como papas y cereales tienden a contener las mayores cantidades de acrilamida; esto se debe principalmente a la presencia natural de compuestos como glucosa, fructosa y asparagina, involucrados en la formación de acrilamida (1). Los efectos neurotóxicos de la acrilamida en humanos han sido bien documentados, sugiriendo la capacidad para causar mutaciones genéticas. Asimismo, la recombinación inducida por el ADN puede interferir en el proceso de replicación genética, lo que favorece la formación de tumores (2). Por otra parte, las bacterias acidolácticas constituyen un grupo de bacterias grampositivas que forman parte importante de la microbiota intestinal debido a que desempeñan un papel trascendente en el buen funcionamiento del organismo y el mantenimiento de la salud (3,4). Además se sabe que las bacterias acidolácticas generan compuestos con actividad antioxidante que neutralizan moléculas tóxicas a nivel intestinal y sistémico (5), además de haber demostrado tener actividades antigenotóxicas y antimutagénicas en modelos *in vitro* e *in vivo* (6,7). El uso de las células no viables de bacterias acidolácticas, o sus componentes y/o extractos, podría tener ventajas de seguridad sobre la utilización de las bacterias completas ya que en los consumidores con sistemas inmunes desequilibrados o comprometidos existe el riesgo de traslocación, infección o aumento de la respuesta inflamatoria, mostrado por algunas cepas de BAL con potencial probiótico. Es por esto que el presente trabajo pretende evaluar el efecto de cepas de *Lactobacillus* y sus extractos intra y extracelulares contra la genotoxicidad y el estrés oxidativo causados por la acrilamida.

METODOLOGÍA

SOLUCIÓN DE TRABAJO DE ACRILAMIDA

Se preparó una solución de acrilamida disolviendo esta en solución de *buffer* de fosfatos salino (0,9 % NaCl en PBS 10 mM, pH = 7,4) para alcanzar una concentración final de 100 mM.

CULTIVO BACTERIANO

Se empleó una cepa de *Lactobacillus casei* Shirota aislada de un producto lácteo fermentado comercial, y una cepa de *Lactobacillus reuteri* NRRL B-14171 que pertenece a una colección de cultivos. Para cada cepa se realizaron dos subcultivos en caldo Man Rogosa y Sharpe (MRS) para obtener concentraciones celulares de 10^9 UFC/mL previo a cada experimento.

PREPARACIÓN DEL CONTENIDO INTRACELULAR DE *L. CASEI* SHIROTA Y L. *REUTERI* ATCC 14171

En breve, se tomó una alícuota (10 ml) de bacterias suspendidas en PBS a la que se le añadió 1 mg/ml de lisozima y se incubó a 37 °C durante 2 h; posteriormente, las células tratadas fueron sometidas a ultrasonicación (70 W) y recuperadas por centrifugación (3600 *g*, 10 min, 4 °C); el sobrenadante se mantuvo en refrigeración y oscuridad hasta su uso y los restos de bacteria se emplearon para obtener los extractos extracelulares.

EXTRACCIÓN DE PARED CELULAR Y ÁCIDOS TEICOICOS DE *L. CASEI* SHIROTA Y *L. REUTERI* NRRL B-14171

Los restos de bacteria obtenidos después de la ruptura para obtener el líquido intracelular fueron tratados con proteinasa K y lisozima para romper la estructura bacteriana. Finalmente, los fragmentos se trataron con dodecilsulfato sódico (SDS) y ácido etilendiaminotetraacético (EDTA). Los fragmentos que se obtuvieron se mantuvieron en congelación hasta su uso para obtener ácidos teicoicos y para realizar los ensayos de micronúcleos y del grado de oxidación. Por otra parte, se tomaron 10 g de los fragmentos de la pared celular aislada de las cepas a evaluar y se incubaron durante 24 h a 37 °C en 5 mL de ácido tricloroacético (TCA) al 10 % sin agitación. Posteriormente, los ácidos teicoicos se recuperaron por precipitación con 5 mL de acetona fría durante 24 h a 4 °C y se recuperaron los ácidos teicoicos por centrifugación (3200 x *g,* 10 min, 4 °C).

EVALUACIÓN DEL EFECTO ANTIOXIDANTE

La capacidad antioxidante se evaluó en los extractos extra e intracelulares de ambas cepas evaluadas mediante la técnica ABTS. En breve, se preparó una solución del radical ABTS (7 mM), la cual se dejó reaccionando con una solución de persulfato de potasio (2,45 mM) durante 16 h a temperatura ambiente y en obscuridad. Trascurrido el tiempo se almacenó a -80 °C en alícuotas de 1 mL hasta el momento de ser requerida. Una vez preparado el radical, se tomó una alícuota de la solución "stock" de ABTS y se ajustó la absorbancia a 0,07 ± 0,05 usando metanol absoluto, y se leyó a 750 nm en un espectrofotómetro UV-VIS (Multiskan Sky); adicionalmente, se preparó una curva de calibración a concentraciones de 5-300 µg/mL utilizando ácido ascórbico (1 mg/mL) como estándar para conocer las concentraciones de las muestras.

EVALUACIÓN DE LA CAPACIDAD ANTIOXIDANTE EN *SACCHAROMYCES CEREVISIAE*

La prueba de protección de la oxidación generada por H_2O_2 se evaluó empleando una cepa de *Saccharomyces cerevisiae*

como modelo celular siguiendo el siguiente diseño experimental: 1) levadura + H_2O_2; 2) levadura; 3) bacteria completa + levadura + H_2O_2; 4) pared celular + levadura + H_2O_2; 5) líquido intracelular + levadura + H_2O_2; 6) ácidos teicoicos + levadura + H_2O_2. La metodología seguida fue la descrita por Oliveira y cols., 2021, en donde 0,1 g de *Saccharomyces cerevisiae* RC 212 (Lalvin bourgovinä) se colocaron en 5 mL de caldo YPD (Yeast extract, Peptone, Dextrose, Bioxonä) y se incubaron por 16 h a 28 °C con agitación a 180 rpm en agitador orbital. Transcurrido el tiempo se tomaron 100 µL, se pasaron a otro tubo con 5 mL de caldo YPD y se incubó el conjunto 16 h a 28 °C con agitación. De este último cultivo se colocaron 100 µL en tubos con 5 mL de caldo YPD y 100 µL de los extractos intra y extracelulares de ambas cepas de acuerdo con el diseño experimental descrito anteriormente, y se llevaron a incubación por 1 h; después se agregaron 7,5 µL de H_2O_2 y se incubaron por 1 hora más. De la mezcla anterior se prepararon diluciones seriadas en caldo YPD hasta 1 x 10^{-5} UFC y se sembraron por vaciado en placa de ágar YPD. Las placas se incubaron a 28 °C por 48 h; transcurrido el tiempo, se realizó el recuento en placa y los resultados se reportaron como UFC/mL de levaduras.

EVALUACIÓN DEL EFECTO ANTIGENOTÓXICO DE *L. CASEI* SHIROTA Y *L. REUTERI* NRRL B-14171

La prueba de formación de micronúcleos en los linfocitos se realizó de acuerdo con lo propuesto por Zamani y cols. (8) siguiendo el siguiente diseño experimental: 1) control (acrilamida); 2) acrilamida + bacteria completa; 3) acrilamida + líquido intracelular; 4) acrilamida + ácidos teicoicos; 5) acrilamida + fragmentos de pared celular. En breve, 0,5 mL de sangre humana se mezclaron con 4,5 mL de medio Roswell Park Memorial Institute (RPMI) 1640 suplementado con suero fetal de ternera al 20 %, penicilina 100 U/mL y estreptomicina 100 mg/mL, a lo cual se añadió fitohemaglutinina-M (1 mg/mL) para estimular el cultivo, incubándose la mezcla a 37 °C durante 72 h. A las 24 h del primer día, las células se trataron de acuerdo con el diseño experimental y, posteriormente, después de 20 h de exposición, se añadió citocalasina B (5 mg/mL) con el objetivo de bloquear la citocinesis celular; 28 h después se obtuvieron los linfocitos por centrifugación. Los linfocitos se sometieron a un tratamiento hipotónico suave con KCl (0,075 M) durante 5 minutos para luego fijarlos en un portaobjetos con una solución de metanol:ácido acético (3:1), repitiendo la fijación 2 veces. Finalmente, una vez fijada, la suspensión celular se tiñó con colorante de Giemsa al 10 % (pH = 6,8) durante 10 min. El porcentaje de micronúcleos se reportó por cada 1000 células observadas utilizando un microscopio de luz óptica.

MEDICIÓN DE LA PEROXIDACIÓN LIPÍDICA EN LINFOCITOS HUMANOS

La medición de la peroxidación lipídica se realizó en los linfocitos cultivados de acuerdo con el diseño experimental descrito en la sección anterior. El contenido de malondialdehído (MDA) se determinó por las sustancias reactivas del ácido tiobarbitúrico (TBA), de acuerdo con lo descrito por Zamani y cols. (8), con algunas modificaciones. En breve, se añadieron 0,25 mL de ácido sulfúrico (0,05 M) a los linfocitos obtenidos de cada grupo para, posteriormente, adicionar 0,3 mL de TBA (0,2 %) y colocarlos en un baño de agua hirviendo durante 30 min. Al finalizar el tiempo, se llevaron los tubos a un baño de hielo, se añadieron 0,4 mL de n-butanol a cada uno y se centrifugaron a 3500 *g* durante 10 min. Finalmente, se midió la cantidad de 1,1,3,3,-tetraetoxipropano (TEP) formado en cada muestra, midiendo la absorbancia del sobrenadante a 532 nm con un lector de ELISA y expresándolo como mmol/L de TEP.

ANÁLISIS ESTADÍSTICO

Los ensayos se realizaron por triplicado y los resultados se presentan como media ± desviación estándar. La significancia estadística ($p < 0,05$) se determinó mediante la prueba estadística ANOVA de una cola con una prueba de Tukey, mediante la cual se buscaron diferencias significativas en la capacidad antioxidante y el número de micronúcleos formados por cada 1000 células observadas al microscopio de luz óptica entre los diferentes tratamientos evaluados. Para el análisis estadístico se empleó el software estadístico Minitab 16.

CONSIDERACIONES ÉTICAS

Este estudio se apegará a lo señalado por la Declaración de Helsinki y lo dispuesto en la Ley General de Salud en materia de investigación. En todo momento se protegió la confidencialidad de la información y se recabó el consentimiento informado de los participantes en la investigación.

RESULTADOS

EVALUACIÓN DEL EFECTO ANTIOXIDANTE DE *L. CASEI* SHIROTA Y *L. REUTERI* NRRL B-14171

En la figura 1 se muestran los resultados referentes a la capacidad antioxidante de los extractos intracelulares y extracelulares de *L. casei* Shirota y *L. reuteri* NRRL B-14171 obtenidos mediante la técnica ABTS. De ambas cepas se obtuvieron valores que oscilaron entre 15,99 y 63,77 µME AA (micromoles de equivalente de ácido ascórbico). Al comparar la capacidad antioxidante de los extractos de ambas cepas se observaron diferencias estadísticamente significativas ($p < 0,05$), siendo el extracto del líquido intracelular de la cepa *L. reuteri* NRRL B-14171 el que presentó la mayor capacidad antioxidante (63,77 µME AA), mientras que los que mostraron la menor capacidad antioxidante fueron los fragmentos de pared celular y los ácidos teicoicos de esta misma cepa con 16,14 y 15,99 µME AA, respectivamente.

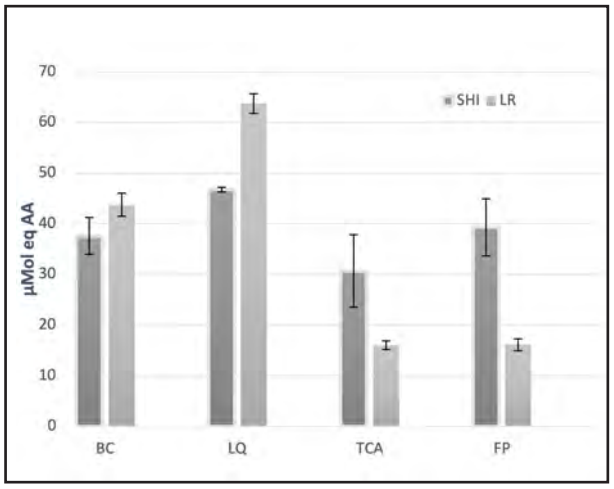

Figura 1.

Capacidad antioxidante de extractos intra y extracelulares de *L. casei* Shirota y *L. reuteri* por la técnica ABTS (SHI: *L. casei* Shirota; LR: *L. reuteri;* BC: bacteria completa; LQ: líquido intracelular; TCA: ácidos teicoicos; FP: fragmentos de pared celular).

EVALUACIÓN DE LA CAPACIDAD ANTIOXIDANTE DE *L. CASEI* SHIROTA Y *L. REUTERI* NRRL B-14171 EN *SACCHAROMYCES CEREVISIAE* RC 212

En la figura 2 se presentan los resultados referentes a la evaluación de la capacidad antioxidante de los extractos intra y extracelulares de *L. casei* Shirota y *L. reuteri* NRRL B-14171 en *Saccharomyces cerevisiae* RC 212, lo cual se demostró cuantificando un aumento en las unidades formadoras de colonias por mililitro (UFC/mL) de levadura en comparación con un control positivo expuesto a peróxido de hidrógeno. De acuerdo a los resultados obtenidos, *L. casei* Shirota mostró un mejor efecto antioxidante al propiciar un mayor crecimiento de *Saccharomyces cerevisiae* RC 212 en presencia de peróxido de hidrógeno; la bacteria completa, así como los fragmentos de pared celular y sus ácidos teicoicos, mostraron la mejor capacidad antioxidante ya que se contabilizó un crecimiento de 1,065 x 10^7 UFC/mL, 1,05 x 10^7 UFC/mL y 1,175 x 10^7 UFC/mL de *Saccharomyces cerevisiae* RC 212 en comparación con el control positivo de peróxido, en el cual se contabilizó un crecimiento de 2,04 x 10^6 UFC/mL de *Saccharomyces cerevisiae* RC 212; comparado con el tratatamiento negativo, esto representó una reducción del crecimiento del 34, 35 y 27 %, respectivamente. Respecto a *L. reuteri* ATCC 14171, de forma general, este mostró la menor protección antioxidante frente al peróxido de hidrógeno y únicamente el líquido intracelular mostró la mejor capacidad antioxidante al contabilizarse un crecimiento de 9,4 x 10^6 UFC/mL de *Saccharomyces cerevisiae* RC 212 en comparación con el control positivo de peróxido; comparado con el tratatamiento negativo, esto representa una reducción del 42,4 % en el crecimiento de *Saccharomyces cerevisiae* RC 212. Por otra parte, la bacteria completa, así como los fragmentos de pared celular y sus ácidos teicoicos, mostraron el menor aumento en el crecimiento de *Saccharomyces cerevisiae* RC 212 al contabilizarse crecimientos de 6,1 x 10^6 UFC/mL, 6,5 x 10^6 UFC/mL y 7,9 x 10^6 UFC/mL, respectivamente.

EVALUACIÓN DEL EFECTO ANTIGENOTÓXICO DE *L. CASEI* SHIROTA Y *L. REUTERI* NRRL B-14171

La reducción en la cantidad de micronúcleos se muestra en la figura 3. Los extractos intra y extracelulares de ambas cepas eva-

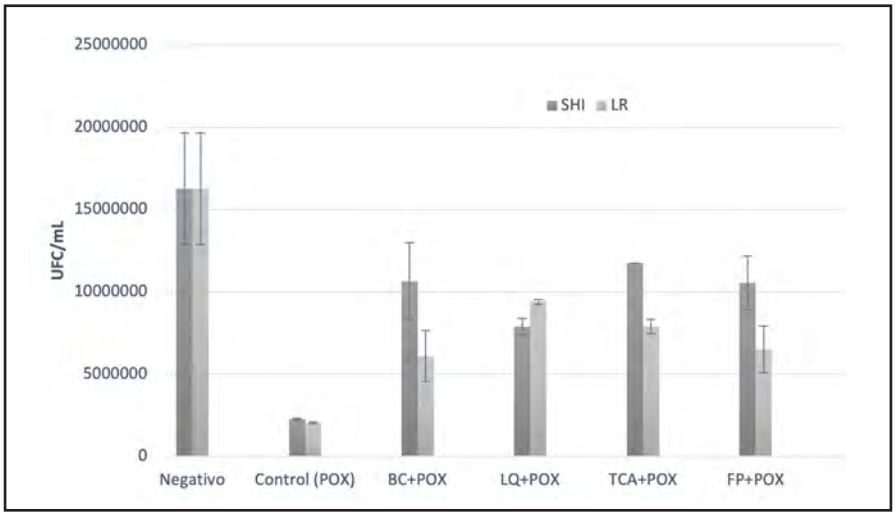

Figura 2.

Capacidad antioxidante de extractos intra y extracelulares de *L. casei* Shirota y *L. reuteri* en *Saccharomyces cerevisiae RC 212* (SHI: *L. casei* Shirota; LR: *L. reuteri*; BC: bacteria completa; LQ: líquido intracelular; TCA: ácidos teicoicos; FP: fragmentos de pared celular; POX: peróxido de hidrógeno).

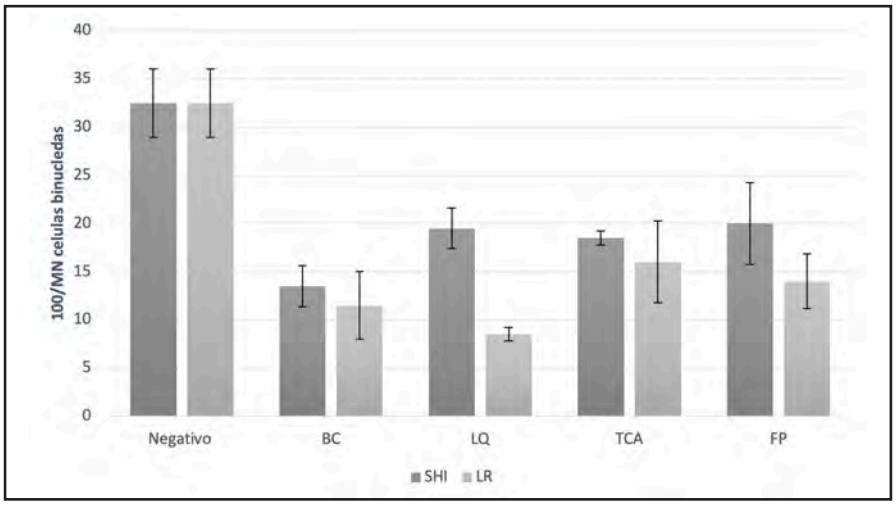

Figura 3.

Efecto antigenotóxico de extractos intra y extracelulares de *L. casei* Shirota y *L. reuteri* sobre la formación de micronúcleos (MN). SHI: *L. casei* Shirota, LR: *L. reuteri,* BC: Bacteria completa, LQ: Líquido intracelular, TCA: Ácidos teicoicos, FP: Fragmentos de pared celular.

luadas mostraron capacidad para reducir la genotoxicidad en los linfocitos causada por la acrilamida. En el líquido intracelular de *L. reuteri* NRRL B-14171 se contabilizaron solo 8,5 núcleos en promedio, comparados con 32,5 registrados en el control tratado con acrilamida, lo cual representa una reducción del 73,8 %; sin embargo, este caso fue estadísticamente similar a la bacteria completa, en la cual se registraron en promedio 11,5 núcleos, lo cual representa una reducción del 64,6 % frente al control. Con respecto a los ácidos teicoicos y la fracción de pared celular, a pesar de que mostraron ser similares estadísticamente, ambos tuvieron un efecto diferente, mostrando una reducción en la formación de micronúcleos de 16 y 14, respectivamente. Por otra parte, el líquido intracelular, los ácidos teicoicos y los fragmentos de pared celular de *L. casei* Shirota tuvieron un efecto similar en la formación de micronúcleos al contabilizarse 19,5, 18,5 y 20 micronúcleos en promedio, lo cual representa una reducción del 40 %, 43 % y 38,4 %, respectivamente, comparados con el control. Únicamente la bacteria completa de *L. reuteri* NRRL B-14171 mostró tener una mayor protección sobre la formación de micronúcleos al contabilizarse una reducción del 64,6 % comparada con el control positivo; sin embargo, esta no fue estadísticamente diferente de *L. casei* Shirota. En la figura 4 se pueden observar los distintos tipos de

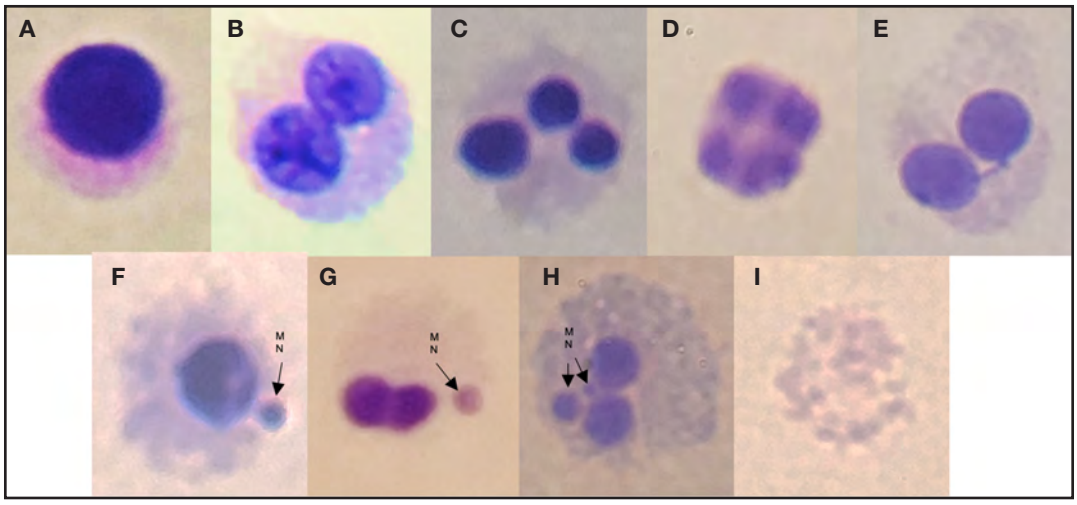

Figura 4.

Linfocitos humanos (A: célula normal (mononucleada); B: célula binucleada; C: célula trinucleada; D: célula multinucleada; E: célula binucleada con puente nucleoplasmático; F: célula mononuclear con micronúcleos (MN); G: célula binucleada con 1 MN; H: célula binucleada con 2 MN; I: célula necrótica).

linfocitos que se observaron en este trabajo, dentro de los cuales aparecen distintas morfologías, como células binucleadas con micronúcleos, células multinucleadas y apoptóticas.

REDUCCIÓN DE LA PEROXIDACIÓN LIPÍDICA EN LINFOCITOS HUMANOS

En la figura 5 se muestra la actividad antioxidante de los extractos intra y extracelulares de *L. casei* Shirota y *L. reuteri* NRRL B-14171 en linfocitos humanos. Los extractos intra y extracelulares de *L. casei* Shirota mostraron tener mayor efecto protector contra la oxidación comparados con los extractos intra y extracelulares de *L. reuteri* NRRL B-14171. La bacteria completa, así como los *ácidos* teicoicos de *L. casei* Shirota, mostró la mayor protección contra la peroxidación lipídica en los linfocitos ya que, en el caso de la bacteria completa, se registraron 0,0004 mMolTEP y en el caso de los ácidos teicoicos 0 mMolTEP, lo cual representa una reducción de la peroxidación de la membrana del eritrocito del 85 y el 100 %m respectivamente para estos extractos comparados con el control. Por otra parte, el líquido intracelular de esta cepa también mostró ser uno de los extractos que más protección mostró ante la peroxidación lipídica, al contabilizarse 0,00057 mMolTEP (80 % menos que el control). Respecto a *L. reuteri* NRRL B-14171, los ácidos teicoicos fueron los únicos extractos que mostraron la mayor reducción de la peroxidación lipídica, al contabilizarse 0,0008 mMolTEP, lo que representa un 70 % de reducción comparada con el control. Por su parte, los ácidos teicoicos de *L. casei* Shirota mostraron el mayor efecto antioxidante, siendo estos significativamente diferentes a los extractos de la pared celular, líquido intracelular y bacteria completa. En el caso de la fracción de pared celular, esta mostró mayor efecto antioxidante que la misma bacteria completa, lo cual podría deberse a que, al estar fraccionada, presenta grupos funcionales o cargas que podrían estar influenciando el efecto antioxidante. Por otra parte, con respecto a *L. reuteri* NRRL B-14171, el extracto intracelular correspondiente al líquido intracelular fue el único que mostró un mayor efecto antioxidante, siendo estadísticamente diferente a los otros extractos. La pared celular presentó un efecto antioxidante similar estadísticamente al de la bacteria completa y los ácidos teicoicos al fragmento de la pared celular.

DISCUSIÓN

De acuerdo con nuestros resultados, las bacterias acidolácticas evaluadas mostraron que eran capaces de proteger contra la oxidación ocasionada por la acrilamida, variando la capacidad antioxidante significativamente en los extractos intra y extracelulares y mostrando una marcada diferencia entre las dos cepas evaluadas, lo cual indica que esta actividad depende de cada cepa. De acuerdo a nuestros resultados, los extractos intracelulares son los que mostraron mayor actividad antioxidante y, de estos, el extracto intracelular de *Lactobacillus reuteri* NRRL B-14171 fue el que presentó mayor capacidad antioxidante (63,77 µMolar de equivalentes de ácido ascórbico), lo cual representa un 45 % más que la bacteria completa, la pared celular y los ácidos teicoicos. Estos resultados son similares a lo reportado por Cuevas-González y cols. (9), que reportaron una alta capacidad antioxidante para el líquido intracelular de las bacterias acidolácticas evaluadas. Adicio-

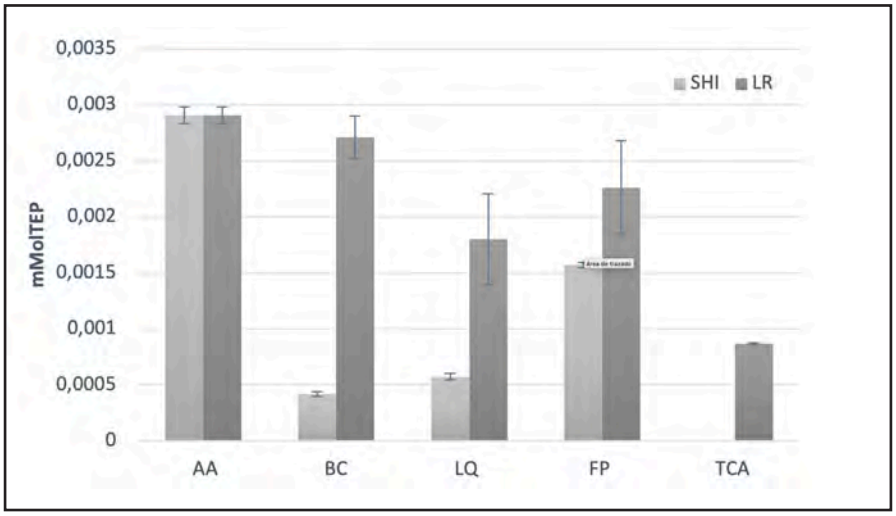

Figura 5.

Reducción de la peroxidación lipídica en linfocitos humanos por los extractos intra y extracelulares de *L. casei* Shirota y *L. reuteri* (SHI: *L. casei* Shirota; LR: *L. reuteri*; AA: acrilamida; BC: bacteria completa; LQ: líquido intracelular; TCA: ácidos teicoicos; FP: fragmentos de pared celular).

nalmente, Aguilar-Toala y cols. (10) reportaron que el líquido intracelular de trece cepas de lactobacilos mostró una mayor actividad antioxidante que la pared celular y que la bacteria completa y, de estas, *Lactobacillus casei* CRL431 presentó la mayor capacidad antioxidante seguida de las cepas *Lactobacillus fermentum* B1932 y *Lactobacillus casei* DCP3968. Estos resultados demuestran que ciertas cepas de lactobacilos podrían ser una buena fuente de posbióticos y una alternativa diferente como protección contra la oxidación causada por compuestos tóxicos adquiridos a través de la dieta.

Diversos autores indican que la actividad antioxidante de algunas cepas de lactobacilos podría atribuirse a la producción de compuestos ubicados en la superficie celular, como polisacáridos extracelulares, ácidos teicoicos y lipoteicoicos (11-13). Con respecto a la actividad antioxidante de los extractos intra y extracelulares de *L. casei* Shirota y *L. reuteri* NRRL B-14171 en los linfocitos humanos, los extractos intra y extracelulares de *L. casei* Shirota mostraron tener mayor efecto protector contra la oxidación comparados con los extractos intra y extracelulares de *L. reuteri* NRRL B-14171. Los ácidos teicoicos de *L. casei* Shirota mostraron mayor efecto antioxidante, siendo estos significativamente diferentes a los extractos de la pared celular, líquido intracelular y bacteria completa. En el caso de la fracción de pared celular, esta mostró mayor efecto antioxidante que la misma bacteria completa, lo cual podría deberse a que, al estar fraccionada, presenta grupos funcionales o cargas expuestos que podrían estar influenciando el efecto antioxidante. Por otra parte, con respecto a *L. reuteri* NRRL B-14171, el extracto intracelular correspondiente al líquido intracelular fue el único que mostró un mayor efecto antioxidante, siendo estadísticamente diferente a los otros extractos; de ellos, la pared celular presentó un efecto antioxidante estadísticamente similar al de la bacteria completa y los ácidos teicoicos al del fragmento de la pared celular.

El uso de levaduras como modelo biológico para el estudio de antioxidantes es un modelo simple pero confiable que puede emplearse para evaluar la protección contra la oxidación a través de la reducción del crecimiento de una célula, además de que varias cepas de lactobacilos han demostrado ser resistentes al peróxido de hidrógeno a diferentes concentraciones (14,15). Al respecto de la capacidad antioxidante de los extractos intra y extracelulares de *L. casei* Shirota y *L. reuteri* NRRL B-14171 en *Saccharomyces cerevisiae* RC 212, *L. casei* Shirota mostró un mejor efecto antioxidante al propiciar un mayor crecimiento de *Saccharomyces cerevisiae* RC 212 en presencia de peróxido de hidrógeno. La bacteria completa, así como los fragmentos de pared celular y sus ácidos teicoicos, mostraron la mejor capacidad antioxidante al permitir solo una reducción del crecimiento de *Saccharomyces cerevisiae* RC 212 del 34, 35 y 27 % para la bacteria completa, los fragmentos de pared celular y los ácidos teicoicos, respectivamente. Estos resultados coinciden con los resultados hallados sobre la capacidad antioxidante de los extractos obtenidos, en donde la pared celular y los ácidos teicoicos de esta cepa fueron los que mostraron la mejor capacidad antioxidante. Adicionalmente, *L. reuteri* NRRL B-14171 mostró la menor protección antioxidante frente al peróxido de hidrógeno y únicamente el líquido intracelular mostró la mejor capacidad antioxidante al permitir la reducción del 42,4 % del crecimiento de *Saccharomyces cerevisiae* RC 212. Este resultado es consistente con los encontrados respecto a la capacidad antioxidante y la protección contra la oxidación evaluada en los linfocitos ya que, en ambos casos, el líquido intracelular de la misma cepa mostró la mejor capacidad antioxidante y protección contra la oxidación.

Respecto a la evaluación del efecto antigenotóxico de los extractos intra y extracelulares mediante la formación de micronúcleos, se observó que todos los extractos analizados presentaron efecto protector contra la genotoxicidad causada por la acrilamida. El análisis estadístico reveló que no hubo diferencias significativas entre los diferentes extractos extra e intracelulares y la bacteria completa con respecto a la cantidad de micronúcleos formados respecto al grupo negativo; sin embargo, el líquido intracelular de *L. reuteri* NRRL B-14171 presentó la menor formación de estructuras binucleadas con un promedio de 8,5 células, correspondiente a una reducción del 73,8 % respecto a las 32,5 células del grupo adicionado solo con acrilamida, lo que lo distingue como el extracto con mayor efecto antigenotóxico, mientras que el de menor protección corresponde al extracto de fragmentos de pared de *L. casei* Shirota, con un 38,4 % de inhibición en la formación de micronúcleos (20 MN). La acrilamida se ha visto involucrada en el desarrollo de múltiples afectaciones comprobadas a partir de análisis tanto *in vivo* como *in vitro*, en donde el daño al material genético es evidente; por ello se buscan alternativas que ayuden a atenuar dichos efectos, tal como lo hicieron Zamani y cols. (8), quienes, de forma similar a nuestra investigación, observaron una disminución de la formación de células binucleadas en los linfocitos de sangre humana, utilizando L-carnitina como agente antioxidante. Salimi y cols. (16), por su parte, utilizaron el ensayo de 8-hidroxi-2'-desoxiguanosina (8-OHdG) para evaluar la disminución del daño al ADN utilizando ácido elágico, observando una disminución significativa en la formación de aductos con 8-OHdG al utilizar concentraciones de 25 y 50 µM del ácido. Por otro lado, se cuenta con poca información sobre la capacidad que tienen los componentes extra e intracelulares de los lactobacilos para contrarrestar la genotoxicidad causada por la acrilamida y solo se ha comprobado que el uso de *Lactobacillus* y de componentes como los ácidos teicoicos puede generar una importante fijación con la acrilamida, favoreciendo su degradación y eliminación (17,18), lo que podría ser un factor clave en la disminución del daño genético.

Estudios previos han indicado que la acrilamida induce la formación de especies reactivas de oxígeno en los linfocitos humanos. La generación de estas es inducida por la acrilamida, pudiendo afectar a macromoléculas importantes, como son las proteínas y lípidos de membrana, e inducir la peroxidación de los lípidos en las células (16). En el presente trabajo, los ácidos teicoicos de ambas cepas evaluadas mostraron la mayor actividad antioxidante cuando se expusieron los linfocitos a la acrilamida. La bacteria completa y los *ácidos* teicoicos de *L. casei* Shirota mostraron la mayor protección contra la peroxidación lipídica en los linfocitos, al contabilizarse una reducción del 85 y el 100 %,

respectivamente, para estos extractos. Por otra parte, el líquido intracelular de esta cepa también mostró ser uno de los extractos de mayor protección ante la peroxidación lipídica, al contabilizarse una reducción del 80 %. Respecto a *L. reuteri* NRRL B-14171, los ácidos teicoicos fueron los únicos extractos que mostraron una mayor reducción de la peroxidación lipídica, al contabilizarse un 70 % de reducción.

CONCLUSIONES

Ambas cepas evaluadas, así como sus extractos intra y extracelulares, mostraron tener capacidad de contrarrestar el estrés oxidativo y la genotoxicidad causados por la acrilamida. Los fragmentos de pared celular de *L. casei* Shirota y *L. reuteri* NRRL B-14171, así como el líquido intracelular de esta última, mostraron la mayor capacidad antioxidante. Sin embargo, se encontraron marcadas diferencias respecto a esta propiedad en ambas cepas. Estas diferencias observadas podrían estar determinadas por la variación de la composición estructural de los ácidos teicoicos y lipoteicoicos, además de la conformación de los peptidoglicanos y de elementos presentes en el líquido intracelular que podrían tener mejor repuesta al liberarse tras el rompimiento celular y que podrían neutralizar los radicales producidos por la acrilamida mediante la liberación de agentes reductores.

Los resultados encontrados sugieren que el empleo de extractos intra y extracelulares de *Lactobacillus reuteri* NRRL B-14171 y *Lactobacillus casei* Shirota podría ser una alternativa para reducir los efectos de genotoxicidad y estrés oxidativo causados por la acrilamida, sin necesidad de requerir una estructura viable sin alteración de su estructura.

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ARÁN

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Trabajo Original

Otros

Low-protein diet supplemented with inulin lowers protein-bound toxin levels in patients with stage 3b-5 chronic kidney disease: a randomized controlled study

La dieta baja en proteínas suplementada con inulina reduce los niveles de toxinas unidas a proteínas en pacientes con enfermedad renal crónica en estadio 3b-5: un estudio controlado aleatorio

Liyang Chang[1], Rongrong Tian[1], Zili Guo[2], Luchen He[1], Yanjuan Li[1], Yao Xu[1], Hongmei Zhang[1]

[1]Department of Renal Centre. Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University. Hangzhou, Zhejiang Province. China. [2]College of Pharmaceutical Sciences. Zhejiang University of Technology. Hangzhou, Zhejiang. China

Abstract

Objective: this study aimed to evaluate whether low-salt low-protein diet (LPD) supplemented with 10 g of inulin could lower serum toxin levels in patients with chronic kidney disease (CKD), thereby providing evidence for adjusting dietary prescriptions of inhospital patients and outpatient nutrition consultants.

Methods: we randomized 54 patients with CKD into two groups. Dietary protein intake compliance was evaluated using a 3-day dietary diary and 24-h urine nitrogen levels. The primary outcomes were indoxyl sulfate (IS) and p-cresyl sulfate (PCS), and secondary outcomes included inflammation marker levels, nutritional status, and renal function. We assessed 89 patients for eligibility, and a total of 45 patients completed the study, including 23 and 22 in the inulin-added and control groups, respectively.

Results: PCS values decreased in both groups after intervention: inulin-added group, ΔPCS -1.33 (-4.88, -0.63) μg/mL vs. LPD group, -4.7 (-3.78, 3.69) μg/mL ($p = 0.058$). PCS values reduced from 7.52 to 4.02 μg/mL ($p < 0.001$) in the inulin-added group ($p < 0.001$). Moreover, IS decreased from 3.42 (2.53, 6.01) μg/mL to 2.83 (1.67, 4.74) μg/mL after adding inulin; ΔIS was -0.64 (-1.48, 0.00) μg/mL, and a significant difference was observed compared with the control group ($p = 0.004$). The inflammation index decreased after intervention.

Conclusion: dietary fiber supplementation may reduce serum IS and PCS levels and modulate their inflammatory status in predialysis CKD patients.

Keywords:

p-cresyl sulfate. Indoxyl sulfate. Inulin. Dietary fiber. Protein-bound toxin. Chronic kidney disease.

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Correspondence:

Hongmei Zhang. Department of Renal Centre. Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University. Hangzhou, Zhejiang Province. China
e-mail: hzzhanghongmei@163.com

Resumen

Objetivo: este ensayo aleatorizado doble ciego comparó el efecto de una dieta baja en proteínas (LPD) con o sin suplementos orales de 10 g de inulina en los niveles de PBUT en pacientes con ERC en prediálisis durante 12 semanas.

Métodos: clasificamos aleatoriamente a 54 pacientes con ERC en dos grupos. El cumplimiento de la ingesta dietética de proteínas se evaluó utilizando un diario dietético de 3 días y nitrógeno en orina de 24 horas. Los resultados primarios fueron IS y PCS y los resultados secundarios incluyeron niveles de marcadores de inflamación, estado nutricional y función renal. Evaluamos la elegibilidad de 89 pacientes y 45 completaron la intervención, incluidos 23 y 22 en los grupos de inulina añadida y de control, respectivamente.

Resultados: el sodio urinario promedio de 24 horas fue de 86 mmol/día y la ingesta promedio de proteínas fue de ~0,7 g/kg/día. Los valores de PCS exhibieron una tendencia decreciente en ambos grupos después de la intervención: grupo con inulina añadida, ΔPCS -1.33 (-4.88, -0.63) µg/mL vs. grupo LPD, -4.7 (-3.78, 3.69) µg/mL) (p =0,058). Los valores de PCS se redujeron de 7,52 a 4,02 µg/mL (p < 0,001) con inulina (p < 0,001). Además, IS disminuyó de 3,42 (2,53, 6,01) µg/mL a 2,83 (1,67, 4,74) µg/mL después de agregar inulina; El ΔIS fue -0,64 (-1,48; 0,00) µg/mL y se observó una diferencia significativa en comparación con el grupo control (p =0,004).

Conclusión: la suplementación con fibra dietética puede reducir las toxinas de unión a proteínas séricas en pacientes con ERC en prediálisis y modular su estado inflamatorio.

Palabras clave:

Sulfato de p-cresil. Sulfato de indoxilo. Inulina. Fibra dietética. Toxina unida a proteínas. Enfermedad renal crónica.

INTRODUCTION

Chronic kidney disease (CKD) is a major public health concern worldwide, with a high prevalence of 10 %-13 % (1). The loss of kidney function in CKD is progressive, engendering the accumulation of toxins that are usually cleared by the kidneys, ultimately causing uremia (2). Owing to various CKD-specific risk factors, including uremic toxin accumulation, metabolic disorders, and systemic inflammation, patients with CKD are at an increased risk of developing cardiovascular diseases, which accounts for approximately 50 % of overall mortality among patients with late-stage CKD (3). By 2040, CKD is estimated to become the fifth leading cause of death globally—one of the largest projected increases among major causes of mortality (4).

The major protein-bound uremic toxins (PBUTs), accounting for approximately 25 % of all currently identified uremic toxins, include indoxyl sulfate (IS) and p-cresyl sulfate (PCS), which are produced via the breakdown of tyrosine and tryptophan in the digestive system, respectively (5,6). IS and PCS accumulate in the serum of patients with CKD because of decreased glomerular filtration rate and augmented toxin-producing microorganism levels (7). IS and PCS accumulation in CKD enhances cytokine expression, induces inflammatory reactions, and promotes renal tubular epithelial and renal interstitial cell degeneration, ultimately causing renal interstitial fibrosis and glomerulosclerosis (8,9). Moreover, IS and PCS are important factors in the development of cardiovascular complications and CKD-mineral and bone disorder (8-11). PBUT enhances oxidative stress in vascular smooth muscles, thereby promoting vascular endothelial damage (12). Consequently, these toxins play an important role in vascular calcification and atherosclerosis (13). Clinical approaches to reduce PBUT in patients with CKD are currently limited. Hemodialysis fails to efficiently remove PBUTs as they are primarily bound to albumin with only a small number of free components (14). Low-protein diet (LPD); intestinal toxin adsorptions, such as AST120; hemoperfusion; and traditional Chinese medicines, such as *chuan xiong,* have been reported to reduce serum IS and PCS levels to a certain extent (15). Nutrition therapy in patients with CKD is an economical and simple treatment method. Recently, dietary fibers have received increasing attention for reducing uremic toxins, attenuating systemic inflammation, and decreasing all-cause mortality in patients with CKD (16,17).

A growing body of evidence has demonstrated that high-fiber diets reduce serum creatinine, serum urea nitrogen, and serum *p*-cresol levels by 24 %-40 % (18,19). The added soluble dietary fiber diet lowers inflammatory biomarkers, such as C-reactive protein (CRP) and interleukin (IL)-6, in patients undergoing maintenance hemodialysis (20). Dietary fiber appears to exert a beneficial effect on renal protection by lowering toxins generated from the gut in the nondialysis CKD population but clinical evidence remains insufficient. Dietary fiber intake in patients with CKD is lower than the recommended dose in both the healthy and CKD populations, approximately 14 g/1000 kcal (21) or 25-30 g/day (22). In early 2013, Fujii H *et al.* retrospectively analyzed the dietary fiber intake of 4399 patients with diabetes and CKD. The average dietary fiber intake was 7.60 ± 0.03 g/1000 kcal, and the author recommended consuming more dietary fibers (23). A previous study reported that the average insoluble dietary fiber intake was 8.85 ± 3.06 g/day; the energy-adjusted intake was approximately 6.31 ± 1.86 g/1000 kcal in Chinese patients with CKD, and the dietary fiber intake was considerably reduced in patients with late-stage CKD due to dietary restrictions on fruits, vegetables, and legumes to lower the risk of hyperkalemia, coupled with gastrointestinal reactions, such as decreased appetite and nausea (24).

Inulin, a common soluble dietary fiber and prebiotic, has a neutral taste and fewer side effects and can increase gut *Bifidobacteriaceae* frequencies (25). Therefore, this study aimed to evaluate the effects of adding inulin to low-salt LPD of Chinese patients with CKD on their serum IS, PCS, and inflammatory biomarker levels.

METHODS

PATIENTS

Predialysis patients with CKD from the outpatient department of the Nephrology Department of a tertiary hospital in Hangzhou were recruited from November 2018 to November 2020.

A sample size of 48 patients was calculated to detect a significant reduction in the serum PCS levels from 7.25 ± 1.74 mg/L to 5.82 ± 1.72 mg/L, with a power of 80 % and an error rate of 5 % based on a previous study (18). Allowing for 10 % dropout, 54 patients were finally recruited.

PASS software was used to calculate

$$n1 = n2 = 2\left[\frac{(Z\alpha + Z\beta)s}{\delta}\right]^2$$

The inclusion criteria were as follows: (1) age >18 years, (2) estimated glomerular filtration rate (eGFR) of ≤ 44 mL/min/1.73 m^2 that was stable for >3 months, (3) received dietary nutrition therapy, and (4) no intellectual or cognitive impairments.

The exclusion criteria were as follows: (1) active gastrointestinal disease or gastrointestinal surgery in the last 3 months; (2) acute pancreatitis, heart failure, malignant tumors, tuberculosis, and other acute infectious diseases; (3) abnormal liver function (aspartate transaminase or alanine transaminase increased by >20 % from the upper limit of the reference value); (4) patients who are using or have received corticosteroids or immunosuppressive drugs and nonsteroidal anti-inflammatory drugs in the past 3 months; and (5) patients participating in other clinical trials.

The data of the patients whose serum creatinine levels doubled or who entered the dialysis treatment during intervention were excluded from the statistical analysis.

MATERIALS AND METHODS

In this randomized controlled double-blind trial, 54 patients were randomly divided into only-LPD and LPD supplemented with dietary fiber (inulin) groups, with 27 cases in each group. The intervention period was 12 weeks.

Enrollment and grouping

Randomized controlled blinding method: SAS software Pro Plan program was used to generate 54 random serial numbers using the Drug Clinical Trials Management Standard Office of the hospital. Then, 54 sequential numbers were randomly assigned to the inulin-added or control group and placed into opaque envelopes. After the patients signed the informed consent, the enrollment-numbered envelopes were removed, and patients were randomly divided into either inulin-added or control group. Blood samples and baseline data were collected.

Intervention

Inulin-added group: LPD plus dietary fiber (10 g/day of inulin). Inulin was added to liquid foods or 100 ml warm water in daily meals and total intake. Inulin (batch number: 20170701) as a dietary fiber was provided by Zhejiang Yingte Food Co., Ltd. Wheat starch and inulin were uniformly packaged by Wuhan Yingnulin Biotechnology Co., Ltd. (10 g/pack) and marked with group label (inulin-added or control), production date, expiry date, and batch number.

Control group: LPD plus placebo (10 g/d of wheat starch). Wheat starch was added to liquid foods or warm water daily. Wheat starch, a colorless and odorless white powder, was used as placebo. The wheat starch (batch no.: 20171201) was provided by Shanghai Yushen Biotechnology Co., Ltd. and produced by Zhejiang Zhuji Shenyi Food Technology Co., Ltd.

LPD and compliance

Dietary intake standard: A low-salt LPD was implemented based on the expert consensus on Protein Nutrition therapy for CKD in China (26). The recommended amount of protein was 0.6-0.8 g/kg/day and calories were 30-35 kcal/kg/day. Salt intake was 100 mmol/day. If the protein intake of participants did not reach the basic treatment target (0.6-0.8 g kg^{-1} d^{-1}, ≥ 50 % of high-quality protein), a run-in period from 0.5 months to 1 month was required to educate them. Individual dietary nutrition education was provided by a single registered dietitian, including the manner of recording the dietary intake quantity by food models and 24-h urine specimen collection methods. After training, the protein intake was assessed again. Dietary compliance of patients in approximately neutral nitrogen balance could be assessed by the estimated total nitrogen excretion. The total nitrogen excretion can be estimated accurately as U + 31mg N/kg/day. The 24-h urea nitrogen was calculated using Maroni et al.'s formula (27) [DPI (g/day) = 6.25 (U + 0.031 × body weight)], and the corresponding intervention was given after reaching the target.

During the research period, dietitians collected 24-h dietary records by telephone once a week. The participants visited a dietitian once a month with a 3-day dietary diary and 24-h urine sample. The 24-h urinary metabolic indicators were primarily collected for estimating 24-h urinary urea nitrogen and sodium levels.

Dietary compliance assessment: Dietary intake according to a 3-day dietary diary and 24-h urine metabolic indicators during the intervention were used to evaluate renal dietary adherence. During the intervention, dietary diaries and 24-h urine indices were evaluated twice, and the average value was obtained as postintervention statistical indices. According to the evaluation criteria of LPD compliance, the average protein intake based on 24-h urea nitrogen was within the research protocol standard range (0.6-0.8 g kg^{-1} d^{-1}), that is, the compliance was good. The amount of inulin intake in the inulin-added and control group was calculated based on the actual follow-up days. Subsequently, five packs were issued each time for temporary delayed follow-up, and the empty packages were recycled after use.

Data collection, input, and analysis of the inulin-added and control groups were performed by postgraduates in this study. The control group was given dietary fiber compensation for 3 months when blindly opened post intervention.

Outcome measurements

The primary outcomes of this study are the serum IS and PCS levels. Fasting blood (3 mL) was drawn in the morning at baseline and at the

postintervention follow-up. Following centrifugation at 3000 rpm for 15 min, the supernatant was stored in a -80 °C refrigerator until use. Ultrahigh-performance liquid chromatography (HPLC) tandem mass spectrometry was used to assess the levels of these toxins (28). HPLC grade acetonitrile and methanol were obtained from Merck (Darmstadt, Germany). Formic acid was procured from Aladdin Chemistry (Shanghai, China). Ultrapure water was obtained using Barnstead TII super Pure Water System (MA, USA). All other analytical grade chemicals used in this experiment were purchased from Yongda Chemical Reagent Company (Tianjin, China). Reference substances, including PCS, IS, PCS-d7, and IS-d4, were purchased from Sigma-Aldrich (St. Louis, MO, USA).

The secondary outcomes of the study included inflammatory markers: serum IL-6, TNF-α, and high-sensitivity CRP, levels of which were measured using enzyme-linked immunosorbent assay (Multi sciences) (ambient temperature, 21°C; relative humidity, 44 %), and nutritional status and renal function, which included serum albumin, prealbumin, and transferrin, used to estimate nutrition status and glomerular filtration rate (eGFR) (required for Modification of Diet in Renal Disease formula), and serum creatinine and blood urea nitrogen levels were collected. The gastrointestinal function score was assessed using the gastrointestinal symptom rating scale (GSRS). It was developed by Swedish researcher Jan Svedlund et al. (29) in 1988 and later improved by Dimenas (30). The subjective global assessment (SGA) score consists of 7 items, including patient's weight, diet, gastrointestinal tract, physiological function, disease impact, and subcutaneous fat and muscle consumption to comprehensively evaluate the patient's nutritional status; the total SGA score ranges from 7 to 35 points. If the total score is within 10, the patient is considered to have a normal nutritional status (31).

STATISTICAL ANALYSIS

Data were analyzed with SPSS 16.0 (IBM Corp, Armonk, NY, USA). Normally distributed continuous variables were presented as mean ± standard deviation and were compared using independent samples t-test between the two groups, and paired t-test was used to compare results pre and post intervention in each group. Continuous variables with skewed distribution were presented as median and interquartile range and compared using nonparametric Mann-Whitney U-test between the two groups. Categorical variables were presented as the frequency and percentage and compared using Pearson Chi-squared test. The correlation between the IS and PCS changes was evaluated using Spearman's correlation. $p < 0.05$ was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS OF THE PARTICIPANTS

In total, 89 patients were assessed for eligibility. Among them, 35 were excluded because of the absence of signed informed consent (n = 25), current steroid or immunosuppressant use (n = 2), advanced tumors (n = 1), remote residence inconvenient for review (n = 2), and other reasons (n = 5). Overall, 54 patients were randomized into two groups (n = 27) and initiated the run-in period. Finally, 45 patients completed the intervention, including 23 in the inulin-added group and 22 in the control group (Fig. 1). In the inulin-added group, four patients dropped out (one could not adhere to the LPD and three were transferred to a local hospital). In the control group, five pa-

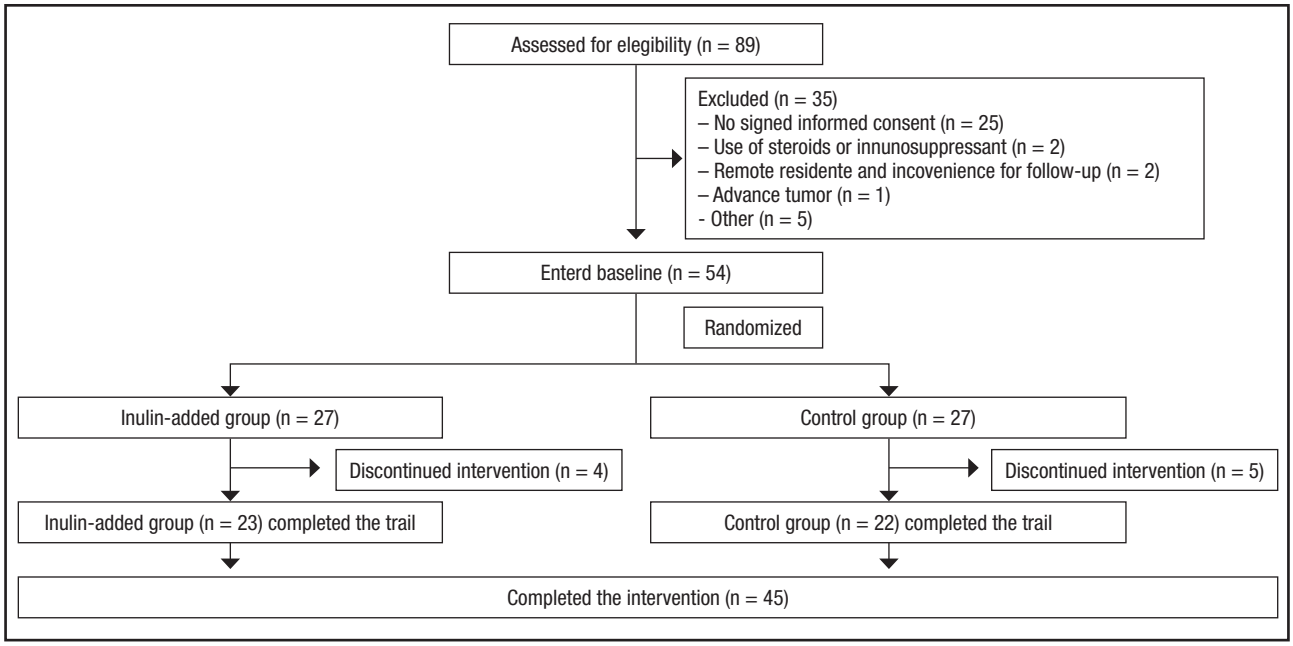

Figure 1.
Flowchart.

tients dropped out because they were unable to adhere to the LPD management. Therefore, 23 patients in the inulin-added group, including 15 males, completed the trial. The primary diseases that caused CKD were chronic nephritis (n = 19), diabetic nephropathy (n = 1), hypertensive nephropathy (n = 1), and polycystic kidney disease (n = 2). Four patients were diagnosed with hyperkalemia at the time of enrollment. In the control group, 22 patients, including 8 males, completed the study. The primary diseases that caused CKD were chronic nephritis (n = 18), diabetic nephropathy (n = 2), hypertensive nephropathy (n = 1), and unknown (n = 1). Five patients were diagnosed with hyperkalemia at the time of enrollment. The two groups showed no statistical differences in terms of demographic data, dietary intake, and biochemical parameters at baseline (Table I).

Table I. Clinical characteristics of the two groups at baseline

Characteristics	Inulin-added group (n = 23)	Control group (n = 22)	*p*-value
Gender (male/%)	15 (65.2%)	8 (36.4%)	0.053
Age (years)	51.30 ± 13.38	51.59 ± 14.64	0.946
CKD4 (n/%)	20 (87%)	16 (72.7%)	0.412
CKD5 (n/%)	3 (13%)	6 (27.3%)	
BMI (kg/m^2)	22.47 ± 2.73	21.85 ± 2.78	0.452
SBP (mmHg)	118.22 ± 10.12	124.91 ± 12.88	0.059
DBP (mmHg)	75.22 ± 8.77	77.05 ± 10.63	0.532
AMC (cm)	24.07 ± 1.56	22.90 ± 2.30	0.051
GFS (points)	7.00 (2.00,12.00)	8.00 (4.00,13.50)	0.654
BSFS (form)	4.00 (3.00,5.00)	4.00 (3.00,6.00)	0.952
24-h urine protein (g/24 h)	1.29 ± 0.93	1.27 ± 0.78	0.959
eGFR (ml/min/1.73 m^2)	24.78 ± 9.16	20.03 ± 7.82	0.068
Hemoglobin (g/L)	107.74 ± 16.60	98.95 ± 15.19	0.071
K (mmol/L)	4.46 ± 0.50	4.61 ± 0.59	0.371
TCH (mmol/L)	4.63 ± 1.28	4.74 ± 0.95	0.745
TG (mmol/L)	1.74 ± 0.89	2.01 ± 1.28	0.346
LDL-C (mmol/L)	2.69 ± 0.97	2.86 ± 0.51	0.460
SCr (μmol/L)	257.33 ± 103.45	299.91 ± 109.98	0.188
BUN (mmol/L)	14.85 ± 5.92	15.50 ± 6.53	0.728
UNa (mmol/d)	120.75 ± 52.97	110.48 ± 35.36	0.603
UK (mmol/d)	30.41 ± 14.68	30.83 ± 15.18	0.973
UUN (g/24 h)	9.05 ± 2.25	7.79 ± 1.76	0.049
eDPI (g/kg/d)	0.99 ± 0.24	0.90 ± 0.20	0.228
Dietary fiber intake (g/d)	9.56 ± 5.52	9.10 ± 2.60	0.825
ACEI (n/%)	7 (30.4%)	6 (27.3%)	0.815
Primary disease (n/%)			0.799
Glomerulonephritis	19 (82.6%)	18 (81.8%)	
Diabetes	1 (4.3%)	2 (9.1%)	
Hypertension	1 (4.3%)	1 (4.5%)	
Polycystic kidney disease	2 (8.7%)	0 (0%)	
Others	0 (0%)	1 (4.5%)	
Keto acid (n/%)	13 (56.5%)	11 (50%)	0.661
Hyperkalemia (n/%)	4 (17.4%)	5 (22.7%)	0.655

Values for continuous variables are presented as means ± standard deviations or medians and interquartile ranges. Categorical variables are expressed as numbers (%). BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; AMC: upper arm muscle circumference; GFS: gastrointestinal function score; BSFS: Bristol Stool Form Scale; eGFR: estimated glomerular filtration rate; K: serum potassium; TCH: total cholesterol; TG: triglycerides; LDL-C: low density lipoprotein-cholesterol; SCr: serum creatinine; BUN: blood urea nitrogen; Una: urine sodium; UK: urine potassium; UUN: urinary urea nitrogen excretion; eDPI: estimated daily protein intake. DFI: dietary fiber intake.

DIETARY COMPLIANCE

During the trial, the average 24-h urinary sodium level was 86 mmol/day, and the average protein intake was approximately 0.7 g/kg/day for all participants (Table II). Nutrient parameters calculated using a 3-day dietary diary showed no significant differences in body weight-adjusted calorie, protein, high-quality protein ratio, and dietary fiber intake between the two groups before intervention. Protein intake in both groups was reduced and stable during the intervention. With changes in the dietary pattern, the actual dietary fiber intake in both groups was reduced; however, the reduction was not significant (Table III).

Table II. Estimated diet protein and salt intake per 24-h urine parameters

Projects	Inulin-added group (n = 23)	Control group (n = 22)	*p*-value
eDPI (g/d) before	56.5 ± 14.05	48.68 ± 11.03	0.049
eDPI (g/d) during	40.58 ± 8.75	38.11 ± 8.81	0.387
p interclass	< 0.001	0.002	
eDPI (g/kg/d) before	0.99 ± 0.24	0.90 ± 0.20	0.228
eDPI (g/kg/d) during	0.71 ± 0.13	0.69 ± 0.13	0.828
p interclass	< 0.001	< 0.001	
UNa (mmol/d) before	120.75 ± 52.97	110.48 ± 35.36	0.603
UNa (mmol/d) during	86.48 ± 35.29	85.39 ± 35.10	0.945
P interclass	0.037	0.170	

Values for continuous variables are presented as means ± standard deviations. eDPI: estimated daily protein intake; Una: urine sodium.

Table III. Macronutrient intake per the 3-day diet diary

Parameters	Inulin-added group	Control group	*p*-value
DEI (kcal/d) before	1750.17 ± 252.90	1562.52 ± 257.54	0.096
DEI (kcal/d) during	1727.33 ± 258.27	1533.17 ± 438.45	0.187
Pinterclass	0.798	0.875	
DEI (kcal/kg/d) before	31.03 ± 4.81	28.73 ± 5.69	0.297
DEI (kcal/kg/d) during	30.33 ± 4.45	28.32 ± 7.59	0.422
Pinterclass	0.659	0.905	
DPI (g/d) before	59.38 ± 11.68	49.11 ± 13.00	0.050
DPI (g/d) during	45.15 ± 7.65	41.63 ± 9.40	0.348
Pinterclass	< 0.001	0.231	
DPI (g/kg/d) before	1.05 ± 0.22	0.89 ± 0.20	0.080
DPI (g/kg/d) during	0.79 ± 0.14	0.77 ± 0.15	0.715
Pinterclass	< 0.001	0.207	
High-quality protein (%) before	37.33 ± 13.16	42.63 ± 12.83	0.350
High-quality protein (%) during	53.53 ± 10.50	44.15 ± 10.49	0.590
Pinterclass	< 0.001	0.808	
DFI (g/d) before	9.56 ± 5.52	9.10 ± 2.60	0.825
DFI (g/d) during	7.52 ± 2.64	7.35 ± 1.80	0.887
Pinterclass	0.186	0.160	

Values for continuous variables are presented as means ± standard deviations. DEI: diet energy intake; DPI: diet protein intake; DFI: dietary fiber intake.

Table IV. Changes in serum p-cresol sulfate and indole sulfate levels of the participants

Parameters	Inulin-added group (n = 23)	Control group (n = 22)	*p*-value
PCS before	7.52 (2.16, 10.75)	7.99 (3.573, 15.085)	0.318
PCS after	4.02 (1.53, 8.43)	8.71 (6.11, 15.18)	0.006
ΔPCS	-1.33 (-4.88, -0.63)	-4.7 (-3.78, 3.69)	0.058
Pinterclass	< 0.001	0.745	
IS before	3.42 (2.53, 6.01)	4.755 (1.98, 6.87)	0.474
IS after	2.83 (1.67, 4.74)	5.69 (3.16, 8.52)	0.003
ΔIS	-0.64 (-1.48, 0.00)	0.825 (-0.61, 1.47)	0.004
Pinterclass	0.006	0.135	

The unit of PCS, IS, and their difference is μg/mL. Values for continuous variables are presented as medians and interquartile ranges. PCS: p-cresol sulfate; IS: indole sulfate. Δ: before-after.

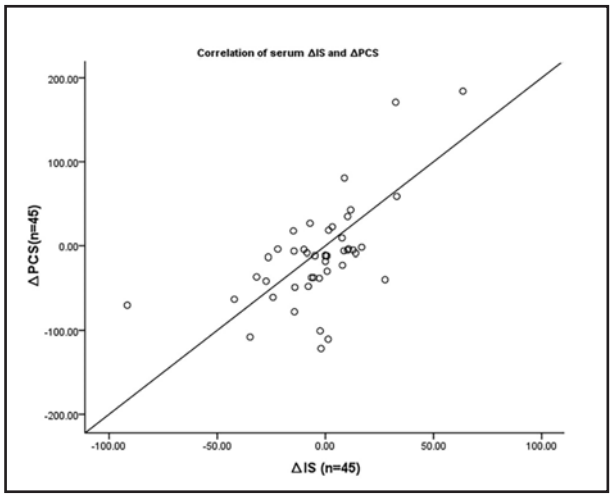

Figure 2.
Correlation of serum ΔIS and ΔPCS.

SERUM IS AND PCS LEVELS

Post intervention, free plasma PCS and IS levels significantly decreased in the inulin-added group ($p < 0.001$ and $p = 0.006$, respectively). ΔPCS in both groups reduced, and a marginal difference was observed ($p = 0.058$). ΔIS in the inulin-added group significantly decreased compared with the control group ($p = 0.004$) (Table IV). The correlation of the IS and PCS level reduction was similar among the study population ($r = 0.570$, $p < 0.05$) (Fig. 2).

RESULTS OF INFLAMMATORY MARKERS

The levels of inflammatory markers in both groups decreased post intervention. A significant decrease in IL6 levels was observed in the inulin-added group compared with the LPD-only group ($p = 0.029$). No significant differences were observed in the levels of other markers (Table V).

NUTRITIONAL MARKERS AND RENAL FUNCTION

All participants were screened with NRS2000 during the study, NRS2000 score less than 3._The nutritional status (Alb and SGA levels) remained stable in both groups, and no significant differences were observed in the serum creatinine and urea nitrogen levels as well as eGFR (Table VI).

Moreover, no serious adverse effects were observed in both groups. Just one patient in the inulin-added group showed an aggravation of constipation after dietary fiber intake for 1 week. A comprehensive analysis conducted by the attending physician and the nutritionist revealed that the patient had insufficient water intake (urine output: 900-1200 ml). After increasing the water intake and performing proper exercises, constipation improved after 1 week of water and lifestyle adjustment.

DISCUSSION

A previous study reported that high dietary fiber ameliorates serum PBUT levels, but the evidence is not well documented (18). This study showed that addition 10 g of inulin to LPD in clinical settings may potential lower serum IS and PCS levels and modulate inflammatory status in patients with stage 3b-5 CKD. Indeed, the dietary fiber intake of patients with CKD is lower than the recommended dose (24). The present study indicated that the addition of inulin to LPD is a safe, economical, and convenient dietary adjustment in CKD nutrition therapy, which can bring clinical benefits of CKD population.

Nutritional therapy is an important strategy in the multidisciplinary treatment of patients with CKD; it is aimed at restricting daily protein and sodium intake and ensuring adequate nutrient intake to avoid developing protein-energy wasting (32). The average salt and actual dietary protein intakes were 86 mmol/day and 0.7 g/kg/day, respectively, during the intervention period, which met the guidelines (33,34). After run-in dietary adjustment, the dietary fiber intake in both groups decreased slightly due to two reasons. First, the patients were advised to select or-

Table V. Changes in the inflammatory indices of the two groups

Parameters	Inulin-added group (n = 23)	Control group (n = 22)	*p*-value
Hs-CRP (mg/L) before	1.53 (0.54, 3.68)	1.07 (0.36, 2.19)	0.242
Hs-CRP (mg/L) after	0.81 (0.38, 2.14)	0.65 (0.32, 1.82)	0.625
ΔHs-CRP(mg/L)	-0.33 (-1.87, 0.04)	-0.29 (-1.19, 0.23)	0.865
Pinterclass	0.019	0.031	
IL-6 (gp/ml) before	23.92 (14.05, 43.59)	21.30 (12.82, 29.12)	0.340
IL-6 (gp/ml) after	10.94 (3.55, 18.68)	14.10 (8.97, 27.00)	0.097
ΔIL-6(gp/ml)	-11.41 (-21.20, -2.81)	-3.71 (-10.86, 5.72)	0.029
Pinterclass	0.001	0.189	
TNF-α (gp/ml) before	78.20 (35.83, 237.96)	108.38 (47.90, 129.62)	0.964
TNF-α (gp/ml) after	63.51 (43.74, 108.52)	98.12 (58.06, 137.52)	0.159
ΔTNF-α (gp/ml)	-30.02 (-117.11, 8.71)	-3.73 (-21.31, 60.19)	0.128
Pinterclass	0.023	0.858	

Values for continuous variables are presented as medians and interquartile ranges. hs-CRP: high-sensitivity C-reactive protein; Hs-CRP: range 0.00-3.00. Δ: before-after.

Table VI. Nutritional markers and renal function of the two groups

Parameters	Inulin-added group (n = 23)	Control group (n = 22)	*p*-value
Alb (g/L) before	37.94 ± 4.80	37.58 ± 3.26	0.773
Alb (g/L) after	40.55 ± 4.41	39.47 ± 2.74	0.33
PA (g/L) before	0.31 ± 0.09	0.30 ± 0.08	0.895
PA (g/L) after	0.35 ± 0.08	0.35 ± 0.07	0.938
TRF (g/L) before	1.94 ± 0.35	1.87 ± 0.30	0.545
TRF (g/L) after	2.35 ± 0.45	2.24 ± 0.33	0.420
SCr (μmol/L) before	257.34 ± 103.45	299.91 ± 109.98	0.188
SCr (μmol/L) after	259.87 ± 115.72	311.18 ± 185.23	0.269
BUN (mmol/L) before	14.83 ± 5.91	15.50 ± 6.53	0.721
BUN (mmol/L) after	13.46 ± 4.40	14.22 ± 6.66	0.655
eGFR (ml/min/1.73 m^2) before	24.78 ± 9.16	20.03 ± 7.82	0.068
eGFR (ml/min/1.73 m^2) after	27.76 ± 11.52	22.07 ± 12.42	0.118
SGA before	10.26 ± 2.63	9.95 ± 2.75	0.705
SGA after	7.83 ± 1.07	8.32 ± 1.78	0.266

Values for continuous variables are presented as means ± standard deviations. Alb: albumin; PA: prealbumin; TRF: transferring; SCr: serum creatinine; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate. m^2: square meter.

dinary staple foods to ensure adequate energy intake during LPD therapy, including wheat starch and vermicelli, which contains lower dietary fiber than whole grains. Second, patients who had experienced hyperkalemia were asked to restrict potassium-rich foods, including some fruits and vegetables. Whole grains, fruits, and vegetables are the main sources of indigestible and complex carbohydrates (35).

We observed that LPD supplemented with inulin decreased serum IS and PCS levels in patients with advanced CKD; this finding was consistent with the findings of previous studies (19,36). PCS reduced from 7.52 to 4.02 mg/L ($p < 0.001$) when LPD was supplemented with 10 g inulin; this finding was consistent with the results of Samen *et al.* (18) Decreased amplitude of PCS in the inulin-added group was marginally higher than that in the LPD group due to small sample size. The IS level significantly decreased after supplementing the diet with inulin, and the decreasing trend of the serum IS and PCS levels was similar since they have similar molecular weights. Notably, a meta-analysis (37) showed that after dietary fiber supplementation, serum PCS level decreased but not IS level. Conversely, Li et al. (38) reported that added dietary fiber (10 g/d inulin-type fructan) significantly decreased the IS level but not the PCS level. However, Ramos et al. (39) did not observe a decreasing trend in serum PCS

and IS levels of patients with CKD after adding dietary fiber (fructose oligosaccharide, 12 g). This discrepancy may be attributable to the diversity of complex polysaccharides associated with bacterial diversity in human gut microbiota (40), which is one of the effect mechanism of dietary fiber can lower PBUTs (7). Inulin contains both low- and high-molecular-weight bioactive carbohydrates, lowers intestinal pH, limits indole-producing bacterial communities, and reduces IS precursor production by the gut microbiome, whereas fructo-oligosaccharides exhibit little effect on gut microbiome species (37,41).

We found that LPD with or without inulin can modulate inflammation; however, inulin-added LPD was more effective; this finding is consistent with the results of a previous study (25). Inulin as a soluble dietary fiber can directly modulate proinflammatory cytokine production in monocytes (42). In another pathway, dietary fiber can modulate CKD-induced microbial dysbiosis (43) and increase the production of short-chain fatty acids, which maintain the gut epithelial structure integrity and function (44). SCFAs are vital nutrients for regulatory T lymphocytes (T-reg). T-reg is essential for maintaining immunological self-tolerance and limiting inflammatory response (45,46).

LPD is associated with a 32 % lower risk of death in patients with CKD compared with the non-LPD group (47). However, clinical implementation of LPD is highly controversial due to high risk of malnutrition (48). We screened all participants with NRS2000 and estimated nutritional status with SGA to ensure safety. In this study, patients' nutritional indexes were stable, consistent with a study of Lu et al. (49). No significant changes in the serum creatinine blood urea nitrogen levels as well as eGFR were observed in both groups, consistent with the results of previous studies (18,25,50). Added dietary fiber to CKD patients' diet plan seems safe and may have potential benefits on reducing uremic toxins. Future nutritional guidelines should consider recommending a higher dose of dietary fiber or potassium-free alternatives, such as prebiotics, for patients with CKD to improve long-term outcomes (51,52).

In conclusion, addition of 10 g inulin to LPD may reduce serum IS and PCS levels and modulate the inflammation level in non-dialysis CKD3b-5 patients. At the same time, inulin-added LPD maintains serum albumin level and has good diet compliance. It provides evidence for adjusting patients' dietary prescriptions and advice about dietary fiber in clinical settings.

This study had certain limitations. First, the sample size was relatively small, and a large gender difference between the groups may have impacted the results. Second, the accuracy of the 3-day dietary diary needs to be improved, and there may be a bias in the estimation of the dietary fiber intake.

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Revisión

Treating asthma patients with probiotics: a systematic review and meta-analysis

Tratamiento de pacientes asmáticos con probióticos: revisión sistemática y metaanálisis

Qiwei Xie, Jiatian Yuan, Yaoweng Wang

The Affiliated Hospital of Medical School. Ningbo University. Ningbo, China

Abstract

Objective: to evaluate the role of probiotics in the treatment of asthma patients by meta-analysis.

Methods: PubMed, Embase, The Cochrane Library, Web of Science, and other databases were searched by computer, and the relevant literature on the treatment of asthma by probiotics that met the inclusion criteria was screened by manual retrieval. Meta-analysis was performed using Revman 5.4 software and the combined effect was evaluated by odds ratio (OR) or mean difference (MD) and 95 % confidence interval (CI).

Results: a total of ten references were included, all of which were randomized controlled studies, and a total of 1,101 people were investigated. Fractional exhaled nitric oxide (FeNO) (MD = -7.17, 95 % CI: -12.81, -1.54), asthma symptom severity (MD = -0.07, 95 % CI: -0.10, -0.04), Childhood Asthma Control Test (CACT) (MD = 2.26, 95 % CI: 1.14, 3.39), and the number of acute episodes of asthma (OR = 0.30, 95 % CI: 0.19, 0.47) in the probiotics group were better than those in the control group. There was no significant difference in forced expiratory volume in the first second (FEV1) (MD = 0.11, 95 % CI: -0.05, 0.26) and FEV1/FVC (%) (MD = 0.32, 95 % CI: -1.48, 2.12).

Conclusion: the use of probiotics in patients with asthma can improve lung inflammation and asthma symptoms, reduce the number of asthma attacks, and have no effect on lung function.

Keywords:

Probiotics. Asthma. Meta.

Resumen

Objetivo: evaluar el papel de los probióticos en el tratamiento de pacientes con asma mediante metaanálisis.

Métodos: se realizaron búsquedas informáticas en PubMed, Embase, The Cochrane Library, Web of Science y otras bases de datos, y se examinó la literatura relevante sobre el tratamiento del asma con probióticos que cumplía con los criterios de inclusión mediante recuperación manual. El metaanálisis se realizó con el *software* Revman 5.4 y el efecto combinado se evaluó mediante la razón de probabilidades (OR) o diferencia media (MD) y el intervalo de confianza (IC) del 95 %.

Resultados: se incluyó un total de diez referencias, todas ellas estudios controlados aleatorios, y se investigó un total de 1.101 personas. El óxido nítrico exhalado (FeNO) (MD = -7,17, IC 95 %: -12,81, -1,54), la gravedad de los síntomas del asma (MD = -0,07, IC 95 %: -0,10, -0,04), la Prueba de Control del Asma (CACT-ACT) (MD = 2,26, IC 95 %: 1,14, 3,39) y el número de episodios agudos de asma (OR = 0,30, IC 95 %: 0,19, 0,47) en el grupo de probióticos fueron mejores que en el grupo de control. No hubo diferencia significativa en volumen espiratorio forzado en el primer segundo (FEV1) (DM = 0,11, IC 95 %: -0,05, 0,26) y FEV1/FVC (%) (DM = 0,32, IC 95 %: -1,48, 2,12).

Conclusión: el uso de probióticos en pacientes con asma puede mejorar la inflamación pulmonar y los síntomas del asma, reducir el número de ataques de asma y no tener efecto sobre la función pulmonar.

Palabras clave:
Probióticos. Asma. Meta.

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Correspondence:

Yaoweng Wang. The Affiliated Hospital of Medical School. Ningbo University. 59 Liuting St. Haishu District. 315016 Ningbo, Zhejiang. China
e-mail: wangyaowennihao@hotmail.com

INTRODUCTION

Asthma is a common chronic inflammatory respiratory disease (1), with high morbidity (2) and mortality. Studies have shown (3) that the proportion of children aged 13-14 and children aged 6-7 suffering from asthma increases by 0.28 % and 0.18 % annually. Due to the high incidence of asthma and the great economic pressure to treat asthma, it has attracted more and more attention from all walks of life in the past (4). The etiology and pathogenesis of asthma have not been fully elucidated (5), which may be related to various factors such as genetics, bacteria, viruses, immunity, nutrition, and environment. Asthma is mainly treated by inhaled corticosteroids, long-acting β-receptor agonists, leukotriene antagonists, and other drugs (6). Recently, the efficacy of probiotics in allergic diseases has received special attention (7). Experiments have shown that probiotics have a clear effect on allergic diseases such as allergic rhinitis (8,9) and eczema (10). However, the current meta-analysis showed that *Lactobacillus* supplementation had a positive effect on asthma prevention (11), while other probiotics had no significant effect on asthma prevention (12) and treatment (13). This is inconsistent with the conclusions of some experiments (14,15). In this study, meta-analysis was used to study the efficacy of probiotics in the treatment of asthma and evaluate it, so as to provide a reference for the selection of treatment options for asthma patients.

METHOD

This study followed the Cochrane manual system evaluation and meta-analysis criteria, according to Prisma statement, clinical registration number: INP LA SY 202270076.

SEARCH STRATEGY

We searched PubMed, Embase, The Cochrane Library and Web of Science databases to collect randomized controlled trials that met the inclusion criteria until July 2022. References for the included studies were also searched to supplement access to relevant information.

STUDY SELECTION

Inclusion criteria were as follows: a) the study is a randomized controlled trial; b) the inclusion of subjects is not limited by age, gender, etiology, or ethnic group; c) asthma diagnosis is consistent with the Global Asthma Initiative (1); d) there was no significant difference in age, gender, course of disease among the groups, and they were comparable; e) the experimental group was treated with probiotics (unlimited strains, doses, and courses of treatment), and the control group was treated with placebo; e) the experiment uses one or more fractional exhaled nitric oxide (FeNO), forced expiratory volume in the first second (FEV1), FEV1/FVC (%), asthma symptom severity, Childhood Asthma Control Test (CACT), Asthma Control Test (ACT), and the number of exacerbations to evaluate the experimental results. Higher FeNO indicates more severe airway inflammation. FEV1, FEV1/FVC (%) correlated with lung function. CACT- ACT indicates the degree of asthma control in the form of a scale. In this study, the assessment of asthma severity using a rating scale was summarized as asthma symptom severity.

Exclusion criteria were: 1) diseases with liver, gastrointestinal, kidney, endocrine, neuronal, cardiovascular, or psychiatric disorders or malignant tumors that may affect the results of the active upper respiratory tract infection study; b) conference papers, reviews, case reports, summaries of experiences, and repeated literature; c) the information contained in the literature is incomplete and cannot be obtained through other information; and d) low quality of literature (Cochrane Handbook < 2).

ASSESSMENT OF RISK OF BIAS

Two commentators independently analyzed the included literature according to the Cochrane bias risk assessment criteria, and the inconsistencies were reached through discussion. The evaluation contents include: a) the generation of the random allocation scheme; b) the concealment of the allocation scheme; c) the implementation of the blind method; d) the integrity of result data; e) non-selective report of results; and f) other biases. “Low risk” means low risk of bias, “high risk” means high risk of bias, and “unclear risk” means that literature does not provide sufficient or certain information for bias assessment.

LITERATURE SCREENING AND DATA EXTRACTION

Two researchers independently screened literature, extracted data and cross-checked them. If there were differences, they were solved through discussion or consultation with a third party. In literature screening, we first read the topic, and after excluding the obviously irrelevant literature, we further read the summary and full text to determine whether it was included. The author of the original study was contacted by email or telephone, if necessary, to obtain undetermined but important information for this study. Data extraction included: research topics, first author, publication year, age, gender, course of disease, follow-up time, intervention measures, outcome indicators.

STATISTICAL ANALYSIS

Statistical analysis was performed using RevMan 5.4 software. For the enumeration data, relative risk (RR) and 95 % confidence interval (95 % CI) were used as efficacy analysis statistics. When there was statistical homogeneity among the studies ($p > 0.1$, $I^2 < 50$ %), a fixed effect model was used for meta-analysis; if there was significant heterogeneity among the

studies ($p < 0.1$, $I^2 > 50$ %), the source of heterogeneity was further analyzed, and a subgroup analysis on factors that may lead to heterogeneity was performed. A random effects model was used for analysis. The funnel plot was used to judge whether there was publication bias in the included literature, and Egger's test could be used when there were at least ten studies. Inspection level was set at $\alpha = 0.05$.

RESULTS

SELECTION OF STUDIES

A total of 2,609 related pieces of literature were obtained from the literature screening process and preliminary examination of results, of which 455 were repetitive publications and 2,121 articles were excluded due to their irrelevant titles and abstracts. After layer-by-layer screening, 33 articles were selected for full-text review, 23 articles assessed as unqualified were excluded, and ten articles were finally included (16-18,21-26), including 1,101 patients. The search and selection steps are shown in figure 1.

The ten articles finally included were all randomized controlled studies from SCI journals. Among them, two articles studied the relationship between probiotics and FeNO, three articles studied the relationship between probiotics and FEV1, four articles studied the relationship between probiotics and FEV1/FVC (%), two articles studied the relationship between probiotics and asthma symptom severity, four articles studied the relationship between probiotics and CACT-ACT, and two articles studied the relationship between probiotics and the number of exacerbations. These ten studies were conducted in different countries, and the types and quantities of probiotics were also different. Table I summarizes the characteristics of each included study.

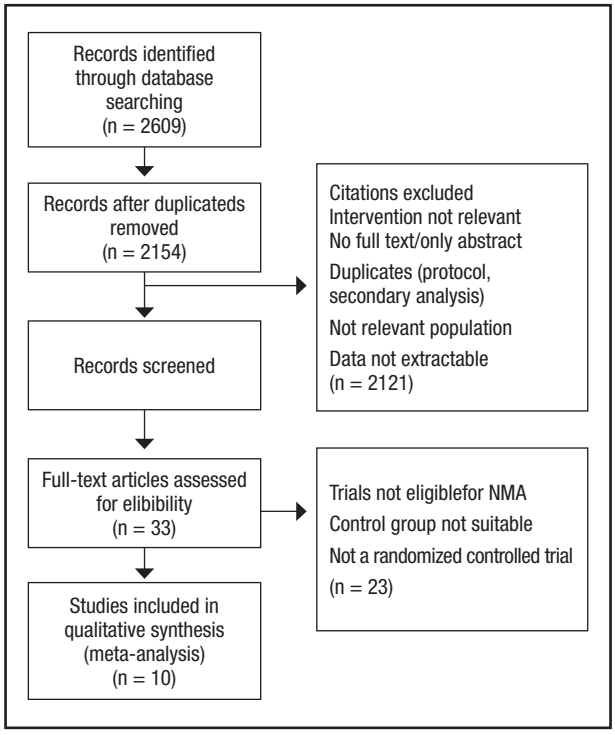

Figure 1.

Flow chart of the stepwise procedure for study selection.

ASSESSMENT OF RISK OF BIAS

The bias risk of included studies was assessed according to the Cochrane manual. The results showed that the research quality of all included randomized controlled trials (RCTs) was high, and the risk bias was mainly due to the midway introduction of research by some subjects. The results of the bias risk assessment included in the study are shown in figures 2 and 3.

META-ANALYSIS

FeNO

Two studies including 99 patients reported FeNO in patients taking probiotics and placebo. We tested the heterogeneity of the two studies, and the results showed $p = 0.11$ and $I^2 = 61$ %, indicating that heterogeneity is high. Therefore, the random effect model was used. After summarizing the data, we found that probiotics were lower than placebo patients, and the difference was statistically significant (MD = -7.17, 95 % CI: -12.81, -1.54). The results are summarized in figure 4.

Asthma symptom severity

Two studies including 252 samples reported asthma symptom severity in patients taking probiotics and placebo. We tested for heterogeneity between two studies which showed $p = 0.29$ and $I^2 = 10$ %, indicating very low heterogeneity; therefore, a fixed effects model was used. After pooling the data, we found asthma symptom severity in patients taking probiotics

It was lower than in the placebo patients, and the difference was statistically significant (MD = -0.07, 95 % CI: -0.10, -0.04). The results are summarized in figure 5.

CACT-ACT

Four studies including 343 samples reported CACT-ACT of patients taking probiotics and placebo. We tested the heterogeneity of the four studies, and the results showed $p = 0.42$ and $I^2 = 0$ %, indicating that heterogeneity was low. Therefore, we used the fixed effect model. After summarizing the data, we found that the CACT-ACT of patients taking probiotics was higher than that of patients taking placebo, and the difference was statistically significant (MD = 2.26, 95 % CI: 1.14, 3.39). The results are summarized in figure 6.

Table I. Characteristics of included studies

Author	Year	Gender	Age (years)	Follow-up (mouth)	Sample	Interventions	Type of probiotics	Outcomes
Yue-Sheng Chen	2010	28/21	8.1 ± 3.0	5	49	Probiotic-treated	*Lactobacillus gasseri* A5	FEV1, FVC, FEV1/FVC (%), PEFR Post-bronchodilator, CACT, PAQLQ
		32/24	9.4 ± 4.1		56	Placebo		
Joanna Jerzynska	2016	-	5-12	5	20	Probiotic	*Lactobacillus rhamnosus* GG	FEV1, FVC, FEV1/FVC (%), FeNO, IL-10 TGF, IL-1, TNF, IL-6, TLR
					24	Placebo		
Lorenzo Drago	2022	121/101	7:0 ± 3:38	19	212	Probiotic	*Ligilactobacillus salivarius* LS01 (DSM 22775) *Bifidobacterium breve* B632 (DSM 24706) mixture	Corticosteroid dose Severity and duration of exacerbations Number and frequency of children with or without asthma exacerbations
		119/81	7.0 ± 2.95		210	Placebo		
M. A. Rose	2010	23/42	16.7 ± 5.52	12	65	Probiotic	*Lactobacillus rhamnosus* (LGG, 1,010 CFU)	IgE, eosinophils, ECP, CACT
		28/38	14.4 ± 5.83		66	Placebo		
Ailing Liu	2021	-	-		29	Probiotic	*Bifidobacterium lactis* Probio-M8 powder and Symbicort Turbuhaler	ACT, CaNO, PEF PEV1, FeNO, IGE, TLC, ECP
					26	Placebo		
Maryam Hassanzad	2019	29/17	6.9 ± 2.7	12	46	Probiotic	Kidilact®	Frequency of medication use, outpatient visits and hospitalizations
		19/16	6.9 ± 2.7		35	Placebo		
Chian-Feng Huang	2018	65/57	7.68 ± 2.21	21	112	Probiotic	*Lactobacillus paracasei* (LP) *Lactobacillus fermentum* (LF)	PAQLQ score, PASS, PEFR, skin prick test reactivity, serum immune biomarker levels and fecal probiotic microbial composition
		18/17	7.86 ± 2.5		35	Placebo		
Jonatas Christian Vieira Moura	2019	7/7	11 ± 2.5	-	14	Probiotic	*Lactobacillus reuteri*	Asthma control test, spirometry and self-report of the symptoms they experienced associated with asthma
		10/6	10.2 ± 2.5		16	Placebo		

(Continues on next page)

Table I (Cont.). Characteristics of included studies

Author	Year	Gender	Age (years)	Follow-up (mouth)	Sample	Interventions	Type of probiotics	Outcomes
Piotr Gutkowski	2010	16/6	6.93 (4.3-9.9)	-	22	Probiotic	Trilac capsules (1.6 × 109 lactic acid bacteria cells: *Lactobacillus acidophilus* – 37.5 % *Bifidobacterium bifidum* 37.5 % *Lactobacillus delbrueckii subsp. bulgaricus* – 25 %)	HLA-DR CD8/CD45RA
		10/14	6.65 (4.2-9.7)		24	Placebo		
Michele Miraglia del Giudice	2017	18/22	9 ± 2.2	2	20	Probiotic	*Bifidobacteria* mixture, *Bifidobacterium longum* BB536 (3 x 109 CFU), Bifantis M-63 (1 x 109 CFU), and B breve M-16 V (1 x 109 CFU)	TSS, QoL
					20	Placebo		

FEV1: forced expiratory volume in the first second; FVC: forced expiratory volume; PEFRs: peak expiratory flow rates; CACT: Childhood Asthma Control Test; FeNO: fractional exhaled nitric oxide; CACT: Childhood Asthma Control Test; PASS: Pediatric Asthma Severity Scores; PAQLQ: Pediatric Asthma Quality of Life Questionnaire; TSS: total symptom score; IL: interleukin; TGF: transforming growth factor; TNF: tumor necrosis factor; TLR: toll-like receptors; ECP: eosinophil cationic protein; HLA: human leukocyte antigen; QoL: quality of life; CFU: colony forming units.

The number of acute episodes of asthma

Two studies, including 503 samples, reported the number of acute episodes in patients taking probiotics and placebos. We tested the heterogeneity of the two studies, and the results showed $p = 0.42$ and $I^2 = 0$ %, indicating that heterogeneity was low. Therefore, the fixed effect model was used. After summarizing the data, we found that the number of acute episodes in patients with probiotics was lower than that in patients with placebo, and the difference was statistically significant (OR = 0.30, 95 % CI: 0.19, 0.47). The results are summarized in figure 7.

Lung function-related indicators

Three studies, including 179 patients, reported FEV1 in patients taking probiotics and placebos. We tested the heterogeneity of the three studies, and the results showed $p = 0.05$ and $I^2 = 66$ %, indicating high heterogeneity. Therefore, the random effect model was used. After summarizing the data, we found that there was no statistically significant difference in FEV1 between probiotics and placebo (MD = 0.11, 95 % CI: -0.05, 0.26). The results are summarized in figure 8.

Four studies, including 125 patients, reported FEV1/FVC (%) in patients taking probiotics and placebos. We tested heterogeneity of the four studies, and the results showed $p = 0.68$ and $I^2 = 0$ %, indicating that heterogeneity was low. Therefore, we used the fixed effect model. After summarizing the data, we found no significant difference in FEV1 between probiotics and placebo (MD = 0.32, 95 % CI: -1.48, 2.12). The results are summarized in figure 9.

TABLE BIAS AND SENSITIVITY ANALYSIS

The funnel plot in figure 10 is basically symmetrical, indicating that there is no potential publication bias and the reliability of the research results is high.

DISCUSSION

In this study, a total of ten RCTs in SCI journals were included for systematic evaluation and meta-analysis. The results showed that probiotics can improve symptoms and airway inflammation in patients with asthma, reduce acute exacerbation of asthma, and have no significant improvement in lung function. This is different from the previous meta-analysis (13).

In our study, we found that the clinical symptoms of asthma patients improved after using probiotics (MD = -0.07, 95 % CI: -0.10, -0.04), and CACT-ACT score increased (MD = 2.26, 95 % CI: 1.14, 3.39). A study (22) showed no significant increase in IgE and IL-12 production in probiotics-treated subjects.

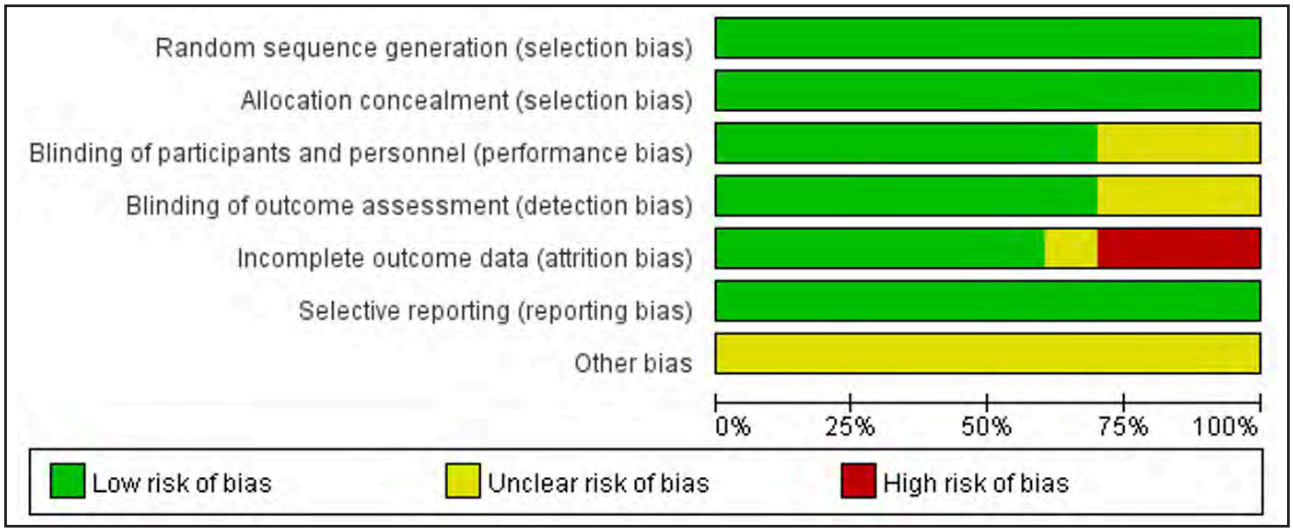

Figure 2.
Risk of bias graph.

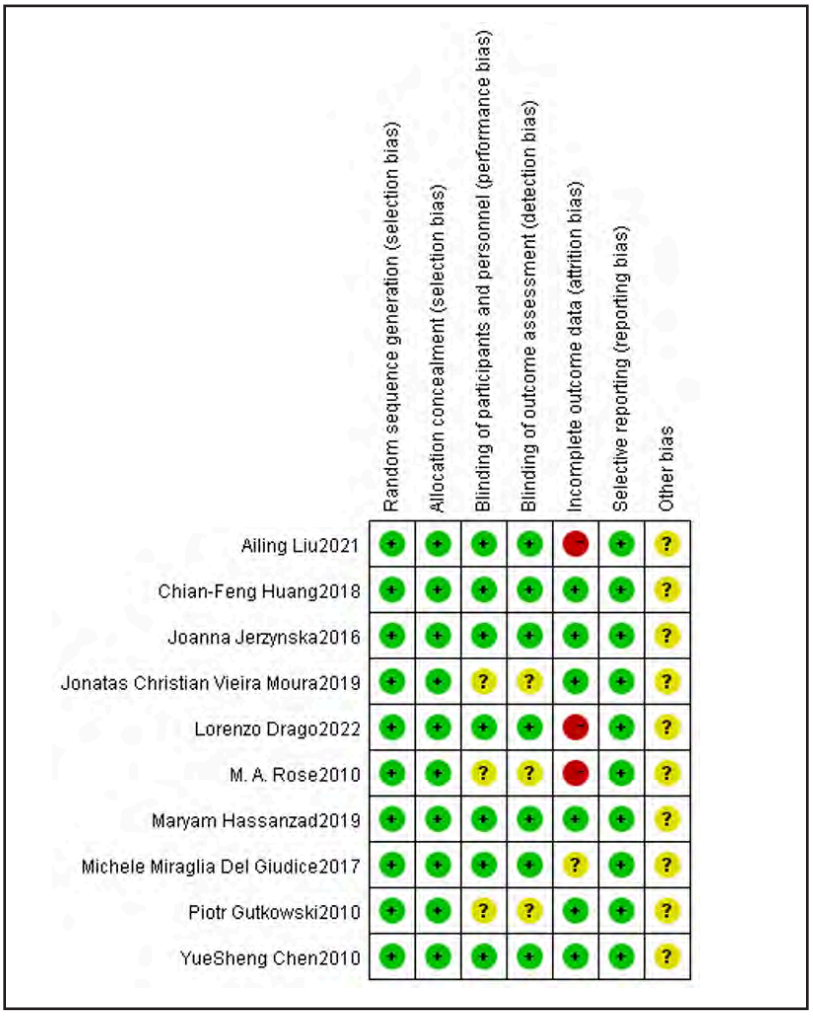

Figure 3.
Risk of bias summary.

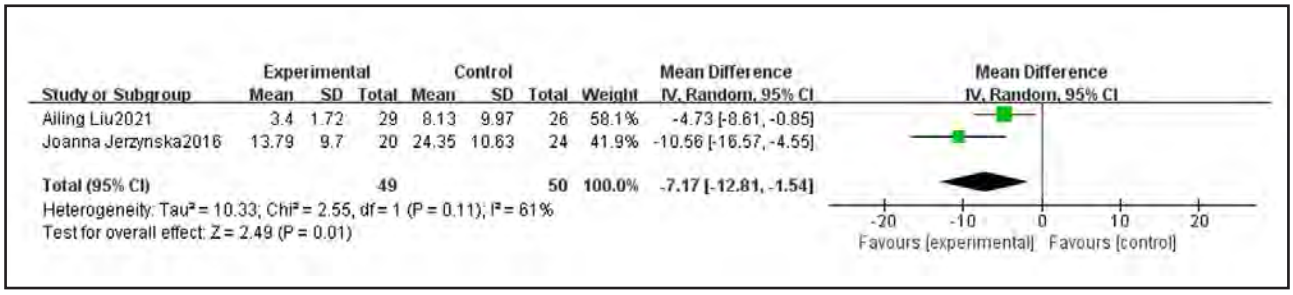

Figure 4.

Comparison of fractional exhaled nitric oxide (FeNO) results between probiotics and control group.

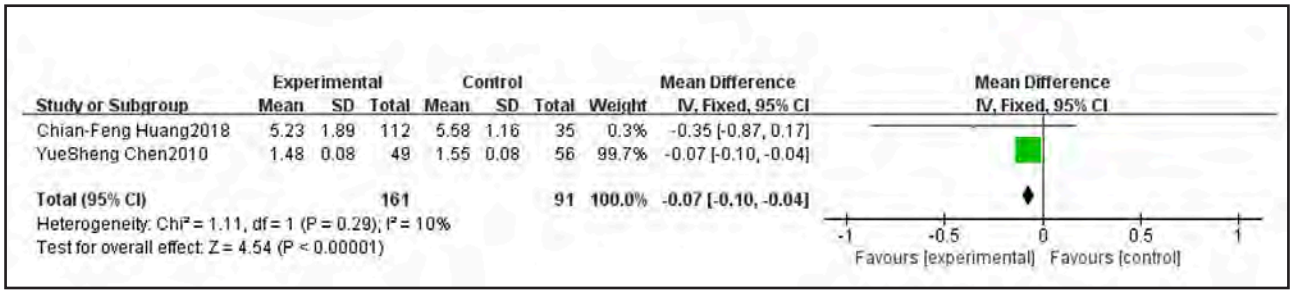

Figure 5.

Comparison of asthma symptom severity between probiotics and control group.

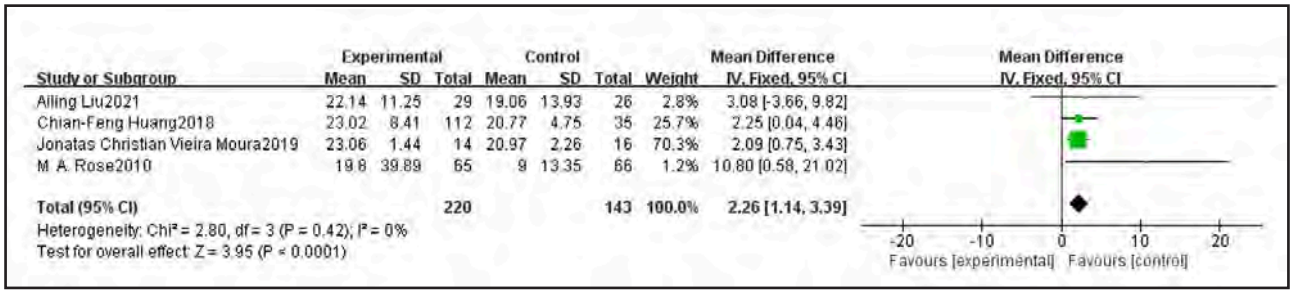

Figure 6.

Comparison of Childhood Asthma Control Test-Asthma Control Test (CACT-ACT) results between probiotics and control group.

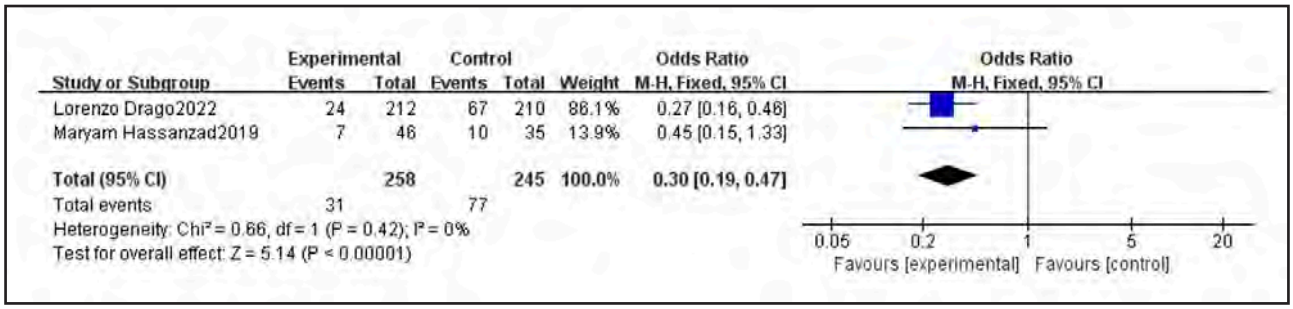

Figure 7.

Comparison of the number of asthma exacerbations between probiotics and control group.

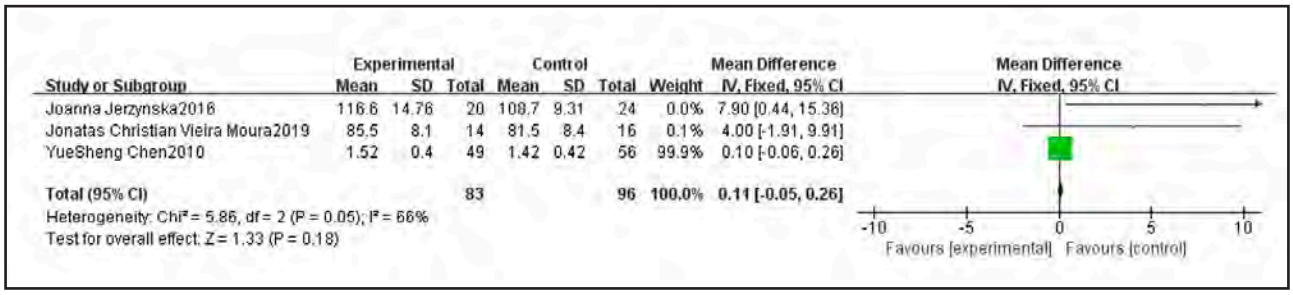

Figure 8.

Comparison of forced expiratory volume in the first second (FEV1) results between probiotics and control group.

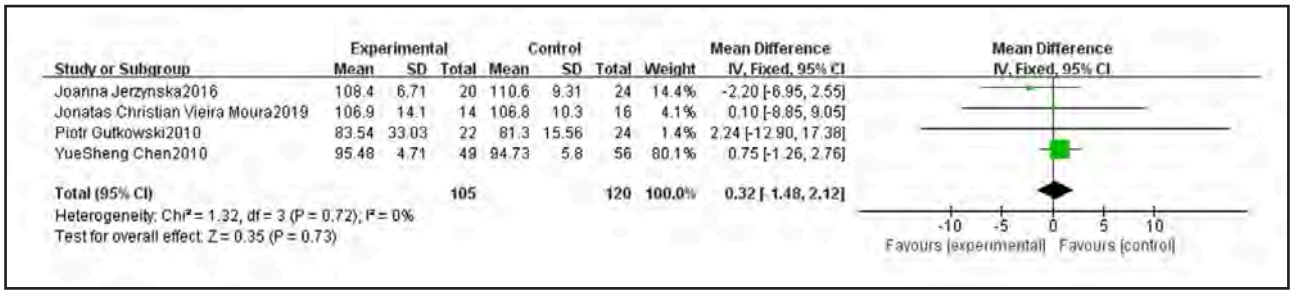

Figure 9.

Comparison of forced expiratory volume in the first second/forced expiratory volume (FEV1/FVC) (%) results between probiotics and control group.

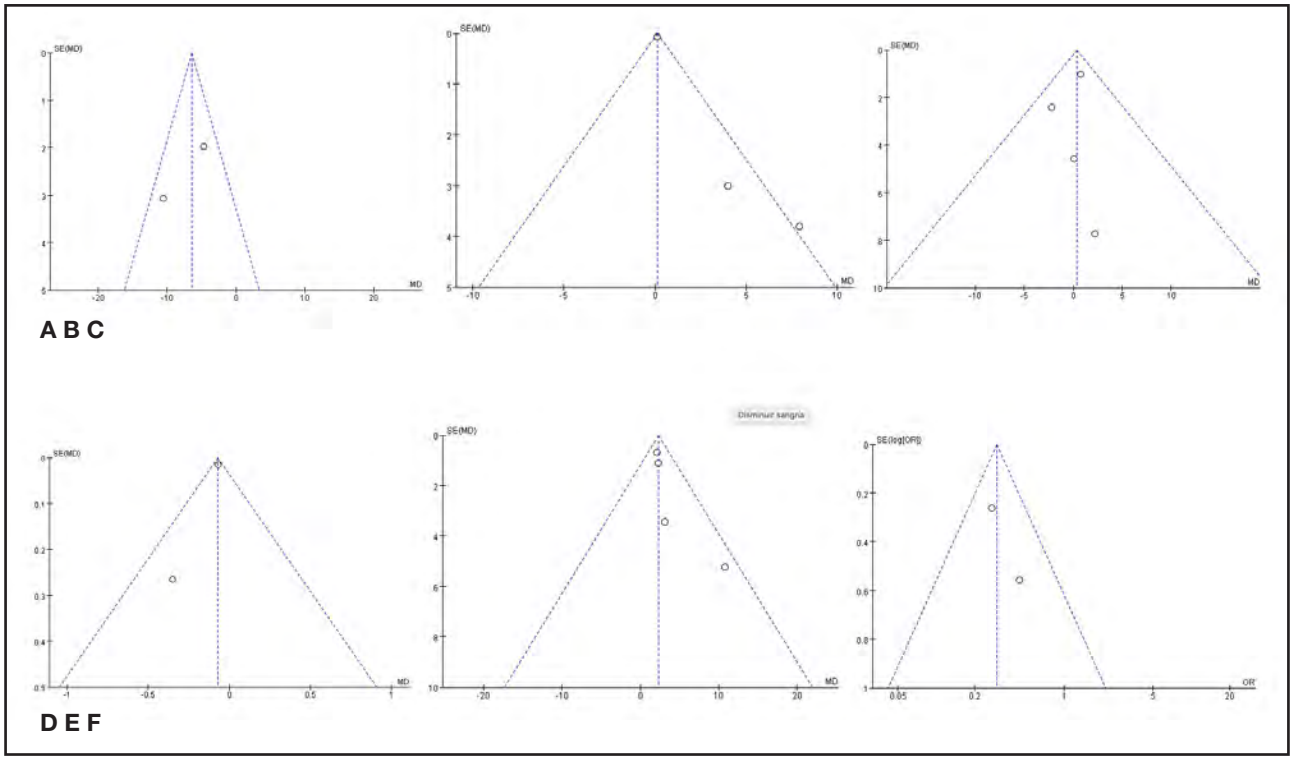

Figure 10.

Publication bias funnel plot.

This suggests that probiotics may not play a role through IgE, and it may control asthma through the intestinal-pulmonary axis, that is, probiotics enter the gastrointestinal tract to produce corresponding immune cells and cytokines, and lactic acid bacteria metabolites directly migrate from the intestine to the respiratory tract through circulation to produce corresponding effects. However, this is not completely consistent with the results of related experiments (27,28). Some experiments (2) have also proved that probiotics treat allergic asthma inflammation and pneumonia induced by OVA-LPS (ovalbumin-lipopolysaccharid) by regulating TLR4/NF-kB signaling pathways. There are some differences and contradictions in the existing research results. Therefore, the mechanism of probiotics affecting asthma needs further research and clarification (29,30).

FeNO reflects the level of airway inflammation in patients with asthma (31,32). In our study, FeNO in the experimental group was lower than that in the control group (MD = -7.17, 95 % CI: -12.81, -1.54). This indicates that the use of probiotics can control airway inflammation of asthma to a certain extent. This is consistent with the result of Kukkonen (19). At the same time, we found that FEV1 (MD = 0.11, 95 % CI: -0.05, 0.26) and FEV1/FVC (%) (MD = 0.32, 95 % CI: -1.48, 2.12) in patients with asthma using probiotics were not significantly different from those in the control group. It is worth noting that the two included studies (17,25) pointed out that probiotics could improve FEV1 in asthma patients, and Michele (20) found that taking probiotics and vitamin D3 simultaneously could also significantly reduce FeNO ($p < 0.01$). In another study (16), although there was a significant difference in FEV1 between the experimental group and the control group, the difference was statistically significant before and after the study ($p = 0.035$). When we did not incorporate the latter data into meta-analysis, the FEV1 results of the experimental group and the control group (MD = 5.50, 95 % CI: 0.87, 10.14) were statistically significant ($p = 0.02$). The number of studies is the main reason for this phenomenon. Although there was no statistical difference in the effect of probiotics on lung function of patients based on the existing data, this result may change with the increase of high-quality randomized controlled trials.

This study showed that the number of acute episodes in patients with asthma after using probiotics was significantly reduced (OR = 0.30, 95 % CI: 0.19, 0.47). Jonatas (25) pointed out that the improvement of asthma symptoms in patients treated with probiotics was mainly concentrated in Wheezing ($p = 0.046$), and there was no statistical difference in cough, tiredness, chest pain, nighttime symptoms, and absence from school. Lorenzo Drago (18) found that the frequency of acute exacerbations, severity and the number of times and doses needed to use drugs in patients with probiotics were lower than those in the control group, and there was statistical difference.

In this included literature, no major or minor adverse reactions occurred in all patients. The adverse reactions caused by probiotics are septicemia, bacteremia and gastrointestinal ischemia (33,34). In general, severe patients, severe infants, postoperative and hospitalized patients and patients with low immune function have more adverse reactions. Overall, however, the safety of probiotics in the treatment of asthma is worth ensuring (35).

Due to the limited number of included studies, no subgroup analysis was conducted. Therefore, the results may be affected by clinical heterogeneity. Studies have found that *Lactobacillus* have a certain preventive effect on asthma, while other probiotics have no effect (11). The duration of intervention, the standard of acute exacerbation of asthma, and patient age may affect the results. At the same time, relatively small sample size limits the accuracy of our analysis.

CONCLUSIONS

The use of probiotics in patients with asthma can improve lung inflammation and asthma symptoms, reduce the number of asthma attacks, and have no significant effect on lung function.

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Nutrición Hospitalaria

Revisión

The effect of perioperative immunonutrition on patients undergoing esophagectomy: a systematic review and updated meta-analysis

Efectos de la inmunonutrición perioperatoria en pacientes sometidos a esofagectomía: revisión sistemática y metaanálisis actualizado

Yun Zhou, Tian-Tian Li, Zhi-liang Yang, Zhi-Ming Tan, Chi-Fen Yang, Zheng Wang

Department of Cardiothoracic Surgery and Abdominal Hernia Surgery. The People's Hospital of Kai Zhou District. Chongqing, P.R. China

Abstract

Background: immunonutrition has been introduced and proposed to have positive modulating effects on inflammatory and immune responses in surgical patients. This meta-analysis aimed to assess whether perioperative enteral immunonutrition (EIN) can reduce postoperative complications or reduce inflammatory responses in esophageal cancer (EC) patients undergoing esophagectomy.

Methods: PubMed, Embase, Web of science, EBSCO, and Cochrane library databases were systematically searched. Randomized controlled trials (RCTs) assessing the effect of EIN before and/or after surgery in EC patients undergoing esophagectomy were identified. Two investigators independently searched articles, extracted data, and assessed the quality of included studies.

Results: ten RCTs involving 1,052 patients were included in the meta-analysis, including 573 patients in the EIN group and 479 patients in the enteral nutrition (EN) group. Overall, no significant difference was observed between the two groups in the incidence of postoperative pneumonia, surgical site infection, intra-abdominal abscess, septicemia, and urinary tract infection. No significant incidence of postoperative anastomotic leakage, acute respiratory distress syndrome (ARDS), and in-hospital mortality was found.

Conclusions: perioperative enteral immunonutrition did not reduce the incidence of infectious complications and anastomotic leakage in EC patients undergoing esophagectomy, nor did it reduce postoperative CRP and IL-6, but did not increase in-hospital mortality.

Keywords:

Pneumonia. Esophagectomy. Enteral nutrition. Meta-analysis.

Resumen

Antecedentes: se ha introducido y propuesto la inmunonutrición para regular activamente la inflamación y la respuesta inmune en pacientes quirúrgicos. El presente metaanálisis fue diseñado para evaluar si la inmunonutrición enteral perioperatoria (EIN, por sus siglas en inglés) puede reducir las complicaciones postoperatorias o la inflamación en pacientes con cáncer de esófago (CE) sometidos a esofagectomía.

Métodos: se realizó una búsqueda sistemática en las bases de datos de PubMed, Embase, Web of Science, EBSCO y Cochrane Library. Se evaluó el efecto de la EIN preoperatoria y/o postoperatoria en un ensayo aleatorizado controlado (RCT) en pacientes con cáncer de esófago sometidos a esofagectomía. Dos investigadores buscaron independientemente artículos, extrajeron datos y evaluaron la calidad de los artículos incluidos.

Resultados: el metanálisis incluyó diez ensayos controlados aleatorios en los que participaron 1.052 pacientes, de los cuales 573 fueron incluidos en el grupo EIN y 479, en el grupo de nutrición enteral (NE). En general, no hubo diferencia significativa en la incidencia de neumonía postoperatoria, infección del sitio quirúrgico, absceso intraperitoneal, sepsis e infección del tracto urinario entre los dos grupos. No hubo diferencia significativa en la incidencia de fístula anastomótica postoperatoria, síndrome de distrés respiratorio agudo (SDRA) y mortalidad hospitalaria.

Conclusión: la inmunonutrición enteral perioperatoria no puede reducir la incidencia de complicaciones infecciosas postoperatorias y fístulas anastomóticas, ni la PCR postoperatoria ni la IL-6. Pero no aumentó la mortalidad hospitalaria.

Palabras clave:

Neumonía. Esofagectomía. Nutrición enteral. Metaanálisis.

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Correspondence:

Zheng Wang. Department of Cardiothoracic Surgery and Abdominal Hernia Surgery. The People's Hospital of Kai Zhou District. 8 Hanfeng Street. 405400 Kaizhou, Chongqing. P.R. China
e-mail: 81045006@qq.com

INTRODUCTION

Esophageal cancer causes more than 500,000 cancer deaths each year, ranking sixth among all cancer-related deaths (1). The five-year overall survival rate for patients with esophageal cancer worldwide ranges from 15 % to 25 % (2), and risk factors for esophageal cancer include alcohol consumption, smoking, lack of fruits and vegetables, obesity, and gastroesophageal reflux disease (3). Esophagectomy is still the main treatment method for esophageal cancer, but severe trauma and postoperative complications, such as esophageal anastomotic leakage, gastroesophageal reflux, and severe infection of esophagectomy may impair the patients' quality of life (4).

Enteral immunonutrition (EIN), which can reduce the production of inflammatory mediators and regulate eicosanoid synthesis, is an enteral formula containing arginine, glutamine, omega-3 fatty acids and nucleotides (5-7). Immunonutrition has been introduced and proposed to improve the nutritional status of the body, enhance the response function of immune cells, regulate the production and release of cytokine and reduce inflammatory markers for surgical patients (8-10). However, the effect of EIN in EC patients remains unclear. Wang et al. (11) have conducted a preliminary analysis of EIN treatment after esophageal cancer and found that EIN did not reduce the incidence of postoperative complications in EC patients. Based on this study, we included ten RTCs and updated the meta-analysis on the relationship between inflammatory markers or postoperative complications with EIN after esophageal cancer surgery.

MATERIALS AND METHODS

SELECTION CRITERIA

The inclusion criteria were as follows: a) published randomized controlled trials (RCTs) of immunonutritional support in EC patients with complete data and no language restrictions; b) subjects: all EC patients who received preoperative and/or postoperative immunonutrition support, and the duration of nutritional support was not limited; c) intervention measures: the experimental group was given immune nutritional support, and the control group was given routine nutritional support; d) outcome measures: the main outcome measures were the incidence of pneumonia, anastomotic leakage, surgical site infection, intra-abdominal abscess, septicemia, urinary tract infection, acute respiratory distress syndrome (ARDS), in-hospital mortality, C-reactive protein (CRP) of postoperative day (POD) 1, POD 3 and POD 7, and IL-6 of POD 1. The exclusion criteria were as follows: a) non-randomized controlled trials, such as reviews, systematic reviews, case reports, disease syndrome definition, etc.; b) non-clinical experiments, such as animal, cell experiments, etc.; and c) incomplete or duplicate information; and d) duplicate literature.

SEARCH STRATEGY

PubMed, Embase, and the Cochrane library were systematically searched from inception to April 2022, with the following keywords: ("oesophagus resection" or "esophagectomy" or "resection of esophagus" or "oesophagectomy" or "esophagus cancer" or "esophageal cancer" or "esophageal squamous cell carcinoma" or "esophageal carcinomas" or "oesophageal cancer" or "oesophageal carcinoma" or "carcinoma of the esophagus" or "carcinoma of esophagus" or "esophageal carcinoma" "esophagus carcinoma") and ("immunonutrition" or "immune-enhancing" or "immune-enhanced" or "immune-modulating"). No limitation was enhanced. To include additional eligible studies, the reference lists of retrieved studies and relevant reviews were also hand-searched and the process above was performed repeatedly until no further article was identified. Conference abstracts meeting the inclusion criteria were also included.

DATA EXTRACTION AND QUALITY ASSESSMENT

Two researchers independently extracted the following information of RCTs according to predefined selection criteria: name of first author, publication year, sample size, baseline characteristics of patients, EIN formula and usage, control, study design, pneumonia, anastomotic leakage, surgical site infection, intra-abdominal abscess, septicemia, urinary tract infection, ARDS, in-hospital mortality, CRP of POD 1, POD 3 and POD 7, and IL-6 of POD 1. The quality assessments of eligible studies were performed using the Cochrane Collaboration's tool published in the Cochrane Handbook (version 5.3).

DATA ANALYSIS

Meta-statistical analysis was performed using RevMan 5.3 software. Input raw data and perform data transformation. Mean differences (MDs) with 95 % confidence intervals (CIs) for continuous outcomes, and risk ratios (RRs) with 95 % CIs for dichotomous outcomes were used to estimate the pooled effects. Each effect size is provided with 95 % CI. If $p \geq 0.05$, $I^2 \leq 50$ %, a fixed-effect model was used for analysis; if $p < 0.05$, $I^2 > 50$ %, it was considered that there was significant heterogeneity among studies, and subgroup analysis was performed or omitting one study at a time. If the heterogeneity cannot be eliminated, the random effects model is used to combine the effect sizes.

RESULTS

LITERATURE SEARCH, STUDY CHARACTERISTICS AND QUALITY ASSESSMENT

The PRISMA flow diagram for the selection process and detailed identification was presented in figure 1. Two hun-

dred and eighty publications were identified through the initial search of databases. After screening, ten RCTs (12-21) were included in the meta-analysis. And the basic characteristics of the ten publications included in this meta-analysis are presented in table I. These ten articles were published from 2007 to 2020, and the sample size included in these articles ranged from 29 to 272 with a total of 1,052, 573 of which received EIN before and/or after surgery and 479 received perioperative enteral nutrition (EN). Two studies included 112 patients who did not receive EN before esophagectomy and started EIN or EN after surgery. One study included 69 patients who received preoperative EIN without postoperative EIN, 68 patients who received postoperative EIN without preoperative EIN, and 77 patients who received both preoperative and postoperative EIN. And seven studies included 668 patients who received postoperative and postoperative EIN or EN.

The quality of each study was evaluated, most of the studies were high-quality RCTs, and their quality assessment is listed in figure 2. The modified Jadad scale was used to evaluate the methodological quality of each RCT included in this meta-analysis. All ten studies were considered to be high-quality ones according to quality assessment.

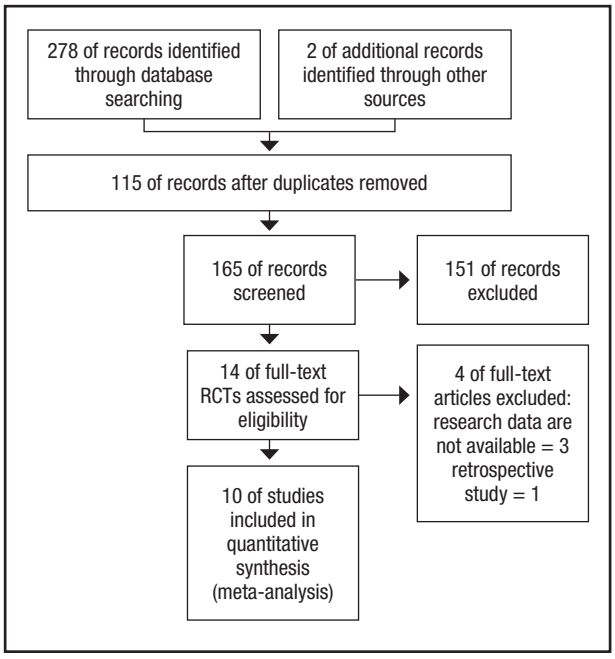

Figure 1.
The PRISMA flow chart. RCT: randomized controlled trial.

Table I. The basic characteristics of involved trials (EN/EIN)

Studies	Region	Sample size (n)	Preoperative nutritional		Preoperative nutritional duration		Postoperative nutritional		Postoperative nutritional duration		Jadad score
			EIN	EN	EIN (day)	EN (day)	EIN	EN	EIN (day)	EN (day)	
Ryan AM, 2009	Ireland	53	ProSure	Ensure® Plus	5	5	ProSure	Ensure® Plus	21	21	6
Sultan J, 2012	UK	195	Oxepa®	Ensure® Plus	7	7	Oxepa®	Ensure® Plus	7	7	7
Kanekiyo 2018	Japan	40	IMPACT	Ensure®	7	7	IMPACT	Ensure®	7	7	5
Kitagawa 2017	Japan	29	MHN-02	MEIBARANCE	5	5	MHN-02	MEIBALANCE	7	7	5
Mudge LA, 2018	Australia	272	(Group A) IMPACT	(Group D) ICSN	7	7	(Group A) IMPACT	(Group D) ICSN	7	7	7
			(Group B) IMPACT				(Group B) ICSN				
			(Group C) ICSN				(Group C) IMPACT				
Healy LA, 2017	Ireland	191	ProSure	Ensure® Plus	5	5	Prosure	Ensure® Plus	30	30	7
Ohkura 2018	Japan	67	-	-	-	-	MEIN	HINE E-GEL®	6	6	5
Sakurai 2007	Japan	30	IMPACT	Ensure®	3	3	IMPACT	Ensure®	14	14	5
Li XK, 2020	China	103	Peptisorb with extra immunonutritional substrates	Peptisorb	7	7	Peptisorb with extra immunonutritional substrates	Peptisorb	30	30	6
Yasunori 2017	Japan	72	-	-	-	-	Experimental diet enriched with EPA, GLA, and Oxepa	Pulmocare®	21	21	7

EIN: enteral immunonutrition; EN: enteral nutrition; EPA: eicosapentaenoic acid; GLA: γ-linolenic acid.

INFECTION-RELATED COMPLICATIONS AND HEMATOLOGICAL INDICATORS

All ten included studies reported the incidence of pulmonary infection, but there was no significant difference in the incidence of pneumonia between the EIN and EN group (RR = 0.96, CI: 0.73-1.27, p = 0.79) (Fig. 3). Eight of the ten included studies reported the incidence of wound infection, but there was no significant difference between the EIN and EN group (RR = 0.80, CI: 0.51-1.24, p = 0.31) (Fig. 4). Two of the ten included studies reported the incidence of intra-abdominal abscess, but there was no significant difference between the EIN and EN group (RR = 1.00, CI: 0.55-1.79, p = 0.99) (Fig. 5). Four of the ten included studies reported the incidence of septicemia, but the incidence of septicemia was not significantly different between the EIN and EN group (RR = 0.97, CI: 0.51-1.85, p = 0.93) (Fig. 6). Two of the ten included studies reported the incidence of urinary tract infection, but there was no significant difference between the EIN and EN group (RR = 1.00, CI: 0.50-2.01, p = 0.99) (Fig. 7). All eligible studies provided the incidence of infection complications, which included CRP of POD 1 in three studies, CRP of POD 3 in two studies, CRP of POD 7 in three studies, and IL-6 of POD 1 in two studies. No significant difference was observed between the two groups in CRP of POD 1 (MD = -9.05, CI: -29.41-11.32, p = 0.38) (Fig. 8), CRP of POD 3 (MD = 12.22, CI: -6.82-31.26, p = 0.21) (Fig. 9), CRP of POD 7 (MD = -3.87, CI: -14.82-7.07, p = 0.49) (Fig. 10), or IL-6 of POD 1 (MD = 26.08, CI: -13.99-66.16, p = 0.20) (Fig. 11).

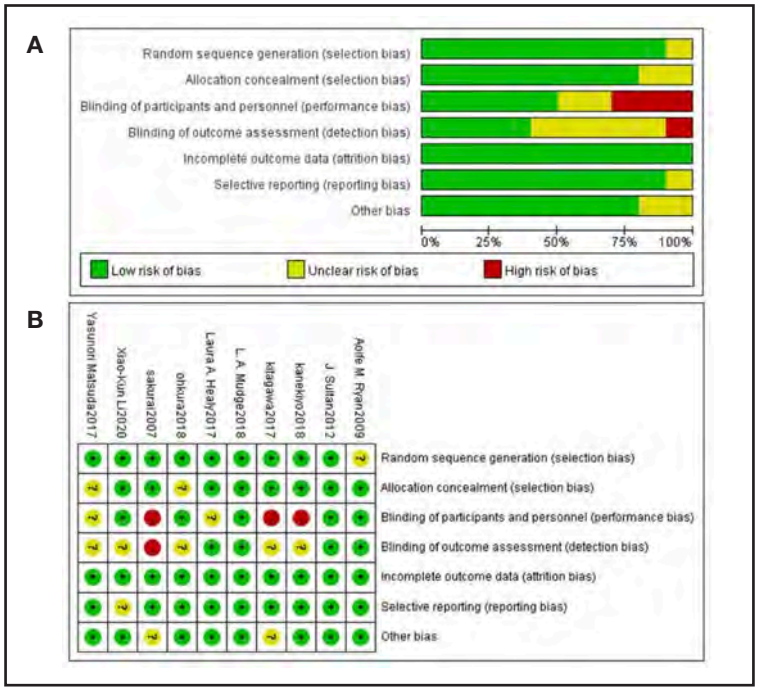

Figure 2.

Risks of bias assessment for each included study (n = 10). A. Risk of bias graph. B. Risk of bias summary.

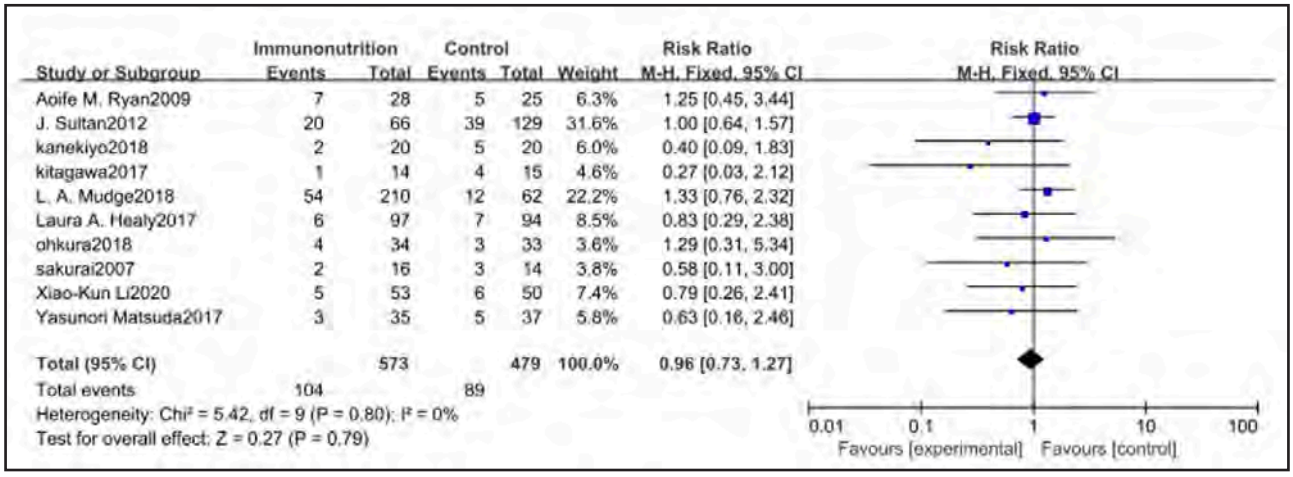

Figure 3.

Forest plot of the incidence of pneumonia between the EIN and EN groups.

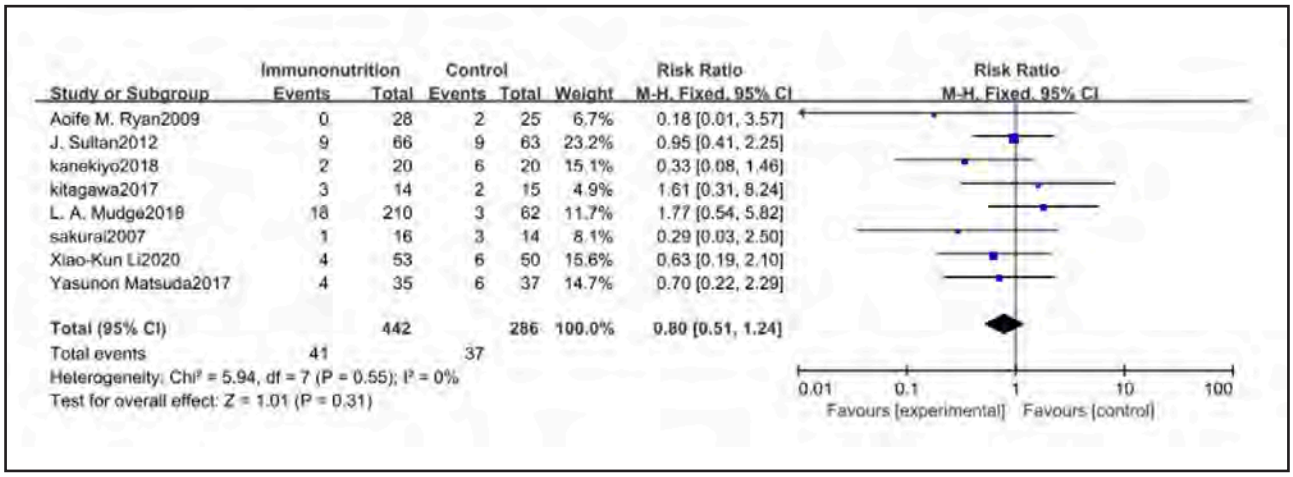

Figure 4.

Forest plot of the incidence of wound infection between the EIN and EN groups.

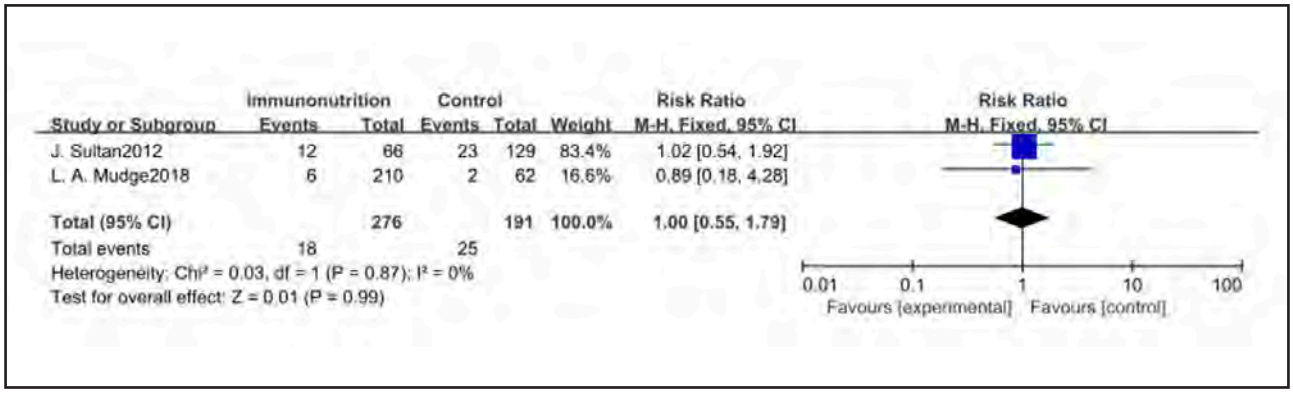

Figure 5.

Forest plot of the incidence of intra-abdominal abscess between the EIN and EN groups.

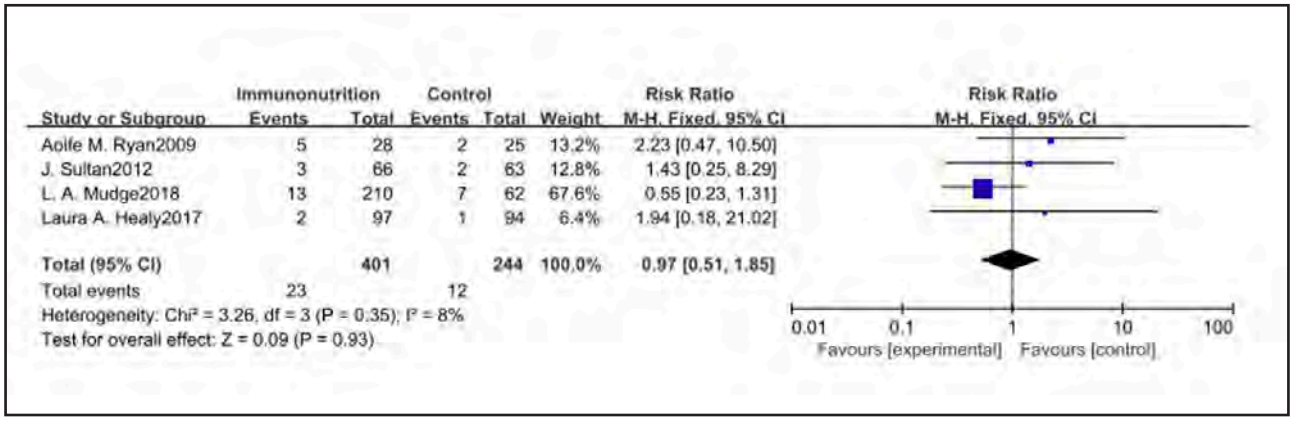

Figure 6.

Forest plot of the incidence of septicemia between the EIN and EN groups.

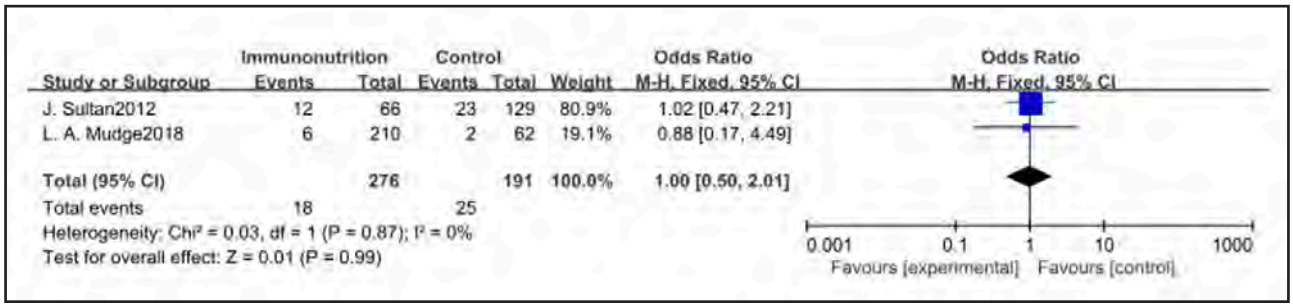

Figure 7.

Forest plot of the incidence of urinary tract infection between the EIN and EN groups.

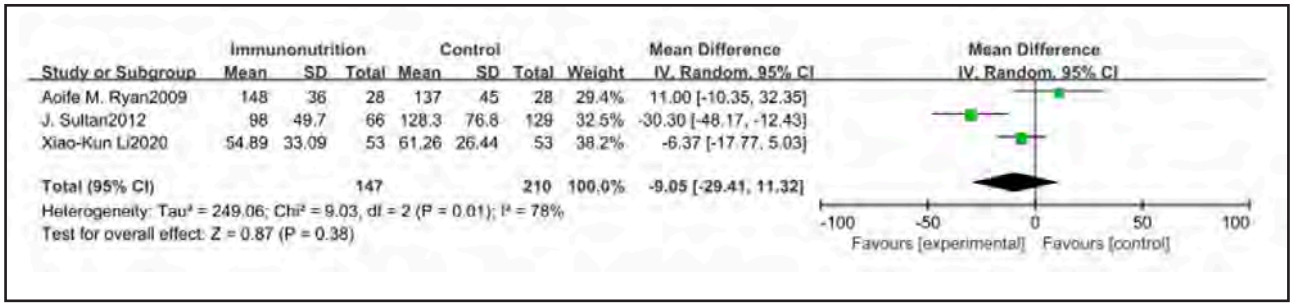

Figure 8.

Forest plot of the CRP of POD 1 between the EIN and EN groups.

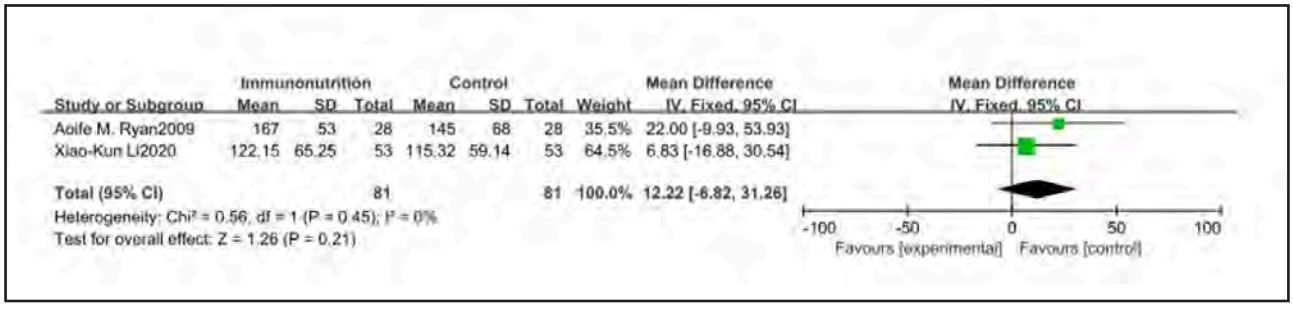

Figure 9.

Forest plot of the CRP of POD 3 between the EIN and EN groups.

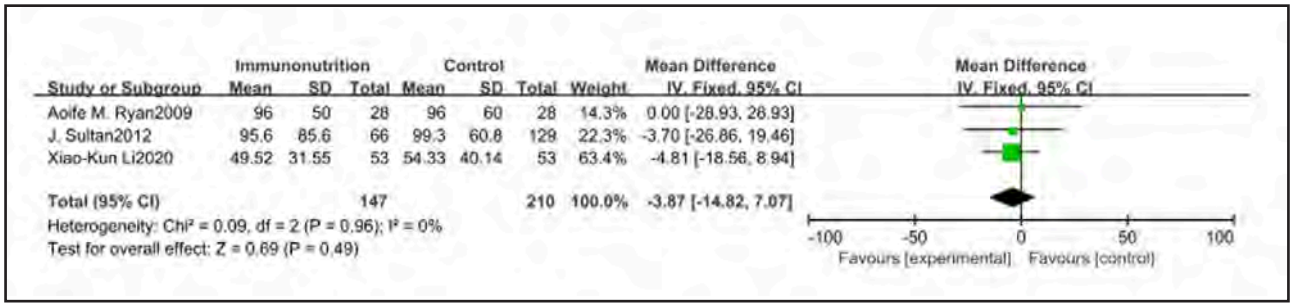

Figure 10.

Forest plot of the CRP of POD 7 between the EIN and EN groups.

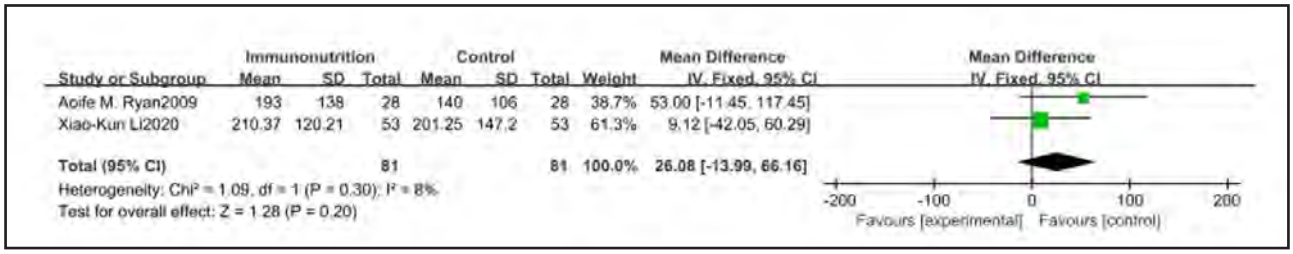

Figure 11.

Forest plot of the IL-6 of POD1 between the EIN and EN groups.

DRUG SAFETY EVALUATION

All ten included studies reported the incidence of anastomotic leakage, but there was no significant difference between the EIN and EN group (RR = 0.70, CI: 0.47-1.05, p = 0.08) (Fig. 12). Seven studies reported the in-hospital mortality rate, but there was no significant difference between the EIN and EN group (RR = 1.09, CI: 0.40-3.02, p = 0.86) (Fig. 13). And three studies reported the incidence of ARDS, but there was no significant difference between the EIN and EN group (RR = 1.44, CI: 0.31-6.68, p = 0.64) (Fig. 14).

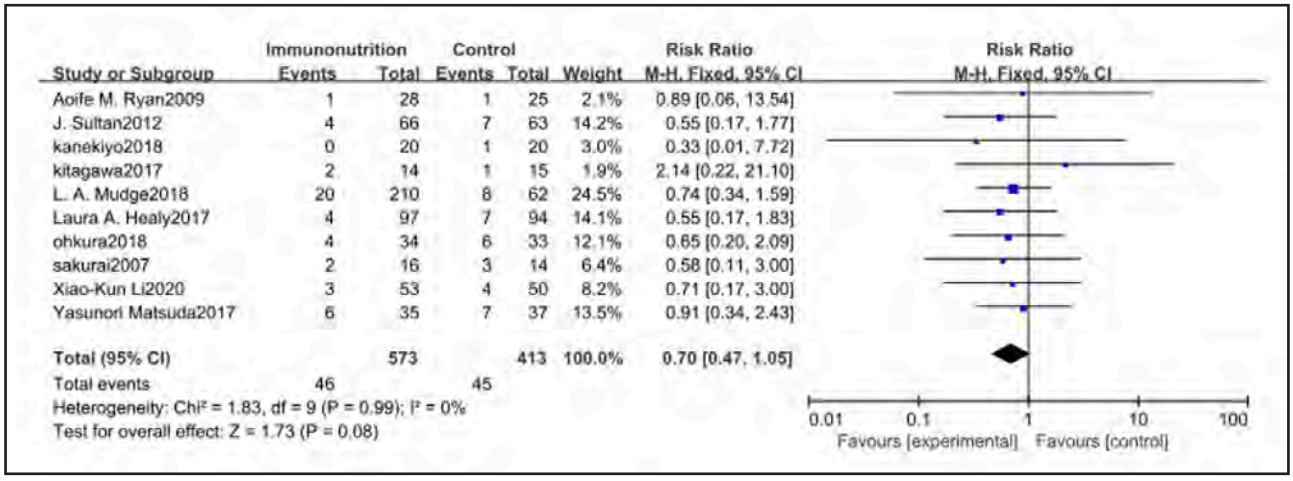

Figure 12.

Forest plot of the incidence of anastomotic leakage between the EIN and EN groups.

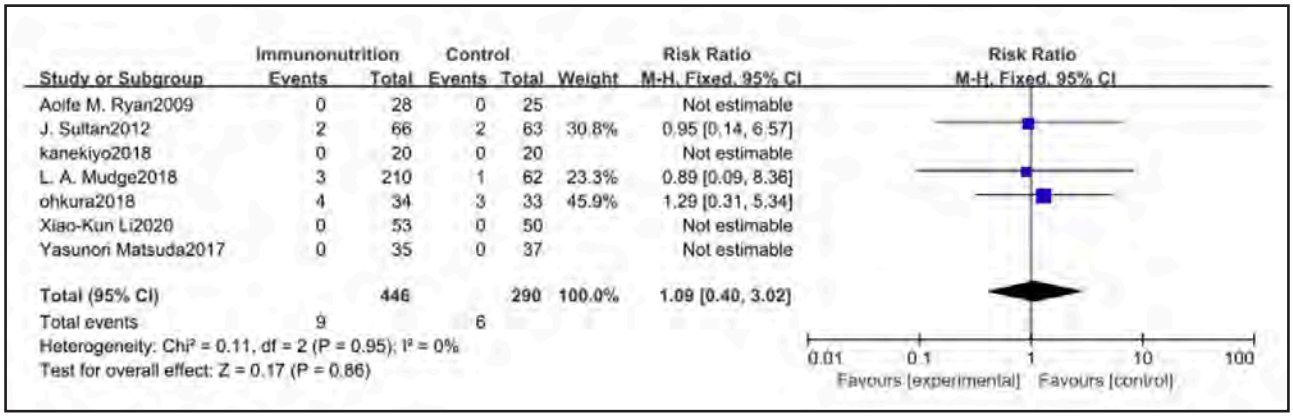

Figure 13.

Forest plot of the in-hospital mortality rate between the EIN and EN groups.

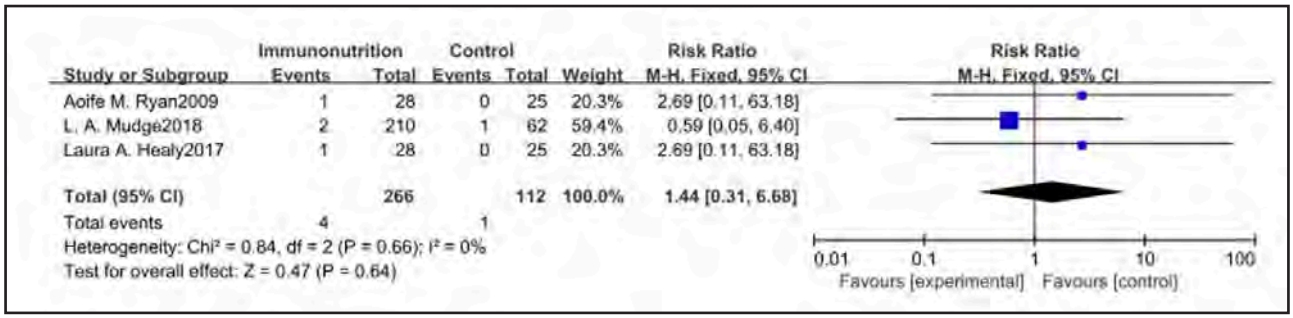

Figure 14.

Forest plot of incidence of ARDS between the EIN and EN groups.

DISCUSSION

Progressive dysphagia, first solid and then liquid, is a typical symptom of esophageal cancer. Therefore, most patients with esophageal cancer face a huge risk of malnutrition (22), and the median weight loss is the highest reported in esophageal cancer patients compared to patients with other malignancies (23). More studies show high risk of malnutrition and preoperative weight loss are associated with worse outcomes (24-29).

A meta-analysis aimed to evaluate the impact of EIN on postoperative infection and mortality in patients undergoing cancer surgery and indicated that EIN can reduce overall infectious complications and surgical-site infection (30). Yu et al. reported that immunonutrition did not reduce sepsis or all-cause mortality in cancer patients treated with surgery, but subgroup analyses revealed that immunonutrition for > 5 days and for ≤ 7 days reduced the rate of respiratory tract infection and the incidence of wound infection (31). However, another meta-analysis showed that there was no significant difference in infectious complications between immunonutritional support and traditional nutritional support after head and neck cancer surgery (32). An increasing number of controlled studies have focused on EIN and esophagectomy, but have not yet achieved ideal results.

Pulmonary infection is one of the most common complications after esophagectomy. It can be caused by many factors, such as surgical trauma, postoperative immunosuppression, sputum accumulation and disconnection of bronchial nerve. The current meta-analysis shows that there is no significant difference in the incidence of pulmonary infection between the EIN group and the EN group (RR = 0.96, CI: 0.73-1.27, p = 0.79). In our opinion, the pain of the surgical incision in esophagectomy inhibits the patient's voluntary cough, and expectoration may have a more significant impact on pulmonary infection, but all studies have not shown the patient's pain score and postoperative analgesia regimen. Consistent with our view, Yin et al. (33) reported that compared with thoracoscopic esophagectomy, transcervical and transhiatal esophagectomy has lower pain score and less pulmonary infections. In addition, Sluis et al. (34) findings show that robot-assisted minimally invasive thoracolaparoscopic esophagectomy has lower mean postoperative pain and lower percentage of pulmonary complications than open transthoracic esophagectomy. On the other hand, the current meta-analysis showed that there was no significant difference in wound infection (RR = 0.80, CI: 0.51-1.24, p = 0.31), septicemia (RR = 0.97, CI: 0.51-1.85, p = 0.93), urethral infection (RR = 1.00, CI: 0.50-2.01, p = 0.99), intra-abdominal abscess (RR = 1.00, CI: 0.55-1.79, p = 0.99) and ARDS (RR = 1.44, CI: 0.31-6.68, p = 0.64) between the EIN group and the EN group. In the general view, the above-mentioned infectious complications may be related to deep venous catheterization, intraoperative aseptic management, and postoperative incision dressing change. Therefore, EIN and EN did not show significant differences in these complications. This meta-analysis showed that although the incidence of anastomotic leakage was lower in the EIN group, it did not show a significant difference compared with the EN group (RR = 0.70, CI: 0.47-1.05, p = 0.08). We deem that the occurrence of anastomotic leakage may be related to the blood supply and the tension of the anastomosis, and the postoperative inflammatory state may be a secondary factor, and only single-factor intervention cannot reduce the occurrence of anastomotic leakage.

Studies have shown that EIN can reduce the inflammatory response in severe patients with Covid-19, severe acute pancreatitis, major abdominal surgery and so on (35-37). But results of this meta-analysis showed that there was no significant difference in CRP of POD 1 (MD = -9.05, CI: -29.41-11.32, p = 0.38), POD 3 (MD = 12.22, CI: -6.82-31.26, p = 0.21), POD 7 (MD = -3.87, CI: -14.82-7.07, p = 0.49) and IL-6 of POD 1 (MD = 26.08, CI: -13.99-66.16, p = 0.20) after esophagectomy between the EIN group and the EN group.

However, the inflammatory factors selected in the included studies may not fully reflect the inflammatory state of patients, therefore, more inflammatory indicators such as procalcitonin, ESR and leukocyte count need to be measured to evaluate the relationship between the body's inflammatory state and EIN. On the other hand, the included studies did not show the administration of antibiotics after operation, and antibiotics may have a more significant inhibitory effect on inflammatory response than EIN. However, there was no significant difference in the in-hospital mortality (RR = 1.09, CI: 0.40-3.02, p = 0.86) and incidence of ARDS (RR = 1.44, CI: 0.31-6.68, p = 0.64) between EN and EIN, which at least suggested that EIN was a safe treatment.

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Nutrición Hospitalaria

Revisión

The impact of docosahexaenoic acid on maternal mental health: scoping review

El impacto del ácido docosahexaenoico en la salud mental materna: revisión sistematizada de la literatura

Olga Masot[1,2], Julio José Ochoa Herrera[3], Elena Paraíso Pueyo[1,2], Judith Roca[1,2], Jèssica Miranda[1,2], Ana Lavedán Santamaría[1,2]

[1]Department of Nursing and Physiotherapy. Universidad de Lleida. Lleida, Spain. [2]Health Care Research Group (GRECS). Instituto de Investigación Biomédica de Lleida Fundación Dr. Pifarré. IRBLleida. Lleida, Spain. [3]Instituto de Nutrición y Tecnología de los Alimentos José Mataix Verdú (INYTA). Department of Physiology. Universidad de Granada. Granada, Spain

Abstract

Docosahexaenoic acid (DHA) is a polyunsaturated essential fatty acid from the omega-3 series that appears to be key to perinatal mental health. For this, the aim of this review is to evaluate the effect of DHA on maternal mental health during pregnancy and lactation with respect to depression and anxiety. The present scoping review was carried out following the methodology of Arksey and O'Malley (2005). The selection of studies was carried out in accordance with PRISMA by means of systematic searches in the PubMed, Scopus, PsycINFO and Medline databases. The results classified according to the effectiveness of DHA. In most (n = 9) of the 14 studies finally included, DHA plasma levels with or without other polyunsaturated omega-3 fatty acids were significantly lower in pregnant women with depressive and anxiety symptoms. However, no study reported a beneficial effect of DHA on mental health during the postpartum period. The majority used detection method was the Edinburgh Postpartum Depression Scale (n = 11). The prevalence of depressive symptoms ranged between 5.9 % and 50 %. As a conclusion, although more research is needed in this area, these exploratory results suggest that DHA could play an important role in preventing the pathogenesis of depression and anxiety during gestation.

Keywords:

Docosahexaenoic acid. Depression. Anxiety. Pregnancy. Postpartum. Review.

Resumen

El ácido docosahexaenoico (DHA) es un ácido graso esencial poliinsaturado de la serie omega-3 que parece ser clave para la salud mental perinatal. Por ello, el objetivo de esta revisión es evaluar el efecto del DHA sobre la salud mental materna durante el embarazo y la lactancia con respecto a la depresión y la ansiedad. La presente revisión se llevó a cabo siguiendo la metodología de Arksey y O'Malley (2005). La selección de estudios se realizó de acuerdo con PRISMA mediante búsquedas sistemáticas en las bases de datos PubMed, Scopus, PsycINFO y Medline. Los resultados se catalogaron según la eficacia del DHA. En la mayoría (n = 9) de los 14 estudios finalmente incluidos, los niveles plasmáticos de DHA con o sin otros ácidos grasos omega-3 poliinsaturados fueron significativamente más bajos en mujeres embarazadas con síntomas de depresión y ansiedad. Sin embargo, ningún estudio informó un efecto beneficioso del DHA sobre la salud mental durante el periodo posparto. El método de detección más utilizado fue la Escala de Depresión Posparto de Edimburgo (n = 11). La prevalencia de síntomas depresivos osciló entre el 5,9 % y el 50 %. Como conclusión, aunque se necesita más investigación en este ámbito, los resultados exploratorios parecen indicar que el DHA juega un papel importante en la prevención de la patogenia de la depresión y la ansiedad durante el periodo de gestación.

Palabras clave:

Ácido docosahexaenoico. Depresión. Ansiedad. Embarazo. Posparto. Revisión.

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Correspondence:

Elena Paraíso Pueyo. Department of Nursing and Physiotherapy. Universidad de Lleida. C/ Montserrat Roig, 2. 25198 Lleida, Spain
e-mail: elena.paraiso@udl.cat

INTRODUCTION

Docosahexaenoic acid (DHA or 22:6n-3) is an omega n-3 polyunsaturated fatty acid (PUFA). Chemically, it is a carboxylic acid like all fatty acids (FAs). DHA is considered as the most important long-chain PUFA of the n-3 family. Physiologically, the human body is able to metabolize DHA through conversion in the organism of alpha linolenic acid (ALA), another n-3 PUFA. This conversion takes place principally in the liver and it is transported as a phospholipid by plasma albumin, almost exclusively, to the brain and retina. In cases of pregnancy, adipose tissue also acts as a temporary reserve, but the degree of conversion is reduced, making it difficult to meet recommended levels of DHA, considered to be an essential prenatal nutrient (1). For this reason, the European Food Safety Authority (EFSA) (2) recommendation ranges from 100 to 200 mg/day.

Factors that can influence low DHA intake in pregnant females include level of education, older age, smoking and insufficient fish and seafood consumption, especially in the second and third trimesters (3). DHA is found in fish oil and some algae. In turn, most DHA in fish and other complex organisms comes from their access to photosynthetic heterotrophic microalgae. Foods that contain it include cold-water fish (like salmon, herring or anchovy), tuna and codfish oil (1). As it can be difficult to reach the recommended amounts through dietary intake, the consumption of DHA supplements with or without other FAs is advised. It should also be noted that omega-3 fatty acid supplements are well tolerated by pregnant and lactating women (4).

In this group of women, this n-3 PUFA participates in different functions (5,6). In terms of mental health, significantly lower levels of DHA, EPA and total n-3 PUFAs have been found in adult patients with depression, suggesting that n-3 PUFAs play a role in the pathogenesis of this illness (7), participating in neurobiological processes including control of serotonergic and dopaminergic function, modulation of brain-derived neurotrophic factor in the hippocampus, regulation of the hypothalamic-pituitary-adrenal axis, and with effects on neuroinflammation (8). In this regard, Lin et al. (7) argued the need for studies examining the specific functions of DHA in different population groups with depressive symptoms. In this context, the present study focuses on maternal mental health.

One possible solution to mental health issues in such situations is the application of prescription drugs. However, because of their potential toxic, teratogenic or even lethal effects on the fetus, the use of many of them is not recommended during pregnancy. In addition, the physiological changes inherent to pregnancy and lactation condition the absorption, transfer, excretion and metabolism of antipsychotics (9). For this reason, nutrition-based treatments have been proposed as an aid to alleviate and/or prevent prenatal anxiety and depression (10). There is therefore an evident need to know the real effect of DHA on mental health during pregnancy and the postpartum period.

Nonetheless, despite the findings of the referenced studies, the relationship between DHA and its effect on mental health in the prenatal stage is not fully clear (7). It can be speculated that different actions can occur simultaneously. On one hand, by maintaining and increasing the brain structures and preserving their function by interacting with phospholipid metabolism and, hence, the modulation of signal transduction. On the other hand, preventing or decreasing the inflammatory status occurring during depression (11). The aim of this scoping review is therefore to evaluate the effect of DHA during pregnancy and the postpartum period on maternal mental health in terms of depressive symptoms and anxiety.

MATERIAL AND METHODS

The scoping review framework adopted was based on the methodological model of Arksey and O'Malley (12), with contributions from the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (13). Following the model, the methodological process was divided into five stages.

IDENTIFYING THE RESEARCH QUESTION

The research question that was formulated was as follows: what are the effects of DHA during pregnancy and the postpartum period on maternal mental health in terms of depression and anxiety?

IDENTIFYING RELEVANT STUDIES

Relevant studies were identified by searching recent literature published between February and March 2021 in the PubMed, Scopus, PsycINFO and Medline databases. The following keywords were used: "Docosahexaenoic Acid"; "Fish Oil"; "Dietary Supplements"; "Pregnancy"; "Maternal-Fetal Exchange"; "Breast Feeding"; "Depression; "Depression, Postpartum"; "Mental Health"; "Behavioral Symptoms"; "Stress, Psychological"; "Affective Symptoms"; "Anxiety"; "Postnatal depression"; and "Antenatal depression".

Articles included in this scoping review met the following specified inclusion criteria: a) analytical studies (i.e., randomised controlled trials [RCT], or mainly observational studies [cross-sectional, cohort and case-control]); b) evaluating the effect of DHA on mental health (depression and anxiety) in pregnant and/or lactating women; c) published in English or Spanish; and d) published between January 2010 and March 2021. The healthcare level at which the study was carried out was not considered as relevant. Studies which were carried out on animals or which focused only on other n-3 PIFAs were excluded.

STUDY SELECTION

Study selection was carried out as described above and following PRISMA (14). First, the search results were imported into Mendeley (https://www.mendeley.com) to perform the duplication check, thus eliminating 563 articles. Of the remaining 964 studies which were subsequently analyzed according to title and abstract, 883 were discarded based on the inclusion

and exclusion criteria, while 81 were found to be potentially eligible articles. Subsequently, the relevance of each of the abstracts was analyzed, eliminating 46 in this process. Finally, the full text of the remaining 35 articles was examined and 14 were chosen for final analysis (Fig. 1). The entire process was recorded using an Excel Information Manager spreadsheet (15).

CHARTING THE DATA

Four specific components were extracted using a standardised form: a) general data (author[s], year of publication and country); b) methodological elements (study design and population); c) data of the intervention/observation carried out (i.e., dose of DHA, measurement of the presence of depression and/or anxiety, etc.); and d) data evaluating the effect of DHA on the mental health of pregnant and/or lactating women.

COLLATING, SUMMARIZING AND REPORTING THE RESULTS

The results were classified according to whether or not taking DHA during pregnancy was effective for maternal mental health. Of the 14 papers, nine reported beneficial effects and five, no beneficial benefits.

RESULTS

The results are set out in three different sections: characteristics of the included studies, studies which show the effectiveness of DHA in terms of maternal mental health, and studies which show no such effectiveness.

CHARACTERISTICS OF INCLUDED STUDIES

The 14 papers came from a total of 11 countries: two from Brazil, United States and Japan; and one each from Australia, The Netherlands, Iran, Kenya, Mexico, Norway, United Kingdom and Taiwan. Exactly half of the papers were published between 2016 and 2018 (n = 7). As for the type of study, six were RCT, four were prospective cohorts, three were cross-sectional studies and one, a longitudinal case-control study. These and other characteristics of the studies are shown in table I.

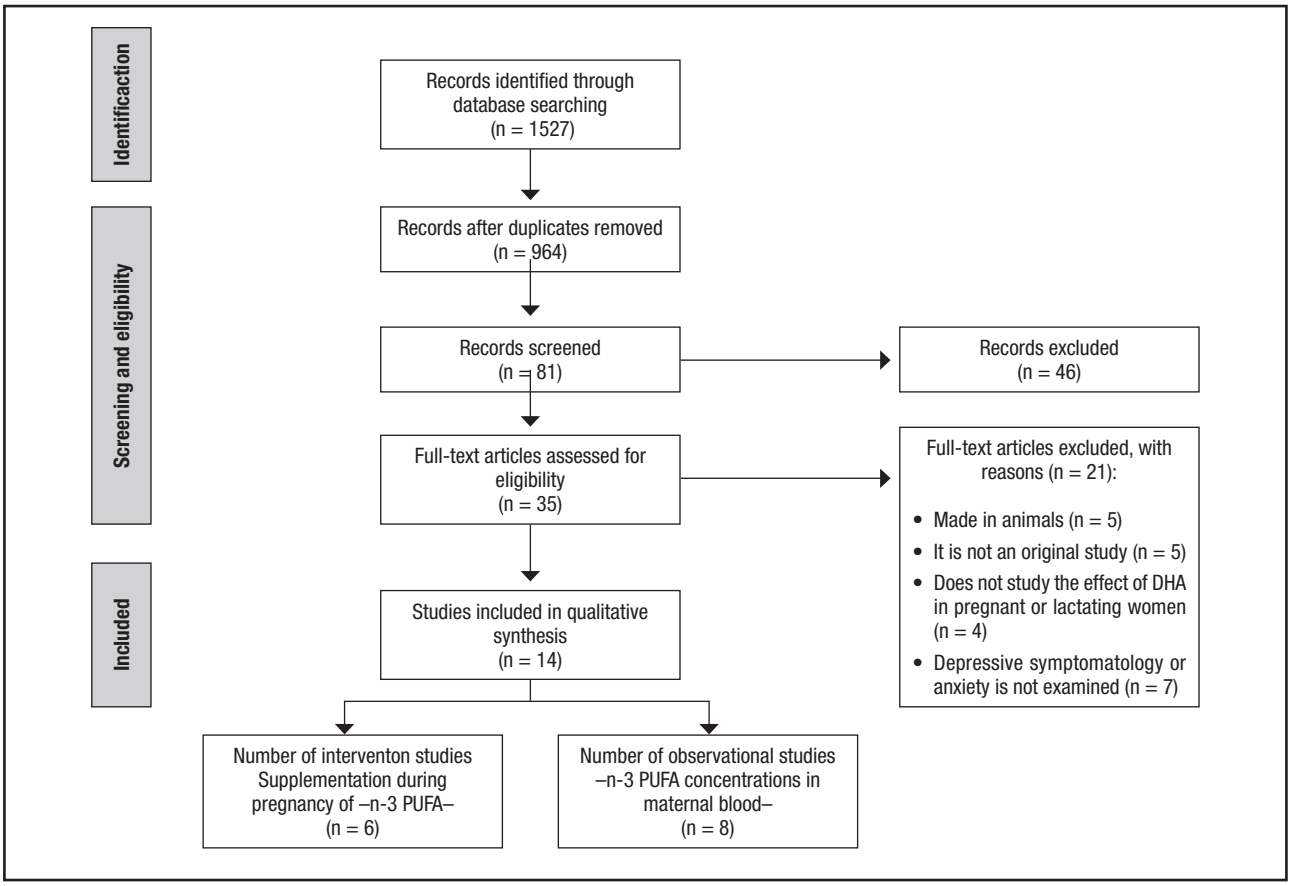

Figure 1.

PRISMA chart. DHA: docosahexaenoic acid; n-3 PUFA: omega-3 polyunsaturated fatty acids.

Table I. Overview of included studies

Author(s), year of publication	Country	Study design	Population	Intervention/observation	DHA effect
Studies where DHA was found to be beneficial for maternal mental health					
Álvarez-Ramírez et al. (16), 2018	Mexico	Cross-sectional study	n = 151 pregnant in second semester	DHA intake: food frequency questionnaire Anxiety: STAI; depression: EPDS (≥ 12 points)	Average daily intake of DHA: 70 mg/day Anxiety: 44.4 %; depression: 17.9 % Anxiety: ↑ STAI score with ↓ DHA intake (p = 0.03) Depression: ↑ EPDS score with ↓ DHA intake (p = 0.01)
Chang et al. (19), 2018	Taiwan	Cross-sectional study	n = 17 with depression (DSM-IV) n = 16 without depression (CG) All were in the 2nd or 3rd trimester	DHA and other FAs in blood Perinatal depression: DSM-IV and EPDS (in medians)	EPDS: 14.6 points (SD: ± 3.6) in the group with depression and 5.3 (SD: ± 3.8) in CG < DHA levels in the depressed group (p = 0.02)
Farshbaf-Khalili et al. (22), 2016	Iran	RCT	IG: n = 75 CG: n = 75 Pregnant	IG: 1,000 mg/day of fish oil supplements (with 120 mg of DHA; 180 mg of EPA and 400 mg of ALA) CG: 1,000 mg/day placebo Follow-up: beginning (WG 16-20), WG 26-30, WG 35-37, and 30-45 days postpartum Depression: EPDS (in medians); serum levels DHA and EPA	After follow-up, significant differences between groups were in mean EPDS score (adjusted mean difference = -1.4 [95 % CI: -2.6 to -0.25]) IG: ↓ mean depression score during pregnancy and the postpartum period (p < 0.05)
Pinto et al. (17), 2016	Brazil	Cohorts, prospective	n = 172 pregnant	DHA and other FAs in blood; depression: EPDS (≥ 11 points) Follow-up between 5-13, 20-26 and 30-36 WG	Depression: 1st trimester = 33.7 %; 2nd = 18.9 %; and 3rd = 17.4 % Advancement of pregnancy = > high concentrations of DHA (OR = 0.96, 95 % CI 0.93-0.99) and other FA and ↓ in depressive symptoms (p < 0.05)
Shiraishi et al. (18), 2015	Japan	Cross-sectional study	n = 329 pregnant (WG 19-23)	Plasma concentrations of DHA (48.6-152.4 µg/ml) and EPA (11.6-107.2 µg/ml); dietary history: BDHQ during the month prior to the study Depression: EPDS (> 8 points)	Depression: 5.9 % ↑ EPDS score with ↓ DHA intake (p = 0.09) and ↓ plasma DHA concentration (p = 0.04)
Judge et al. (23), 2014	USA	RCT (pilot study)	IG: n = 20 pregnant CG: n = 22 pregnant	IG: DHA (300 mg of DHA) CG: placebo (without DHA, corn oil capsule) Consumption of capsules from 24 to 40 WG (1 capsule 5 days/week) Depression during pregnancy: CES-D; postpartum (up to 6 months): PDSS (in means)	CES-D: means IG 12.6 (SD: ± 8.3) and CG 9.5 (SD: ± 8.3) PDSS: means between 46.03 and 47.65 ↓ total PDSS scores in IG: with less anxiety/insecurity (p = 0.03), emotional lability (p = 0.04) and loss of self (p = 0.02)

(Continues on next page)

Table I (Cont.). Overview of included studies

Author(s), year of publication	Country	Study design	Population	Intervention/observation	DHA effect
Studies where DHA was found to be beneficial for maternal mental health					
Sallis et al. (29), 2014	UK	Cohorts, prospective	n = 306 with perinatal depression n = 2,357 without depressive symptoms	DHA and EPA: changes in their presence in erythrocytes (1 % in DHA and 0.1 % in EPA) Perinatal, antenatal and postnatal depression: EPDS (≥ 12 points)	Perinatal depression: 11.5 % Positive association of EPA (OR = 1.07, 95 % CI: 0.99-1.15) and DHA (OR = 1.08, 95 % CI: 0.98-1.19) with perinatal depression There were no associations with the other types of depression
Markhus et al. (21), 2013	Norway	Cohorts, prospective	n = 35 women who completed the follow-up	FA in erythrocytes (28 WG) Depression: EPDS (≥ 10 points) measured at 3 months postpartum	Depression: 6.9 % Significant association between low levels of DHA with higher depression scores ($p = 0.006$)
Mozurkewich et al. (24), 2013	USA	RCT	IG^1: n = 39 IG^2: n = 38 CG: n = 41 All pregnant at the beginning of pregnancy had risk of depression	IG^1: EPA (1,060 mg EPA + 274 mg DHA) IG^2: DHA (900 mg of DHA + 180 mg of EPA) CG: placebo (soybean oil) Depression: Beck Depression Inventory + Mini International Neuropsychiatric Interview at the time of enrolment, 26-28 WG, 34-36 WG, and 6-8 weeks postpartum Serum AF: on admission and between 34 and 36 WG	↑ DHA (IG^2) concentrations at 34-36 WG, ↓ BDI scores ($p < 0.05$) IG^1 and CG were not significant
Studies that do not demonstrate the effectiveness of DHA on maternal mental health					
Urech et al. (26), 2020	The Netherlands	Case-controls, longitudinal	n = 9 with major depression n = 10 with anxiety n = 8 with mixed anxiety-depression disorder CG: 40 healthy pregnant	DHA and other FAs in maternal erythrocytes and breast milk Depression: EPDS (in means) Prenatal anxiety: DSM-IV	Mean scores ↑ in groups with major depression (9.5 ± 6.1), in mixed disorder (7.6 ± 7.6), and with anxiety (5.1 ± 1.8) than in healthy (3.0 ± 3.8) No significant associations were found between prenatal depression and/or anxiety and DHA in milk or maternal erythrocytes
Opiyo et al. (29), 2018	Kenya	RCT	IG: n = 109 CG: n = 107 All HIV-positive pregnant women	IG: daily dose of fish oil rich in n-3 (EPA = 2.15 g; DHA = 1.02 g) CG: daily dose of soybean oil (SFA: 0.178 g, MUFA: 0.299 g, PUFA: 0.985 g, with traces of EPA: 0.115 g) Follow-up: 8 weeks between WG 14 and 27 Depression: Beck's Depression Inventory (< 14)	Mild depression: 95.3 % in the IG and 97.9 % in the CG There were no significant differences between the two groups in the reduction of symptoms of depression in HIV-positive pregnant women

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Table I (Cont.). Overview of included studies

Author(s), year of publication	Country	Study design	Population	Intervention/observation	DHA effect
Studies that do not demonstrate the effectiveness of DHA on maternal mental health					
Dos Santos Vaz et al. (30), 2017	Brazil	RCT	IG: n = 32 CG: n = 28 All pregnant at risk of depression	GI: 1.8 g (1.08 g EPA and 0.72 g DHA) CG: placebo Supplementation began at 22-24 WG (T1) and lasted 16 weeks Depression: EPDS (≥ 11 points) at 5-13 WG (T0), 22-24 WG (T1), 30-32 WG (T2) and 4-6 weeks postpartum (T3)	Depression in IG: 50 % (T0), 25 % (T1), 28.6 % (T2) and 25 % (T3) Depression in CG: 46.9 % (T0), 37.5 % (T1), 34.4 % (T2) and 25 % (T3) There were no differences between IG and CG in the prevalence of depression from pregnancy to postpartum IG women with depression had a greater reduction in EPDS from the second to the third trimester (p = 0.029)
Kobayashi et al. (27), 2017	Japan	Cohorts, prospective	n = 967 puerperal women (1 month after delivery) n = 710 women (6 months after delivery)	DHA consumption during 26-40 WG: sFFQ Depression: EPDS (≥ 9 points)	Depression: 19.8 % and 12.8 % in the puerperium No significant associations were observed between EPA, DHA, and n-3 PUFA intake at the end of pregnancy and postpartum depression at both one month and six months of follow-up
Makrides et al. (28), 2010	Australia	RCT	GI: n = 1,197 women CG: n = 1,202 women n = 694 newborns	GI: fish oil capsules with DHA (800 mg/day) CG: vegetable oil capsules without DHA Both from the beginning of the study until birth Postpartum depression: EPDS (> 12 points); cognitive and language development of the baby: Bayley scale	Postpartum depression: in IG 9.7 % and in CG 11.2 % IG compared to CG did not give lower levels of postpartum depression nor did it improve cognitive and language development in early childhood

DSM-IV: Diagnostic and Statistical Manual, 4th edition; IG: intervention group; CG: control group; WG: gestation week; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; STAI: State-Trait Anxiety Inventory (Spanish version); EPDS: Edinburgh Postpartum Depression Scale; FA: fatty acids; ALA: alpha-linolenic acid; BDHQ: self-administered diet history questionnaire; CES-D: Center for Epidemiologic Studies Depression Scale; PDSS: Postpartum Depression Screening Scale; HIV: human immunodeficiency virus; n-3: omega-3; SFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; sFFQ: semi-quantitative food frequency questionnaire; n-3 PUFA: omega-3 polyunsaturated fatty acids.

STUDIES THAT REPORT EFFECTIVENESS OF DHA WITH RESPECT TO MATERNAL MENTAL HEALTH

Of the 14 analyzed papers, nine found that the consumption of either DHA alone or in combination with other FAs during pregnancy was beneficial for maternal mental health. Of these, six (16-21) measured plasma levels in the mother while only three (22-24) studied dietary supplements during the pregnancy.

With respect to the consumption of DHA alone, without other FAs, this was only performed by Judge et al. (23). Significantly lower scores ($p = 0.016$) were recorded on the Postpartum Depression Screening Scale in the IG (46.03 ± 2.17) compared to the control group (CG) (52.11 ± 2.4).

The effect of the combination of DHA with other FAs has also been studied. Daily intake of DHA varied between 70 mg/day and 325 mg/day and the prevalence of depressive symptoms between 5.8 % and 33.7 % (16-18,21). Pinto et al. (17) reported a 5 % decrease in the probability of having depressive symptoms for each one-week increase in the pregnancy. In all (16-18,21), it was found that pregnant women with lower dietary intake and blood concentrations of DHA had higher scores on the Edinburgh Postpartum Depression Scale (EPDS) ($p < 0.05$). Likewise, lower plasma concentrations of other FAs, such as EPA (16-18,21), docosapentaenoic acid (DPA) (17,21), total n-3 (17,21), the n-3/n-6 ratio and highly unsaturated fat (21) were correlated with higher scores on the EPDS. Finally, it should be noted that no statistically significant results were obtained for the postpartum period (20,21). As for anxiety, Álvarez-Ramírez et al. (16) reported a prevalence of 44.4 % (STAI > 40 points) and an increase in the STAI score for pregnant women with a lower intake of DHA and EPA ($p = 0.03$).

Two observational studies carried out a follow-up of a group of pregnant females diagnosed with perinatal depression (IG) and another with no prior pathology (CG). In the first of these, Chang et al. (19) found that the IG had significantly lower levels of DHA ($p = 0.020$), total n-3 ($p = 0.026$), and EPA ($p = 0.019$). In the second study (20), an 11.5 % prevalence of perinatal depression was found, along with a positive association between DHA and EPA, and perinatal depression. However, as in the previous cases, no statistically significant correlations were found between DHA and EPA plasma concentrations and postnatal depression.

The final two papers that reported a beneficial effect of DHA were RCTs. In the first of these (22), after the follow-up it was found that fish oil supplements significantly reduced the mean EPDS score during pregnancy ($p < 0.05$). In the second study, Mozurkewich et al. (24) used two IGs and a CG (with soybean oil). EPA-rich fish oil was administered to the first IG and DHA-rich fish oil to the second. At the third of four visits (at 24-36 weeks' gestation), the Beck Depression Inventory (BDI) score was significantly predicted by serum DHA ($p < 0.05$), BDI at enrollment ($p < 0.001$) and admission to having stopped taking the capsules ($p < 0.01$). None of the three dietary supplements significantly predicted the BDI scores at 6-8 weeks postpartum.

STUDIES THAT REPORTED NO EFFECTIVENESS OF DHA WITH RESPECT TO MATERNAL MENTAL HEALTH

In this section, a description is offered of the five studies which reported no beneficial effect of DHA on maternal mental health. In the observational studies, an analysis was undertaken of the concentration of n-3 PUFAs in blood samples. In the most recent of the studies, carried out by Urech et al. (26), a longitudinal follow-up was made of four groups of pregnant women. Mean scores increased more in the groups with a mental disorder than in the healthy group (CG). Moreover, women with a major depression disorder did present lower levels of n-3 ($p = 0.018$) and EPA ($p = 0.006$), and those diagnosed with a mixed anxiety-depression disorder had lower levels of EPA ($p = 0.015$) and higher levels of DPA ($p = 0.001$). No statistically significant association was found between the anxiety disorder group and any FA. In addition, no FA was significantly associated with postpartum depression. In the other observational study (27), a total of 967 women were screened for postpartum depression. Depression was recorded in 19.8 % of the women one month after delivery, a value which fell to 12.8 % at six months. No significant associations were observed between postpartum depression and intakes of DHA, EPA and n-3 PUFA.

Just one study, that of Makrides et al. (28), administered only DHA supplements (800 mg/day) to an IG. No significant differences were found between the percentage of women who reported depressive symptoms during the first six months postpartum in the IG and CG (9.67 % against 11.19 %; adjusted OR 0.85; 95 % CI: 0.70-1.02; $p = 0.09$). Depressive symptoms were commoner among women with a prior or current diagnosis of depression at enrolment.

The two RCTs in which DHA was studied in combination with other FAs were published by Opiyo et al. (29) and Dos Santos Vaz et al. (30). In the first of these (29), all participants were HIV-positive pregnant women. At the end of the follow-up, most of the participants had mild depressive symptoms (95.3 % in the IG and 97.9 % in the CG), with the difference not being statistically significant. Finally, in the study by Dos Santos Vaz et al. (30), depression was detected using the EPDS ($\geq$ 11 points) in different gestation weeks. At weeks 30-32 of gestation, the IG had higher serum concentrations of EPA, DHA and lower n-6/n-3 ratio compared to the CG. However, there were no differences between the IG and CG in the prevalence of EPDS scores over time. Only women in the IG with a previous history of depression had a higher reduction in the EPDS score between the second and third trimester compared to the CG ($p = 0.038$). In their conclusions, the authors argued that a daily dietary supplement of 1.8 g of n-3 PUFAs during 16 weeks had no effect in terms of preventing maternal depressive symptoms.

DISCUSSION

The results were classified according to whether the studies showed beneficial effects or otherwise of the intake of DHA dur-

ing pregnancy on maternal mental health in terms of depressive symptoms and anxiety. The observational ones almost all show that the DHA has an important effect in relation to maternal mental health (6 yes, 2 no). On the other hand, the experimental ones do not show that effect so clear (3 yes, 3 no). This lower effect in the experimental ones may be due to various causes (i.e., the different doses, the sample size and even the different countries in which the studies have been performed, since it is known that there are clear differences in diets [31]).

According to the analysis of the papers that has been undertaken, dose is one of the conditioning factors that may affect the effectiveness of DHA. Different doses were administered in the RCTs (22-24) (Table I). These doses meet the recommended daily DHA intake of the EFSA (2) (a range from 100 to 200 mg/day). It should also be noted that the effectiveness of DHA reported in these studies may be affected by the exclusion criteria of a prior history of depression, anxiety or certain other illnesses.

In other RCTs with higher doses of DHA, no beneficial effect on mental health was reported, though this may be due to how the studies were developed. In the case of Dos Santos Vaz et al. (30), the inclusion criteria were a prior history or risk of depression. Likewise, in the study of HIV-positive pregnant women (29), the illness itself could imply a bias in the results given the different physiological and psychological conditioning factors of this group of women. Finally, it should be noted that in the study by Makrides et al. (28), a dietary DHA supplement of 800 mg/day was found to be ineffective in the prevention or reduction of depressive symptoms. However, as limitations to their study, the authors reported that they did not verify the clinical diagnosis of depression before the start of the RCT. In addition, they associated the lower than expected rate of depressive symptoms in the CG to the so-called Hawthorne effect (33), according to which the mere fact of participation in a trial with a high degree of contact with researchers helps to prevent such symptoms. Finally, in relation to the non-effectiveness of DHA in pregnant women with an established diagnosis of prenatal depression, a recent study by Mezquida et al. (34) reported the association of a specific pattern of obstetric complications with a more severe clinical symptomology like depression. All of this may be influential in terms of the results of the non-effectiveness of DHA in this population with a history of mental illness.

On the other hand, Makrides et al. (28) only analyzed the effect of DHA in the postpartum period, while the effectiveness of DHA was only found to be statistically significant in other studies during pregnancy (16-24). In this regard, a total of five studies (24,26-29) found, after analyzing the effect of DHA in the postpartum period, no positive effect in terms of the prevention or reduction of depressive or anxiety symptoms. This may be because the dietary supplements were administered during pregnancy and, therefore, the concentrations of DHA would have lowered considerably in the postpartum period. However, the importance of DHA for maternal mental health in the third trimester has been shown. This appears to be a critical period to ensure adequate levels of maternal DHA to facilitate optimal cognitive development at the end of infancy (35). In this regard, the potential effects of DHA during infancy and adulthood are becoming more widely recognized, suggesting at the same time that DHA levels can play a role in cognitive decline and in relation to the main psychiatric disorders (36). The effect may be related to the intake of DHA supplements increasing the concentrations of 17-hydroxy-docosahexaenoic acid in maternal and umbilical cord blood ($p = 0.02$) (37).

Finally, another conditioning factor that may have affected the results is the way depressive symptoms were measured. One of the scales used, in the study by Judge et al. (23), was the Center for Epidemiologic Studies Depression scale (CES-D) (38). In the study, a Cronbach's α coefficient of 0.89 in the IG and 0.90 in the CG was reported. A noteworthy result if compared with the original coefficients of 0.85 and 0.9, respectively (38). For this reason, Judge et al. (23) concluded that the maternal CES-D score during pregnancy was a significant predictor of postpartum depressive symptoms. This finding also supports previous research that identified psychological disturbance during the prenatal period as a significant predictor of postpartum depression (39,40). However, this scale was not used in the other studies, where the most commonly used scale was the EPDS (25) ($n = 11$). This scale measures depression and the emotional feelings of mothers in the last weeks of gestation. The prevalence of depression ranged between 5.9 % and 50 % (16-22,24,26-28,30). The EPDS has been used with different cut-off values (≥ 12 points, ≥ 11, ≥ 10, ≥ 9 and > 8) or simply the mean values. Although a high EPDS score (25) cannot confirm a diagnosis of depression, it is considered that a score higher than 12 may indicate a probable depressive disorder (28). A score of 10 to 12 represents a crossover point and a score of 0 to 9, the absence of postpartum depression (41). In contrast, Markhus et al. (21) argue that the cut-off value should be ≥ 10, as this is the value commonly used in Primary Care settings.

LIMITATIONS

The selected studies were carried out in different countries with large sociocultural and dietary differences, making generalizations difficult. In addition, there are important gaps in the body of knowledge with respect to the influence of other nutrient deficiencies (i.e., genetic polymorphisms that affect the synthesis of n-3 FAs and the total intake of FAs) or the real influence of other n-3 FAs (i.e., EPA) in maternal mental health. Data on dietary intake of fats and measures of fatty acid status in blood are not collected or, at least, not specified in most papers.

The studies are also limited in many instances by a small sample number or the inclusion/exclusion criteria that were used in relation to mental health issues prior to pregnancy. For the above reasons, the results of these studies cannot be considered to be conclusive.

CONCLUSIONS

This scoping review focuses on identifying the effectiveness of DHA with respect to maternal mental health. In most of the

studies analyzed (n = 9), higher serum concentrations of this n-3 PUFA, whether due to a high natural intake or dietary supplements, were shown to influence reducing the prevalence of depressive and anxiety symptoms. Although more research is needed, these exploratory results therefore seem to indicate that DHA plays an important role in the prevention of the pathogenesis of these two mental illnesses during the gestation period. However, it appears to lose effectiveness in the postpartum period, since no studies analyzed in this review had shown an effect of DHA on depressive or anxiety symptoms. The findings lend support to the hypothesis of the implication of phospholipids in depression. However, further research in this area is required. Future investigations should aim to replicate findings in larger data sets and clarify possible pathophysiological mechanisms. Another research line would be to investigate what happens with multiple pregnancies given that all the studies made to date have concentrated on singleton pregnancies. It should also be noted that very few of the papers have considered only the use of DHA, with most studying DHA in combination with other PUFAs like EPA. Further research is therefore required to know the individual effect of DHA on maternal mental health.

Finally, different scales were used to detect depressive symptoms, with the EPDS being the most frequently employed. However, there appears to be no consensus on the cut-off value. Clarifying this question is key in terms of the healthcare implications for the systematic detection of depression during pregnancy and the postnatal period and, in this way, ensuring early intervention and the correct tackling of the disorder.

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ARÁN

Nutrición Hospitalaria

Artículo Especial

Guía Práctica ESPEN: nutrición enteral domiciliaria

ESPEN practical guideline: Home enteral nutrition

Stephan C. Bischoff[1], Peter Austin[2,3], Kurt Boeykens[4], Michael Chourdakis[5], Cristina Cuerda[6], Cora Jonkers-Schuitema[7], Marek Lichota[8], Ibolya Nyulasi[9,10], Stéphane M. Schneider[11], Zeno Stanga[12], Loris Pironi[13,14], Ana Cantón[15,*]

[1]Departamento de Nutrición Clínica. Universität Hohenheim. Stuttgart, Alemania. [2]Departamento de Farmacia. Oxford University Hospitals NHS Foundation Trust. Oxford, Reino Unido. [3]School of Pharmacy. University College London. Londres, Reino Unido. [4]Unidad de Soporte Nutricional. Hospital AZ Nikolaas. Sint-Niklaas, Bélgica. [5]Escuela de Medicina. Facultad de Ciencias de la Salud. Universidad Aristóteles de Tesalónica. Tesalónica, Grecia. [6]Unidad de Nutrición. Hospital General Universitario Gregorio Marañón. Madrid. [7]AMC. Centro Médico Universitario de Ámsterdam. Ámsterdam, Países Bajos. [8]Asociación de Pacientes con Fallo Intestinal "Appetite for Life". Cracovia, Polonia. [9]Departamento de Nutrición. Departamento de Rehabilitación, Nutrición y Deporte. Universidad de La Trobe. Melbourne, Australia. [10]Departamento de Medicina. Universidad de Monash. Melbourne, Australia. [11]Gastroenterología y Nutrición. Centre Hospitalier Universitaire. Université Côte d'Azur. Niza, Francia. [12]Servicio de Diabetes, Endocrinología, Nutrición y Metabolismo. Hospital Universitario de Berna. Universidad de Berna. Berna, Suiza. [13]Departamento de Medicina y Cirugía. Alma Mater Studiorum. Universidad de Bolonia. Bolonia, Italia. [14]Centro de Fallo Intestinal Crónico. Unidad de Nutrición Clínica y Metabolismo. IRCCS Azienda Ospedaliero-Universitaria di Bologna. Bolonia, Italia. [15]Servicio de Endocrinología y Nutrición. Hospital Clínico Universitario de Santiago de Compostela. Santiago de Compostela, La Coruña

Resumen

Esta guía práctica de la European Society for Clinical Nutrition and Metabolism (ESPEN) proporciona información a médicos, enfermeras, dietistas, farmacéuticos, cuidadores y otros proveedores de nutrición enteral domiciliaria (NED) de forma concisa, sobre las indicaciones y contraindicaciones de la NED, así como sobre su administración y seguimiento. Esta guía también ofrece información a los pacientes interesados que necesiten NED. La nutrición parenteral domiciliaria no está incluida, pero se abordará en otra guía de la ESPEN. La guía se basa en la guía científica de la ESPEN publicada anteriormente, que consta de 61 recomendaciones (que se han reproducido y renumerado), junto con los comentarios asociados (que se han resumido en relación a la guía científica). Se indican los grados de evidencia y los niveles de consenso. La ESPEN encargó y financió la guía y seleccionó también a los miembros del grupo.

Palabras clave:

Nutrición enteral domiciliaria. Nutrición por sonda. Equipo de soporte nutricional. Fórmula enteral. Seguimiento.

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Correspondencia:

Stephan C. Bischoff. Zentrum für Klinische. Ernährung. Universität Hohenheim. Schloß Hohenheim 1. 70599 Stuttgart, Alemania
e-mail: bischoff.stephan@uni-hohenheim.de

Sobre la traducción al español: Ana Cantón Blanco. Servicio de Endocrinología y Nutrición. Hospital Clínico Universitario de Santiago de Compostela. Rúa da Choupana, s/n. 15706 Santiago de Compostela, A Coruña
e-mail: Ana.Canton.Blanco@sergas.es

Abstract

This ESPEN practical guideline will inform physicians, nurses, dieticians, pharmacists, caregivers and other home enteral nutrition (HEN) providers in a concise way about the indications and contraindications for HEN, as well as its implementation and monitoring. This guideline will also inform interested patients requiring HEN. Home parenteral nutrition is not included but will be addressed in a separate ESPEN guideline. The guideline is based on the ESPEN scientific guideline published before, which consists of 61 recommendations that have been reproduced and renumbered, along with the associated commentaries that have been shorted compared to the scientific guideline. Evidence grades and consensus levels are indicated. The guideline was commissioned and financially supported by ESPEN and the members of the guideline group were selected by ESPEN.

Keywords:

Enteral formula. Home enteral nutrition. Monitoring. Nutrition support team. Tube feeding.

INTRODUCCIÓN

Desde su introducción en la década de 1970, la nutrición enteral domiciliaria (NED) se ha afianzado como una intervención nutricional fiable y eficaz, algo especialmente relevante dada la confianza creciente en la atención ambulatoria. La NED se inicia generalmente durante una estancia en el hospital y se continúa después como terapia domiciliaria a largo plazo. En general, las diferencias en cuanto a la indicación de la nutrición enteral (NE) hospitalaria y domiciliaria son mínimas. Sin embargo, en el caso de la NED hay que considerar criterios adicionales, como el pronóstico, la calidad de vida relacionada con la salud (CVRS) y aspectos éticos. Para iniciar la NED, el principio que se debería seguir es que sin la NE sería esperable un deterioro significativo del estado nutricional del paciente, que afectaría al pronóstico y a la CVRS, lo que supone una decisión compleja, especialmente si no existe un tratamiento eficaz para la enfermedad subyacente.

El tratamiento nutricional enteral es un tratamiento médico, pero las decisiones en cuanto a la vía, la composición y la gestión del tratamiento nutricional se toman mejor desde los equipos de soporte nutricional multidisciplinares.

Esta guía proporciona información basada en la evidencia sobre el uso de la NED. Hay numerosas enfermedades, a menudo complejas, que pueden hacer necesaria una NED. Su descripción no forma parte de la presente guía, pero se incluyen:

- Trastornos de la deglución por enfermedades neurológicas.
- Obstrucciones por tumores malignos.
- Caquexia por cáncer.
- Enfermedad pulmonar obstructiva crónica.
- Enfermedades cardiacas.
- Infecciones crónicas.
- Malabsorción/maldigestión a causa de enfermedades hepáticas, pancreáticas o intestinales.

Los requerimientos nutricionales específicos de estas enfermedades se describen detalladamente en otras guías de la European Society for Clinical Nutrition and Metabolism (ESPEN) recientemente publicadas (véase la web de la ESPEN y la revista *Clinical Nutrition*). La presente guía se centra en la metodología y la práctica clínica de la NED, el seguimiento correspondiente y las estrategias para evitar complicaciones.

METODOLOGÍA

La presente guía práctica consta de 61 recomendaciones y se basa en la guía de la ESPEN sobre NED, la versión práctica (1) y la versión científica (2). En este caso, la guía original se ha acortado al restringir los comentarios a la evidencia recopilada y la bibliografía en las que se basan las recomendaciones. Las recomendaciones no se han modificado, pero se ha transformado la presentación del contenido en una presentación gráfica, con diagramas de flujo para la toma de decisiones, siempre que ha sido posible. La guía original se elaboró según el procedimiento operativo estándar (POE) para las guías ESPEN (3). Este POE está basado en la metodología de la Scottish Intercollegiate Guidelines Network (SIGN). Se han realizado búsquedas en la literatura y se han clasificado del 1 al 4 según la evidencia. Asimismo, se crearon recomendaciones que se clasificaron en cuatro clases (A/B/0/GPP). Entre paréntesis se indican los números de la recomendación original (R1, R2, etc.) y la clasificación. El grupo de trabajo incluía médicos, un farmacéutico, una enfermera y dietistas, así como un representante de los pacientes. El proceso de elaboración de la guía fue financiado exclusivamente por la ESPEN. La guía abreviada y la difusión fueron financiadas en parte por la sociedad United European Gastroenterology (UEG) y también por la ESPEN. Para obtener más detalles sobre la metodología, véanse la versión completa de la guía ESPEN (2) y el POE de la ESPEN (3).

RECOMENDACIONES

Esta guía práctica incluye 61 recomendaciones estructuradas en cinco capítulos principales y diversos subcapítulos (Fig. 1).

INDICACIÓN Y CONTRAINDICACIÓN DE LA NED (FIG. 2)

¿CUÁLES SON LAS INDICACIONES DE LA NED?

1. *Se debería ofrecer tratamiento con NED a los pacientes con riesgo nutricional o desnutridos que no puedan alcanzar sus necesidades de nutrientes mediante una ingesta dietética normal, que tengan un tracto gastrointestinal funcionante, que puedan recibir la terapia fuera de un entorno de cuidados de agudos y que estén de acuerdo y sean capaces de cumplir el tratamiento con NED, con el objetivo de mejorar el peso corporal, el estado funcional o la CVRS.*

(Recomendación 1, grado GPP, consenso fuerte, 97 % de acuerdo)

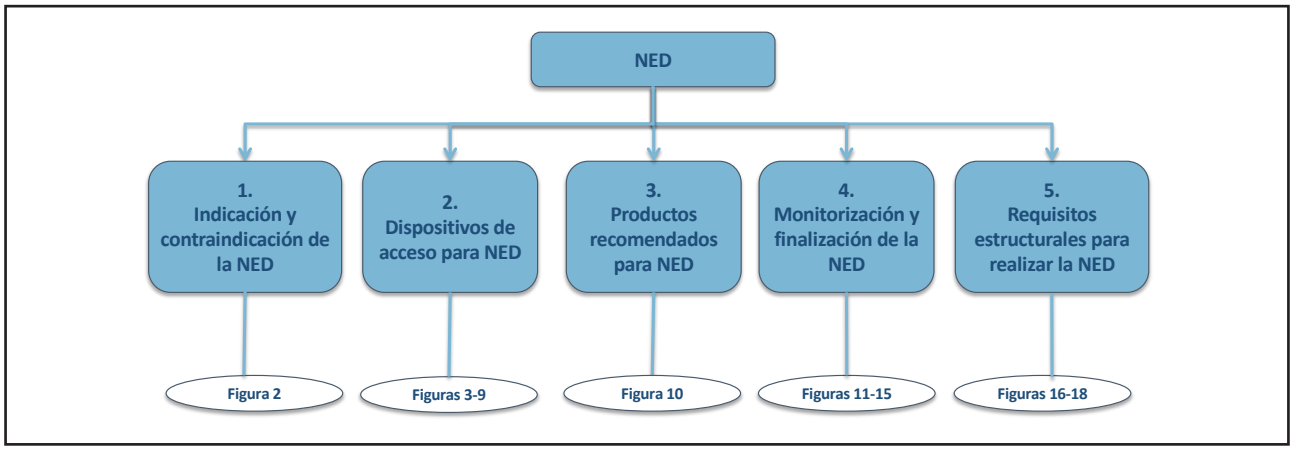

Figura 1.

Estructura principal de la guía práctica de la ESPEN sobre NED. La guía consta de cinco capítulos que se presentan en las figuras 2-18. Para más detalles, véase el texto. NED: nutrición enteral domiciliaria.

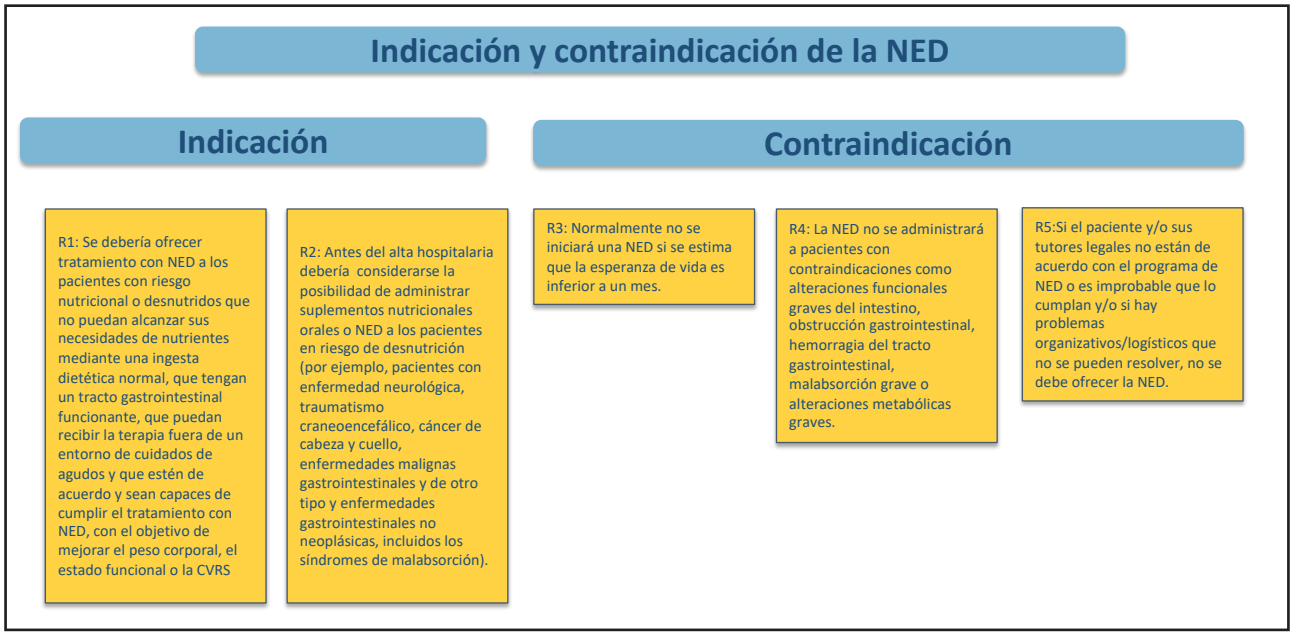

Figura 2.

Indicación y contraindicación de la NED. NED: nutrición enteral domiciliaria; CVRS: calidad de vida relacionada con la salud.

Comentario

La NED está indicada en pacientes con alto riesgo nutricional o desnutridos, que no pueden satisfacer sus requerimientos nutricionales por vía oral y que presentan un tracto gastrointestinal funcionante (4). Así, la NED puede definirse como una terapia de mantenimiento de la vida y debería plantearse si se considera probable que la ingesta nutricional de un paciente sea cualitativa o cuantitativamente insuficiente durante una semana o más.

Se considera que un estado nutricional es inadecuado cuando el paciente no puede comer durante una semana o si la ingesta energética es inferior al 60 % de sus necesidades estimadas durante 1-2 semanas (normalmente, inferior a 10 kcal/kg/d o un déficit de 600-800 kcal/d) (5-8). Se presume que la ingesta nutricional es deficiente cuando no se puede realizar una ingesta de alimentos normal, que alcanzaría las necesidades individuales, a pesar de la optimización del tratamiento médico y dietético. En esta situación, la NE se debería iniciar en la primera semana. Se debe asumir que existe un deterioro significativo del estado nutricional cuando el paciente ha perdido > 5 % de su peso corporal en 1-3 meses (9). El estado nutricional puede deteriorarse si la absorción de alimentos es inferior al 75 % de las

necesidades diarias (10,11), si ha habido una pérdida de peso previa o procesos catabólicos concomitantes o si está implicado un tratamiento con quimioterapia (12).

Un ensayo controlado aleatorizado (ECA) multicéntrico en el que se evaluaron pacientes sometidos a esofagectomía o gastrectomía total demostró que la NED a través de una yeyunostomía como práctica habitual era factible, segura y aceptable para los pacientes y sus cuidadores. Además, los autores demostraron un incremento sustancial de los parámetros antropométricos y funcionales, así como del coste eficiencia tras seis meses de seguimiento (13). En dos estudios que incluían pacientes con cáncer y con enfermedad de Crohn se demostró la eficacia de la NED en los resultados clínicos (14,15).

2. *Antes del alta hospitalaria debería considerarse la posibilidad de administrar suplementos nutricionales orales o NED a los pacientes en riesgo de desnutrición (por ejemplo, pacientes con enfermedad neurológica, traumatismo craneoencefálico, cáncer de cabeza y cuello, enfermedades malignas gastrointestinales y de otro tipo y enfermedades gastrointestinales no neoplásicas, incluidos los síndromes de malabsorción).*

(Recomendación 2, grado B, consenso fuerte, 96 % de acuerdo)

Comentario

En los datos epidemiológicos recogidos de 3.246 pacientes italianos a lo largo de un periodo de once años, se pudo observar un incremento anual progresivo del tratamiento con NED (16). La incidencia media fue de 406 ± 58 pacientes/millón de habitantes/año para los pacientes que vivían en su domicilio y de 319 ± 44 para los pacientes que vivían en residencias de ancianos (tasa de prevalencia media ± DE: 464 ± 129 casos/millón de habitantes en domicilio frente a 478 ± 164 en residencias de ancianos) (16).

Según varios estudios epidemiológicos y registros nacionales europeos, las indicaciones más frecuentes de la NED en adultos son las enfermedades neurológicas (neurovasculares y degenerativas), el cáncer de cabeza y cuello, el cáncer gastrointestinal y otros cánceres, la parálisis cerebral, las enfermedades gastrointestinales no neoplásicas (por ejemplo, fístulas, estenosis esofágica, enfermedad inflamatoria intestinal), traumatismos craneales, síndromes de malabsorción (por ejemplo, síndrome de intestino corto), trastornos graves de la motilidad intestinal, enfermedades metabólicas hereditarias y fibrosis quística (4,14,16-24).

Un estudio retrospectivo italiano encontró que la duración media de la NED era de unos 196 días (22). Desglosada por patologías, la duración fue de 261 días para la enfermedad neurovascular, 251,5 días para la enfermedad neurodegenerativa, 118 días para el cáncer de cabeza y cuello, 82,5 días para el cáncer abdominal, 788 días para los traumatismos craneales y 387 días para las enfermedades congénitas. Solo el 7,9 % de los pacientes reanudaron la nutrición oral y la mediana de supervivencia fue de 9,1 meses (22).

¿CUÁNDO NO SE DEBE RECOMENDAR LA NED? (CONTRAINDICACIÓN)

3. *Normalmente, no se iniciará una NED si se estima que la esperanza de vida es inferior a un mes.*

(Recomendación 3, grado GPP, consenso, 78 % de acuerdo)

Comentario

Esta recomendación se basa en una recomendación previa de la Sociedad Alemana de Nutrición Clínica (25). Para garantizar una atención óptima, se debería hacer un esfuerzo para estimar la esperanza de vida (26). Para más recomendaciones sobre la NED, se debería consultar la guía de la ESPEN sobre los aspectos éticos de la nutrición e hidratación artificial (27) y la guía de nutrición clínica en Neurología (28).

4. *La NED no se administrará a pacientes con contraindicaciones como alteraciones funcionales graves del intestino, obstrucción gastrointestinal, hemorragia del tracto gastrointestinal, malabsorción grave o alteraciones metabólicas graves.*

(Recomendación 4, grado GPP, consenso, 84 % de acuerdo)

Comentario

Esta recomendación se basa en la buena práctica clínica y no es específica para la NED. Se aplica de forma similar a la nutrición enteral en general.

5. *Si el paciente y/o sus tutores legales no están de acuerdo con el programa de NED o es improbable que lo cumplan y/o si hay problemas organizativos/logísticos que no se pueden resolver, no se debe ofrecer la NED.*

(Recomendación 5, grado GPP, consenso fuerte, 97 % de acuerdo)

Comentario

Esta recomendación se ha tomado de la guía alemana sobre nutrición artificial ambulatoria (25) y se ajusta a la guía de ética de la ESPEN (27).

DISPOSITIVOS DE ACCESO PARA NED (FIG. 3)

DISPOSITIVOS DE ACCESO (FIG. 4)

NED de corta duración (< 6 semanas)

6. *La NED se puede administrar a través de una sonda nasogástrica en pacientes que necesitan NED durante un corto periodo de tiempo (hasta 4-6 semanas).*

(Recomendación 6, grado 0, consenso, 90 % de acuerdo)

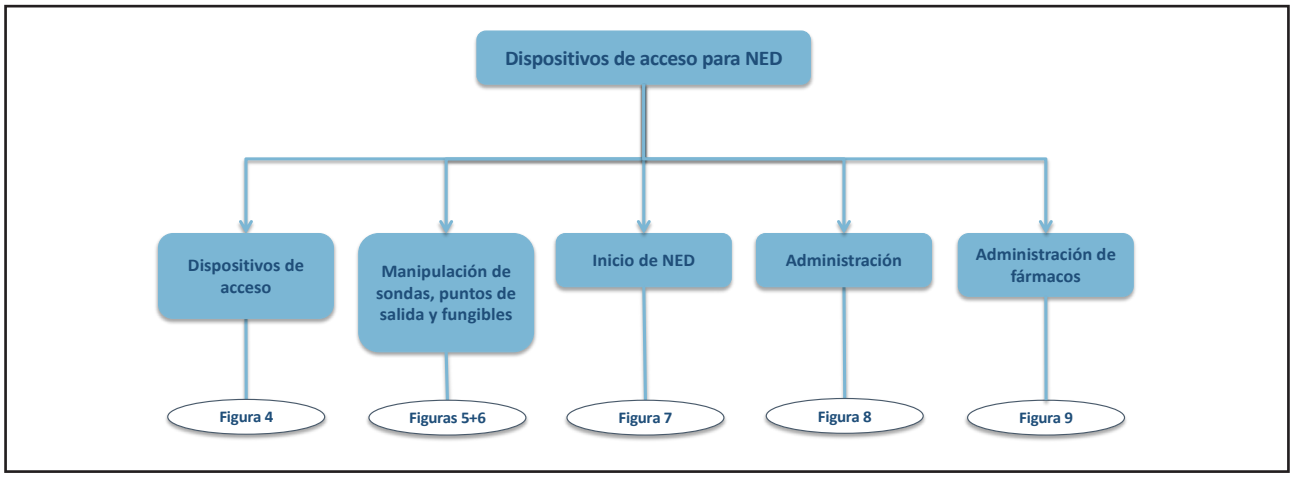

Figura 3.

Dispositivos de acceso para la NED: una visión general. NED: nutrición enteral domiciliaria.

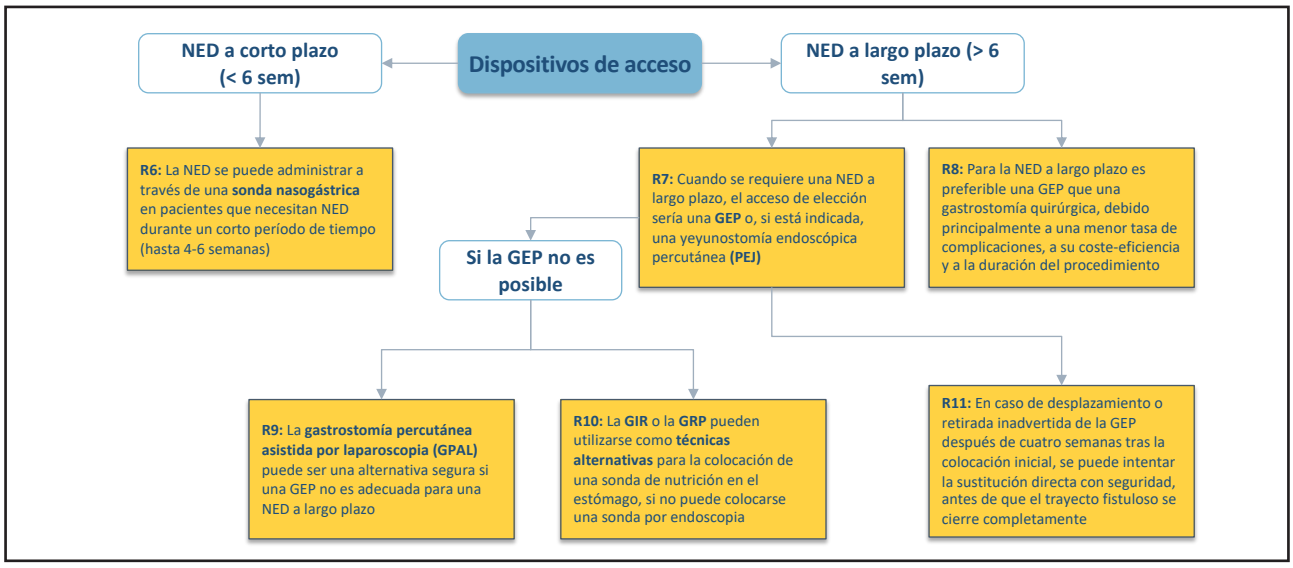

Figura 4.

Dispositivos de acceso para la NED a corto y largo plazo. NED: nutrición enteral domiciliaria; GEP: gastrostomía endoscópica percutánea; PEJ: yeyunostomía endoscópica percutánea; GPAL: gastrostomía asistida por laparoscopia percutánea; GRP: gastrostomía radiológica percutánea; GIR: gastrostomía insertada radiológicamente.

Comentario

La vía más adecuada para el tratamiento nutricional ambulatorio depende del funcionamiento, la accesibilidad y la capacidad digestiva y/o de absorción del tracto gastrointestinal. La vía de administración de la nutrición debería seleccionarse cuidadosamente (teniendo en cuenta las contraindicaciones). Si la NED es necesaria durante un tiempo limitado (hasta seis semanas), puede utilizarse una sonda nasogástrica. Dichas sondas, sobre todo las de pequeño calibre, se podrían utilizar durante periodos más largos, cuando la gastrostomía endoscópica percutánea (PEG) o la gastrostomía insertada radiológicamente (GIR) (22,29) no son una opción adecuada a largo plazo. Si ya existe un acceso *in situ* que pueda utilizarse para la administración de NE, debe considerarse su uso.

NED de larga duración (> 6 semanas)

7. *Cuando se requiere una NED a largo plazo, el acceso de elección sería una PEG o, si está indicada, una yeyunostomía endoscópica percutánea (JEP).*

(Recomendación 7, grado B, consenso fuerte, 93 % de acuerdo)

Comentario

La recomendación de utilizar una PEG o una JEP para NED a largo plazo se basa en un ECA (30) citado en la guía de la ESPEN sobre el cáncer (5), en el que se compararon las PEG y las sondas nasogástricas en pacientes con cáncer de cabeza y cuello, tres revisiones sistemáticas sobre el mismo tema (31-33) y una revisión sistemática que comparaba las PEG con las sondas nasogástricas en pacientes con disfagia (34). El peso corporal se mantenía de forma similar tanto con la PEG como con la sonda nasogástrica (33), mientras que el riesgo de pérdida de la sonda era menor (33,34) y la CVRS era probablemente mejor (30), aunque las sondas nasogástricas se asociaron con menos disfagia (33) y un destete más temprano tras la finalización de la radioterapia (31,33). Estas ventajas suponen una limitación frente a la clara recomendación de la PEG sugerida por los estudios anteriores y conducen al grado de recomendación B en lugar de A. Una revisión sistemática que incluía once ECA reportaba un menor número de fracasos de la intervención y una mejoría superior del estado nutricional en el grupo de PEG en comparación con el grupo de sonda nasogástrica (34). Además, la CVRS (por ejemplo, las molestias, la incomodidad, la alteración de la imagen corporal y de las actividades sociales) fue favorable a la PEG. No hubo diferencias significativas en las tasas de mortalidad y de neumonía por aspiración entre los dos grupos. Otra revisión sistemática no permitió extraer conclusiones firmes sobre si la nutrición con PEG era beneficiosa o no en comparación con la nutrición a través de sonda nasogástrica en pacientes mayores con disfagia no asociada a accidente cerebrovascular (35). En ancianos hospitalizados, el uso de la PEG se asoció a una mayor supervivencia, fue mejor tolerada y se asoció a una menor incidencia de aspiración (36) en comparación con la nutrición por sonda nasogástrica. El uso de una sonda JEP o PEG/J (PEG con extensión yeyunal) para la NED puede ser adecuado en caso de trastornos de la motilidad gastroduodenal, estenosis de la salida gástrica o alto riesgo de aspiración (37,38).

8. *La gastrostomía percutánea asistida por laparoscopia (GPAL) puede ser una alternativa segura si una PEG no es adecuada para una NED a largo plazo.*

(Recomendación 9, grado 0, consenso fuerte, 93 % de acuerdo)

Comentario

Existe una gran aceptación de la PEG frente a la gastrostomía quirúrgica convencional como técnica de inserción de elección debido a su menor coste, simplicidad, tiempo de procedimiento y menos complicaciones (39,41). Sin embargo, hay pacientes que no son candidatos apropiados para una PEG o en los que hay intentos fallidos de colocación de la misma (42). Una revisión sistemática y un metaanálisis solo pudieron demostrar que la PEG tiene menos complicaciones que la gastrostomía quirúrgica en los estudios aleatorizados incluidos en el análisis (39). Un gran estudio observacional en el que se compararon la GPAL, la PEG, la gastrostomía radiológica percutánea (GRP) y la gastrostomía quirúrgica convencional demostró que la tasa de complicaciones más baja correspondía al grupo de la GPAL (43).

En una revisión sistemática de Yuan y cols. (44) tanto la PEG como la GRP fueron eficaces para la NE a largo plazo en individuos seleccionados, aunque otra revisión indicó que la PEG se asociaba a una menor mortalidad a los 30 días en comparación con la GIR, lo que sugiere que la PEG debería considerarse como de primera elección para la NE a largo plazo (45). Por último, una revisión retrospectiva reveló que las tasas de pérdida de la sonda eran significativamente mayores en el grupo de GIR en comparación con el grupo de PEG (46).

9. *La GIR o la GRP pueden utilizarse como técnicas alternativas para la colocación de una sonda de nutrición en el estómago, si no puede colocarse una sonda por endoscopia.*

(Recomendación 10, grado 0, consenso fuerte, 97 % de acuerdo)

Comentario

El riesgo de peritonitis y mortalidad disminuye si la gastrostomía se coloca mediante una técnica endoscópica en lugar de radiológica (46-48). Las técnicas radiológicas deberían reservarse para aquellos pacientes en los que no es posible una técnica endoscópica. Sin embargo, tanto la PEG como la GRP son eficaces para la NE a largo plazo en individuos seleccionados (44).

10. *En caso de desplazamiento o retirada inadvertida de la PEG después de cuatro semanas tras la colocación inicial, se puede intentar la sustitución directa con seguridad antes de que el trayecto fistuloso se cierre completamente.*

(Recomendación 11, grado GPP, consenso fuerte, 93 % de acuerdo)

Comentario

Un trayecto fistuloso maduro es un requisito para la sustitución de una PEG después de su retirada inadvertida, extracción, oclusión o rotura. Los pacientes con riesgo de extracción involuntaria (por ejemplo, con demencia o delirio) requieren medidas preventivas para proteger la sonda. La adhesión del estómago a la pared abdominal se produce normalmente en un plazo de siete a 14 días, pero puede retrasarse en pacientes con problemas de cicatrización (49). La retirada involuntaria de una sonda de gastrostomía percutánea colocada recientemente (menos de cuatro semanas) es una urgencia.

En las dos primeras semanas, el recambio se realizará por vía endoscópica o radiológica a través de la misma ubicación. Entre dos y cuatro semanas después de la colocación inicial, se puede intentar la reposición a ciegas (por decisión médica), además de la sustitución endoscópica, si se comprueba posteriormente la posición adecuada de la sonda mediante un estudio con contraste hidrosoluble (50). La reposición debe realizarse rápidamente para mantener la permeabilidad y evitar el cierre del trayecto (37). Para el recambio a ciegas se utilizan generalmente las sondas de balón. Si se puede planificar el primer recambio de

sonda, se recomienda realizarlo en un hospital. Los posteriores podrían ser realizados por una enfermera en el domicilio o en una residencia de ancianos, si los pacientes no son capaces de hacerlo (51).

Si no se dispone de una sonda de gastrostomía de diámetro similar para la sustitución inmediata, se puede utilizar temporalmente una sonda Foley de balón del mismo diámetro para mantener el trayecto abierto y, si es necesario, administrar NE, líquidos o medicamentos, aunque actualmente es más difícil con los conectores universales de seguridad (por ejemplo, ENFit®) (51). Si existe alguna duda sobre la adecuada ubicación tras el recambio a ciegas, debería confirmarse endoscópica o radiológicamente la posición correcta, utilizando un contraste hidrosoluble, antes de utilizar la sonda. Las técnicas alternativas para comprobar la posición correcta son la confirmación del pH del contenido gástrico (pH 5 o inferior), la irrigación de la sonda con 3-50 ml de agua estéril sin resistencia ni fugas alrededor del estoma, la evaluación de la longitud externa de la sonda y la manipulación de la sonda mediante rotación y movimientos de entrada y salida (59,60).

11. *Para la NED a largo plazo es preferible una PEG que una gastrostomía quirúrgica, debido principalmente a una menor tasa de complicaciones, a su coste-eficiencia y a la duración del procedimiento.*

(Recomendación 8, grado B, consenso fuerte, 100 % de acuerdo)

Comentario

Véase el comentario a la recomendación 8.

MANIPULACIÓN DE SONDAS, PUNTOS DE SALIDA Y FUNGIBLES

Aspectos de enfermería (Fig. 5)

12. *El punto de salida de la PEG debería vigilarse diariamente y mantenerse limpio y seco (mediante el cuidado de la herida de forma aséptica) hasta que se forme el trayecto fistuloso y la incisión esté curada (generalmente, hasta 5-7 días después del procedimiento).*

(Recomendación 12, grado B, consenso fuerte, 100 % de acuerdo)

Comentario

Durante la primera semana tras la inserción de la PEG, uno de los objetivos es prevenir la infección del tracto del estoma. No es necesario aplicar tracción durante las primeras 24 horas al sistema de sonda PEG recién insertado para lograr una mejor adaptación de la sonda gástrica a la pared abdominal (52). Debe vigilarse diariamente el punto de salida de la PEG (para detectar signos de sangrado, dolor, eritema, induración, fugas e inflamación) y limpiarse con cloruro sódico al 0,9 %, agua estéril o agua recién hervida y enfriada (para eliminar cualquier resto). Se suele utilizar una gasa estéril (que no desprenda fibras) en Y para comprimir, colocada bajo la placa de disco externa, con un apósito transpirable respetuoso con la piel. Cuando la gasa se coloca bajo el disco externo, hay que evitar la tensión (51,53). Deben evitarse los apósitos oclusivos porque favorecen un ambiente húmedo y pueden provocar la maceración de la piel (52,53).

De acuerdo con las guías anteriores (61,62), la calificación de la recomendación 12 se ha elevado a una B, aunque la evidencia bibliográfica previa utilizada se ajusta más bien a un 0. Dentro de estas guías, falta una comparación directa de "sin cuidados" con "cuidados asépticos"; y en su lugar solo se examinó la "limpieza" frente a la "desinfección" por razones obvias (éticas).

13. *Cuando el tracto de la gastrostomía se ha curado (después de, aproximadamente, una semana), la sonda debe girarse diariamente y debe moverse hacia dentro al menos una vez por semana (como mínimo 2 cm, hasta 10 cm).*

(Recomendación 17, grado GPP, consenso, 87 % de acuerdo).

Comentario

El síndrome de enterramiento del tope interno de la gastrostomía (BBS) es una complicación grave en la que el dispositivo de fijación interna migra a lo largo del trayecto fistuloso hacia el exterior del estómago. El dispositivo puede acabar en cualquier localización entre la mucosa del estómago y la superficie de la piel (54). El BBS es generalmente una complicación a largo plazo, infrecuente y grave, pero que se puede prevenir con unos cuidados de enfermería adecuados. Las señales de alarma son cualquier dificultad para movilizar la sonda, las fugas alrededor del lugar de inserción cuando se intenta lavar la sonda, las alarmas frecuentes de la bomba de infusión (que pueden indicar obstrucción), el dolor abdominal, las infecciones crónicas de la zona o la resistencia a la administración de NE o líquidos (38). El factor de riesgo más importante para un BBS es la compresión excesiva del tejido entre el dispositivo de fijación interno y el externo (con mayor frecuencia en el caso de los dispositivos internos rígidos o semirrígidos) (55). La distancia entre los dos topes no debe ser ni demasiado holgada ni demasiado ajustada. La sonda debe avanzar en el estómago un mínimo de unos 2-3 cm, pero con pequeños movimientos se corre el riesgo de que solo se mueva la pared abdominal, por lo que lo ideal sería llegar hasta 5-10 cm (56). Esto puede hacerse, como pronto, cuando haya pasado aproximadamente una semana tras la inserción ya que antes podría provocar dolor local y dañar la formación del trayecto fistuloso. Una PEG también puede "incrustarse" en la mucosa gástrica y permitir igualmente girar la PEG. Esto puede ocurrir cuando una "bolsa" de mucosa gástrica ha crecido por encima y alrededor del tope interno (56). Cuando hay puntos de sutura porque el estómago está fijado a la pared abdominal (gastropexia), la movilización de la sonda puede retrasarse hasta que se hayan retirado las suturas (normalmente, después de dos semanas). Si hay una extensión yeyunal dentro de la sonda o si la

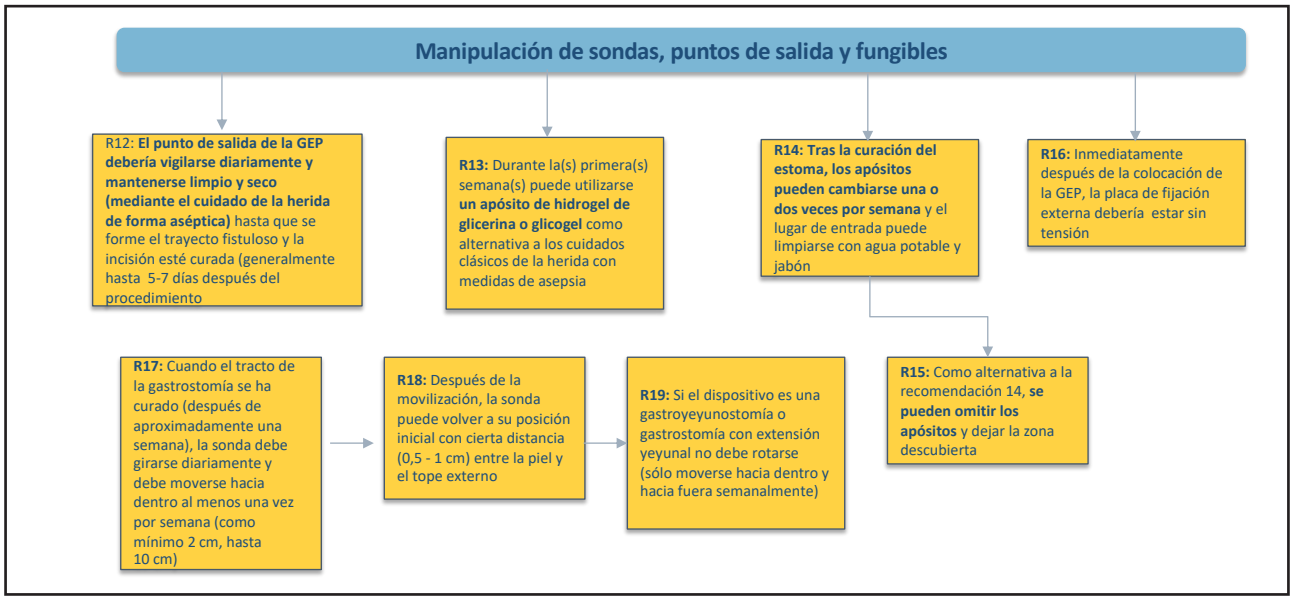

Figura 5.

Manipulación de sondas, puntos de salida y fungibles. Aspectos de enfermería. GEP: gastrostomía endoscópica percutánea.

sonda es una gastroyeyunostomía, el dispositivo no debe girarse (sino solo moverse hacia dentro y hacia fuera) (53,57).

14. *Después de la movilización, la sonda puede volver a su posición inicial con cierta distancia (0,5-1 cm) entre la piel y el tope externo.*

(Recomendación 18, grado 0, consenso fuerte, 93 % de acuerdo)

Comentario

Véase el comentario a la recomendación 13.

15. *Si el dispositivo es una gastroyeyunostomía o gastrostomía con extensión yeyunal no debe rotarse (solo moverse hacia dentro y hacia fuera semanalmente).*

(Recomendación 19, grado GPP, consenso fuerte, 92 % de acuerdo)

Comentario

Véase el comentario a la recomendación 13.

16. *Durante la(s) primera(s) semana(s) puede utilizarse un apósito de hidrogel de glicerina o glicogel como alternativa a los cuidados clásicos de la herida con medidas de asepsia.*

(Recomendación 13, grado B, consenso fuerte, 97 % de acuerdo)

Comentario

Dos ECA en adultos compararon unos apósitos diferentes para heridas con los apósitos estándar. El estudio más reciente demostró una reducción estadísticamente significativa de la infección al final de la primera y la segunda semana, utilizando un apósito para heridas de hidrogel de glicerina (aplicado al día siguiente de su colocación y cambiado semanalmente durante cuatro semanas) (52,58). Sin embargo, el otro estudio no demostró ninguna ventaja de un apósito de glicogel en cuanto a la infección periestomal después de una semana de uso (59). Ambos estudios concluyeron que, al evitar los cambios diarios de los apósitos habituales, esta otra técnica puede ser una alternativa coste-efectiva. Los resultados se confirmaron en un ECA muy reciente en el que se utilizó un hidrogel en niños (60).

De acuerdo con las guías anteriores (61,62), la calificación de la recomendación 16 se ha elevado a una B, aunque la evidencia bibliográfica previa utilizada se ajusta más bien a un 0.

17. *Tras la curación del estoma, los apósitos pueden cambiarse una o dos veces por semana y el lugar de entrada puede limpiarse con agua potable y jabón.*

(Recomendación 14, grado 0, consenso fuerte, 90 % de acuerdo)

Comentario

Después de una semana aproximadamente (o si está bien curado), el área del estoma puede limpiarse dos veces por semana con una toalla limpia, utilizando agua fresca del grifo y jabón y secando la piel después suave y completamente. Si el orificio del estoma está bien curado, también es posible ducharse, bañarse y nadar (es aconsejable cubrir la zona con un apósito impermeable cuando se nade en piscinas públicas) al cabo de unas semanas. Para algunos pacientes puede ser aconsejable utilizar una fijación o sujeción adicional para minimizar la tracción en el lugar del estoma (53).

Una vez que el paciente es dado de alta, es importante garantizar una atención posterior competente y de alta calidad mediante una comunicación verbal clara y materiales escritos o visuales para los cuidadores y/o los pacientes. También debe señalarse a qué servicio o departamento se puede acudir en caso de urgencia (61).

18. *Como alternativa a la recomendación 14, se pueden omitir los apósitos y dejar la zona descubierta.*

(Recomendación 15, grado GPP, consenso fuerte, 92 % de acuerdo)

Comentario

Véase el comentario a la recomendación 17.

19. *Inmediatamente después de la colocación de la PEG, la placa de fijación externa debe estar sin tensión.*

(Recomendación 16, grado GPP, consenso fuerte, 93 % de acuerdo)

Comentario

Véase el comentario a la recomendación 13.

Complicaciones (Fig. 6)

Fugas

20. *En caso de fuga periestomal de contenido gástrico, la piel circundante puede protegerse adecuadamente utilizando protectores cutáneos a base de óxido de zinc.*

(Recomendación 20, grado 0, consenso fuerte, 93 % de acuerdo)

Comentario

En la primera semana tras la colocación puede producirse una pequeña salida de líquido periestomal, pero la fuga de contenido gástrico (muy a menudo en combinación con signos de infección periestomal o ensanchamiento de la gastrostomía) puede provocar problemas graves e incluso la pérdida de la sonda. Los factores de riesgo de fuga periestomal incluyen la infección de la piel, el aumento de la secreción de ácido gástrico, la gastroparesia, el aumento de la presión abdominal, el estreñimiento, la torsión lateral de la sonda, el aumento de la tensión entre el tope interno y externo, el BBS y la presencia de tejido de granuloma en el trayecto fistuloso (51,62,63). Además, los factores relacionados con el paciente pueden dificultar la cicatrización de la herida, como la diabetes, la inmunosupresión y la desnutrición.

En cualquier caso, para minimizar el daño de la piel debido a las fugas, se puede aplicar un producto tópico como un agente absorbente en polvo o una película de barrera, pasta o crema (que contenga óxido de zinc) (64). Asimismo, pueden utilizarse apósitos de espuma en vez de gasas para reducir la irritación local de la piel (la espuma separa el líquido de la piel, mientras que las gasas pueden contribuir a una mayor maceración). Las infecciones locales por hongos también pueden estar asociadas a fugas y pueden tratarse con agentes antifúngicos tópicos. Es importante verificar que la tensión entre los dos topes sea adecuada, evitando el movimiento innecesario de la sonda o la excesiva presión. La torsión lateral, que da lugar a un trayecto del estoma demasiado grande, se puede corregir estabilizando la sonda mediante un dispositivo de sujeción o cambiando a una sonda de bajo perfil (49). Si se trata de una sonda con balón como sistema de retención, el volumen del balón se debe ajustar a las recomendaciones del fabricante y comprobar regularmente (por ejemplo, una vez por semana). En el caso de una gastros-

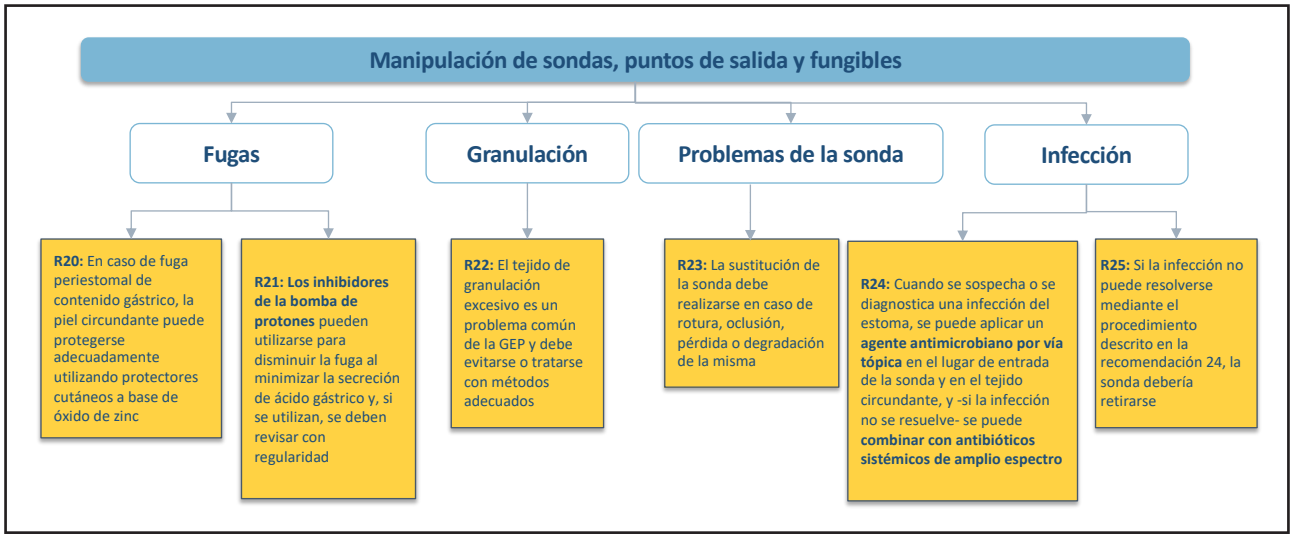

Figura 6.

Manipulación de sondas, puntos de salida y fungibles: complicaciones. GEP: gastrostomía endoscópica percutánea.

tomía de botón, hay que asegurarse de que el tamaño del globo y la longitud de la sonda son correctos (53). En algunos casos refractarios se puede intentar retirar la sonda durante 24-48 horas, lo que permitiría un ligero cierre espontáneo del trayecto, con el objetivo de que la sonda de sustitución se ajuste mejor (65). Si todas las medidas mencionadas fracasan, hay que colocar una nueva gastrostomía en una nueva ubicación.

21. *Los inhibidores de la bomba de protones pueden utilizarse para disminuir la fuga al minimizar la secreción de ácido gástrico y, si se utilizan, se deben revisar con regularidad.*

(Recomendación 21, grado 0, consenso fuerte, 96 % de acuerdo)

Comentario

La descompresión gástrica y el inicio de los inhibidores de la bomba de protones y/o los procinéticos pueden ser útiles mientras se optimiza simultáneamente el estado nutricional (por ejemplo, con el inicio de la NP) y la situación médica (66).

Granulación

22. *El tejido de granulación excesivo es un problema común de la PEG y debe evitarse o tratarse con métodos adecuados.*

(Recomendación 22, grado GPP, consenso fuerte, 93 % de acuerdo)

Comentario

El desarrollo de un exceso de tejido de granulación alrededor de la sonda de gastrostomía es una complicación común en pacientes con una sonda PEG. El tejido de granulación es vascular, por lo que sangra fácilmente y a veces es doloroso. Las causas más comunes de su desarrollo son un exceso de humedad, mucha fricción o movimiento de una sonda mal fijada y la colonización crítica, la fuga o la infección (recomendaciones 22 y 24). Se puede utilizar una película o crema de barrera para proteger la piel circundante si el tejido de granulación es exudativo. La piel afectada debería limpiarse con un antimicrobiano como mínimo una vez al día. Además, existe una gran variedad de opciones de tratamiento, como la aplicación de un agente antimicrobiano tópico bajo el dispositivo de fijación, o un apósito de espuma o de plata sobre la zona afectada que debería cambiarse solo si hay exudación significativa (pero al menos, semanalmente). Otra opción es cauterizar directamente el tejido de granulación en exceso con nitrato de plata. Como alternativa, se puede administrar una crema o pomada tópica de corticoides durante 7-10 días en combinación con un apósito de espuma. Por último, se han descrito en la literatura la resección quirúrgica y la coagulación con argón. Si los pasos anteriores resultan ineficaces, puede probarse una marca comercial diferente o un tipo alternativo de sonda de gastrostomía (38,53,67).

Problemas de la sonda

23. *La sustitución de la sonda debe realizarse en caso de rotura, oclusión, pérdida o degradación de la misma.*

(Recomendación 23, grado GPP, consenso fuerte, 93 % de acuerdo)

Comentario

La mayoría de las sondas de gastrostomía colocadas por vía transoral pueden durar muchos años. La duración de una sonda PEG se relaciona fundamentalmente con un manejo cuidadoso de la misma. No es necesario cambiar la sonda regularmente (52). En algún momento habrá que sustituirla por rotura, oclusión, pérdida de la misma o degradación (38). Un dispositivo de acceso enteral percutáneo que muestre signos de colonización fúngica con deterioro del material y compromiso de la integridad estructural debería ser sustituido de forma no urgente (37). En el caso de una sonda con tope interno, la retirada se realiza cortando la sonda a nivel de la piel abdominal y empujando el tope interno hacia la luz intestinal (técnica de "cortar y empujar") (68). La migración no suele presentar problemas, incluso en el caso de las sondas de gran calibre (69). No obstante, se recomienda la extracción endoscópica del tope interno en los casos de cirugía intestinal previa y en los pacientes con riesgo de estenosis o íleo, que podrían dificultar la migración espontánea y la eliminación del fragmento seccionado (38). La sustitución puede realizarse de muchas maneras: por vía endoscópica, radiológica, quirúrgica o a pie de cama (según el tipo de sonda de gastrostomía que se sustituya) (53). Las sondas de balón son las que se utilizan principalmente para la sustitución a ciegas a través del mismo trayecto fistuloso maduro. El balón se infla con agua estéril (no suero salino) (normalmente, de 5 a 10 ml) y se comprueba el volumen de agua cada semana para prevenir que el balón se desinfle espontáneamente por pérdida de agua. Este tipo de sonda puede necesitar su sustitución cada tres o cuatro meses debido a la degradación del balón (38,70).

Infección

24. *Cuando se sospecha o se diagnostica una infección del estoma, se puede aplicar un agente antimicrobiano por vía tópica en el lugar de entrada de la sonda y en el tejido circundante, y si la infección no se resuelve, se puede combinar con antibióticos sistémicos de amplio espectro.*

(Recomendación 24, grado 0, consenso fuerte, 93 % de acuerdo)

Comentario

La infección del estoma es una complicación común después de la colocación de la gastrostomía por vía transoral (71). Los pacientes con diabetes, obesidad, mal estado nutricional y los

que reciben tratamiento crónico con corticosteroides u otra terapia inmunosupresora tienen un mayor riesgo de infección (72). Además, la piel hiperhidratada o inflamada, debido a las fugas, puede favorecer el crecimiento de microorganismos (véanse las recomendaciones 20 y 21). La prevención consiste en un buen cuidado de la herida con técnica aséptica tras su colocación y en la detección temprana de signos y síntomas de infección, como pérdida de la integridad de la piel, eritema, exudado purulento y/o maloliente, fiebre y dolor (73). Hay que asegurarse de que el tope externo no está demasiado apretado, causando demasiada presión entre el tope interno y el externo. Se puede realizar un frotis de la zona para detectar infecciones bacterianas y fúngicas. Se puede utilizar una pomada antimicrobiana o un apósito con un agente antimicrobiano de liberación sostenida en el estoma de la gastrostomía: estos apósitos suelen obtener su actividad antimicrobiana de la plata, el yodo o el polihexametileno biguanida y están disponibles en diferentes formas (por ejemplo, espumas, hidrocoloides o alginatos). Hay que tener en cuenta las alergias a cualquiera de los componentes del producto y que los apósitos de plata no pueden usarse durante la realización de una resonancia magnética. Pueden utilizarse antibióticos sistémicos o (si se ha comprobado) agentes antifúngicos, en combinación con el tratamiento tópico local. No deben utilizarse antibióticos tópicos.

25. *Si la infección no puede resolverse mediante el procedimiento descrito en la recomendación 24, la sonda debería retirarse.*

(Recomendación 25, grado GPP, consenso, 86 % de acuerdo)

Comentario

En caso de obstrucción, de infección periestomal que persiste a pesar del tratamiento antimicrobiano adecuado, de excoriación de la piel o de una infección por hongos (especialmente si se trata de una sonda de silicona) es aconsejable retirar y/o sustituir la sonda de gastrostomía (53,73).

INICIO DE LA NED (FIG. 7)

26. *La NED puede iniciarse cuando el paciente esté médicamente estable y: a) se verifique la posición correcta de la sonda; b) se demuestre la tolerancia a la nutrición enteral prescrita (volumen y fórmula); y c) el paciente y/o quien administre la nutrición tenga los conocimientos y habilidades adecuadas para manejar la NED.*

(Recomendación 26, grado GPP, consenso fuerte, 100 % de acuerdo)

Comentario

Los pacientes hospitalizados que inician la nutrición enteral deberían recibir ya un tratamiento nutricional estable antes del alta hospitalaria. Debe confirmarse que el paciente tolera el volumen y el tipo de nutrición que se le administrará en su domicilio. Si el paciente ha ingresado para un procedimiento de un día con el fin de (re)colocar una sonda, se debe comprobar la función gastrointestinal antes del alta para garantizar la seguridad. El inicio de la NED depende del tipo y la posición de la sonda. Debe verificarse la posición correcta de todos los tipos de sonda y, si se ha realizado un procedimiento intervencionista (por ejemplo, la inserción de una gastrostomía o yeyunostomía), es necesario un periodo de observación para garantizar que no haya ninguna complicación quirúrgica. Los pacientes con NED y sus cuidadores necesitan formación en el manejo de la NE por parte de un

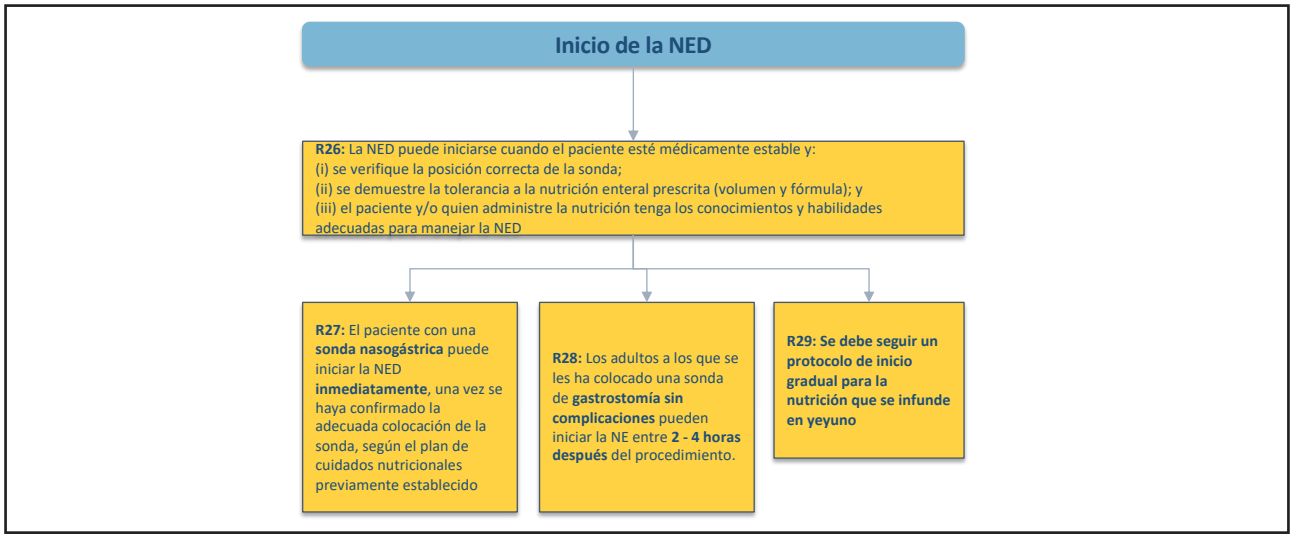

Figura 7.

Requisitos previos al inicio y calendario de la NED. NED: nutrición enteral domiciliaria; NE: nutrición enteral.

equipo multidisciplinar (74). Antes de ser dados de alta, deben ser capaces de demostrar su competencia en la administración de la nutrición, el manejo del equipo y la resolución de problemas básicos en caso de fallo de la sonda o del equipo (75).

27. El paciente con una sonda nasogástrica puede iniciar la NED inmediatamente, una vez se haya confirmado la adecuada colocación de la sonda, según el plan de cuidados nutricionales previamente establecido.

(Recomendación 27, grado GPP, consenso fuerte, 96 % de acuerdo)

Comentario

Una vez se haya confirmado la posición de la sonda nasogástrica, la NED puede comenzar o continuar según el plan de cuidados nutricionales previamente establecido. No hay evidencia de que la fórmula nutricional deba diluirse al inicio de la NED solo por motivos de dilución, a menos que se necesite líquido adicional en forma de agua (76). Cualquiera que sea el acceso por sonda que se utilice, debe tenerse precaución si se sospecha un síndrome de realimentación. En estos casos, deberían seguirse las guías adecuadas para evitar complicaciones metabólicas.

28. Los adultos a los que se les ha colocado una sonda de gastrostomía sin complicaciones pueden iniciar la NE entre dos y cuatro horas después del procedimiento.

(Recomendación 28, grado A, consenso fuerte, 100 % de acuerdo)

Comentario

Tradicionalmente, tras la inserción de la gastrostomía, la NE se iniciaba con agua o solución salina lentamente y con un incremento gradual, y posteriormente se iniciaba la fórmula enteral. Un metaanálisis reciente de ECA no mostró diferencias en cuanto a las complicaciones cuando se iniciaba en menos de cuatro horas o se iniciaba tardíamente o al día siguiente (38). No hay evidencia que apoye la administración de agua antes de comenzar la NE a través de la gastrostomía (52,77,78).

29. Se debe seguir un protocolo de inicio gradual para la nutrición que se infunde en yeyuno.

(Recomendación 29, Grado B, consenso fuerte, 93 % de acuerdo)

Comentario

Los estudios recomiendan una infusión inicial de 10 ml/h de cloruro sódico al 0,9 % en las primeras 24 horas tras la inserción de la sonda, seguida del inicio de la NE a 10 ml/h durante 24 horas y luego del aumento de la velocidad en 20 ml/h hasta que se alcance el objetivo nutricional, generalmente al sexto día (79). En un ensayo prospectivo aleatorizado realizado por Han-Geurts en 2007 se utilizó una pauta de inicio de 1,0 kcal/ml administrada en infusión continua por bomba, iniciando a 30 ml/h el primer día postoperatorio y aumentando a 84 ml/h el tercer día, según tolerancia (80). El 90 % de los pacientes toleraron esta pauta nutricional y alcanzaron completamente sus objetivos nutricionales.

Una revisión sistemática de las vías para nutrición precoz tras una esofagectomía informó de que la NE que se iniciaba en el primer día postoperatorio y se incrementaba gradualmente para satisfacer las necesidades nutricionales al tercer día era bien tolerada (81). No obstante, en algunos centros las pautas de progresión de la nutrición hacían que solo la mitad de los pacientes alcanzasen su objetivo al octavo día. Cuando no se ha realizado ningún procedimiento quirúrgico, no están bien definidas en la literatura las pautas de inicio de la nutrición yeyunal, sin embargo, dado que no hay resección del tracto gastrointestinal y posiblemente menos posibilidad de íleo, las pautas de inicio tienden a ser más liberales.

ADMINISTRACIÓN (FIG. 8)

Equipo de soporte nutricional

30. El método de administración de la NED debería ser una decisión del equipo de soporte nutricional (ESN) multidisciplinar implicado en el cuidado del paciente, teniendo en cuenta la enfermedad del mismo, el tipo de sonda, la tolerancia a la nutrición y la preferencia del paciente.

(Recomendación 30, grado GPP, consenso fuerte, 100 % de acuerdo)

Comentario

El nivel de actividad del paciente, su entorno social y sus capacidades individuales deberían tenerse en cuenta a la hora de elegir el método de administración (82). En algunas situaciones hay que tener en cuenta los costes atribuibles al tratamiento con NED, ya que podrían influir en la elección del método de administración.

Necesidad de una bomba

31. A través de una bomba se puede administrar tanto la nutrición en bolos como la infusión continua intermitente o la infusión continua, en función de la necesidad clínica, la seguridad y el nivel de precisión requerido.

(Recomendación 31, grado GPP, consenso fuerte, 92 % de acuerdo)

Comentario

El procedimiento de infusión en bolos supone dividir el volumen total de nutrición entre cuatro y seis tomas a lo largo del día. El volumen de infusión suele estar entre 200 y 400 ml administrados durante un periodo de 15 a 60 minutos, en función

de su tolerancia y las necesidades de nutrientes del paciente. Las infusiones en bolos se utilizan cuando el paciente tiene una sonda nasogástrica *in situ* o una sonda de gastrostomía. Las tomas se administran con una jeringa de 50 ml, con o sin émbolo. La nutrición en bolos en el estómago se considera la más fisiológica (83). La infusión continua de fórmula enteral suele realizarse a través de una bomba. Las bombas de nutrición enteral pueden infundir soluciones con precisión (84). El uso de una bomba de nutrición enteral permite infundir con seguridad pequeños volúmenes de solución durante periodos de tiempo variables (85). Esto se considera una ventaja en la nutrición yeyunal, ya que el yeyuno depende del suministro controlado de sustratos isotónicos. Los bolos de nutrición de fórmula hipercalórica deberían administrarse preferentemente mediante una bomba de nutrición. La infusión nocturna de la nutrición mediante una bomba permite a los pacientes estar activos durante el día para realizar trabajos/estudios y otras actividades sociales. La nutrición nocturna mediante bomba permite a los pacientes tener un sueño ininterrumpido sin necesidad de ajustar los flujos durante la noche. Las bombas de nutrición pueden ser estáticas o móviles, colocando el dispositivo en una mochila especialmente diseñada. Pueden colocarse en la espalda del paciente o acoplarse, por ejemplo, a una silla de ruedas. Las bombas de nutrición han evolucionado para ser más ligeras y más intuitivas en su manejo, lo que permite una mayor facilidad en la administración de NED por los pacientes y los cuidadores (84).

Lavado con agua

32. El lavado con agua antes y después de la nutrición de manera rutinaria puede prevenir la obstrucción de la sonda y debería formar parte de la educación del paciente/cuidador.

(Recomendación 32, grado GPP, consenso fuerte, 100 % de acuerdo)

Comentario

Independientemente de la vía de administración (gástrica o yeyunal), las sondas de nutrición son proclives a obstruirse, principalmente por la composición química de las soluciones ricas en proteínas, la viscosidad del fluido y el pequeño diámetro de la luz de la sonda. Este problema se agrava aún más cuanto más larga sea la sonda de nutrición y si se administran medicamentos a través de ella. Las sondas deberían lavarse con al menos 30 ml de agua potable antes de empezar y después de terminar la nutrición en caso de administración en bolos o cada cuatro horas si la nutrición es en infusión continua (86).

ADMINISTRACIÓN DE FÁRMACOS (FIG. 9)

33. Una sonda enteral utilizada para la NE también puede ser utilizada para la administración de fármacos si se puede confirmar la eficacia de la administración de los mismos.

(Recomendación 33, grado GPP, consenso fuerte, 92 % de acuerdo)

Comentario

La administración de medicamentos a través de sondas de nutrición enteral es una práctica muy extendida, pero una encuesta reciente realizada en Reino Unido (87) descubrió que más del 30 % de los cuidadores de pacientes que requieren la administración de medicamentos a través de sondas de nutrición enteral no recibieron información. Además, esa encuesta se llevó a cabo a través de un grupo nacional de apoyo a los pacientes, por lo que podría ser que en una población más amplia incluso menos cuidadores recibieran dicha información. Cuando se utiliza una sonda de nutrición enteral para la administración de medicamentos, es importante que la sonda no se obstruya y que quienes prescriban, suministren y administren los medicamentos sean conscientes

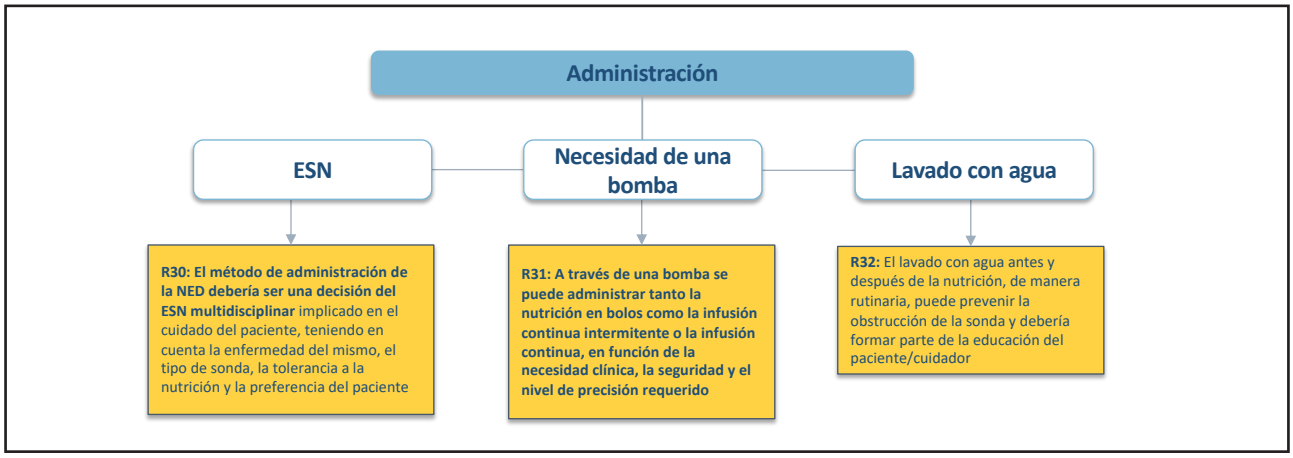

Figura 8.

Administración de la NED. NED: nutrición enteral domiciliaria; ESN: equipo de soporte nutricional.

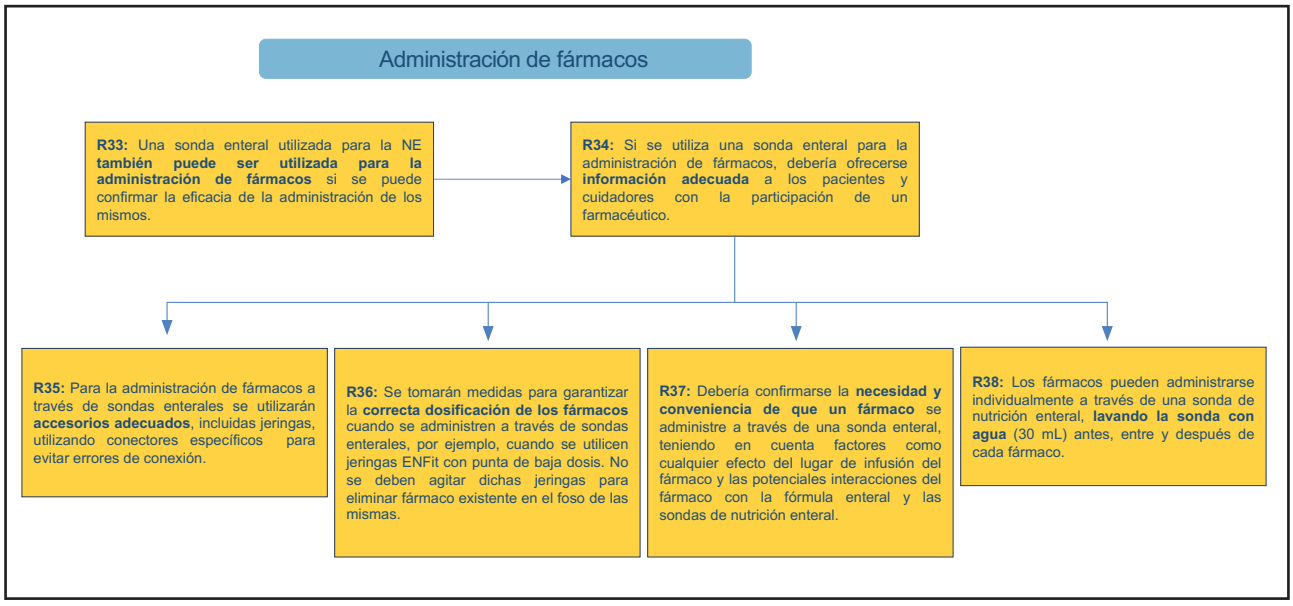

Figura 9.

Administración de fármacos a través de una sonda de nutrición. NE: nutrición enteral.

de su responsabilidad ante cualquier acontecimiento adverso derivado del uso de medicamentos no autorizados o del uso de medicamentos autorizados fuera de ficha técnica.

Debería consultarse el correspondiente resumen de las características del producto para ayudar a comprender la situación legal en relación a cada una de las prescripciones y formas farmacéuticas. El uso de un producto fuera de los términos del resumen de las características del producto conlleva una responsabilidad adicional que debería ser aceptada antes de la prescripción, suministro o administración del medicamento. Siempre que sea posible, debe evitarse triturar los medicamentos dados los riesgos potenciales de exposición al fármaco y a las imprecisiones en la dosificación del mismo. La elección de la forma de dosificación para la administración a través de una sonda de nutrición enteral también presenta consideraciones prácticas. Por ejemplo, aunque es posible que haya una incidencia generalmente mayor de oclusiones de la sonda cuando se utilizan formas farmacéuticas sólidas a través de sondas nasogástricas y GEP de silicona, hay que tener cuidado con los medicamentos líquidos, ya que pueden contener sorbitol, que se ha notificado que contribuye a la diarrea (48 % de los casos de diarrea osmótica, n = 14) (88) o a tener una osmolaridad > 500-600 mOsm/kg, lo suficientemente alta como para provocar alteraciones intestinales (73).

34. *Si se utiliza una sonda enteral para la administración de fármacos, debería ofrecerse información adecuada a los pacientes y cuidadores con la participación de un farmacéutico.*

(Recomendación 34, grado GPP, consenso fuerte, 100 % de acuerdo)

Comentario

Un farmacéutico está en una posición ideal para asesorar sobre la administración de medicamentos a través de sondas de nutrición enteral y, de hecho, en las guías nacionales se ha recomendado la participación de los farmacéuticos (73). El farmacéutico puede sugerir medicamentos alternativos u otras opciones de tratamiento del paciente cuando se le pide que asesore sobre la administración de un medicamento concreto a través de una sonda de nutrición enteral.

35. *Para la administración de fármacos a través de sondas enterales se utilizarán accesorios adecuados, incluidas jeringas, utilizando conectores específicos para evitar errores de conexión.*

(Recomendación 35, grado A, consenso fuerte, 100 % de acuerdo)

Comentario

Véase el comentario a la recomendación 36.

36. *Se tomarán medidas para garantizar la correcta dosificación de los fármacos cuando se administren a través de sondas enterales, por ejemplo, cuando se utilicen jeringas con punta de baja dosis ENFit®. No se deben agitar dichas jeringas para eliminar fármaco existente en el foso de las mismas.*

(Recomendación 36, grado GPP, consenso fuerte, 100 % de acuerdo)

Comentario

La reconocida norma ISO 80369-3 para sondas enterales (ENFit®) se ha introducido a raíz de errores de conexión, que incluían errores fatales. Esta norma exige que las sondas y los accesorios, incluidas las jeringas, tengan un diseño específico para que no puedan conectarse con sondas y accesorios destinados a la administración por una vía diferente.

Dada la preocupación por la exactitud de la administración de fármacos con las jeringas ENFit® y, en particular, con las jeringas con punta de baja dosis ENFit®, se actualizó el diseño de las jeringas de 1 ml y 3 ml para incorporar una punta de jeringa de baja dosis. Aunque la punta de baja dosis podría mejorar la precisión de la dosis, también podría dar lugar a un remanente de fármaco en el foso de la jeringa que podría alterar inadvertidamente la cantidad de fármaco administrado. Por lo tanto, se deben tomar medidas para evitar una dosificación inexacta cuando se utilicen jeringas ENFit® de baja dosis para administrar medicamentos a través de sondas enterales. Agitar una jeringa para eliminar el fármaco del foso de la jeringa expone el ambiente y a las personas al fármaco y podría afectar a la dosis administrada, por lo que, en ausencia de evidencia, no es una práctica recomendada.

37. *Debería confirmarse la necesidad y conveniencia de que un fármaco se administre a través de una sonda enteral, teniendo en cuenta factores como cualquier efecto del lugar de infusión del fármaco y las potenciales interacciones del fármaco con la fórmula enteral y las sondas de nutrición enteral.*

(Recomendación 37, grado GPP, consenso fuerte, 100 % de acuerdo)

Comentario

El lugar de la punta de la sonda enteral y, por tanto, el lugar de infusión del fármaco es un factor importante a la hora de establecer la eficacia probable del fármaco. Por ejemplo, un estudio sobre la trovafloxacina administrada en estómago mostró una eficacia similar con o sin la administración simultánea de la fórmula enteral, pero la infusión a través de una sonda directamente en el duodeno en lugar del estómago condujo a una menor disponibilidad del fármaco (89). Desgraciadamente, en esta publicación no se indica el tipo o el material de la sonda nasogástrica utilizada.

No se ha notificado ninguna diferencia entre la NE en bolos o continua en relación a la obstrucción de la sonda ($p = 0,33$) (88) cuando se utiliza una sonda de nutrición enteral para la administración de medicamentos. Sin embargo, la elección entre nutrición en bolos y continua podría afectar a la administración en la práctica de determinados medicamentos, como los que se unen a la fórmula enteral y, por tanto, algunos medicamentos administrados a través de una sonda de nutrición enteral podrían tener que ser administrados separados de la fórmula enteral. Se han notificado interacciones entre medicamentos específicos y la fórmula enteral que reducen la eficacia de los mismos, así como interacciones directas entre medicamentos y sondas de nutrición enteral. Por ejemplo, se ha reportado que la fenitoína se une directamente a la fórmula enteral, así como a las sondas de nutrición enteral de poliuretano lubricadas con polivinilpirrolidona (siendo el pH un factor importante) (90). También se ha sugerido que las PEG de poliuretano son preferibles a las de silicona cuando se considera la administración de medicamentos a través de una sonda de nutrición enteral, debido al mayor mantenimiento de la permeabilidad y la consiguiente posibilidad de seguir utilizando la sonda (88).

38. *Los fármacos pueden administrarse individualmente a través de una sonda de nutrición enteral, lavando la sonda con agua (30 ml) antes, entre y después de cada fármaco.*

(Recomendación 38, grado 0, consenso fuerte, 100 % de acuerdo)

Comentario

Está casi universalmente aceptado que los medicamentos no deben mezclarse antes de su administración a través de una sonda de nutrición enteral debido a los riesgos que conlleva, entre ellos, las interacciones farmacológicas, y que es necesario un lavado adecuado de la sonda entre la nutrición y/o los medicamentos. El uso de al menos 30 ml de agua para la irrigación cuando se administran medicamentos o cuando se lavan las sondas nasogástricas de pequeño diámetro puede reducir el número de obstrucciones de la sonda (88). Una encuesta realizada a 105 farmacéuticos belgas de la comunidad reveló que tenían un conocimiento limitado sobre la administración de medicamentos a través de sondas de nutrición enteral. Por ejemplo, menos de la mitad sabía si los medicamentos debían mezclarse o no antes de su administración (91). Otra encuesta similar (92) realizada por el mismo grupo, pero esta vez en centros residenciales belgas para personas con discapacidad intelectual, reveló que menos del 40 % del personal sabía si los medicamentos podían mezclarse antes de su administración. Además, en el mismo tipo de centro se constató que no se seguían las recomendaciones para la administración de medicamentos a través de sondas de nutrición enteral (93). En la práctica, más de dos tercios de los medicamentos preparados se mezclaban antes de su administración, y en algunos casos hasta ocho medicamentos a la vez, a pesar de que casi la mitad del total de los registros de medicación contenían al menos una interacción farmacológica (94). La administración inadecuada de medicamentos se atribuyó a factores como la falta de tiempo y unos conocimientos limitados (95).

FÓRMULAS NUTRICIONALES RECOMENDADAS PARA NED (FIG. 10)

SITUACIÓN BASAL

39. *Se puede utilizar una fórmula comercial estándar, a menos que haya una justificación específica para un triturado natural.*

(Recomendación 39, grado 0, consenso fuerte, 92 % de acuerdo)

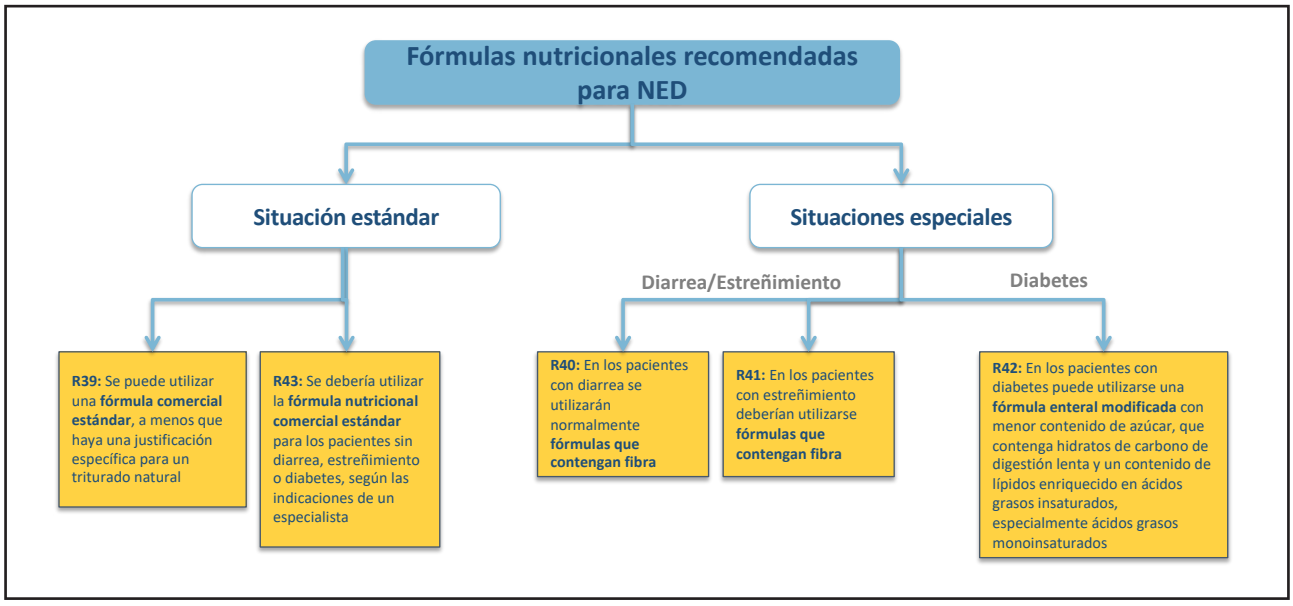

Figura 10.

Productos recomendados para NED. NED: nutrición enteral domiciliaria.

Comentario

No hay diferencias fundamentales en cuanto a los productos nutricionales preferibles en NED para pacientes que pueden tener una enfermedad benigna o maligna. Frecuentemente se han utilizado alimentos naturales a través de la sonda en lugar de fórmulas comerciales. Se ha considerado que la nutrición por sonda con alimentos naturales requiere mucho tiempo y, por lo tanto, es laboriosa, y un estudio encontró que el tiempo y los costes no nutricionales podían suponer más del 50 % del coste total de la nutrición (96). El mismo estudio también concluyó que la estandarización de los alimentos naturales por sonda era deficiente y que existía riesgo de contaminación microbiana e inestabilidad del producto. Cabe destacar que cuatro de los cinco autores de este estudio en particular estaban relacionados con empresas de nutrición enteral comercial. Sin embargo, otros también han expresado su preocupación por la mayor contaminación microbiana de los alimentos naturales en comparación con las fórmulas enterales comerciales (97,98). Además, cuando 203 pacientes polacos pasaron de la nutrición por sonda con alimentos naturales administrada en bolos de 50-100 ml entre cinco y seis veces al día a la nutrición por sonda con formula comercial administrada en bolos o en infusión continua bajo el control de un especialista, presentaron menos ingresos en el hospital y en Cuidados Intensivos, y una menor frecuencia de neumonía, infección del tracto urinario y anemia que requiriera hospitalización (99). En este estudio, además de la fórmula comercial por sonda, se proporcionó a los pacientes información sobre cuidados, lo que complica la interpretación de los resultados comunicados (99). En otro estudio, se observó durante un periodo de ocho meses, en pacientes con cáncer de cabeza y cuello, que la fórmula comercial era relativamente más beneficiosa en comparación con preparados con alimentos naturales por sonda o la dieta triturada utilizada como nutrición por sonda (100). La nutrición con triturados naturales, aunque sin un beneficio claro en comparación con la nutrición comercial, se sigue utilizando ocasionalmente en pacientes crónicos en casa, pero no en los hospitales. Si se utiliza, debería administrarse a través de una sonda grande (14 de diámetro) o una PEG para evitar que se obstruya.

40. *Se debería utilizar la formula nutricional comercial estándar para los pacientes sin diarrea, estreñimiento o diabetes, según las indicaciones de un especialista.*

(Recomendación 43, grado GPP, consenso fuerte, 96 % de acuerdo)

Comentario

Hay información más limitada sobre otras situaciones especiales, que incluyen un papel potencial de la dieta baja en yodo para nutrición enteral hecha en casa para la preparación para la exploración y el manejo del carcinoma diferenciado de tiroides (101). En un estudio de NE en pacientes con enfermedad de Crohn (que se complica porque a todos los participantes en el estudio se les administraron 200 ml de lípidos de soja al 10 % por vía intravenosa diariamente durante un periodo indeterminado), la fórmula elemental fue beneficiosa para la remisión de la enfermedad, así como para el mantenimiento de la remisión, en comparación con la fórmula elemental más tratamiento farmacológico (prednisolona o sulfasalazina), solo tratamiento farmacológico (y una dieta baja en residuos) o ninguna intervención (102). Se ha lanzado un mensaje general en relación a garantizar la

claridad por parte del prescriptor de los objetivos nutricionales si se utilizan módulos proteicos, ya que los diferentes productos no son clínicamente equivalentes para la misma cantidad de aminoácidos (103). Otros informes parecen ser actualmente menos relevantes desde el punto de vista clínico. Por ejemplo, la nutrición enteral estándar por sonda resultó beneficiosa en 14 pacientes HIV positivos con emaciación, sin grupo control (104); la suplementación de la nutrición enteral con enzimas digestivas no tuvo efectos significativos en las concentraciones totales de proteínas y albúmina en 16 ancianos residentes en un centro de cuidados (105); y la disponibilidad únicamente de información limitada sobre los intentos de modificar la microflora intestinal mediante la incorporación de fructooligosacáridos a la nutrición por sonda (106).

SITUACIONES ESPECIALES

Diarrea/estreñimiento

41. En los pacientes con diarrea se utilizarán normalmente fórmulas que contengan fibra.

(Recomendación 40, grado A, consenso fuerte, 92 % de acuerdo)

Comentario

En un estudio cruzado en el que se investigaba el efecto de la fibra en NE en diez residentes de un centro de cuidados crónicos médicamente estables, se descubrió que con la fibra casi se duplicaban tanto la frecuencia deposicional como el peso húmedo de las heces (ambos $p < 0,05$), sin diarrea (107). Cuando los residentes israelíes de centros de cuidados de larga estancia recibieron durante un periodo de ocho semanas una nutrición por sonda que contenía fibra, en lugar de una que no la contenía, se observó una reducción en la glucosa y un aumento de la albúmina y la hemoglobina, aunque las dos fórmulas tenían otras diferencias más allá de la fibra, por ejemplo, en la densidad de aminoácidos y micronutrientes (108). Además, los residentes no fueron aleatorizados a una u otra fórmula nutricional. Más recientemente, en una revisión sistemática y un metaanálisis sobre los efectos de la fórmula enteral con fibra tanto en un entorno de enfermedad aguda como de crónicos, se observaron beneficios estadísticamente significativos de la fórmula enteral que contenía fibra (especialmente, mezclas de fibra) para los pacientes con diarrea, así como una tendencia de beneficio de la fórmula enteral que contenía fibra para los pacientes con estreñimiento (109).

42. En los pacientes con estreñimiento deberían utilizarse fórmulas que contengan fibra.

(Recomendación 41, grado B, consenso fuerte, 96 % de acuerdo)

Comentario

Véase el comentario a la recomendación 41.

Diabetes

43. En los pacientes con diabetes puede utilizarse una fórmula enteral modificada con menor contenido de azúcar, que contenga hidratos de carbono de digestión lenta y un contenido de lípidos enriquecido en ácidos grasos insaturados, especialmente ácidos grasos monoinsaturados.

(Recomendación 42, grado 0, acuerdo mayoritario, 60 % de acuerdo)

Comentario

En los pacientes con diabetes se pueden utilizar formulas específicas con un menor contenido de azúcar, que son comparables a las fórmulas estándar en tolerancia (110). Por ejemplo, se observó una mejoría del control glucémico de los residentes de un centro de larga estancia con diabetes tipo 2 que recibieron una fórmula enteral con un tercio menos de energía procedente de los azúcares (111). Una limitación de este estudio (111) que ya se ha planteado previamente (110) es que no se informó de la proporción de fórmula enteral recibida por cada grupo del estudio. En otro estudio de NE específica para diabetes se observó una disminución tanto en las necesidades de insulina como en la HbA1c tras 84 días en pacientes con diabetes tipo 2 con disfagia neurológica (112). Uno de los pacientes del grupo de nutrición enteral con menos azúcar tuvo diarrea en relación a la fórmula enteral y uno de los pacientes del grupo con formula estándar tuvo una hiperglucemia grave "posiblemente relacionada con el tratamiento". Una revisión sistemática de fórmulas enterales específicas para diabetes (definidas como suplementos orales o fórmulas enterales que contienen una alta proporción [> 60 %] de lípidos, fructosa y fibra) encontró mejoría del control glucémico en comparación con la fórmula enteral estándar (113).

Para un contenido fijo de azúcar, el aumento del contenido de lípidos y proteínas de la fórmula enteral específica para diabetes puede afectar al control glucémico. Por ejemplo, en una revisión sistemática de los efectos de distintos macronutrientes sobre la glucemia posprandial, se vio que se necesitaba más insulina después de las ingestas ricas en grasas/proteínas (114).

MONITORIZACIÓN Y FINALIZACIÓN DE LA NED (FIG. 11)

¿CUÁNDO Y CÓMO DEBERÍAN SER MONITORIZADOS LOS PACIENTES CON NED? (FIG. 12)

44. Los pacientes con NED deberían ser monitorizados en relación a la eficacia y las complicaciones de la NED, lo que requiere una buena planificación y comunicación entre las personas implicadas (médicos, enfermeras, cuidadores, etc.).

(Recomendación 44, grado GPP, consenso fuerte, 96 % de acuerdo)

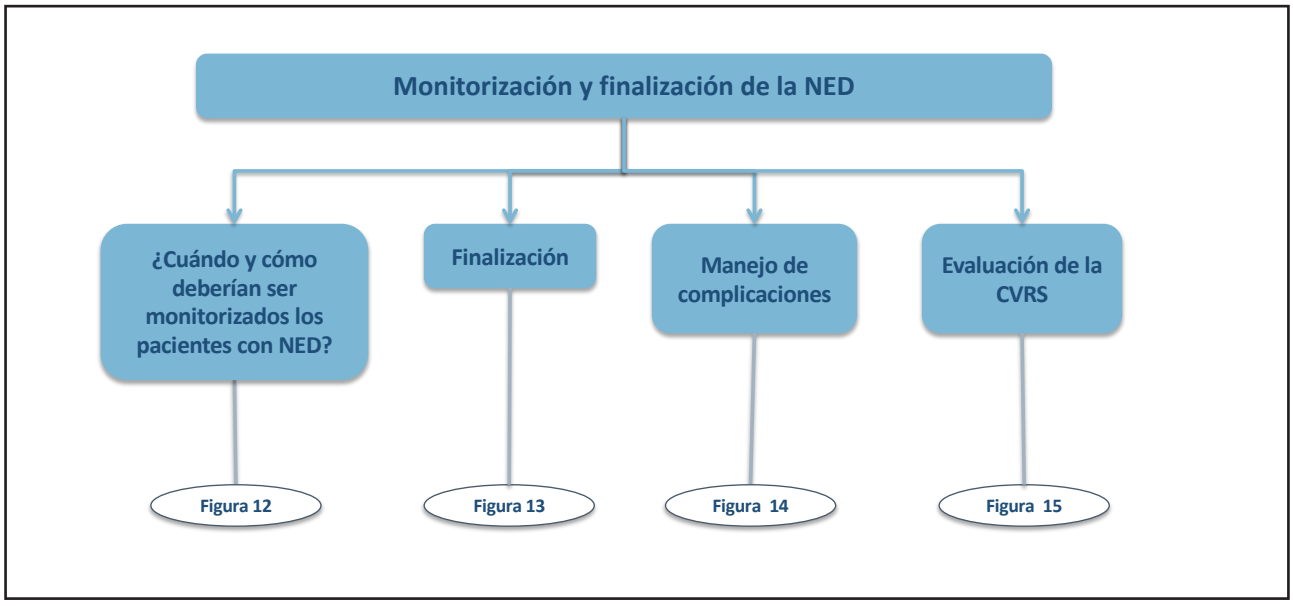

Figura 11.

Monitorización y finalización de la NED: una visión general. NED: nutrición enteral domiciliaria; CVRS: calidad de vida relacionada con la salud.

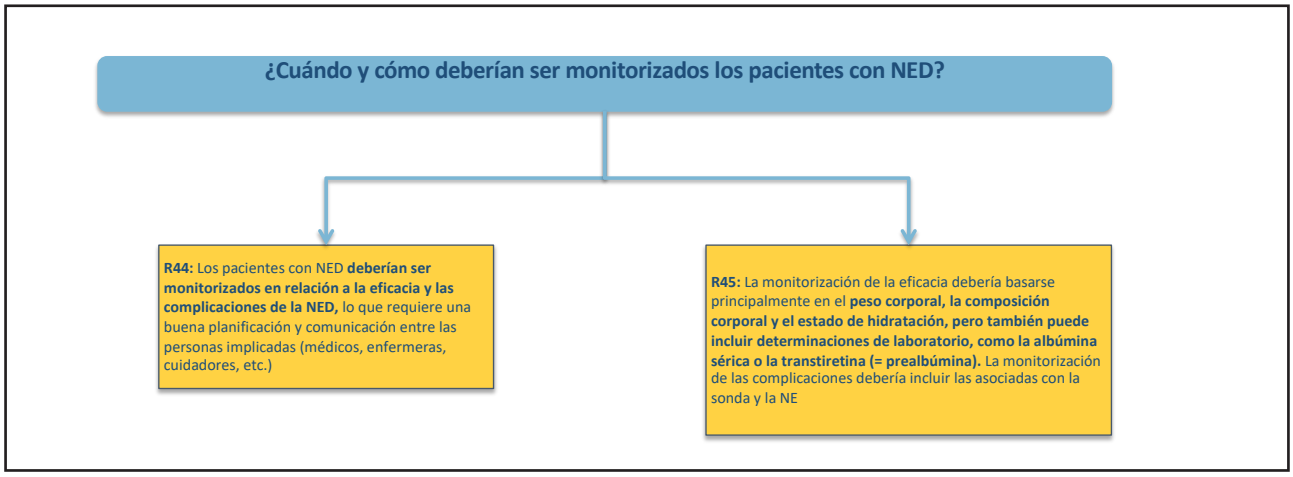

Figura 12.

Monitorización y finalización de la NED: ¿cuándo y cómo? NE: nutrición enteral; NED: nutrición enteral domiciliaria.

Comentario

La monitorización debería depender de muchos factores, relacionados con el paciente (enfermedad subyacente, estado nutricional al alta, tratamiento activo o cuidados paliativos) y relacionados con la estructura (presencia o ausencia de un equipo multidisciplinar encargado del seguimiento, legislación del país sobre la atención domiciliaria que exige la renovación de la prescripción a determinados intervalos, etc.).

Puede implicar al equipo multidisciplinar prescriptor (médico, dietista, enfermero, farmacéutico), al médico y al enfermero de Atención Primaria, a los cuidadores en domicilio, así como al propio paciente, reforzando la importancia de formar a los pacientes y/o cuidadores en el cuidado de la sonda, en temas de higiene y seguridad y en la resolución de problemas básicos.

45. *La monitorización de la eficacia debería basarse principalmente en el peso corporal, la composición corporal y el estado de hidratación, pero también puede incluir de-*

terminaciones de laboratorio, como la albúmina sérica o la transtiretina (= prealbúmina). La monitorización de las complicaciones debería incluir las asociadas con la sonda y la NE.

(Recomendación 45, grado GPP, consenso, 83 % de acuerdo)

Comentario

La monitorización se llevará a cabo en el domicilio o en el lugar donde se originó la prescripción. Puede incluir:

- Para la eficacia: peso corporal, composición corporal (masa libre de grasa o masa muscular), hidratación, fuerza y rendimiento muscular, ingesta de alimentos y transtiretina sérica (debido a una vida media mucho más corta que la de la albúmina).
- Para la tolerancia: complicaciones relacionadas con la sonda (fugas, obstrucción, desplazamiento, complicaciones locales del estoma) y tolerancia respiratoria y digestiva.

El seguimiento prospectivo sistemático de una cohorte española de 365 pacientes con NED por diversos motivos mostró, tras un promedio de 148 ± 104 (media ± DE) días, una mejoría de todos los parámetros antropométricos (peso, circunferencia del brazo) y bioquímicos (albúmina, transtiretina, transferrina, linfocitos) (18). En un estudio prospectivo de 150 pacientes de 70 ± 8 años (media ± DE) a los que se les colocó una PEG por varias enfermedades, entre los 72 que sobrevivieron al menos 60 días no hubo cambios significativos en el peso o la albúmina sérica después de cuatro meses (115). Entre los 80 pacientes que fueron aleatorizados para recibir NED complementaria, nutrición parenteral domiciliaria (NPD) o nada después de una cirugía abdominal mayor y que fueron evaluados hasta un año después del alta, hubo una disminución global del peso corporal (aunque con mantenimiento de la masa magra corporal) y un aumento de la albúmina sérica con el tiempo, sin diferencias entre los grupos (116). Un seguimiento a distancia puede resultar útil: un estudio prospectivo de 188 pacientes con NED mayores de 65 años mostró que la incorporación de una consulta telemática con el equipo del hospital a la visita mensual a domicilio permitió reducir las complicaciones metabólicas (117).

FINALIZACIÓN (FIG. 13)

46. *La NED debería finalizarse cuando se haya alcanzado el peso deseado y la ingesta oral del paciente se ajuste a sus necesidades de mantenimiento.*

(Recomendación 46, grado GPP, consenso fuerte, 92 % de acuerdo)

Comentario

Aparte de los casos de cuidados al final de la vida, hay varias situaciones en las que finalizará la NED:

- Restablecimiento de la nutrición oral.
- Complicación grave (diarrea intratable, neumonía por aspiración), que conlleva una contraindicación prolongada para la NED.
- Traslado a un centro de cuidados de larga estancia.
- Finalización de la NED indicada como nutrición trófica (síndrome del intestino corto).

La primera situación es la más frecuente. Los pacientes pueden evolucionar de la NE total a la NE complementaria y a la autonomía oral completa. Una cohorte de 417 pacientes con NED se sometió a seguimiento durante un periodo de 24 a 103 meses. La NED se había finalizado por fallecimiento en el 75,2 %, por retirada en el 32,6 % y por otros motivos en el 6,7 %; solo el 5,5 % era todavía dependiente de la NED (23). En una cohorte española se observó en 365 pacientes con NED seguidos durante 148 ± 104 días (media ± DE) que era el mismo número de pacientes (47,2 %) el que había recuperado la autonomía oral que el que seguía necesitando la NE (47,8 %) (18). Dos estudios de cohortes regionales reportaron que era mucho más frecuente la recuperación de la autonomía oral en pacientes con enfermedades digestivas que en pacientes con cáncer o enfermedades neurológicas (4,23).

La situación de los cuidados al final de la vida ha sido abordada por la reciente guía de la ESPEN sobre los aspectos éticos de la nutrición e hidratación artificial (27), en la que se dice que "en caso de que la viabilidad o eficacia de la nutrición artificial sea incierta, es aconsejable administrar el tratamiento a modo de prueba. En caso de complicaciones o si no se consigue el éxito deseado, debería suspenderse el intento".

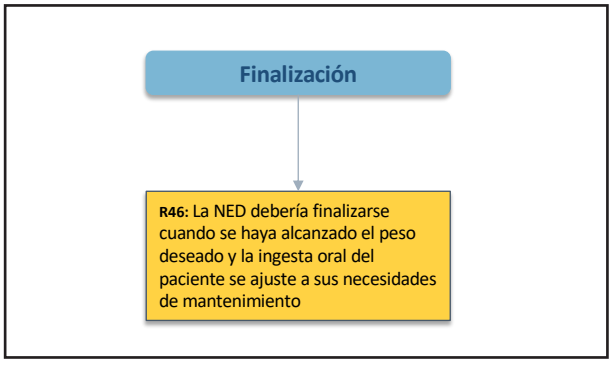

Figura 13.

Monitorización y finalización de la NED. NED: nutrición enteral domiciliaria.

MANEJO DE LAS COMPLICACIONES (FIG. 14)

47. *Para reducir las complicaciones mecánicas de la NED (obstrucción, desplazamiento) deberían utilizarse sondas percutáneas en lugar de sondas nasales para nutrición a largo plazo (al menos 4-6 semanas).*

(Recomendación 47, grado B, consenso fuerte, 98 % de acuerdo)

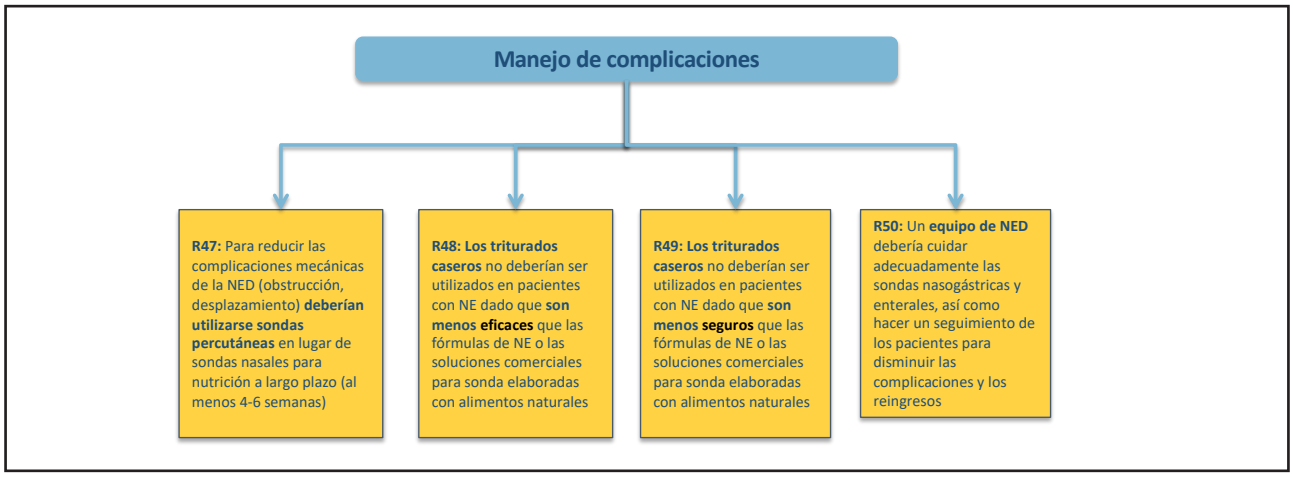

Figura 14.

Monitorización y finalización de la NED. Manejo de complicaciones. NE: nutrición enteral; NED: nutrición enteral domiciliaria.

Comentario

Las complicaciones de la NE en general se aplican a los pacientes con NED y pueden ser clasificadas como complicaciones mecánicas, aspirativas, gastrointestinales, metabólicas y del estoma. La frecuencia de estas complicaciones se ha evaluado en varios estudios retrospectivos y prospectivos que han incluido diferentes tipos de pacientes y de accesos enterales (118-121). En una revisión sistemática Cochrane, la nutrición a través de una PEG demostró una menor probabilidad de fracaso de intervención (definida como interrupción de la nutrición, obstrucción o fuga de la sonda, o falta de adherencia al tratamiento), lo que sugiere que el procedimiento endoscópico es más eficaz y seguro que la nutrición por sonda nasogástrica (121).

Las complicaciones mecánicas tales como el desplazamiento y la obstrucción de las sondas son más frecuentes en las sondas nasales, especialmente en las nasoyeyunales, que en las sondas PEG (118). En los casos de obstrucción persistente, algunos expertos, pero no todos, recomiendan la infusión con bebidas carbonatadas que contienen cola o enzimas pancreáticos para desobstruir la sonda (122). Sin embargo, esta maniobra no es recomendable por varias razones; una de ellas es que el contenido de azúcar de los refrescos aumenta el riesgo de contaminación bacteriana de la sonda. Otros recomiendan el uso de una solución de bicarbonato sódico al 8,4 % para desobstruir la sonda; sin embargo, esto tampoco es medicina basada en la evidencia. Si es necesario, y en manos expertas, se podría utilizar una guía metálica o un dispositivo comercial para desobstruir en el caso de sondas PEG (38). La aspiración puede ocurrir en pacientes que no son capaces de proteger sus vías respiratorias, especialmente los pacientes con problemas neurológicos. Se ha informado que la incidencia de aspiración alcanza el 20 % y se han estudiado varias estrategias para reducir la aspiración. Estas incluyen la elevación de la cabecera de la cama, la nutrición pospilórica (por vía nasoyeyunal, gastroyeyunostomía percutánea o PEJ) y la administración de agentes procinéticos para estimular el vaciado gástrico (38,122). Las complicaciones gastrointestinales incluyen estreñimiento, diarrea, vómitos y dolor abdominal. Estas complicaciones pueden estar causadas por la enfermedad subyacente, el tratamiento farmacológico, la fórmula enteral y el método de administración (38,122). Las complicaciones metabólicas incluyen hiperglucemia, alteraciones electrolíticas, deficiencia de micronutrientes y síndrome de realimentación (38,122). Las complicaciones del estoma son frecuentes en los pacientes con gastrostomía e incluyen exceso de tejido de granulación, fugas, infección periestomal y BBS (38,52).

48. No deberían utilizarse triturados caseros en pacientes con NE dado que son menos eficaces que las fórmulas de NE o las soluciones comerciales para sonda elaboradas con alimentos naturales.

(Recomendación 48, grado GPP, acuerdo mayoritario, 63 % de acuerdo)

Comentario

Véase el comentario a la recomendación 49.

49. No deberían utilizarse triturados caseros en pacientes con NE dado que son menos seguros que las fórmulas de NE o las soluciones comerciales para sonda elaboradas con alimentos naturales.

(Recomendación 49, grado GPP, consenso, 76 % de acuerdo)

Comentario

Las soluciones de triturados caseros son todavía populares en muchos países debido a su bajo coste en comparación con la fórmula enteral. Sin embargo, dichas soluciones no están es-

tandarizadas en cuanto a la composición de macronutrientes y micronutrientes y pueden suponer un mayor riesgo de contaminación, así como una manipulación y una administración más engorrosas (123). En un estudio observacional, el uso de una fórmula enteral y de un ESN en comparación con las soluciones de triturados mejoró el peso y disminuyó las complicaciones infecciosas, los ingresos hospitalarios y los costes, pero no tuvo ningún efecto sobre otras complicaciones (124).

Véase también la recomendación 39.

50. *Un equipo de NED debería cuidar adecuadamente las sondas nasogástricas y enterales, así como hacer un seguimiento de los pacientes para disminuir las complicaciones y los reingresos.*

(Recomendación 50, grado B, consenso fuerte, 100 % de acuerdo)

Comentario

La formación adecuada del paciente/cuidador y la continuidad de los cuidados tras el alta hospitalaria son factores clave para el éxito de la NED (125). La mayoría de las complicaciones potenciales a largo plazo dependen exclusivamente de la calidad de los cuidados posteriores de las sondas y pueden evitarse eficazmente si se toman las medidas adecuadas. En un estudio prospectivo que incluyó a 108 pacientes de edad avanzada en Italia, con un seguimiento de 12 meses, los autores constataron una baja tasa de complicaciones, la mayoría de ellas leves. La mortalidad tras el primer mes y al año fue del 7,4 % y 23,1 %, respectivamente, con una supervivencia media de 674 días, que es casi tres veces mayor que la de la literatura. Los autores atribuyen sus mejores resultados respecto a otras series de pacientes a la continuidad de los cuidados por parte del mismo equipo de nutrición (126). En una investigación cuasi experimental realizada en Taiwán con evaluaciones antes y después en 233 pacientes con nutrición por sonda nasogástrica, la intervención sistemática de enfermería, que incluía folletos educativos detallados y educación a través de vídeos, en comparación con la educación habitual mejoró significativamente los conocimientos y las habilidades de los cuidadores principales y disminuyó la incidencia de complicaciones a los tres meses (127). En ausencia de un cuidado adecuado de la gastrostomía, las tasas de reingreso hospitalario a los seis meses alcanzaban el 23 %. En un estudio prospectivo de 313 pacientes con gastrostomía seguidos por un equipo de NED, se presentaron 371 complicaciones y la mayoría se resolvieron sin hospitalización. Los reingresos hospitalarios relacionados con la gastrostomía se redujeron significativamente del 23 al 2 % ($p < 0,0001$) (128).

EVALUACIÓN DE LA CVRS (FIG. 15)

51. *Durante el tratamiento con NED, la CVRS debería medirse periódicamente.*

(Recomendación 51, grado GPP, consenso fuerte, 92 % de acuerdo)

Comentario

La CVRS es uno de los resultados relacionados con el paciente necesarios para evaluar el efecto de los tratamientos. La NED tiene un efecto considerable física, social y psicológicamente en la vida de los pacientes y sus cuidadores. El apoyo en el momento de la colocación de la sonda, y de manera regular y continua, puede ayudar a minimizar el impacto en ambos, permitiéndoles aprovechar al máximo su vida diaria, dormir mejor y disfrutar de una mayor CVRS en general (129).

La CVRS debería medirse al inicio de la NED y periódicamente durante el tratamiento para evaluar el impacto de esta intervención. En estos pacientes se ha investigado la CVRS utilizando principalmente cuestionarios genéricos, como el SF-36, el SF-12, el CVRS-BREF de la Organización Mundial de la Salud (OMS) y el EQ-5D, con un resultado inferior al de la población general. Entre los principales factores que pueden influir en la CVRS del paciente con NED se encuentran la enfermedad subyacente, la edad, el sexo y la presencia del cuidador. Además, la evaluación del cuidador puede ser útil para tener una aproximación a la

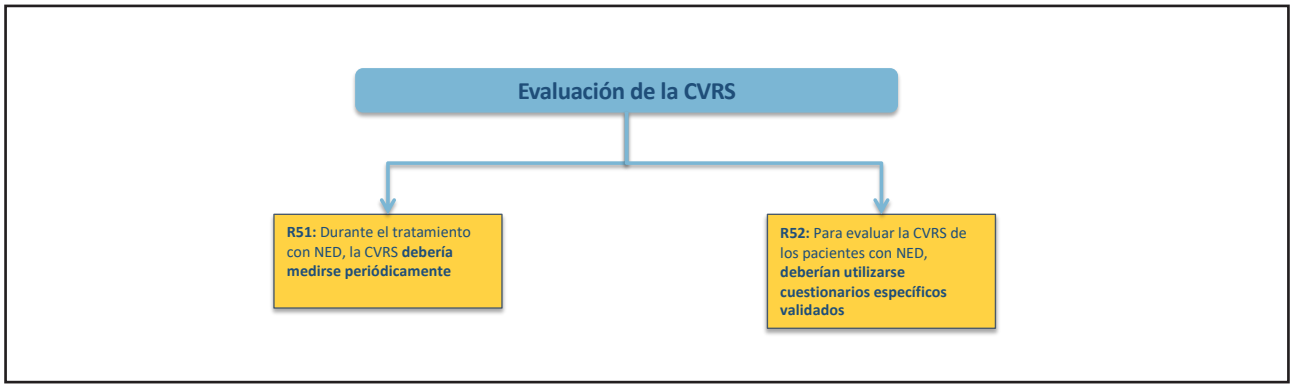

Figura 15.

Monitorización y finalización de la NED. Evaluación de la CVRS. NED: nutrición enteral domiciliaria; CVRS: calidad de vida relacionada con la salud.

percepción del paciente cuando este no tiene capacidad de comunicarse (130).

52. Para evaluar la CVRS de los pacientes con NED, deberían utilizarse cuestionarios específicos validados.
(Recomendación 52, grado GPP, consenso, 88 % de acuerdo)

Comentario

Las Medidas de Resultados Comunicadas por los Pacientes deberían desarrollarse mediante un proceso estandarizado (131). El proceso de validación de estas herramientas conlleva la medición de las siguientes propiedades psicométricas (viabilidad, fiabilidad o reproductibilidad, respuesta, determinación de la diferencia mínima clínicamente significativa y validez). Para medir la CVRS en pacientes con NED podemos utilizar cuestionarios genéricos o específicos. Las herramientas genéricas carecen de sensibilidad para reflejar los problemas de los pacientes y las diferencias en la CVRS entre subgrupos según las enfermedades o durante el seguimiento. Los cuestionarios específicos se elaboran a partir de los síntomas, limitaciones y problemas de los pacientes en su vida diaria y son más sensibles a los cambios. Para estudiar la CVRS en la NED, algunos autores han utilizado cuestionarios específicos para diferentes patologías como el IBDQ, el QOL-EF de cáncer de cabeza y cuello y el EORTC QLQ-C30 (132,133). Existen otros cuestionarios específicos para la PEG, pero con algunas limitaciones metodológicas. En un estudio multicéntrico en población española que incluyó 355 sujetos, se validó un cuestionario específico para evaluar la CVRS en pacientes con NED. Este cuestionario, NutriQoL®, consta de 17 ítems y evalúa la CVRS en dos dimensiones (rendimiento físico, actividades de la vida diaria y aspectos sociales). Este cuestionario es válido, fiable y, aunque poco sensible al cambio, parece ser útil para medir la CVRS en esta población (134,135).

REQUISITOS ESTRUCTURALES PARA REALIZAR LA NED (FIG. 16)

EDUCACIÓN Y ESN (FIG. 17)

53. Todos los profesionales sanitarios que participan directamente en la atención al paciente deben recibir educación y formación, necesaria para sus funciones, sobre los diferentes aspectos relacionados con la provisión segura de NED y la importancia de proporcionar una nutrición adecuada.
(Recomendación 55, grado B, consenso fuerte, 100 % de acuerdo)

Comentario

El número de pacientes que reciben NED ha aumentado considerablemente en los últimos años (75). Se calcula que actualmente hay más del doble de pacientes que reciben NE en la comunidad que los que la reciben en el hospital (136). La NED es una terapia compleja y debería ser monitorizada de manera próxima (136); de no ser así, se podrían producir complicaciones graves, como neumonía por aspiración, desplazamiento de la sonda, complicaciones gastrointestinales, etc. El tratamiento suele iniciarse en Atención Especializada, pero los médicos de Atención Primaria también pueden remitir pacientes para NED electiva con inserción de una sonda de nutrición de forma ambulatoria. Las sondas de gastrostomía son las vías de acceso más fáciles de manejar en la comunidad. Todos los hospitales que den de alta a pacientes con NED deberían disponer de al menos una enfermera especializada en tratamiento nutricional y una dietista (137). Estos hospitales deberían contar con una comisión de nutrición que proporcionase protocolos para una NED segura. La composición de este equipo puede variar según el entorno y las disposiciones locales, pero debería estar formado al menos por un médico, un dietista, una enfermera de soporte nutricional y,

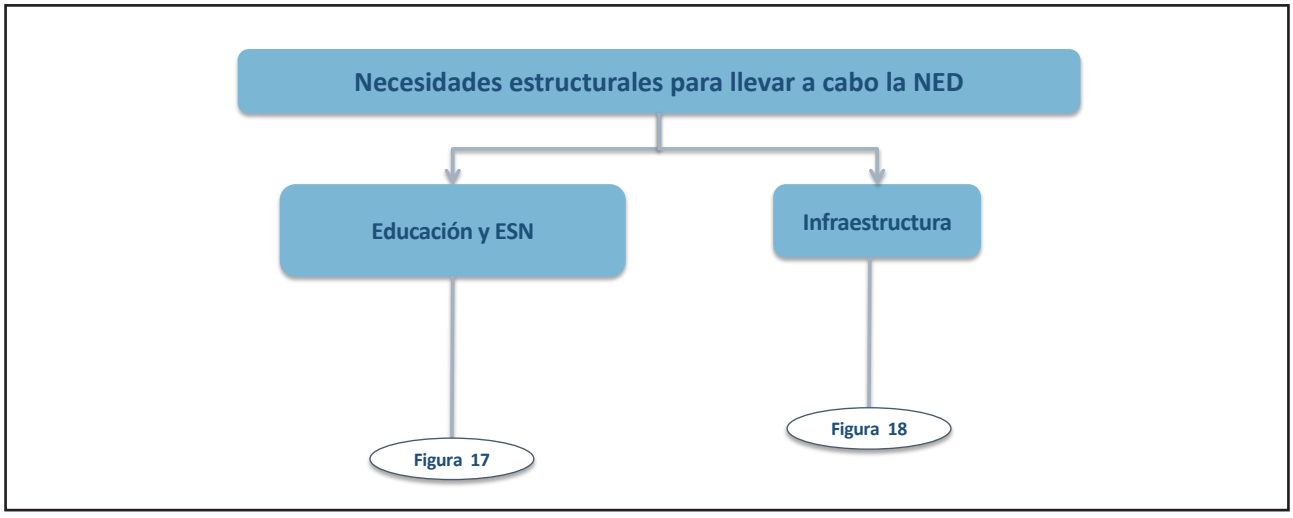

Figura 16.
Necesidades estructurales para llevar a cabo la NED: una visión general. NED: nutrición enteral domiciliaria; ESN: equipo de soporte nutricional.

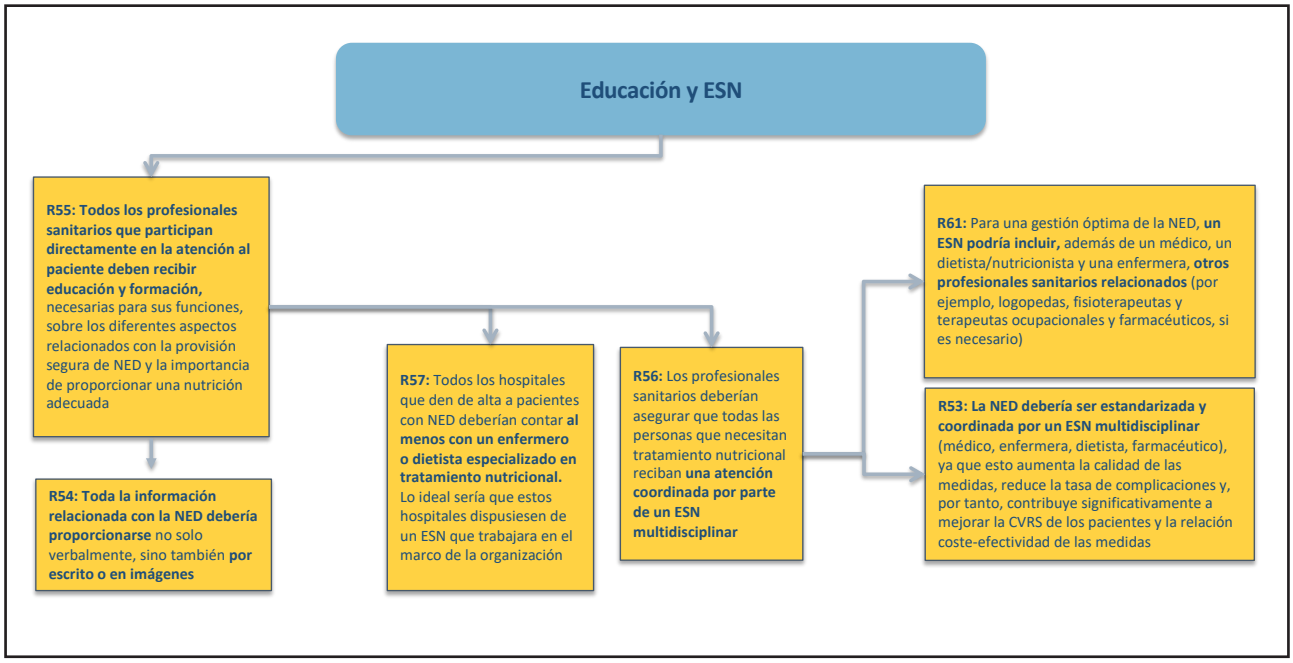

Figura 17.

Necesidades estructurales. Educación y ESN. NED: nutrición enteral domiciliaria; ESN: equipo de soporte nutricional; CVRS: calidad de vida relacionada con la salud.

si es posible, un farmacéutico y un fisioterapeuta. La estrecha colaboración con el médico de Atención Primaria es importante para el seguimiento y en caso de complicaciones. Es recomendable la intervención educativa (por ejemplo, tres cursos modulares de una semana durante seis meses) (125) para todos los profesionales sanitarios, en particular, personal médico, dietistas y enfermeras, incluidos aquellos que trabajan con personas con demencia. El efecto sobre el cuidado de los pacientes (estado nutricional, duración de la estancia en el hospital, frecuencia de las visitas del médico de Atención Primaria, complicaciones y CVRS) debería compararse con la ausencia de educación formal (129). La mayoría de los países cuentan con empresas de servicios ("proveedores de atención domiciliaria") que proporcionan a los pacientes en domicilio las fórmulas enterales, las bombas y el material fungible (138). El reembolso de los productos enterales, los fungibles y el alquiler de las bombas debería discutirse con las compañías de seguros o con el Gobierno para poder proporcionar la NED a todos los pacientes (138,139).

54. *Toda la información relacionada con la NED debería proporcionarse no solo verbalmente, sino también por escrito o en imágenes.*

(Recomendación 54, grado B, consenso fuerte, 100 % de acuerdo)

Comentario

Cada vez es mayor el número de pacientes adultos que necesitan continuar la nutrición enteral tras el alta hospitalaria (75,136). La NED hace referencia a la nutrición proporcionada en el domicilio del paciente a través de una sonda de nutrición directamente en el tracto gastrointestinal cuando un individuo no puede ingerir, masticar o tragar alimentos, pero puede digerir y absorber los nutrientes. Permite al paciente volver a su entorno familiar, en el que el propio paciente puede continuar la nutrición enteral y donde la familia, los amigos o los cuidadores profesionales pueden prestarle apoyo (84,85). La prescripción debería realizarse en el entorno hospitalario o en el domicilio. Se debería proporcionar información escrita que incluya vías de contacto en caso de que se produzcan complicaciones y/o se necesiten más aclaraciones (129,137-140).

55. *Todos los hospitales que den de alta a pacientes con NED deberían contar al menos con un enfermero o dietista especializado en tratamiento nutricional. Lo ideal sería que estos hospitales dispusiesen de un ESN que trabajara en el marco de la organización.*

(Recomendación 57, grado B, consenso fuerte, 96 % de acuerdo)

Comentario

Véase el comentario a la recomendación 53.

56. *Los profesionales sanitarios deberían asegurar que todas las personas que necesitan tratamiento nutricional reciban una atención coordinada por parte de un ESN multidisciplinar.*

(Recomendación 56, grado B, consenso fuerte, 100 % de acuerdo)

Comentario

Véase el comentario a la recomendación 53.

57. *Para una gestión óptima de la NED, un ESN podría incluir, además de un médico, un dietista/nutricionista y una enfermera, otros profesionales sanitarios relacionados (por ejemplo, logopedas, fisioterapeutas y terapeutas ocupacionales y farmacéuticos, si es necesario).*

(Recomendación 61, grado GPP, consenso fuerte, 97 % de acuerdo)

Comentario

El equipo de NED da apoyo a los pacientes que se alimentan a través de una sonda de nutrición enteral en la comunidad. Sin embargo, la organización de los servicios de apoyo al creciente número de personas que reciben NED varía según las regiones. Las guías del National Institute for Health and Care Excellencce (NICE) de Reino Unido señalan que las personas que reciben NED en la comunidad deberían "recibir el soporte de un equipo multidisciplinar coordinado" (136). Parece que un modelo de coordinación de cuidados estandarizado que incluya un equipo multidisciplinar podría mejorar los resultados y reducir los costes relacionados con la atención sanitaria. No obstante, no se dispone de datos suficientes para determinar específicamente el grado de eficacia de dicha intervención o la composición del equipo. Los beneficios de introducir en la comunidad los ESN vienen principalmente de trabajo observacional, que ha permitido contemplar beneficios (por ejemplo, las auditorías realizadas tras la introducción de control por expertos de la NED) en cuanto a reducción de costes y mejoría de los resultados. Los miembros del equipo multidisciplinar más mencionados en diferentes países fueron las enfermeras y las dietistas, mientras que también se incluyeron en la mayoría de los diferentes enfoques de un equipo multidisciplinar los médicos de Atención Primaria y médicos especialistas. En algunos casos, también se consideraron logopedas y otros trabajadores sanitarios (141).

58. *La NED debería ser estandarizada y coordinada por un ESN multidisciplinar (médico, enfermera, dietista, farmacéutico), ya que esto aumenta la calidad de las medidas, reduce la tasa de complicaciones y, por tanto, contribuye significativamente a mejorar la CVRS de los pacientes y la relación coste-efectividad de las medidas.*

(Recomendación 53, grado B, consenso fuerte, 96 % de acuerdo)

Comentario

Véase el comentario a la recomendación 54.

INFRAESTRUCTURA (FIG. 18)

59. *El entorno de los pacientes que reciben NED debería ser seguro para administrar la NE sin riesgo de complicaciones.*

(Recomendación 58, grado B, consenso fuerte, 100 % de acuerdo)

Comentario

Véase el comentario a la recomendación 53.

60. *Deberían establecerse normas de higiene para prevenir la contaminación del producto enteral y prevenir las infecciones relacionadas con la NED.*

(Recomendación 59, grado GPP, consenso fuerte, 100 % de acuerdo)

Comentario

Véase el comentario a la recomendación 53.

61. *Todos los pacientes que reciben NED deberían tener acceso a un profesional para la evaluación del procedimiento y, especialmente en caso de complicaciones y urgencias, para una intervención adecuada.*

(Recomendación 60, grado GPP, consenso fuerte, 100 % de acuerdo)

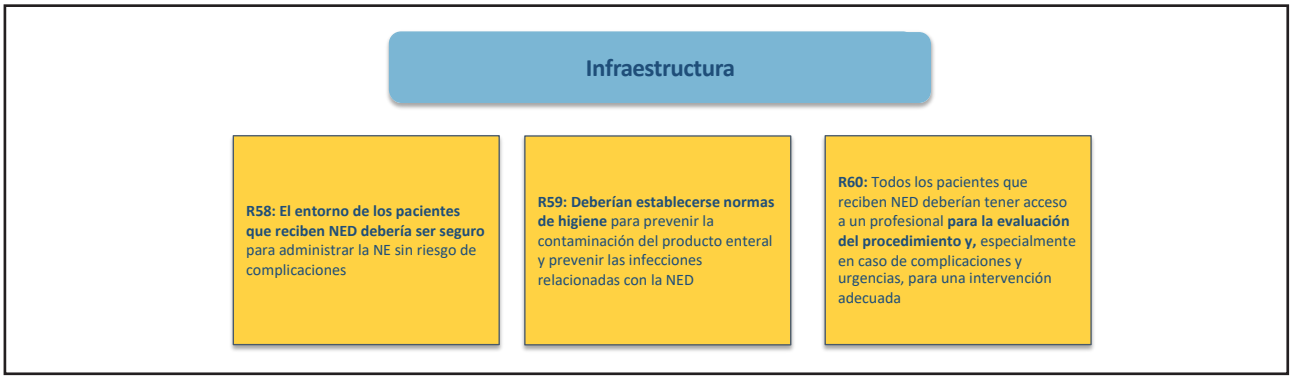

Figura 18.

Necesidades estructurales. Infraestructura. NE: nutrición enteral; NED: nutrición enteral domiciliaria.

Comentario

Véase el comentario a la recomendación 53.

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ARÁN

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Revisión sobre la experiencia en vida real de teduglutida

Review of real-life teduglutide experience

Cristina Campos-Martín[1], Cristina Tejera-Pérez[2], Nuria Virgili-Casas[3], José A. Irles-Rocamora[4]

[1]Coordinadora. Grupo de Trabajo NADYA-SENPE. Hospital Universitario Virgen Macarena. Sevilla. [2]Hospital Naval. Complejo Hospitalario Universitario de Ferrol. Ferrol, A Coruña. [3]Hospital Universitari de Bellvitge. L´Hospitalet de Llobregat, Barcelona. [4]Hospital Universitario Nuestra Señora de Valme. Sevilla

Resumen

Introducción: la teduglutida es un agonista del péptido relacionado con glucagón (aGLP2) eficaz como tratamiento de pacientes con síndrome de intestino corto (SIC) una entidad que afecta a la calidad de vida, suele precisar de nutrición parenteral domiciliaria (NPD) y genera importantes costes sanitarios. El objetivo de la presente revisión narrativa fue evaluar la experiencia en vida real reportada con teduglutida.

Métodos y resultados: en vida real un metaanálisis y estudios publicados con 440 pacientes, indican que teduglutida es efectivo pasado el periodo de adaptación intestinal posterior a la cirugía, reduciendo las necesidades de NPD y en algunos casos permite incluso suspenderla. La respuesta es heterogénea, aumenta progresivamente hasta 2 años después del inicio del tratamiento y alcanza el 82 % en algunas series. La presencia de colon en continuidad es factor predictivo negativo de respuesta precoz, pero un factor predictivo positivo para la retirada de NPD. Los efectos adversos más frecuentes son de origen gastrointestinal en las primeras etapas del tratamiento. Hay complicaciones tardías relacionadas con el estoma o con la aparición de pólipos de colon, aunque la frecuencia de estas últimas es muy baja. En adultos son escasos los datos en mejoría de calidad de vida y en coste eficacia.

Conclusiones: teduglutida es efectivo y seguro confirmándose en vida real los datos de los ensayos pivotales para tratamiento de pacientes con SIC y permite reducir o incluso suspender en algunos casos la NPD. Aunque parece coste efectivo son necesarios más estudios para identificar aquellos pacientes con mayor beneficio.

Palabras clave:

Teduglutida. Síndrome de intestino corto. Insuficiencia intestinal. Nutrición parenteral en domicilio.

Abstract

Background: teduglutide is an agonist of glucagon-related peptide (aGLP2) effective as a treatment for patients with short bowel syndrome (SBS), an entity that affects quality of life, usually requires home parenteral nutrition (HPN) and generates significant health costs. The objective of the present narrative review was to assess the real-life experience reported with teduglutide.

Methods and results: in real life, one meta-analysis and studies published with 440 patients indicate that Teduglutide is effective after the period of intestinal adaptation after surgery, reducing the need for HPN and in some cases even allowing it to be suspended. The response is heterogeneous, increasing progressively up to 2 years after the start of treatment and reaching 82 % in some series. The presence of colon in continuity is a negative predictor of early response, but a positive predictive factor for the withdrawal of HPN. The most common side effects are gastrointestinal in the early stages of treatment. There are late complications related to the stoma or the occurrence of colon polyps, although the frequency of the latter is very low. In adults, data on improved quality of life and cost-effectiveness are scarce.

Conclusions: teduglutide is effective and safe and data from pivotal trials for the treatment of patients with SBS are confirmed in real life and can reduce or even stop HPN in some cases. Although it seems cost-effective, more studies are needed to identify those patients with the greatest benefit.

Keywords:

Teduglutide. Short bowel syndrome. Intestinal failure. Parenteral nutrition home.

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Correspondencia:

José Antonio Irles Rocamora. Hospital Universitario Nuestra Señora de Valme. Avda. Bellavista, s/n. 41014 Sevilla

e- mail: irles irles@us.es

INTRODUCCIÓN

El síndrome de intestino corto (SIC) se produce como resultado de la pérdida de segmentos de intestino por resecciones quirúrgicas extensas debidas a isquemia, enfermedad inflamatoria, enteritis rádica, traumatismo o tumores, y es la causa más frecuente del fallo intestinal crónico. Se trata de una entidad compleja en la que la reducción de la absorción de nutrientes, electrolitos y agua, requiere de la administración intravenosa de los mismos, e incluso la necesidad de soporte con nutrición parenteral domiciliaria (NPD) para mantener la salud (1).

La prevalencia de SIC en España se estima en 4,18 pacientes por millón de habitantes/año (2). El uso de NPD varía entre países europeos, desde 12,7 / millón de habitantes en Dinamarca a 4,2 / millón de habitantes en España. No existen datos precisos, pero se estima que el 50 % de pacientes con SIC requieren NPD de forma permanente y aunque esta técnica permite la supervivencia durante décadas no está exenta de complicaciones a largo plazo como: alteraciones electrolíticas, sepsis o trombosis por catéter, enfermedad hepática y ósea, entre otros. Por otra parte, además de afectar a la calidad de vida, genera importantes costes sanitarios (3).

Aunque existen tratamientos farmacológicos para el SIC con el objeto de mejorar el control de síntomas o favorecer la adaptación intestinal, ninguno ha sido efectivo a largo plazo. Teduglutida es el primer tratamiento aprobado a largo plazo para adultos y niños con SIC tanto en Estados Unidos como en Europa, pero tiene la categoría de medicamento huérfano. En España está registrado y autorizado como uso compasivo desde 2017 y está indicado para el tratamiento del SIC en situación estable tras el periodo de adaptación intestinal posterior a la cirugía (1). Existe un registro en España, y un registro europeo, pero aún no hay datos publicados.

Teduglutida es un análogo de péptido similar al glucagón 2 (GLP-2) secretado por las células L intestinales, que determina un efecto de hipertrofia en la mucosa intestinal, reduce la secreción de ácido gástrico, retrasa el vaciado gástrico, estimula el flujo sanguíneo intestinal y contrarresta los estímulos inflamatorios. De este modo produce un aumento global de la capacidad de absorción intestinal reduciendo las necesidades de NPD, considerándose criterio de respuesta la reducción de NPD ≥ 20 % y en algunos casos permite incluso suspenderla (4-6). Los datos de un metaanálisis en adultos (7) muestran una tasa de respuesta de hasta el 82 % en tratamientos de duración superior a 2 años; y por otro lado, la tasa de destete de NPD alcanza el 21 % en más de 2 años.

Aunque costoso en términos económicos se considera que es un tratamiento coste eficaz. Según un estudio en EE. UU. la teduglutida no cumple con el umbral tradicional de los estudios de coste efectividad, si se compara con el coste la NPD, pero en subpoblaciones que demuestran el máximo beneficio, podría ser coste efectivo, y su falta de uso total podría conducir a pérdidas económicas (8). Según el estudio de coste-efectividad realizado por NICE 2022 es poco probable que el ICER para niños estuviera por encima £ 20 000 por QALY ganado y es muy poco probable que supere los £ 30 000 por QALY ganado, por lo que recomienda el tratamiento para niños, pero no así en adultos en los que el comité no puede hacer una recomendación para la teduglutida, y solicita un análisis más detallado debido a que existen incertidumbres en cuanto la estimación y puede haber beneficios que no hayan sido captados por los estudios de coste efectividad actuales (9). En España el coste de tratamiento por año, tanto en adultos como en niños asciende a 111.383,4 €, pero en este cálculo solo se ha incluido el coste del medicamento, y no se han analizado las complicaciones que evita (10).

Estudios previos han demostrado (4-6) que la respuesta a teduglutida es muy heterogénea, muy probablemente debido a las diferencias en la etiología del SIC, la anatomía intestinal y el volumen de NPD pretratamiento. Sin embargo, en la práctica clínica habitual la experiencia clínica reportada es escasa y no se conocen bien los efectos adversos, y el grado de respuesta terapéutica.

El objetivo de la presente revisión narrativa fue evaluar la experiencia en vida real reportada con teduglutida en términos de seguridad y eficacia, analizándose también los posibles factores predictores de respuesta y los resultados en términos de calidad de vida.

MATERIAL Y MÉTODOS

El proceso de búsqueda bibliográfica y la selección de estudios estuvo a cargo de tres revisores independientes. Las disparidades se resolvieron por consenso. Se consultaron las siguientes bases de datos electrónicas hasta el 1 abril 2023: PubMed/Medline, biblioteca Cochrane y Scielo. La estrategia de búsqueda se realizó utilizando una combinación de términos de búsqueda relevantes específicos de la base de datos para identificar estudios pertinentes sobre la eficacia y seguridad de pacientes adultos con SIC. Se emplearon palabras clave (MeSH) así como los términos de búsqueda de texto libre. El término "teduglutida" se combinó con otras palabras clave como intestino corto, insuficiencia intestinal, nutrición parenteral en domicilio, soporte parenteral, complicaciones y cáncer. Se identificaron 71 publicaciones de las cuales se seleccionaron 27, la mayoría de adultos y solo 3 de niños. En lo que se refiere al diseño de los estudios evaluados fueron un metaanálisis, 3 RCT, 7 estudios de cohorte, y del resto de estudios clínicos la mayoría fueron series de casos. También se incluyó una base datos amplia.

SELECCIÓN DE CANDIDATOS Y NÚMERO DE PACIENTES TRATADOS

Si bien en todos los trabajos publicados los pacientes comparten la característica común de presentar SIC, existen peculiaridades según cada estudio. A la hora de plantear el tratamiento con teduglutida, el candidato ideal es aquel que cumple los siguientes ítems: a) paciente estable desde el punto de vista clínico, con enfermedad de base no obstructiva ni de carácter

maligno; b) realizar un tratamiento optimizado desde el punto de vista dietético y farmacológico y que pese a ello precise soporte de NP/fluidoterapia; c) paciente optimizado tanto a nivel nutricional como a nivel hidroelectrolítico; d) predispuesto a reducir/suspender la NP/fluidoterapia; y e) compromiso de administración diaria subcutánea de teduglutida (5,6,11).

En la tabla I, se resumen las características de los pacientes que han participado en los estudios con teduglutida procedentes de bases de datos en vida real o bien extensión de ensayos clínicos a largo plazo y en práctica clínica diaria. La dosis empleada de teduglutida fue, la señalada en ficha técnica de 0,05 mg/kg/día. Se trata de 8 estudios de cohorte (5,12-18), que en total suman 440 pacientes.

En población pediátrica, los datos publicados proceden del análisis de los ensayos clínicos en este subgrupo (19). En total, se han reportado datos de 89 pacientes con una media de exposición al tratamiento de 51,7 semanas rango (5-94). Su edad media fue de 5,6 años y la causa más frecuente de SIC fue la gastrosquisis (33,7 %), seguida de vólvulo (28,1 %) y enterocolitis necrotizante (16,9 %). La longitud media de intestino remanente fue de 45,9 cm y conservaban válvula ileocecal en el 25,6 % de los casos. La mayor parte de los pacientes presentaban colon remanente (92,1 %). Los participantes recibían de media 62,7 mL/kg/día de soporte parenteral (media 45,1 kcal/kg/día).

Ramos y cols. (20) han presentado la experiencia en España de 17 pacientes pediátricos que recibieron teduglutida, analizados a los 12 meses de tratamiento. Los participantes recibían de media 55 mL/kg/día de soporte parenteral (media 33 kcal/kg/día). La causa más frecuente de SIC en esta población fue la enterocolitis necrotizante (35 %) y todos los participantes presentaban SIC desde la etapa neonatal. La media de intestino remanente fue de 52 cm. No tenían colon remanente en 3 casos mientras que en el resto conservaba o bien colon total o bien al menos una parte. Tres pacientes conservaban válvula ileocecal.

FACTORES PREDICTORES DE RESPUESTA

Desde las primeras experiencias con teduglutida se ha buscado cuáles son las características del paciente que podrían predecir una mejor respuesta al mismo (4,6,11). Pese a su elevado coste ha demostrado ser un fármaco coste-eficiente (8) y capaz de mejorar notablemente la calidad de vida de los pacientes con SIC (18,21,22).

A partir de los datos *post hoc* del ensayo pivotal fase III de teduglutida (4) los pacientes que obtuvieron mejor respuesta fueron aquellos con unos mayores requerimientos basales de volumen, con yeyuno o ileostomía y que presentaban una enfermedad inflamatoria intestinal de base. En cambio, el efecto fue menor en participantes con más del 50 % del colon en continuidad sin colostomía y en participantes con menos del 50 % colon remanente o colostomía.

En vida real, a mayor duración de la exposición al tratamiento con teduglutida, mejor es la respuesta, si bien esta, puede ser tanto precoz como tardía, lo cual sugiere esperar un tiempo prudencial hasta ver el efecto clínico antes de suspender el tratamiento por falta de eficacia (5). De hecho, se han observado mejores tasas de respuesta de tratamiento y destete cuando el tratamiento supera el año de duración (7).

También, en los datos en práctica clínica habitual, la presencia de colon en continuidad redujo la tasa de respuesta a teduglutida mientras que en su ausencia, esta probabilidad de respuesta mejora (5,12-16). También se han descrito tasas de respuesta superiores en caso de mayores necesidades basales de volumen aportado de soporte parenteral, mayor duración del tiempo de dependencia de este soporte, pacientes con yeyunostomía o ileostomía (5,12-16). No se ha descrito una mejor tasa de respuesta en función de la enfermedad de base, si bien existe una tendencia no significativa a mejor respuesta y mayor probabilidad de destete en pacientes con enfermedad de Crohn (5,12-16). Se ha descrito con teduglutida un aumento significativo del grosor de la pared del intestino delgado de forma precoz de 4,5 mm de media, demostrado por pruebas de imagen, y el incremento de ese grosor se relacionó con una mejor respuesta clínica (23).

En población pediátrica, si bien en vida real, los efectos beneficiosos de teduglutida superan a los descritos en adultos (20), no se han podido definir claramente factores predictores de respuesta debido a la heterogeneidad de los pacientes.

COMPLICACIONES

Las reacciones adversas que han definido el perfil de seguridad de teduglutida se observaron a partir de 4 estudios pivotales, dos ensayos clínicos aleatorizados (ECA) en fase III, controlados con placebo; estos fueron los estudios STEPS y CL0600-004, en pacientes con SIC y dependientes de soporte parenteral; y sus respectivos estudios de extensión abiertos STEPS-2 y CL0600-005. Fueron realizados entre mayo de 2004 y enero de 2013 y fueron un total de 173 pacientes los que recibieron teduglutida en los estudios iniciales y/o los de extensión (11).

En cuanto a los dos primeros estudios, se llevaron a cabo con 109 pacientes tratados con dosis de 0,05 y 0,10 mg/kg/día, durante un máximo de 24 semanas; de ellos, 77 pacientes recibieron 0,05 mg/kg/día y 32 recibieron 0,10 mg/kg/día; 59 pacientes conformaron el grupo placebo. Posteriormente estos pacientes tuvieron la oportunidad de entrar en los mencionados estudios de extensión, en los que participaron 153 pacientes. Durante el STEPS-2, los 88 pacientes recibieron durante un máximo de 2 años 0,05 mg/kg/día: 37 que habían recibido el mismo tratamiento en STEPS, 39 que habían recibido placebo y 12 testados previamente pero no aleatorizados en STEPS. En CL0600-005 los pacientes que recibieron teduglutida en el estudio previo siguieron con la misma dosis: 25 con 0,05 y 27 con 0,10 mg/kg/día; 13 que habían recibido placebo fueron aleatorizados para 0,05 ($n = 6$) y 0,10 mg/kg/día ($n = 7$), hasta 28 semanas. Por todo ello, hubo 173 pacientes que recibieron teduglutida en los estudios iniciales y/o los de extensión; el tiempo medio de tratamiento de estos pacientes fue de 66,9 semanas (0,6-143,3) y de ellos 107 fueron tratados durante al menos 48 semanas.

Tabla I. Características de los pacientes participantes en estudios en vida real/extensión de ensayos clínicos a largo plazo con teduglutida

Autor/año/ Ref.	Diseño estudio	*n* =	Duración	Sexo (% hombres)	Edad (años)	Etiología SIC (EC, V, otras)	ID Remanente (cm)	% colon continuidad	Volumen parenteral (L/semana)	Años NP
Schwar 2016 (5)	CP	88	24 m	46,6	50,9	12,8/33/48,8	50	61,4	12,2	6,4
Pevny 2018 (12)	CR	27	45 sem	48,1	51	14,8/44,4/40,8	74	77,8	13,7	4,3
Schoele 2018 (13)	CP	14	48 sem	35,7	50,5	50/35,7/14,3	50	64,3	12,2	5,2
Jolly 2020 (14)	CR	54	24 sem	64,8	52,3	29,6/38,9/31,5	62	64,8	11,2	9,8
Puello 2021 (15)	CR	18	60 m	44,4	54,4	55,6/16,7/27,7	100	50	9,9	3,3
Solar 2021 (16)	CP	17	5 a y 9 m	52,9	40,2	0/47,1/52,9	38	94,1	12,1	6,5
Greif 2022 (18)	CR	52	> 12 m	42	49	40/31/29	80	58	13,4	2
Loufty 2022 (17)	Base datos	170	ND	29,4	45-69*	41,2/52,9/5,9	ND	58,8 %	ND	ND

*SIC: síndrome intestino corto; NP: nutrición parenteral; ID intestino delgado; EC: enfermedad de Crohn; V: vascular; ND: no disponible. *La mayoría con edad entre 45-69 a.; CP: cohorte prospectiva; CR: cohorte retrospectiva.*

Los eventos adversos se clasificaron en: leves si no interfirieron con actividad diaria, no necesitaron tratamiento y fueron transitorios (menos de 48 horas); moderados si interfirieron con la actividad diaria y necesitaron tratamientos sencillos; y severos si necesitaron una intervención terapéutica importante. Asimismo, se distinguió entre eventos adversos derivados del tratamiento (EADT) y los eventos adversos serios derivados del tratamiento (EASDT): aquellos que comportan un riesgo vital, discapacidad permanente o significativa, requieren hospitalización o necesitan intervención médica o quirúrgica para evitar una mala evolución. En cuanto a la frecuencia, se han clasificado en muy frecuentes > 1/10, frecuentes > 1/10 a < 1/100, poco frecuentes > 1/1000 a < 1/100 y de frecuencia no conocida.

El número total de eventos adversos registrados fue: 778 EADT y 80 EASDT en el grupo ECA/teduglutida de los dos estudios iniciales; 2235 EADT y 259 EASDT en el grupo ECA/extensión teduglutida, 372 EADT y 34 EASDT en el grupo ECA/placebo. En la tabla II se describen los eventos adversos para cada estudio.

Los EADT más frecuentes en el grupo de los 173 pacientes que recibieron teduglutida en los estudios iniciales y/o los de extensión fueron: complicaciones del estoma en el 45,6 % de los participantes con estoma ($n = 68$); dolor abdominal en el 41,6 %, infección del tracto respiratorio superior 28,9 %, náuseas en el 26,6 %, cefalea y astenia en el 20,2 %. Los eventos adversos más frecuentes en el grupo con teduglutida con respecto a los del grupo placebo fueron el dolor abdominal, las complicaciones relacionadas con el estoma, las infecciones respiratorias y la distensión abdominal.

Los efectos adversos también difirieron según la duración del tratamiento. Los trastornos gastrointestinales fueron más frecuentes en las primeras 12-24 semanas, mientras que los efectos adversos relacionados con el catéter, pérdida de peso, astenia e infecciones del tracto urinario se presentaron con mayor frecuencia a partir de las 48 semanas de tratamiento. En el estudio STEPS-3 (6), con 14 pacientes procedentes del STEPS-2 (5) 5 de ellos del grupo con teduglutida desde el STEPS (4) y 14 no aleatorizados o con placebo previo, con tratamiento total entre 36 y 42 meses, los eventos adversos más frecuentes fueron astenia y diarrea, entre leve y moderada.

Los trastornos gastrointestinales en el grupo ECA/extensión ocurrieron con mayor frecuencia en pacientes con enfermedad inflamatoria intestinal como causa de SIC, y en las primeras semanas del tratamiento, más que en los pacientes con SIC por causas vasculares. Según el tipo anatómico de intestino corto, los pacientes con SIC de tipo I (intestino delgado remanente con estoma y sin colon en continuidad) tendieron a comunicar mayor número de trastornos gastrointestinales (84,2 %), comparados con los pacientes de grupo 2 (colon remanente sin estoma y con colon en continuidad) y el grupo 3 (colon remanente o colostomía), 58,4 % y 70,4 % respectivamente. En la tabla III se detallan estos eventos adversos.

Por otra parte, los síntomas gastrointestinales son esperables en el contexto del SIC y además de poder explicarse con el mecanismo de acción del análogo de GLP-2, asimismo se han relacionado con el empleo de opiáceos como moduladores de la motilidad intestinal que muchos de estos pacientes incluidos en los estudios tenían en su tratamiento (24).

Tabla II. Eventos adversos en función de su gravedad en los estudios de extensión (modificado de UF Pape 2020)

	Grupo ECA teduglutida *n* = 109 *n* (%)	**Grupo ECA/extensión teduglutida *n* = 173 *n* (%)**	**Grupo ECA placebo *n* = 59 *n* (%)**
Cualquier EADT	99 (90,8)	167 (96,5)	49 (831)
Gravedad de EADT			
EADT leve	84 (77,1)	151 (87,3)	45 (76,3)
EADT moderado	74 (67,9)	140 (80,0)	34 (57,6)
EADT grave	31 (28,4)	83 (48,0)	16 (27,1)
Cualquier EASDT	39 (35,8)	101 (58,4)	17 (28,8)
Gravedad de cualquier EASDT			
EASDT leve	13 (11,9)	29 (16,8)	5 (8,5)
EASDT moderado	18 (16,5)	59 (34,1)	7 (11,9)
EASDT grave	16 (14,7)	56 (32,4)	8 (13,6)
EADT con discontinuación de tratamiento	10 (9,2)	34 (19,7)	4 (6,8)
EADT éxitus	0	3(1,7)	0

EADT: eventos adversos derivados del tratamiento; EASDT: eventos adversos serios derivados del tratamiento; ECA: ensayo clínico aleatorizado.

Tabla III. Eventos adversos más frecuentes en estudios en vida real/extensión de ensayos clínicos a largo plazo con teduglutida

	Grupo ECA teduglutida *n* = 109 *n* (%)	**Grupo ECA/ extensión teduglutida *n* = 173 *n* (%)**	**Grupo ECA placebo *n* = 59 *n* (%)**	**Loufty *n* = 170**
Trastornos gastrointestinales				
Complicación estoma	17 (37,8)	31 (45,6)	3 (13,6)	20 (11,8)
Dolor abdominal	42 (38,5)	72 (41,6)	16 (27,1)	70 (41,2)
Náuseas	29 (26,6)	46 (26,6)	12 (20,3)	40 (23,5)
Distensión abdominal	18 (16,5)	32 (18,5)	1 (1,7)	ND
Vómitos	15 (13,8)	26 (15,0)	6 (10,2)	ND
Diarrea	7 (6,4)	24 (13,9)	7 (11,9)	ND
Obstrucción intestinal	6 (5,5)	12 (6,9)	0	30 (17,6)
Trastornos infecciosos				
Infecciones tracto respiratorio superior	30 (27,5)	50 (28,9)	8 (13,6)	ND
Sepsis relacionada con catéter	9 (8,3)	29 (16,8)	8 (13,6)	20 (12 %)
Trastornos generales				
Cefalea	18 (16,5)	35 (20,2)	9 (15,3)	ND
Astenia	14 (12,8)	35 (20,2)	7 (11,9)	ND
Fiebre	10 (9,2)	29 (16,8)	7 (11,9)	ND
Pérdida de peso	2 (1,8)	26 (15,0)	6 (10,2)	ND
Sobrecarga de volumen	11 (10,1)	23 (13,3)	4 (6,8)	ND
Reacción en sitio de inyección	22 (20,2)	33 (19,1)	7 (11,9)	ND

En cuanto a los eventos adversos serios relacionados con el tratamiento (EASDT) ocurrieron en los tres grupos, siendo más frecuentes en el grupo ECA/extensión teduglutida (58,4 %). Los principales fueron: sepsis relacionada con el catéter, que ocurrió en los tres grupos pero con frecuencia similar en el grupo ECA teduglutida y el grupo ECA placebo (13,8 % y 15,3 %) y en un 24 % del grupo ECA/extensión. Le siguieron: estenosis gastrointestinal y obstrucción, trastornos biliares y complicaciones del estoma, 4,6 %, 4,6 % y 4,4 % en el grupo ECA/extensión, menor frecuencia en el grupo ECA teduglutida y ningún episodio en el grupo placebo. Los EADT que causaron discontinuación del tratamiento en más pacientes fueron el dolor abdominal (4,6 %) y las complicaciones del estoma (4,4 %). Suspendieron el tratamiento por efectos adversos el 9,2 % de pacientes del grupo ECA/teduglutida y el 19,7 % en el grupo ECA/extensión.

En el grupo ECA/extensión se detectaron en 50 pacientes que se realizaron colonoscopia 7 pólipos de nueva aparición: pólipos colónicos en 3 pacientes, pólipos rectales en 2 y pólipo duodenal en 1 paciente, y un pólipo intestinal en 1 paciente del grupo placebo que provocó la discontinuación del estudio, ninguno displásico o maligno. En otra cohorte de 170 pacientes a los cuales se les había prescrito teduglutida, se detectó un 5,9 % de pólipos colónicos posteriormente al inicio del tratamiento (17). Tres pacientes fueron diagnosticados de neoplasia durante STEPS-2, 1 de ellos de adenocarcinoma metastásico en hígado (considerado relacionado con el tratamiento) y 2 de neoplasia pulmonar de células no pequeñas no considerados relacionados con el tratamiento; los 2 primeros fueron éxitus. Otro paciente falleció durante STEPS-2 por sepsis relacionada con el catéter e infección del tracto urinario, este evento se consideró no relacionado con el tratamiento.

Se detectó el desarrollo de anticuerpos frente a teduglutida en los pacientes incluidos en STEPS-2 (5), sobre todo en el grupo que había recibido el fármaco desde el inicio del estudio previo; fueron el 49 % (n = 18/37) en el mes 30. También se detectó aumento asintomático de la proteína C reactiva, con valores promedio de 25 mg/L durante la primera semana de tratamiento, disminuyendo posteriormente hasta un aumento promedio de 1,5 mg/l a las 24 semanas.

Sobre efectos adversos en vida real la mayor serie publicada n = 170 es una retrospectiva de una base de datos de prescripción de teduglutida en USA Explorys (17). Reporta síntomas comunes como dolor abdominal (41,2 %) y náuseas (23,5 %), y otras complicaciones más relevantes como obstrucción intestinal (17,76 %) y complicaciones del estoma (11,8 %). Estos porcentajes fueron concordantes con los referidos previamente. Presentaron formación de pólipos de colon después del tratamiento (5,9 %). Aunque el antecedente de insuficiencia cardíaca es una contraindicación relativa, n = 30 (17,6 %) en esta situación recibieron teduglutida. No fue posible obtener información individualizada del grado de respuesta terapéutica ni de la duración del tratamiento y esta es una limitación importante de este estudio (17).

Las directrices sugieren la interrupción temporal de teduglutida y reanudar el tratamiento una vez se ha resuelto la complicación en caso de obstrucción o náuseas, pero no se conoce bien la tasa de abandonos por efectos adversos que en los datos del estudio ECA extensión fue de 19 % (11).

En pacientes pediátricos se ha evaluado la seguridad del fármaco en dos estudios fase III y sus estudios de extensión; los estudios iniciales reclutaron niños entre 1 y 7 años con SIC dependientes de soporte parenteral, en uno de ellos, de 12 semanas de duración los 42 pacientes recibieron soporte estándar o teduglutida, 0,0125, 0,025 o 0,05 mg/kg y día; en el otro, de 24 semanas de duración con 59 pacientes repartidos en un brazo de cuidado estándar y dos aleatorizados doble ciego con 0,025 y 0,05 mg/kg día de teduglutida. Posteriormente estos pacientes pudieron entrar en los estudios de extensión, donde recibieron 0,05 mg/kg/día de teduglutida durante 24 semanas seguidas de un periodo de seguimiento de 4 semanas de observación, reintroduciendo o no el fármaco según la evolución clínica. En total 89 pacientes recibieron teduglutida en algún momento, con una mediana de tratamiento de 52 semanas y un periodo de seguimiento prospectivo de 83 semanas.

Todos los pacientes tuvieron efectos adversos, se consideraron relacionados con el tratamiento en 35 pacientes (39,3 %). Los más frecuentes fueron: vómitos 51,7 %, pirexia en 43,8 %, infecciones del tracto respiratorio superior en 41,6 %, tos en 33,7 % y complicaciones infecciosas del catéter en 29,2 %. Se comunicaron eventos adversos serios en 69 pacientes (77,5 %), se consideraron derivados del tratamiento en 3 pacientes: íleo adinámico, acidosis láctica (2 episodios en el mismo paciente) y fecaloma. En los 3 se discontinuó el tratamiento y se reinició posteriormente. No se comunicaron neoplasias. En 34 de 82 pacientes con colon remanente (41,5 %) se realizó colonoscopia y se encontró 1 pólipo cecal, no biopsiado. La prevalencia de anticuerpos contra el fármaco alcanzó el 33,3 % en la semana 36 y se mantuvo estable hasta la semana 72. Se detectaron anticuerpos neutralizantes en un máximo de 10 % de pacientes en la semana 72.

RESPUESTA TERAPÉUTICA

La respuesta terapéutica al tratamiento con teduglutida se definió en los ensayos como una reducción del volumen del soporte parenteral semanal de al menos el 20 % con respecto al basal previo. También se tuvo en cuenta como objetivo secundario, el destete del soporte parenteral.

Solo hay un metaanálisis sobre eficacia (7), que incluyó 10 estudios, 8 de ellos observacionales, sobre 411 pacientes, y encontró una tasa de respuesta clínica del 64 %, 77 % y 82 % a los 6 meses, 1 año y 2 años respectivamente, con independencia de NP/fluidoterapia del 11 %, 17 % y 21 % a los 6 meses, 1 y 2 años. La presencia de colon remanente se asoció con menor tasa de respuesta (-17 %, 95 %CI: (-31 %, -3 %) pero con mayor tasa de independencia (+16 %, 95 %CI: (+6 %, +25 %). Hubo una tendencia a mejor respuesta, aunque no significativa en pacientes con enfermedad de Crohn como etiología del SIC.

El estudio (STEPS-2) (5) de 24 meses de duración es una ampliación del estudio inicial controlado con placebo para evaluar la seguridad y eficacia a largo plazo de teduglutida en pacientes con SIC. Los pacientes habían completado 24 semanas de teduglutida (TED/TED) o placebo (PBO/TED) en el inicial, o bien fueron calificados para ese estudio, pero no fueron tratados (NT/TED) debido a reclutamiento completo. Todos fueron tratados con teduglutida 0,05 mg/kg/día durante un máximo de 24 meses (NT/TED y PBO/TED) o hasta 30 meses (TED/TED).

En los pacientes que completaron el estudio STEPS-2, que fueron 65, la respuesta clínica se logró en 28/30 (93 %) TED/TED, 16/29 (55 %) PBO/TED, y 4/6 (67 %) pacientes con NT/TED. Las reducciones medias del volumen de NP desde el inicio fueron 7,6 (66 %), 3,1 (28 %) y 4,0 (39 %) l/semana en los grupos TED/TED, PBO/TED y NT/TED, respectivamente. Trece pacientes alcanzaron plena autonomía enteral.

En la serie reportada de 54 pacientes (14) se consiguió respuesta terapéutica a la semana 24 de tratamiento en 85 % de ellos, con reducción del volumen semanal en un 51 %, reducción media de 1,5 días de infusión e independencia de la NP en 13 de ellos (24 %). Esta respuesta se asoció significativamente a un aumento en la ingesta oral basal (2.540 *vs.* 1.875 kcal/día), también fue mejor la respuesta en caso de presencia de colon en continuidad (85 % de los pacientes independizados) y con un menor volumen semanal de NP (738 *vs.* 1867 mL/día). En una serie de 13 pacientes (25) con un seguimiento medio de 107 semanas, se consiguió respuesta clínica en todos los pacientes con reducción media de NP semanal entre el 82,5 y el 100 %, entre la semana 24 y 144 de tratamiento. En total, 12 de los 13 consiguieron independencia de la NP. En otra serie de 6 pacientes (26) todos consiguieron la independencia, que fue más temprana en 3 de ellos con colon en continuidad y con menor volumen semanal de NP. Según un estudio retrospectivo más reciente sobre 52 pacientes, después de un año con teduglutida respondieron el 68 % con una reducción de más de 20 % de la NP, y el 14 % suspendieron la NP (18).

CALIDAD DE VIDA

Los pacientes con fallo intestinal por síndrome de intestino corto que son dependientes de soporte parenteral experimentan en su vida diaria gran cantidad de síntomas y comorbilidades como astenia, además de las complicaciones asociadas a la nutrición parenteral y las derivadas del catéter Asimismo, sufren restricciones en su movilidad, interrupciones del sueño y de las actividades de la vida diaria, todo ello produce una repercusión negativa en la capacidad para desarrollar su trabajo, en el ocio y en la vida social y familiar, como consecuencia de todo ello manifiestan una disminución en su calidad de vida (27).

Utilizando el cuestionario SBS-QoL (28) durante el ensayo clínico STEPS-3, se analizó el impacto del tratamiento con teduglutida sobre la calidad de vida en los participantes, se comparó la puntuación obtenida en el momento basal con la obtenida en los subgrupos tratados con teduglutida *vs.* placebo; en el grupo tratado con teduglutida se observó una reducción de -8,6 puntos, lo que indica mejora en la percepción de calidad de vida, en la puntuación del SBS-QoL a la semana 24. El impacto fue mayor en pacientes en el tercer tercil (mayor) de necesidades basales de volumen del soporte parenteral (-27,3, 95 %CI -50,8 a -3,7) y con enfermedad inflamatoria intestinal (-29,6, 95 % CI -46,3 a 12,9) (22).

La reducción de necesidades de NP y de días de infusión semanales, incluso llegando a alcanzar la independencia del soporte intravenoso, es una consecuencia de la mejora funcional del intestino delgado tras el tratamiento con teduglutida (29). Un estudio de cohorte en 52 pacientes indica que después de más de 1 año de tratamiento la disminución en los días NP y la menor manipulación del catéter central podrían reducir el riesgo de complicaciones de la NP y del catéter. Se ha documentado una mejora en los hábitos dietéticos, en la frecuencia y consistencia de las deposiciones, reducción de las interrupciones del sueño de más del 50 %, y mejora de calidad de vida (18). Y es la principal motivación de los pacientes para estar dispuestos a iniciar el tratamiento con teduglutida, la posibilidad de reducir o prescindir del soporte parenteral, en una exploración cualitativa desde el punto de vista de pacientes y familiares con NPD (30).

LIMITACIONES

Las limitaciones de esta revisión son el escaso número de publicaciones sobre el tema, debido a que lleva relativamente poco tiempo en el mercado, a que los estudios en vida real no suelen tener alto número de reportes, a que es un tratamiento de alto coste para una enfermedad rara y a que ha sido incluido en las guías de ESPEN con un grado de evidencia moderada, pero solo para pacientes seleccionados con esta patología rara. El que exista actualmente un registro con más de 1.800 casos en ClinicalTrials.gov NCT01990040 para evaluar el perfil de seguridad a largo del tratamiento con teduglutida en un entorno clínico habitual, hace previsible que tengamos en el futuro más información sobre el tema.

CONCLUSIONES

Después de su introducción en España en 2017, la teduglutida se ha mostrado como tratamiento eficaz a largo plazo para la reducción y/o interrupción de la NP en pacientes con SIC. En este sentido, presenta un beneficio que aumenta de forma progresiva con el tiempo de tratamiento, en la mayoría de casos hasta al menos un año desde el inicio del tratamiento, aunque hay casos de repuesta tardía incluso hasta los 2 años especialmente en casos de colon en continuidad. El estándar de eficacia es una reducción de al menos el 20 % de la NP con respecto al basal previo, lo que se consigue hasta en el 82 % de los pacientes tratados a 2 años, permitiendo así reducir en un porcentaje relevante de pacientes la dependencia de NPD y alcanzar autonomía nutricional. En cuanto a los factores predictores de respuesta

se confirma que la presencia de colon en continuidad es factor predictivo negativo de respuesta recoz , pero un factor predictivo positivo para el destete de NP.

Teduglutida tiene un perfil de seguridad consistente con los datos previos y no se han identificado nuevos problemas de seguridad. Los efectos adversos notificados con mayor frecuencia fueron de origen gastrointestinal, y compatibles con la enfermedad subyacente y las acciones intestinotróficas de teduglutida sobre la enfermedad de base, pero también lo fueron las complicaciones asociadas con la NP y los trastornos electrolíticos. La alta frecuencia de estos efectos adversos hace necesario un programa intensivo de control y seguimiento especialmente en las primeras etapas del tratamiento y posteriormente de vigilancia de otras complicaciones tardías relacionadas con el estoma o con la aparición de neoplasias del área gastrointestinal, aunque la frecuencia de estas últimas es baja. La tasa de abandono de tratamiento por complicaciones es alta en vida real, del 19 %, en ese sentido se debe extremar la vigilancia y en caso de aparición de las mismas, discontinuar temporalmente el tratamiento como indican las guías. En adultos son escasos los datos en mejoría de calidad de vida y en coste-eficacia.

En conclusión, existe una evidencia creciente y ya las guías ESPEN recomiendan con un nivel de evidencia moderado el tratamiento con teduglutide para pacientes seleccionados con síndrome de intestino corto (31), confirmándose en vida real los datos de los ensayos pivotales sobre eficacia y seguridad de teduglutida, pero son necesarios más estudios que apoyen estos datos, especialmente en cuanto a la identificación de aquellos grupos de pacientes con mayor beneficio terapéutico.

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Carta al Director

¿CUÁNDO ES NECESARIO UN RESUMEN DE REVISIONES SISTEMÁTICAS?

Sr. Editor:

Un resumen de revisiones sistemáticas, también conocido como revisión paraguas u *overview,* corresponde a un diseño de investigación secundario que consiste en resumir múltiples revisiones sistemáticas previas con el objetivo principal de proveer una sinopsis de la evidencia, incluyendo una combinación de diferentes intervenciones, desenlaces, condiciones, problemas o poblaciones (1,2).

¿Cuáles son las razones metodológicas que justificarían su realización?

Según el capítulo 5 del Manual Cochrane de revisiones sistemáticas de intervenciones (3), los motivos para resumir revisiones sistemáticas en un solo documento son:

1. Resumir la evidencia de más de una revisión sistemática de intervenciones diferentes para la misma afección o problema.
2. Resumir la evidencia de más de una revisión sistemática de la misma afección o problema en la que se abordan resultados diferentes en distintas revisiones sistemáticas.
3. Resumir la evidencia de más de una revisión sistemática de la misma intervención para diferentes afecciones, problemas o poblaciones.
4. Resumir la evidencia acerca de los efectos adversos a partir de una intervención de más de una revisión sistemática del uso de la intervención para una o más afecciones.
5. Proporcionar un resumen exhaustivo de un área con la inclusión de estudios que no se hayan incluido en revisiones sistemáticas.

¿Y cuáles son las razones desde el punto de vista de la práctica clínica?

Este tipo de revisiones debiera nacer de la necesidad de compilar la información proveniente de revisiones sistemáticas dispersas sobre un tema particular (2), básicamente como un insumo para los tomadores de decisiones, quienes, en general, no tienen los recursos para resumir la evidencia de manera oportuna. Esta necesidad de información a veces se relaciona con problemas amplios que se generan en los complejos sistemas de salud y otras veces se relaciona con problemas puntuales como los que enfrentan los clínicos en su práctica cotidiana. De esta manera, los resúmenes de revisiones se convierten en un insumo importante para la práctica basada en evidencias, lo que debiera redundar en mejores resultados de salud, a nivel general en el sistema de salud o a nivel individual con un paciente en particular.

Para ejemplificar esto, analizaremos el siguiente estudio: *"*Rehabilitación para personas con esclerosis múltiple: una *overview* de revisiones Cochrane*"* (4). El objetivo de esta *overview* es proporcionar un resumen de la efectividad de las terapias de rehabilitación utilizadas para la esclerosis múltiple (EM). Los investigadores incluyeron 15 revisiones sistemáticas, las cuales comprenden 164 estudios clínicos aleatorizados y cuatro estudios controlados, con un total de 10.396 personas con EM. Las revisiones incluidas evaluaron una amplia gama de intervenciones de rehabilitación: terapia física, terapia ocupacional, ejercicios de fuerza, resistencia y aeróbicos, elongación, ortesis, terapia hiperbárica, estimulación eléctrica transcutánea, hipoterapia, terapia vibratoria, rehabilitación vocal, acupuntura, intervención psicológica, intervención nutricional, práctica mental, educación y programas de rehabilitación específicos (telerrehabilitación, manejo de la fatiga, rehabilitación de miembros superiores y manejo de la espasticidad). Dentro de los resultados principales, la evidencia de calidad moderada sugiere que la terapia física (ejercicio y actividad física) mejora los desenlaces funcionales (movilidad, fuerza muscular); también redujo la fatiga y mejoró la participación (calidad de vida). En relación con los programas de rehabilitación multidisciplinaria para pacientes hospitalizados o ambulatorios, se produjeron ganancias a largo plazo en los

Conflicto de intereses: los autores declaran no tener conflicto de intereses.

niveles de actividad y participación. Por otro lado, evidencia de baja calidad sugiere que las intervenciones neuropsicológicas, los programas de manejo de síntomas (espasticidad), la terapia vibratoria y la telerrehabilitación mejoraron solo algunos desenlaces. En relación con las otras modalidades de rehabilitación analizadas, la evidencia no fue concluyente debido a la falta de estudios sólidos. La evidencia presentada en la *overview* analizada (4) respalda la estrategia de utilizar enfoques variados para la rehabilitación y que el tipo de tratamiento y el entorno (hospitalización, comunidad) deben individualizarse en función de las necesidades específicas de cada paciente. La evidencia mostró que, aunque había una gran cantidad de intervenciones de rehabilitación disponibles para tratar a las personas con EM, la gran mayoría de estas no cuentan con evidencia de alta calidad que pueda conducir al clínico a tomar una decisión con una certeza aceptable; pero lo más importante es que logró discriminar las pocas intervenciones, específicamente de terapia física, que con una certeza moderada sugieren buenos resultados, lo que debiera entonces influir en que sean estas las intervenciones escogidas.

Con este ejemplo, en relación al impacto para la práctica clínica que representa una *overview*, podemos concluir que proporciona, en un solo documento, un resumen global y crítico de las revisiones sistemáticas pertinentes a una pregunta para tomar una decisión clínica informada, ayudando al clínico con escaso tiempo para leer, evaluar y discriminar a tomar decisiones informadas por la evidencia.

Finalmente, es importante puntualizar que una *overview* no debe realizarse de forma aleatoria sin tener presente su objetivo primordial, que es el apoyar las decisiones contingentes; para eso, la íntima relación que debe haber entre la evidencia, la experiencia clínica y las necesidades de los usuarios debe ser la triada que oriente las preguntas a responder a través de este diseño de investigación secundario.

Raúl Alberto Aguilera-Eguía[1,2], Héctor Fuentes-Barria[3], Pamela Serón-Silva[4]

[1]Departamento de Salud Pública. Facultad de Medicina, Carrera de Kinesiología. Universidad Católica de la Santísima Concepción. Concepción, Chile. [2]Doctorado en Metodología de la Investigación Biomédica y Salud Pública. Universidad Autónoma de Barcelona. Barcelona, España. [3]Programa Magíster en Ciencias de la Actividad Física y Deportes Aplicadas al Entrenamiento, Rehabilitación y Reintegro Deportivo. Facultad de Salud. Universidad Santo Tomás. Santiago, Chile. [4]Departamento de Ciencias de la Rehabilitación. Facultad de Medicina. Universidad de La Frontera. Temuco, Chile

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Carta al Director

NO NOS OLVIDEMOS DE PRISMA-P

Sr. Editor:

La elaboración de un protocolo de investigación (PI) se considera un componente esencial en el proceso de una revisión sistemática (RS) (1). Así lo argumenta el manuscrito publicado previamente en su prestigiosa revista, titulado: *"Hacia la elaboración del Protocolo de Investigación y su registro"* (2). También se debe considerar que el PI garantiza que la RS esté planificada y que todo aquello que fue organizado se encuentre previamente documentado antes de que comience la RS, promoviendo la coherencia del equipo, la responsabilidad, la integridad y la transparencia de la revisión (1).

No hay que olvidar que, para la elaboración de un PI de una RS, se deben utilizar los ítems de referencia para publicar protocolos de Revisiones Sistemáticas y Metaanálisis: Declaración PRISMA-P 2015 (1,3). Por el contrario, para elaborar una RS, se deben considerar los ítems de referencia para publicar Revisiones Sistemáticas y Metaanálisis: Declaración PRISMA (4). En relación con esto, el propósito del presente manuscrito es describir brevemente PRISMA-P y plasmar su lista de verificación.

PRISMA-P corresponde a directrices que orientan a los autores en la preparación de PI para la planificación de RS y metaanálisis, a través de un conjunto mínimo de ítems de inclusión en el protocolo (1) (Tabla I). Los investigadores deben preparar un protocolo de la revisión con antelación a su registro en PROSPERO (5), de manera que los detalles que necesiten mayor consi-

Tabla I. Lista de verificación de PRISMA-P 2015: ítems recomendados para su inclusión en un protocolo de revisión sistemática

Sección/tema	N.º ítem	Ítem de la lista de verificación
Información administrativa		
Título		
Identificación	1a	Identificar el documento como protocolo de una revisión sistemática
Actualización	1b	Si el protocolo está destinado a una actualización de una revisión sistemática previa, identificarlo como tal
Registro	2	Si está registrado, proporcionar el nombre del registro (*p.* ej., PROSPERO) y el número de registro
Autores		
Contacto	3a	Proporcionar nombre, afiliación institucional y dirección de correo electrónico de todos los autores del protocolo, aportar dirección postal del autor para la correspondencia
Contribuciones	3b	Describir las contribuciones de los autores del protocolo e identificar al responsable de la revisión
Correcciones	4	Si el protocolo supone una corrección de un protocolo completado previamente o publicado, identificarlo como tal y enumerar la lista de cambios; en caso contrario, declarar la estrategia para documentar las correcciones importantes del protocolo

(Continúa en página siguiente)

Conflicto de intereses: los autores declaran no tener conflicto de intereses.

Tabla I (Cont.). Lista de verificación de PRISMA-P 2015: ítems recomendados para su inclusión en un protocolo de revisión sistemática

Sección/tema	N.º ítem	Ítem de la lista de verificación
Información administrativa		
Apoyo		
Fuentes	5a	Indicar fuentes de financiación de la revisión sistemática y otros tipos de apoyo
Patrocinador	5b	Aportar el nombre del financiador o patrocinador de la revisión
Papel del patrocinador/ financiador	5c	Detallar el papel desempeñado por parte del(los) financiador(es), patrocinador(es), y/o institución(es), si los hay, en la elaboración del protocolo
Introducción		
Justificación	6	Describir la justificación de la revisión en el contexto de lo que ya se conoce sobre el tema
Objetivos	7	Plantear de forma explícita las preguntas que se desea contestar en relación con los participantes, las intervenciones, las comparaciones y los desenlaces o resultados (PICO)
Métodos		
Criterios de elegibilidad	8	Especificar las características de los estudios (*p.* ej., PICO, diseño del estudio, contexto, duración del seguimiento) y detallar las características (*p.* ej., años abarcados, idioma o estatus de publicación) utilizadas como criterios de elegibilidad para la revisión
Fuentes de información	9	Describir, con las fechas de cobertura previstas, todas las fuentes de información (*p.* ej., bases de datos y periodos de búsqueda, contacto con los autores de los estudios, registros de los estudios y otras fuentes de literatura gris)
Estrategia de búsqueda	10	Presentar el borrador de la estrategia de búsqueda que será utilizada en al menos una base de datos electrónica, incluidos límites propuestos, de manera que pueda repetirse
Registro de estudios		
Gestión de datos	11a	Detallar los mecanismos que se utilizarán para gestionar los datos y los registros durante la revisión sistemática
Proceso de selección	11b	Exponer el proceso que se utilizará para seleccionar los estudios (*p.* ej., dos revisores independientes) en cada fase de la revisión (es decir: cribado, elegibilidad e inclusión en un metaanálisis)
Proceso de extracción de datos	11c	Describir el método planteado para la extracción de datos de las publicaciones (*p.* ej., uso de formularios para la extracción uniforme de datos *[piloting forms],* por duplicado y de forma independiente) y cualquier proceso destinado a la obtención y confirmación de los datos por parte de los investigadores
Lista de datos	12	Enumerar y definir todas las variables para las que se buscarán datos (*p.* ej., PICO, fuente de financiación) y cualquier asunción o simplificación de dichos datos planeada de antemano
Resultados esperados y priorización	13	Enumerar y detallar todos los desenlaces o resultados esperados para los que se buscarán datos, incluidas la priorización y justificación de los resultados principales y los adicionales
Riesgo de sesgo en los estudios individuales	14	Detallar los métodos previstos para evaluar el riesgo de sesgo de los estudios individuales, incluyendo si se aplicarán a nivel del desenlace esperado, a nivel del estudio o de ambos; exponer cómo se utilizará esta información en la síntesis de los datos
Datos		
Síntesis	15a	Describir los criterios que permitirán sintetizar cuantitativamente los datos de los estudios
	15b	Si los datos son adecuados para su síntesis cuantitativa, describir las medidas planificadas para resumirlos, métodos de tratamiento de datos y métodos de combinación de datos, incluido cualquier análisis de consistencia interna (*p.* ej., I2, tau de Kendall)
	15c	Detallar todo análisis adicional propuesto (*p.* ej., sensibilidad o análisis de subgrupo, metarregresión)
	15d	Si la síntesis cuantitativa no resulta adecuada, describir el tipo de resumen de datos planificado
Metasesgo(s)	16	Especificar todas las evaluaciones de metasesgo(s) planificadas (*p.* ej., sesgo de publicación entre los diferentes estudios, la presentación de información selectiva en los estudios)
Confianza en la evidencia acumulada	17	Describir de qué manera se evaluará la solidez del conjunto de pruebas (evidencia) (*p.* ej., GRADE)

PRISMA-P Preferred Reporting Items for Systematic review and Meta-Analysis Protocols. Extraído de: Ítems de referencia para publicar Protocolos de Revisiones Sistemáticas y Metaanálisis: Declaración PRISMA-P 2015.

deración dispongan de la reflexión previa necesaria, lo cual evita la necesidad de múltiples rectificaciones en la información del registro (1). Los ítems de PRISMA-P derivan en gran medida de la lista de verificación de PRISMA (6) y de los ítems del registro PROSPERO, a fin de facilitar un proceso de registro fluido.

Para concluir, PRISMA-P es fundamental en el proceso de elaboración de un PI para publicar protocolos de RS y metaanálisis. No hay que olvidar que el objetivo de un PI es principalmente proporcionar de forma previa tanto la justificación de la revisión como el enfoque metodológico, análisis estadístico que presentará la RS. Por tanto, es recomendable preparar el PI con antelación a su registro prospectivo. Los ítems de PRISMA-P derivan de la lista de verificación PRISMA y de los ítems presentes en el registro PROSPERO, con el fin de dar fluidez al proceso.

Raúl Aguilera-Eguía[1], Cristian Yáñez-Baeza[2], Héctor Fuentes-Barria[3], Ángel Roco-Videla[4]

[1]Departamento de Salud Pública. Facultad de Medicina. Universidad Católica de la Santísima Concepción. Concepción, Chile. [2]Departamento de Ciencias Clínicas y Preclínicas. Facultad de Medicina. Universidad Católica de la Santísima Concepción. Concepción, Chile. [3]Escuela de Odontología. Facultad de Odontología. Universidad Andrés Bello. Concepción, Chile. [4]Facultad de Salud y Ciencias Sociales. Universidad de las Américas. Santiago, Chile

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Carta al Director

FRACTURA DE CADERA EN ADULTOS MAYORES DURANTE LA PANDEMIA Y EFECTO DE LA VITAMINA D

Sr. Editor:

Leímos el artículo de Sanz y cols. (diciembre de 2022) (1), en el que señalan la importancia de manejar protocolos sobre pacientes que ingresan para cirugía de cadera con comorbilidades de diabetes, a fin de optimizar resultados y disminuir tiempos por complicaciones de esta cirugía. Según esto, es significativo revisar qué sucedió con los traumas en adultos mayores en pandemia. Hay estudios en Chile que mencionan que la tasa de hospitalización por caídas disminuyó en un 20,8 %, así como la de hospitalización semanal en un 18,5 %. Esto se debe a que este periodo de confinamiento disminuyó la movilidad producto del distanciamiento social, los adultos mayores estuvieron más acompañados por su familia y ellos son más autosuficientes (2).

La fractura de cadera es la más frecuente por fragilidad osteoporótica producto de baja energía por caídas en el grupo etario de adultos mayores (2) y afecta a cada tercera mujer y a cada quinto hombre mayores de 50 años.

En Chile, han ido disminuyendo las fracturas de cadera en adultos mayores, con la cifra más baja en año 2020, 18,33 %, en periodo de pandemia (2).

Hay estudios que revelan que el mayor porcentaje de caídas ocurre en el sexo femenino de centros geriátricos, con consumo de antihipertensivos y niveles bajos de vitamina D (3), de ahí la importancia del consumo de vitamina D, así como de tomar el sol.

El consumo diario de leche fortificada con calcio y vitamina D en mujeres posmenopáusicas sanas mejoró significativamente el estado de la vitamina D, aumentó significativamente la densidad mineral ósea (DMO) femoral y tuvo efectos beneficiosos sobre los perfiles de glucosa y lípidos (4).

Al administrarse este suplemento de vitamina D con dosis mayor a la habitual, tiene efectos positivos en la consolidación ósea en pacientes con fractura de cadera.

Otra forma de disminuir riesgo de fractura de cadera en mujeres es el consumo de estrógenos y progesteronas como estradiol para mejorar densidad ósea (5).

Como medida de prevención de la fractura de cadera, cuya mayor prevalencia se da a consecuencia de caídas, es importante la evaluación de los factores de riesgo con instrumentos certificados, ya sea en pacientes institucionalizados o que vivan solos, y valorando las condiciones de riesgo de su vivienda.

En Chile se está aplicando la hospitalización domiciliaria debido a que permite una mejor visualización de los adultos mayores y descongestionar el sistema de salud, dando movilidad a las camas de hospitalizados y permitiendo que los pacientes se encuentren en su medio ambiente, con un personal dedicado exclusivamente a ellos que les brinda todos sus cuidados.

Además, son importantes las políticas públicas para implementar programas enfocados en prevenir, mantener o corregir la salud del adulto mayor y que permitan realizar ejercicios adecuados según su condición física para que pueda ser autovalente y se logre disminuir el riesgo de caídas.

Finalmente, en estos adultos mayores se debe realizar un trabajo multidisciplinario puesto que no existe una atención rutinaria y adecuada. Cada persona es única con sus necesidades insatisfechas, por lo que se debe realizar un diagnóstico correcto, sumado a un plan de tratamiento y una ejecución acorde a sus cuidados.

Mónica Zúñiga González[1], Ángel Roco Videla[2]
[1]Escuela de Enfermería, y [2]Facultad de Salud y Ciencias Sociales. Universidad de las Américas. Santiago, Chile

Conflicto de intereses: los autores declaran no tener conflicto de intereses.

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MEJORANDO LA CALIDAD DE LA ATENCIÓN SOCIOSANITARIA Y LA INVESTIGACIÓN A TRAVÉS DE LA INTEGRACIÓN DE COMPETENCIAS DIGITALES EN LA EDUCACIÓN DE PREGRADO

Sr. Editor:

Agradecemos la valiosa publicación de Caviedes-Olmos y Roco-Videla (1), la cual destaca la necesidad de utilizar herramientas de automatización y sistemas de inteligencia artificial para optimizar la búsqueda y el análisis de información. Esta situación nos lleva a reflexionar sobre la relevancia de incorporar la adquisición de competencias digitales en los currículos de pregrado, lo cual resulta esencial en un mundo donde el volumen de información es cada vez mayor.

La Organización Mundial de la Salud (OMS) ha enfatizado la necesidad de desarrollar competencias digitales en el personal de salud, para mejorar la calidad y eficiencia de la atención sanitaria (2). La inclusión de estas competencias en los currículos de pregrado permite a los futuros profesionales adquirir habilidades necesarias para la búsqueda, el análisis y la aplicación de la información en sus prácticas laborales (3).

Diversos estudios han demostrado que la adopción de competencias digitales en la educación salubrista mejora la capacidad de los estudiantes para acceder, evaluar y aplicar la información científica de manera efectiva, lo que resulta en una mejor atención a los usuarios-pacientes (4). Además, la integración de tecnologías de la información y la comunicación (TIC) en la formación académica fomenta el desarrollo de habilidades colaborativas y de trabajo en equipo (5).

La implementación de programas de capacitación en competencias digitales es fundamental para preparar a los estudiantes para enfrentar los desafíos actuales y futuros en su campo laboral. Estos programas deben abordar aspectos como el uso de herramientas de búsqueda, la gestión de bases de datos, la interpretación de resultados y la comunicación efectiva de la información (6).

Es esencial que las instituciones académicas incorporen la adquisición de competencias digitales en los currículos de pregrado, para formar profesionales de la salud capacitados en el manejo de información y tecnologías emergentes. Esto permitirá mejorar la calidad de la atención sanitaria, así como la eficiencia en la realización de revisiones sistemáticas y metaanálisis (1).

Claudio Aránguiz Bravo

Escuela TENS. Facultad de Salud y Ciencias Sociales. Universidad de las Américas. Santiago, Chile

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DEFICIENCIA DE VITAMINA D EN PACIENTES CON EPILEPSIA: CONSIDERACIONES A TENER EN CUENTA

Sr. Editor:

Nos parece interesante la publicación realizada recientemente sobre un estudio preliminar, cuyo objetivo era encontrar una posible asociación entre epilepsia con deficiencia de vitamina D y alteraciones antropométricas como sobrepeso/obesidad (1). En este estudio se incluyeron 32 pacientes adultos mayores de 18 años con diagnóstico de epilepsia quienes estaban en seguimiento por neurología en una institución de Brasil. Evaluaron la composición corporal y midieron niveles de vitamina D, encontrando que el 75 % de los pacientes tenían sobrepeso, 21,9 % peso normal y 3,1 % bajo peso, y los niveles séricos de vitamina D estaban en un 78 % de los pacientes por debajo de 30 ng/ml, aunque no hubo asociación estadística entre sobrepeso y la deficiencia de vitamina D ($p > 0,05$).

Es importante resaltar que sí se han encontrado en múltiples estudios una asociación clara entre epilepsia y deficiencia de vitamina D, secundario al uso de fármacos anticrisis (2). En condiciones fisiológicas, esta vitamina regula la concentración de calcio, aumentando la absorción intestinal y reclutando células madre en el hueso que se convierten a osteoblastos maduros (3). Se han descrito varios mecanismos por los cuales los fármacos anticrisis generan una disminución de esta vitamina. Uno de ellos, y el más descrito es la inducción del citocromo P450 hepático, lo cual genera un aumento del catabolismo del a vitamina D, produciendo a metabolitos inactivos, y generando consigo una reducción de la absorción del calcio por vía intestinal, con posterior elevación de la paratohormona (PTH), que produce un aumento de resorción ósea (4). Otro mecanismo es el aumento de la excreción biliar de la vitamina D por vía biliar (5). También se ha visto que pueden activar los receptores nucleares de esteroides y pregnano en el riñón (SXR y PXR), los cuales aumentan la transducción de la enzima 25-hidroxivitamina D3-24-hidroxilasa, cuya función es catalizar la conversión de la vitamina D a un metabolito inactivo (6) (Fig. 1).

Dentro de los factores de riesgo descritos para desarrollar deficiencia de esta vitamina se encuentra la politerapia anticonvulsiva (definido como el uso de 2 o más medicamentos), epilepsia refractaria (requieren uso de mayores dosis de anticonvulsivos) y el uso prolongado de estos medicamentos (especialmente ácido valproico, levetiracetam y carbamazepina) (7-9).

Actualmente no hay recomendaciones sobre el tamizaje o conductas a realizar en estos pacientes con exposición crónica a fármacos anticrisis. Se han descrito las siguientes pautas a tener en cuenta para estos pacientes (10):

- Medición anual de niveles de vitamina D y calcio.
- Si hay exposición mayor a 5 años a fármacos anticonvulsivantes, especialmente al ácido valproico, o si hay algún factor de riesgo adicional, solicitar densitometría ósea.
- Si se llega a detectar deficiencia de vitamina D, se debe suplementar 2000 UI día si es pediátrico, o 4000 UI día si es adulto.
- Si se detecta osteoporosis, se debe escoger el fármaco de acuerdo a las condiciones del paciente, similar a las guías de manejo de osteoporosis.
- Dado que los pacientes con epilepsia suelen ser evaluados por múltiples especialidades (aparte de neurología), es necesario sensibilizarse y realizar un adecuado tamizaje.

Juan Martín Mancera, Lina María Rodríguez Vélez
Departamento de Medicina Física y Rehabilitación. Universidad del Valle. Hospital Universitario del Valle ESE. Cali, Colombia

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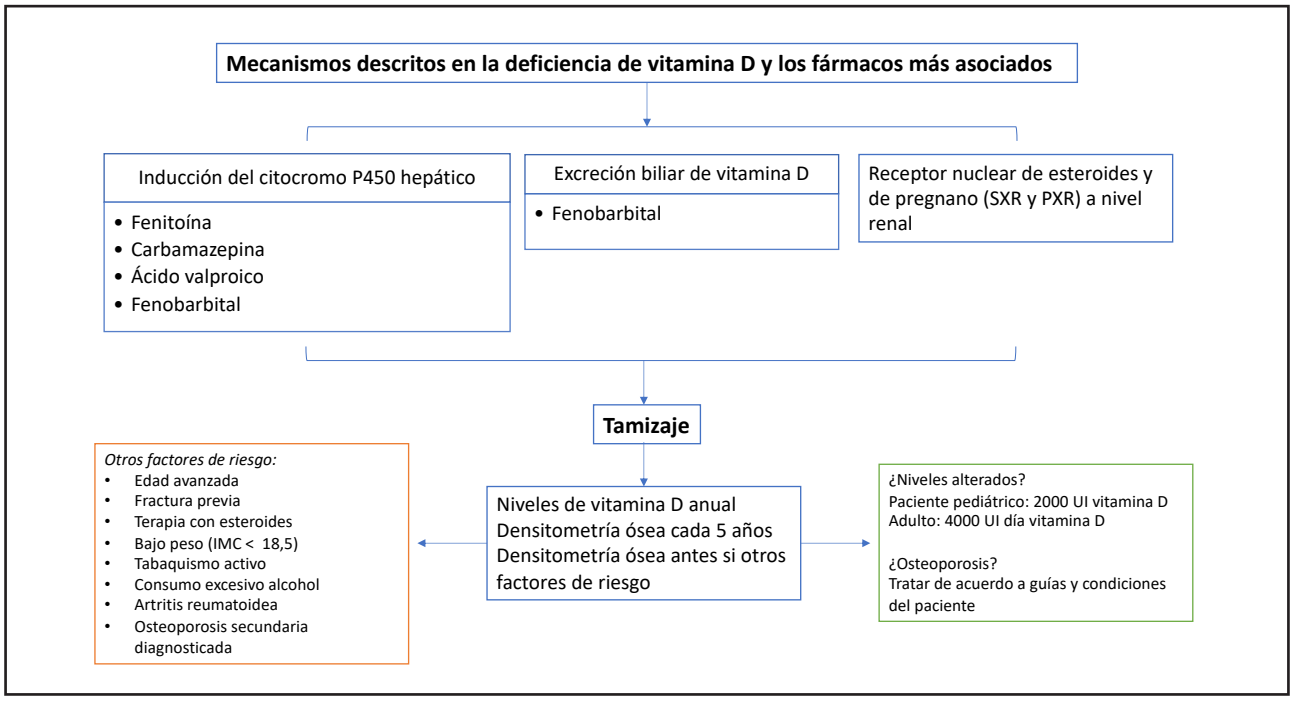

Figura 1.

Se ilustran las anteriores recomendaciones, además se relacionan los mecanismos asociados al déficit de dicha vitamina y los respectivos fármacos.

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DESNUTRICIÓN Y SARCOPENIA EN PACIENTES CON CIRROSIS HEPÁTICA

Sr. Editor:

Leímos el artículo de Aldana-Ledesma y cols. (marzo-abril 2023) (1), en el que concluyen que en los pacientes con cirrosis hepática son comunes la sarcopenia y la desnutrición, realizándose un tamizaje con la utilización de herramientas seguras y de fácil acceso: valoraciones antropométricas, fuerza de agarre de la mano y el RFH-SGA (Royal Free Hospital-Subjetive Global Assessment).

Podemos agregar que la desnutrición/sarcopenia están asociadas con una mayor tasa de complicaciones y son predictoras independientes de menor sobrevida (2). Es más evidente en pacientes con cirrosis hepática descompensada que compensada, debido frente a este escenario, es fundamental el diagnóstico precoz de desnutrición para realizar un tratamiento nutricional oportuno para evitar mal pronóstico.

Al analizar las cifras (3) tenemos pacientes con cirrosis compensada en los que un 20 % presenta desnutrición y más de 50 % de pacientes tienen enfermedad hepática descompensada. En cirrosis hepática hay entre un 50 y 70 % que presentan como complicación la sarcopenia (4), debido al aumento de los niveles de amonio sérico y miostatina, y para tratar esta hiperamonemia se ha administrado L-ornitina L-aspartato (LOLA), mejorando la masa corporal magra, fuerza de presión manual y el diámetro promedio de la fibra muscular.

En esta patología es importante la prevención y podemos destacar que Chile tiene medidas similares de prevención primaria recomendadas internacionalmente (5), como tamizaje con cuestionario Audit, intervenciones en tamizaje positivo, implementación en políticas públicas con restricción de consumo (edad, lugares y horarios), reducción de disponibilidad de impuestos, campañas de etiquetado, en oposición a los enfoques de prevención secundaria y terciaria con un tratamiento incompleto de la cirrosis alcohólica y sus complicaciones.

A nivel secundario no existen protocolos o guías de prácticas clínicas del Minsal ni de la Sociedad Chilena de Gastroenterología, en comparación internacional que, frente a la sospecha de la patología, se deben de tomar niveles plasmáticos de enzimas hepáticas, evaluación de elastografía según enzimas alteradas y biopsia según criterios de solicitud.

A nivel terciario se concuerdan parcialmente en Chile con el nivel internacional las medidas estandarizadas como en ascitis; existe terapia de paréntesis evacuadora y esto no esta presente en guías chilenas; en síndrome hepatorrenal a nivel internacional se usan quinolonas y en Chile no existe; con respecto a encefalopatía hepática corresponde tratamiento de trasplante y en Chile no se considera frente a esta complicación. No existen medidas en Chile frente a manejo de cirrosis hepática compensada, varices esofágicas y trasplante.

Finalmente podemos concluir según los autores (6) que la evaluación nutricional de la cirrosis juega un papel vital en el manejo de la cirrosis. La enfermedad hepática es crónica porque afecta pronóstico y respuesta al trasplante hepático, por esta razón es primordial realizar una valoración nutricional completa, adecuada y precoz. Esto puede ser una tarea difícil en esta población para lo cual se recomienda un enfoque holístico de la nutrición y personal en cada paciente.

La evaluación nutricional detallada incluye: evaluación de la masa muscular, herramienta de evaluación nutricional global y una evaluación exhaustiva de la ingesta de alimentos, permitiendo un manejo integral de la cirrosis hepática.

Mónica Zúñiga González, Ángel Roco Videla
Escuela de Enfermería y Técnicos de nivel superior en Enfermería. Facultad de Salud y Ciencias Sociales. Universidad de las Américas. Santiago, Chile

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Crítica de Libros

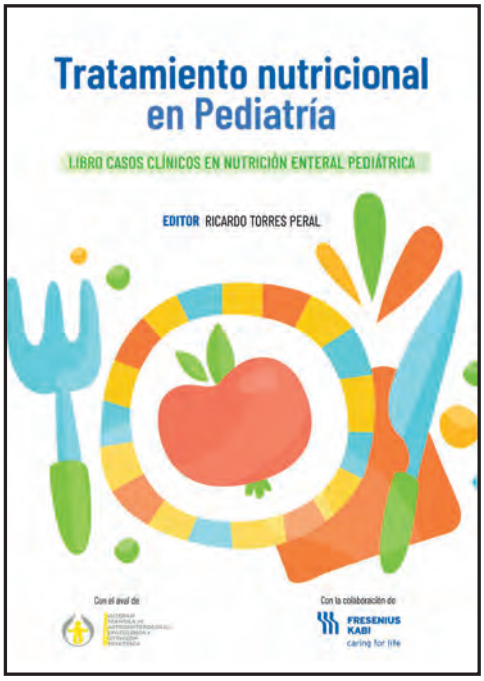
TRATAMIENTO NUTRICIONAL EN PEDIATRÍA

Ricardo Torres. Ergón, 2023

Mi buen amigo, el gastroenterólogo infantil Ricardo Torres, acaba de publicar este libro breve, dedicado al tratamiento nutricional en Pediatría, fundamentalmente al soporte nutricional por vía enteral. Es, como tantas obras en el campo de la Nutrición, una obra coral en la que participan un buen número de especialistas españoles, la mayoría al cargo o formando parte de las Unidades de Soporte Nutricional, presentes en los grandes hospitales españoles. Como bien señala el coordinador de esta edición, el crecimiento del soporte nutricional ha venido de la mano de la mejora en la atención y en el tratamiento de niños con patologías complejas. Tan solo con mira un poco hacia atrás vemos que los primeros productos de nutrición enteral diseñados específicamente para niños (fuera de las fórmulas para lactantes, tanto sanos como con patología) tienen apenas 30 años.

El libro, organizado en 19 capítulos, abarca desde la importancia del cribado nutricional hasta el tratamiento nutricional del niño con síndrome inflamatorio multisistémico por COVID-19, pasando por el abordaje nutricional de paciente neurológico, con especial atención a la disfagia, el paciente oncológico o con una cardiopatía congénita, entre otros.

La estructura de cada capítulo está basada en un caso clínico, con la presentación del problema nutricional, el planteamiento de manejo a la luz de la evidencia científica y, finalmente, los resultados de la intervención.



Bienvenido este nuevo libro dedicado al paciente pediátrico con necesidad de soporte nutricional y enhorabuena al coordinador y a los autores por llevar a buen puerto la iniciativa.

Dr. José Manuel Moreno Villares
Director de *Nutrición Hospitalaria*