

Nutrición Hospitalaria



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Sociedad Española de Nutrición Parenteral y Enteral ■ Sociedad Española de Nutrición ■ Federación Latino Americana de Nutrición Parenteral y Enteral ■ Federación Española de Sociedades de Nutrición, Alimentación y Dietética

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Órgano Oficial

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Cribado nutricional en aras de la eficiencia

Nutrition screening: looking for the efficiency

Las medidas de lucha contra la desnutrición relacionada con la enfermedad (DRE), propuestas e implementadas por los principales países de nuestro entorno, incorporan, como un pilar básico de la atención de los sujetos enfermos, la identificación de aquellos que pudieran estar desnutridos o en riesgo de desnutrición. De ahí la relevancia de considerar las herramientas de cribado nutricional.

Si bien resulta casi una misión imposible definir la DRE, como se aprecia en las últimas publicaciones de consensos de expertos de la European Society for Clinical Nutrition and Metabolism (ESPEN) y la American Society for Parenteral and Enteral Nutrition (ASPEN) (1,2), existe un acuerdo unánime en que el cribado nutricional es el primer paso para el abordaje del paciente enfermo en riesgo nutricional. La complejidad del cuidado y tratamiento integral del paciente en riesgo de desnutrición y desnutrido obliga a buscar herramientas eficientes que permitan identificar adecuadamente a los pacientes en riesgo, para optimizar la funcionalidad de los equipos asistenciales (3).

En este punto nos podríamos preguntar si el cribado nutricional cumple los criterios de Frame y Carlson para ser definido como tal (4). Estos autores, hace más de 40 años, definieron las condiciones que debían cumplir las medidas preventivas para ser consideradas como un cribado. Estas eran: que la enfermedad buscada sea una causa común de morbilidad (enfermedad prevalente); que sea detectable en etapa presintomática; que, además, las pruebas diagnósticas deban ser efectivas y eficaces (sensibilidad y especificidad aceptables, sencillas y baratas) y que el tratamiento temprano sea mejor que en la etapa sintomática y, por supuesto, que el daño potencial de la intervención deba ser menor que en el tratamiento no precoz.

Entendemos el cribado nutricional como un procedimiento estandarizado que permite identificar a los individuos desnutridos o con riesgo de desnutrición que se pueden beneficiar de un apropiado cuidado y tratamiento nutricional. Debe ser sencillo, válido, fiable, reproducible y práctico. Además, debe estar asociado a protocolos específicos de actuación y tener "precisión diagnóstica" que se expresa como sensibilidad, especificidad, valor predictivo positivo y valor predictivo negativo; en definitiva, debe ser eficiente.

La importancia del papel de las herramientas de cribado nutricional ha avanzado de la mano del conocimiento de la desnutrición y sus consecuencias. Desde que en 1936, un cirujano, Hiram O Studley (5), llamara la atención a la comunidad científica acerca de cómo impacta la pérdida de peso en la evolución de los pacientes postquirúrgicos con úlcera péptica, la evolución en el concepto de la DRE y los avances tecnológicos en su tratamiento se han venido desarrollando.

En la actualidad, son más de 20.000 las referencias bibliográficas recogidas en PubMed relativas a "nutritional screening". Aunque, probablemente los primeros cribados nutricionales descritos fueron los de Setzler en 1979 y Potosnak en 1983, no fue hasta la publicación de la Valoración Subjetiva Global (VSG), en 1987 por Destky (6), cuando se comenzó a integrar el concepto de las herramientas de despistaje para identificar pacientes en riesgo nutricional y cuestionarios de evaluación nutricional estructurados. A partir del año 2000 se registra la mayor proliferación de publicaciones relativas a herramientas de cribado nutricional.

Hay más de 70 herramientas descritas. El Comité de Expertos de ESPEN define como componentes fundamentales de un cribado nutricional: el índice de masa corporal; la pérdida de peso reciente involuntaria; la reducción de la ingesta y la gravedad de la enfermedad (7). Los métodos identificados como patrón oro para

editorial

ESPEN son el Nutrition Risk Screening (NRS 2002) recomendando su utilización en el ámbito hospitalario. El Malnutrition Universal Screening Tool (MUST) de uso predominante en el ámbito comunitario y el Mini Nutritional Assessment Short Form (MNA-SF) de utilización en población geriátrica. La ASPEN, por su parte, apuesta por Valoración Subjetiva Global (VSG) y el Malnutrition Screening Tool (MST). A pesar de estas recomendaciones cuesta definir qué herramienta de cribado se ajusta más a los criterios que se establezcan como definitivos para determinar DRE.

La selección de la herramienta de cribado nutricional en cada caso deberá responder a preguntas relacionadas con la población a estudio (enfermedad relacionada, edad, etc.) o el objetivo del cribado, entre otras. Podríamos considerar dos objetivos del cribado. Por un lado, predecir la probabilidad de un pronóstico desfavorable debido a los factores nutricionales, y por otro identificar a los sujetos que pueden beneficiarse del tratamiento nutricional (8).

Los estudios como el de Castro-Vega y cols. (9) validando un método de cribado nutricional como el MST, comparándolo con la Valoración Nutricional Completa y otros cribados nutricionales en distintos ámbitos sanitarios, publicado en este número de la revista *Nutrición Hospitalaria*, aportan luz para poder hacer una selección acertada. Este trabajo se presenta como un subanálisis del estudio sobre la prevalencia del riesgo de desnutrición y desnutrición establecida en población ambulatoria, institucionalizada y hospitalizada en un departamento de salud valenciano (10).

Los autores, con una adecuada metodología, han demostrado la utilidad del MST en el cribado nutricional en más de 800 pacientes ambulatorios, institucionalizados y hospitalizados y no solo en el paciente oncológico, colectivo para el que ya está validado el método. El MST diagnostica en este estudio más del 80% de los pacientes en riesgo nutricional con alta sensibilidad (69,4%) y especificidad (94,2%), así como una buena concordancia y validez respecto a la valoración nutricional completa. Su aportación en nuestro medio es muy interesante identificando los sujetos en riesgo nutricional y evitando los falsos positivos. Esta última circunstancia añade valor a esta herramienta ya que permite limitar la utilización de recursos (profesionales y tiempo), en pacientes que no son subsidiarios de un plan atención nutricional integral que incluye, como paso inmediato al cribado, realizar una valoración nutricional completa.

Castro- Vega y cols. destacan también entre las bondades de este método, cuando se compara con el resto de los estudiados en esta publicación (MUST y MNA-SF), que ofrece la versatilidad de poder ser realizado por personal sanitario, el propio paciente o sus familiares, lo que evidentemente se aprecia como una ventaja sobre el resto de los estudiados. Este hecho y el de permitir evitar los falsos positivos, constituyen los aspectos de mayor interés, a nuestro juicio, en aras de la eficiencia nutricional.

La implantación de métodos de cribado nutricional en los distintos niveles asistenciales resulta ser uno de los pilares fundamentales de la lucha contra la DRE en Europa. Modelos como el holandés con el desarrollo del SNAQ (Screening Nutritional Assessment Questionary) en sus distintas variantes según nivel asistencial, o el británico con la creación del MUST aportando un interesante algoritmo de actuación encadenado a los resultados del mismo muestran, con sus buenos resultados, un modelo a imitar.

En España, la Sociedad Española de Nutrición Parenteral (SENPE) junto a la Fundación Abbott lideran el movimiento Alianza Masnutridos (www.alianzamasnutridos.org). En su Plan de Lucha contra la DRE uno de los principios de su decálogo establece la necesidad de la realización de un cribado universal. El desarrollo de este movimiento, que arranca del Proyecto Masnutridos, ha potenciado la realización de estudios piloto en diferentes comunidades autónomas. La instauración de una metodología de cribado, escogida en cada centro según sus necesidades, ha permitido hacer una foto de nuestra realidad local y nacional, iniciar procedimientos de buenas prácticas e implementar medidas generales en las distintas comunidades autónomas que han podido evaluar el impacto de sus resultados.

Sin embargo, compartimos con distintos autores que existe una serie de factores que influyen negativamente, dificultando la implantación de métodos de cribado nutricional en los distintos ámbitos sanitarios. Entre ellos queremos destacar la falta de formación y sensibilidad de los profesionales sanitarios, en ocasiones provocado por el exceso de confianza de los equipos médicos y de enfermería en sus apreciaciones personales a la hora de valorar a los pacientes, asociado a una falta de rutina en la incorporación del registro de la medida de los resultados de los test estandarizados.

Tampoco podemos olvidar la falta de recursos, especialmente el tiempo ante una importante sobrecarga asistencial y, en ocasiones, la disponibilidad de peso y tallímetro.

Por último, uno de los principales factores limitantes de éxito en esta empresa estriba en la falta de una política claramente definida y la dificultad para identificar el método de cribado más adecuado. Por todo esto, la información de los estudios de validación de cribado nutricional, como el que se publica en este

número, añaden conocimiento, iluminan y facilitan la toma de decisiones en el abordaje integral del sujeto enfermo en riesgo de DRE.

editorial

Julia Álvarez Hernández

Sección de Endocrinología y Nutrición. Hospital Universitario Príncipe de Asturias. Alcalá de Henares, Madrid
(julia.alvarez@movistar.es)

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Trabajo Original

Nutrición artificial

Multicenter study of parenteral nutrition in non-critically ill elderly patients compared to younger patients - Study IAIOS-PN (Incidence and Assessment of Iatrogenesis in Older Subjects receiving Parenteral Nutrition)

Estudio multicéntrico de nutrición parenteral en pacientes ancianos no críticos comparados con pacientes más jóvenes - Estudio IAIOS-PN (Incidencia y Valoración de Iatrogenia en Sujetos Ancianos que reciben Nutrición Parenteral)

Javier Mateu-de Antonio¹, David Berlanda², Montserrat Pons-Busom³, Maria B. Badia-Tahull⁴, María Teresa Miana-Mena⁵, Beatriz Martínez-Castro⁶, Neus Sunyer-Esquerrà⁷, Mónica Sanmartín-Suñer⁸, Juan González-Valdivieso⁹, Elisabet Leiva-Badosa⁴, Eva Martínez-Bernabé¹⁰, Anna Murgadella-Sancho¹¹, Nuria Mirerachs-Aranda¹², Anna Vila-Bundó¹³, Jordi Fernández-Morató¹⁴ and María Teresa Vitales-Farrero¹⁵

¹Pharmacy Department. Hospital del Mar. Barcelona, Spain. ²Pharmacy Department. Hospital Universitari Vall d'Hebron. Barcelona, Spain. ³Pharmacy Department. Hospital Universitari Sagrat Cor. Barcelona, Spain. ⁴Pharmacy Department. Hospital Universitari Bellvitge - IDIBELL. Hospitalet de Llobregat, Spain. ⁵Pharmacy Department. Hospital Clínic de Barcelona. Barcelona, Spain. ⁶Pharmacy Department. Hospital Universitari Arnau de Vilanova. Lleida, Spain. ⁷Pharmacy Department. Hospital Universitari de Girona Dr. Josep Trueta. Girona, Spain. ⁸Pharmacy Department. Quironsalud Hospital General de Catalunya. Sant Cugat del Vallès, Spain. ⁹Pharmacy Department. Consorci Sanitari de Terrassa. Terrassa, Spain. ¹⁰Pharmacy Department. Corporació de Salut del Maresme i la Selva. Blanes, Spain. ¹¹Pharmacy Department. Hospital Dos de Maig. Barcelona, Spain. ¹²Pharmacy Department. Fundació Hospital Esperit Sant. Santa Coloma de Gramenet, Spain. ¹³Pharmacy Department. Fundació Sanitària Mollet. Mollet del Vallès, Spain. ¹⁴Pharmacy Department. Centro Médico Teknon. Barcelona, Spain. ¹⁵Pharmacy Department. Consorci Hospitalari de Vic. Vic, Spain

Abstract

Objective: this study assessed the incidence of hyperglycemia, hypertriglyceridemia, and liver function test (LFT) alterations among patients older and younger than 65 years receiving parenteral nutrition (PN). A secondary objective was to compare the incidence of any of these three events.

Material and methods: inclusion criteria were non-critically ill adult inpatients receiving PN for ≥ 7 days in 15 hospitals in Spain. Exclusion criteria were hyperglycemia, hypertriglyceridemia, LFT alterations, sepsis, shock, pancreatic/hepatobiliary surgery, renal failure, diabetes mellitus (DM) type 1, insulin-treated DM type 2, acute DM complications, or obesity prior to PN. Patients were classified into groups YOUNG (aged 35-64) and OLD (aged 65-95).

Results: this study recruited 200 patients. Group YOUNG included 63 (31.5%) patients and OLD, 137 (68.5%). Hyperglycemia appeared in 37 (18.5%) patients, eight (12.7%) in group YOUNG and 29 (21.2%) in group OLD ($p = 0.174$). Hypertriglyceridemia appeared in only one (0.7%) patient. LFT alterations appeared in 141 (70.5%) patients, 44 (69.8%) in group YOUNG and 97 (70.8%) in group OLD ($p = 1.000$). The model for hyperglycemia included DM type 2, previous surgical procedure, and use of hyperglycemia-inducing medications. The model for LFT alteration included previous surgical procedure, amount of lipids and amino acids, medications causing LFT alterations and a trend for age group. The model for any event included surgical procedure, DM type 2, and medications causing alterations.

Conclusion: patients of ≥ 65 years receiving PN had similar incidences of hyperglycemia, hypertriglyceridemia, and LFT alterations as younger patients. Additionally, older patients had trends toward lower LFT alterations.

Resumen

Objetivo: valorar la incidencia de hiperglicemia, hipertrigliceridemia y alteraciones de los parámetros bioquímicos hepáticos (PBH) en pacientes mayores de 65 años frente a pacientes más jóvenes con nutrición parenteral (NP). El objetivo secundario fue comparar la incidencia de cualquiera de los tres eventos.

Material y métodos: se incluyeron adultos no críticos hospitalizados que recibieron NP durante siete días o más en 15 hospitales españoles. Se excluyeron pacientes con hiperglicemia, hipertrigliceridemia, alteración de los PBH, sepsis, shock, cirugía biliopancreática, insuficiencia renal, diabetes tipo 1 o tipo 2 insulinodependiente, complicaciones diabéticas agudas y obesidad previas a la NP. Los pacientes se clasificaron en dos grupos: YOUNG (35-64 años) y OLD (65-95 años).

Resultados: se incluyeron 200 pacientes; 63 (31,5%) en el grupo YOUNG y 137 (68,5%) en el OLD. Se detectó hiperglicemia en 37 (18,5%) pacientes, ocho (12,7%) en el grupo YOUNG y 29 (21,2%) en el OLD ($p = 0,174$). Solo hubo un caso (0,7%) de hipertrigliceridemia. Alteraciones de PBH aparecieron en 141 (70,5%) pacientes, 44 (69,8%) en el grupo YOUNG y 97 (70,8%) en el OLD ($p = 1,000$). El modelo para hiperglicemia incluyó como variables diabetes tipo 2, cirugía previa y el uso de medicamentos hiperglicemiantes. El modelo para alteración de PBH incluyó cirugía previa, dosis de lípidos y aminoácidos y medicaciones hepatotóxicas. Hubo una tendencia a menor alteración por la edad. El modelo global para cualquier evento incluyó cirugía previa, diabetes tipo 2 y medicaciones que causen las alteraciones estudiadas.

Conclusión: los pacientes de 65 años o más que recibieron NP tuvieron incidencias similares de hiperglicemia, hipertrigliceridemia y alteración de PBH a las de los pacientes más jóvenes. Hubo una tendencia a menor alteración de PBH en los pacientes mayores.

Key words:

Aged. Drug-induced liver injury. Hyperglycemia. Hypertriglyceridemia. Liver disease. Parenteral nutrition.

Palabras clave:

Ancianos. Fármacos hepatotóxicos. Hiperglucemia. Hipertrigliceridemia. Hepatopatía. Nutrición parenteral.

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Correspondence:

Javier Mateu-de Antonio. Pharmacy Department. Hospital del Mar. Passeig Marítim, 25-29. 08003 Barcelona, Spain
e-mail: FMateu@hospitaldelmar.cat

INTRODUCTION

Life expectancy has increased steadily in developed countries during the last century and the health status of people aged ≥ 65 years is therefore of growing importance. This age group is known to present increased risk of several diseases that are associated with greater use of health resources. Currently, older age is not a contraindication for surgical procedures (1,2) or for admission to intensive care units (ICU) (3), but older patients do experience more surgical complications and have increased risk of adverse outcomes (1,3). Older age is also not a contraindication for parenteral nutrition (PN) (4). To our knowledge, no specific studies have been published on the prevalence of PN support in older patients in comparison to younger patients in general hospitals. In a retrospective-cohort study on critically-ill adult patients in 125 USA hospitals, PN usage declined slightly and similarly, around 6%, over time in all age groups, including elderly patients, during an eight-year period (5). A cross-sectional study on PN use over three months in 15 acute care hospitals in the north of England found that patients receiving PN had a median age > 65 years (6). Thus, older patients seem to be exposed to PN in at least the same proportions as younger patients. However, few studies have assessed the effect of PN in the elderly compared to young patients (7,8). These retrospective studies did not find differences in nutritional and inflammatory markers, biochemical outcomes and associated morbidity of PN when compared to younger controls. However, older patients may present metabolic alterations during PN as diminished plasma lipoprotein-lipase activity (9), limited capacity to mobilize fat stores (10), and lower glucose oxidation (11) or have comorbidities that could increase PN complications (4).

The main purpose of this study was to assess metabolic complications of PN, comparing the incidence of adverse events (hyperglycemia, hypertriglyceridemia, and liver function test [LFT] alterations) in non-critically ill adult inpatients receiving PN between those patients ≤ 64 years and those ≥ 65 . A secondary purpose was to compare the incidence, as a first appearance, of any of these three adverse events, as a variable of overall metabolic complications between the two groups.

MATERIAL AND METHODS

A retrospective analysis of a prospectively collected data set was performed on a cohort of medical and surgical non-critically ill adult inpatients receiving PN in 15 hospitals in Catalonia (Spain) from January 1st 2014 to December 31st 2014. The study was reviewed and approved by the ethics committees of Hospital Universitari Sagrat Cor, Parc de Salut Mar, and Hospital Clínic de Barcelona, Spain. The rest of the hospitals adhered to these approvals.

PATIENTS

Patients were classified into two groups depending on age: group YOUNG included adult patients aged between 35 and

64 years (middle age and older adulthood), and group OLD, senior patients aged between 65 and 95 years (younger and older old age). They were followed-up until PN was discontinued for any reason or oral or enteral nutrition started, or they were admitted to ICU or to Post-Anesthesia Care Unit (PACU) for three days or longer, or were transferred to another hospital.

INCLUSION AND EXCLUSION CRITERIA

Patients who entered the study met the following inclusion criteria: non-critically ill, recent weight available, and PN duration longer than six days. In addition, PN, including peripheral PN containing lipid emulsions, had to be the unique source of nutritional support covering at least 80% of the equation-calculated resting energy expenditure (cREE) (12).

The following acute conditions at the beginning of PN were exclusion criteria: sepsis; hypovolemic or cardiogenic shock; renal failure with a calculated glomerular filtration rate (cGFR) < 30 ml/min/1.73 m² (13); triglyceridemia > 250 mg/dl; any LFT (total bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma glutamyl transferase [GGT], or alkaline phosphatase [ALP]) value > 1.5 -fold the upper limit of normal range (ULN); a glycemia test > 180 mg/dl 24 hours before the beginning of PN; biliary or hypertriglyceridemia-induced pancreatitis; and admission due to hyperosmolar hyperglycemia, diabetic ketoacidosis, or hypoglycemia under 70 mg/dl. Chronic conditions considered as exclusion criteria were: chronic liver disease, hepatobiliary disease, diabetes mellitus type 1, insulin-treated diabetes mellitus type 2, and body mass index (BMI) > 35 kg/m². Patients were also excluded if they underwent biliopancreatic or liver surgical procedures, or they were admitted for longer than three days to ICU or PACU within the first 72 hours of PN course.

VARIABLES

Main outcomes were the comparison of the incidence of hyperglycemia, hypertriglyceridemia, and LFT alterations between the two groups defined above. The secondary variable was defined as the combined variable of the presence of any of the above-mentioned complications (hyperglycemia, hypertriglyceridemia, or LFT alterations).

Hyperglycemia was defined as capillary or plasma glycemia ≥ 180 mg/dl. If it was registered by capillary test, it had to be measured at least twice daily. Hypertriglyceridemia was defined as plasma triglycerides > 400 mg/dl. LFT alteration was defined as any liver enzyme increase > 2 -fold the ULN, conjugated bilirubin > 2 mg/dl, or total bilirubin > 2.5 mg/dl. Blood clinical chemistry parameters were obtained at least once weekly.

DATA COLLECTED

At the beginning of the study, data collected were demographics (sex, age, and BMI), main diagnosis, ward area (medical, sur-

gical or trauma), date of surgical procedure if relevant, Charlson comorbidity index (14), indication for and date of PN initiation, and cREE calculated by the Mifflin-St Jeor equation (12). Additional data were registered when any alteration in main variables was detected and at the end of PN: amounts of macronutrients (amino acids, glucose, and lipids) delivered in PN, and the ratio of kilocalories provided by PN and cREE; biochemical parameters (glycemia, triglyceridemia, albumin, creatinine, total bilirubin, conjugated bilirubin, AST, ALT, GGT, ALP); ICU or PACU admission for three days or longer; the reason for PN discontinuation when it occurred, and PN duration. As overall health outcomes, hospital length of stay (LOS) and mortality during hospital admission were recorded.

As the co-administration of some medications might alter the variables studied, the number of medications affecting glycemia, triglyceridemia, or LFTs was collected when they were administered for at least three days during PN. A list of medications to be monitored relating to hyperglycemia (nine medications) (15), hypertriglyceridemia (12 medications) (16), and LFT alterations (53 medications) was obtained from several sources (17-19).

PARENTERAL NUTRITION

PN was prepared following usual hospital practices as an "all-in-one" admixtures containing amino acids, glucose and lipid emulsions. They were administered in a 24-hour perfusion through central catheters or peripheral lines.

STATISTICAL ANALYSIS

Descriptive statistics were reported by age category. Continuous variables were reported as mean $\pm$ standard deviation (SD), and categorical variables were reported as frequency and percent. To assess for equivalency between groups, continuous variables (age, Charlson comorbidity index, BMI, kilojoules from PN) were compared using Student's t-tests. The categorical variables (sex and admission diagnosis category) were compared using the Chi-squared test or Fisher's exact test.

Unadjusted incidence rates of complication outcomes (hyperglycemia, hypertriglyceridemia, and LFT alterations) were reported by age group. Using an adjusted Cox proportional hazard model, age categories were compared with regard to each complication outcome assessed (hyperglycemia, hypertriglyceridemia, and LFT alteration). Potential factors associated with the occurrence of each complication outcome studied were evaluated by the use of univariate analysis. For each complication assessed, variables with a two-tailed p-value below 0.10 in the univariate analysis or those that were deemed clinically relevant were selected for inclusion in a multivariate Cox proportional hazard model to identify variables associated with occurrence of the complication evaluated. The final model was determined using backward elimination variable selection (Wald statistic). The initial model contained all the independent variables selected.

In the same way, the secondary outcome was assessed by adding all potential factors found in a multivariate Cox proportional hazard model to identify variables associated with the occurrence of any of the complications studied.

Additional analyses were performed to compare the rate of patients free of any adverse event over time (Kaplan-Meier plot) between groups.

In all analyses, p values were two-tailed, and a $p < 0.05$ was considered as statistically significant. SPSS Version 12 statistical software for Microsoft Windows (SPSS Inc., Chicago, IL, USA) was used for all analyses.

RESULTS

This study recruited 200 patients. Group YOUNG included 63 (31.5%) patients and group OLD, 137 patients (68.5%). Both groups differed in several baseline parameters (Tables I and II). Group OLD presented lower cREE, cGFR, triglycerides, cholesterol, and albumin, but higher Charlson comorbidity index. This group received smaller amounts of macronutrients, but the same ratio of kilocalories provided/cREE during a similar period.

Hyperglycemia was detected in 37 (18.5%) patients, eight (12.7%) in group YOUNG, and 29 (21.2%) in group OLD ($p = 0.174$). Surgical patients showed greater rates of hyperglycemia and LFT alterations than non-surgical patients. Hypertriglyceridemia appeared in only one (0.7%) patient in group OLD. LFT alterations were detected in 141 (70.5%) patients, 44 (69.8%) in group YOUNG and 97 (70.8%) in group OLD ($p = 1.000$). Patients with LFT alterations showed differences in baseline cGFR, albumin, and ALP, and amounts of glucose and amino acids administered compared with those without alterations. Complication outcome incidence rates and differences found are listed in table III.

Table IV shows hazard ratios for hyperglycemia and LFT alterations, both adjusted for age group, surgical procedure, and medication use. Multivariate Cox models were additionally adjusted for differences found: for the hyperglycemia model, and for diabetes mellitus type 2 and amount of glucose administered. For the liver-function-test-alteration model, adjustments were for baseline FA, albumin, cGFR and amount of macronutrients administered. The final model for hyperglycemic events included diabetes mellitus type 2, surgical procedures, and use of medications that increase glycemia. For LFT alterations, the final model included surgical procedures, amounts of lipid and amino acid administered, use of more than one medication related to liver alteration, and age group.

The Cox proportional hazards regression for predictor variables on secondary outcome (the incidence of any of the three adverse events) found three variables as significant predictors: surgical procedure, diabetes mellitus type 2, and use of medications causing hyperglycemia, hypertriglyceridemia, or LFT alterations (Table IV). Amino acid amounts were also included in the final model. Since only one patient showed hypertriglyceridemia, no statistical analysis was performed for this complication.

Table I. Patients' diagnoses and parenteral nutrition indications

Variable	Group YOUNG Patients (%)	Group OLD Patients (%)	p
Diagnoses			
Lower gastrointestinal tract neoplasm	14 (22.2%)	54 (39.4%)	0.074
Non-neoplasm gastrointestinal disease	9 (14.3%)	23 (16.8%)	
Upper gastrointestinal tract neoplasm	10 (15.9%)	21 (15.3%)	
Inflammatory bowel disease	7 (11.1%)	9 (6.6%)	
Others	23 (36.5%)	30 (21.9%)	
Parenteral nutrition indication			
Post-operative ileus	13 (20.6%)	54 (39.4%)	0.066
Intolerance to oral or enteral feeding	11 (17.5%)	21 (15.3%)	
Small-bowel occlusion	13 (20.6%)	15 (10.9%)	
Other post-operative complications	6 (9.5%)	15 (10.9%)	
Others	20 (31.7%)	32 (23.4%)	

Adverse events were detected at day 6.01 ± 3.99 without differences between groups ($p = 0.952$). Hyperglycemia appeared at day 4.68 ± 4.45 ; the only hypertriglyceridemia was detected at day 7 and LFT alterations appeared at day 6.79 ± 4.12 .

Amongst those patients who suffered adverse events, patients of group OLD had the same number of days of PN (12.91 ± 7.48 vs 13.85 ± 6.66 ; $p = 0.462$), LOS (27.01 ± 16.41 vs 28.11 ± 13.82 ; $p = 0.691$) and mortality ($10/104$ vs $2/4$; $p = 0.343$) as those of group YOUNG.

There was no difference in the rates of patients free of any adverse event over time between the two groups ($p = 0.808$) as shown by the Kaplan-Meier curve in figure 1.

There were no differences between groups in the rates of incidence of variables from the beginning to the end of PN except for triglyceridemia, which increased more in group OLD (Table V).

DISCUSSION

In our study, older patients did not present a greater incidence of metabolic complications during PN than younger patients. In addition, older age was not related to the appearance of adverse events. In our patients, the main predictors for the adverse events studied were surgical procedures, diabetes mellitus type 2, and the concomitant use of medications related to metabolic disorders.

Our findings were in accordance with previous studies reporting no differences between older and younger non-critically ill patients

Table II. Baseline patient parameters and PN characteristics

Variable	Group YOUNG Mean $\pm$ SD	Group OLD Mean $\pm$ SD	p
Patient parameters			
Age, years	52.19 ± 7.62	76.77 ± 6.53	< 0.001
BMI, kg/m ²	24.86 ± 4.08	25.54 ± 3.69	0.240
cREE, kcal/kg/day	20.6 ± 1.9	18.7 ± 2.0	< 0.001
Charlson comorbidity index, points	2.95 ± 2.48	5.50 ± 4.25	< 0.001
Creatinine, mg/dl	0.70 ± 0.26	0.85 ± 0.28	0.001
cGFR, ml/min/1.73 m ²	104.1 ± 18.9	78.4 ± 17.9	< 0.001
Glycemia, mg/dl	112 ± 24	114 ± 28	0.570
Total bilirubin, mg/dl	0.47 ± 0.26	0.47 ± 0.27	0.998
ALT, U/l	19.5 ± 13.6	19.0 ± 13.0	0.815
AST, U/l	19.0 ± 10.0	20.8 ± 10.1	0.274
GGT, U/l	43.2 ± 24.5	37.6 ± 23.5	0.137
ALP, U/l	72.2 ± 29.9	74.0 ± 23.8	0.640
Triglycerides, mg/dl	127.1 ± 50.2	108.2 ± 43.0	0.008
Cholesterol, mg/dl	120.7 ± 44.2	101.9 ± 38.6	0.009
Total protein, g/dl	5.24 ± 0.83	4.97 ± 0.89	0.119
Albumin, g/dl	2.96 ± 0.58	2.57 ± 0.65	< 0.001
PN characteristics			
Amino acids, g/kg/day	1.24 ± 0.03	1.06 ± 0.23	< 0.001
Glucose, g/kg/day	3.07 ± 0.77	2.77 ± 0.58	0.002
Fat, g/kg/day	0.81 ± 0.29	0.78 ± 0.22	0.502
kcal/kg/day	25.33 ± 6.8	23.15 ± 4.7	0.009
Ratio kcal provided/cREE	1.23 ± 0.30	1.25 ± 0.26	0.679
Days of PN	14.1 ± 8.0	12.7 ± 7.2	0.208

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; cGFR: calculated glomerular filtration rate; GGT: gamma glutamyl transferase; cREE: resting energy expenditure.

receiving PN (7,8). Nonetheless, differences were found on baseline characteristics as well as amount of nutrients administered between the two groups assessed. However, differences found have been assessed with regression models in order to manage them.

In an early study, aging was reported to increase glycemia during PN in a heterogeneous cohort including critically-ill patients (20) but rates of hyperglycemia were not assessed. Diminished insulin response in the injured elderly might have contributed to this finding (20). In a study on a cyclic 6-hour PN regimen with high energy low protein content, glucose oxidation was about 30% lower and glycemia was about 20% higher with comparable insulinemia in elderly patients when compared with middle-aged patients (11).

Table III. Complication outcome incidence rates

Variable		Liver function test alteration		p	Hyperglycemia		p
		Yes	No		Yes	No	
Group YOUNG (≤ 64)		44 (69.8)	19 (30.2)		8 (12.7)	55 (87.3)	
Group OLD (≥ 65)		97 (70.8)	40 (29.2)	1.000	29 (21.2)	108 (78.8)	0.174
Medications*	Yes	116 (76.8)	35 (23.2)		26 (32.1)	55 (67.99)	
	No	25 (51.0)	24 (49.0)	0.001	10 (9.3)	98 (90.7)	< 0.001
Surgery	Yes	107 (76.4)	33 (23.6)		32 (22.9)	108 (77.1)	
	No	34 (56.7)	26 (43.3)	0.007	5 (8.3)	55 (91.7)	0.017
Amino acids, g/kg/day		1.05 (0.30)	1.16 (0.21)	0.010	1.08 (0.30)	1.12 (0.29)	0.498
Glucose, g/kg/day		2.74 (0.77)	2.97 (0.61)	0.033	2.71 (0.64)	2.87 (0.65)	0.188
Fat, g/kg/day		0.81 (0.47)	0.82 (0.19)	0.861	0.75 (0.18)	0.79 (0.26)	0.273
kcal/kg/day		23.28 (7.61)	24.76 (4.62)	0.167	22.71 (4.98)	23.97 (5.59)	0.208
ALT, U/l		19.59 (13.10)	18.06 (13.22)	0.455	22.10 (15.48)	18.47 (12.47)	0.129
AST, U/l		20.74 (10.29)	19.03 (9.37)	0.302	21.69 (10.11)	19.90 (10.02)	0.353
GGT, U/l		39.69 (23.79)	38.40 (24.44)	0.756	39.46 (22.87)	39.36 (24.16)	0.983
ALP, U/l		70.7 (20.8)	80.1 (34.4)	0.020	71.1 (21.1)	74.0 (26.8)	0.546
Total bilirubin, mg/dl		0.48 (0.26)	0.46 (0.27)	0.591	0.42 (0.19)	0.48 (0.29)	0.167
Albumin, g/dl		2.64 (0.60)	2.81 (0.75)	0.096	2.58 (0.5)	2.72 (0.7)	0.246
cGFR, ml/min/1.73 m ²		84.4 (21.8)	91.5 (21.0)	0.036	84.3 (18.7)	87.0 (22.4)	0.490

*For the analysis, the presence of more than one medication affecting liver function tests or glycemia, depending on the statistical test, was considered. Variables presented as value (%) or value ($\pm$) depending on the variable shown. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; cGFR: calculated glomerular filtration rate; GGT: gamma glutamyl transferase.

Table IV. Hazard ratios (HRs) for occurrence of liver function test alteration, hyperglycemia and any complication

Variable	Hyperglycemia	Liver function test alteration	Any event
Age group (older)	Not included, $p = 0.74$	0.69 (0.47-1.02), $p = 0.06$	Not included, $p = 0.26$
Medication use	3.47 (1.65-7.32)*, $p < 0.01$	1.86 (1.19-2.92) [†] , $p < 0.01$	1.59 (1.01-2.50) [‡] , $p = 0.04$
Surgery	3.27 (1.26-8.48), $p = 0.02$	1.86 (1.25-2.78), $p < 0.01$	2.04 (1.38-3.00), $p < 0.01$
Diabetes type 2	4.48 (2.11-9.51), $p < 0.01$	----	2.19 (1.25-3.82), $p < 0.01$
Amino acids, g/kg/day	-----	0.20 (0.09-0.44), $p < 0.01$	0.56 (0.28-1.10), $p = 0.09$
Fat, g/kg/day	-----	2.66 (1.50-4.73), $p < 0.01$	Not included, $p = 0.61$
Glucose, g/kg/day	Not included, $p = 0.36$	Not included, $p = 0.18$	Not included, $p = 0.81$

Presented as hazard ratio (95% confidence interval). *Medications related to hyperglycemia. [†]Medications related to liver alterations. [‡]Medications related to any of the events assessed (liver alteration or hyperglycemia).

In a more recent study to determine the prevalence of diabetes, prediabetes, stress hyperglycemia, and factors affecting hyperglycemia (> 180 mg/dl) in non-critically ill patients receiving PN, age ≥ 65 years showed a significant relationship to the development of hyperglycemia compared with younger age groups (21). However, age was not found to be a factor for hyperglycemia in the present study maybe because we excluded diabetes mellitus type 1 and insulin-treated diabetes mellitus type 2 patients. This discrepancy could be also related to the glucose doses received.

Older and younger patients received similar glucose loads in these former studies. In our study, older patients received about 0.3 g of glucose/kg/day and about 2.18 kcal/kg/day less than younger patients. This is consistent with the fact that older patients have less cREE than younger patients (22,23), but our older patients received the same ratio of kcal provided/cREE as younger ones (Table II).

Studies on fat oxidation rates have shown inconclusive results in older adults compared to younger ones (23).

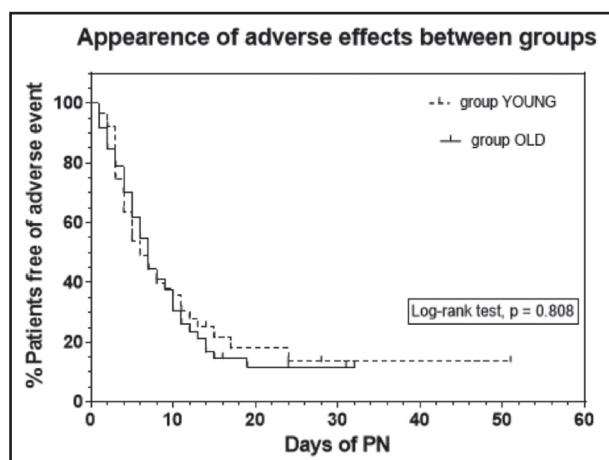


Figure 1.

Comparison of the rate of patients free of any adverse event over time.

Table V. Evolution of variables during PN

Variable	Differences between final and initial values during PN		
	Group YOUNG Mean $\pm$ SD	Group OLD Mean $\pm$ SD	p
Creatinine (mg/dl)	-0.07 $\pm$ 0.1	-0.13 $\pm$ 0.29	0.065
Glomerular filtration rate, ml/min/1.73 m ²	5.5 $\pm$ 11.2	9.2 $\pm$ 15.3	0.058
Glycemia, mg/dl	2.8 $\pm$ 29.0	3.8 $\pm$ 39.5	0.839
Total bilirubin, mg/dl	-0.04 $\pm$ 0.30	-0.01 $\pm$ 0.26	0.458
ALT, U/l	24.3 $\pm$ 43.8	21.2 $\pm$ 48.8	0.664
AST, U/l	12.5 $\pm$ 28.4	15.9 $\pm$ 50.4	0.646
GGT, U/l	204.6 $\pm$ 274.0	178.9 $\pm$ 234.4	0.496
ALP, U/l	81.8 $\pm$ 97.8	75.9 $\pm$ 92.0	0.688
Triglyceridemia, mg/dl	31.0 $\pm$ 61.7	50.2 $\pm$ 56.8	0.035

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase.

Specifically, older patients presented roughly 30% higher lipid oxidation, 35% higher FFA blood levels, and a lower respiratory quotient, but comparable triglyceridemia levels (11). In other study, older subjects presented higher FFA blood levels, about 65% lower lipoprotein lipase activity, and about 15% lower fat oxidation rates than younger patients, but triglyceridemia remained comparable in both groups. The authors concluded that elderly subjects can metabolize intravenous fat emulsions similarly to young individuals (9). In our study, at the end of PN, older patients showed higher triglyceridemia than younger patients while receiving a fat load of around 0.8 g/kg/day (Table V), but only one hypertriglyceridemic episode was detected. Our findings seem to be in agreement with the aforementioned studies, showing that older patients can main-

tain triglyceridemia levels similarly to younger patients, despite differences in fat oxidation. In contrast, in other study hypertriglyceridemia was detected in 36% of older patients (≥ 80 years) versus 8% in younger patients (< 80 years), but the authors did not show nutritional loads and mean triglyceridemia. Additionally, they defined hypertriglyceridemia as > 168 mg/dl whilst we set the cut-off point at 400 mg/dl in accordance with current European guidelines (24) and PN hypertriglyceridemia literature (25).

The influence of age has not been studied extensively in PN in association with liver alterations in adults. Reilly et al. found no differences in maximum values of ALT, ALP, and bilirubin in patients < 80 years when compared to older patients. However, the group of older patients represented only 13% of the entire cohort (8). In a study using a cumulative logit model and including 162 patients receiving home PN for > 6 months, age was not a relevant factor in the development of liver disease (26). In another study on home PN, age was not a factor for chronic biochemical cholestasis in a cohort of 113 patients (27). Additionally, age was not a factor for liver dysfunction associated with specialized nutrition support in a prospective cohort of 725 critically ill patients (28). Indeed, in our study, age ≥ 65 showed a trend to a reduced incidence of this adverse event. We hypothesized that already diminished bile acid production and excretion, as occurs in older patients (29), could have been an influence in our findings.

Parenteral nutrition liver disease (PNALD) and LFT alterations associated to PN are considered to be of multifactorial origin and have a decreased incidence in adults compared to infants. Main factors in its development are excess caloric intake of macronutrients, specially fats, infectious or septic events, inflammation, oxidative stress, nutrient deficiencies, and contaminants in parenteral products (30). In general, our findings are in agreement with this knowledge: surgery as a pro-inflammatory factor and increased fat load.

Nevertheless, amino acid load has been found to reduce its incidence in our study. This parameter has not been studied extensively in adults and usually has not been considered to play a role in PNALD currently (17). To our knowledge, only one prospective study found that a load > 1 g protein/kg/day was deleterious for liver parameters (31). The role of amino acid load in LFT alterations during PN would require further studies.

In PN, the contribution of concomitant medications to adverse events has not been assessed in depth. The simultaneous use of some medications during PN has been shown to be of relevance for developing hyperglycemia (15,21) or hypertriglyceridemia (16), but we could not find studies for LFT alterations or PNALD. In our work, the simultaneous use of two or more medications has been associated with a moderate contributory influence in LFT alterations and a strong influence in hyperglycemia. These results on the effect of medications in PN toxicity warrant further investigation.

This is the first multicenter study that has evaluated the metabolic complications of PN in patients of ≥ 65 years compared to younger patients, but our study had several limitations. They include its observational design, and differences in amount of nutrients administered. Regression models adjusted by some of these limitations have been used to manage them. Besides, obser-

vational cohort studies can provide a reflection of daily clinical practices. The groups had several differences that replicated the differences that would be expected to be found between younger and older patients. Older patients have usually more comorbidities, worse renal function, and lower albuminemia.

Nutritional loads were different between the two groups, but both received the same amount of energy intake in relation to their cREE. This approach would be acceptable in our opinion. In clinical trials, it has been acceptable to use different medication doses in older people to reach the same efficacy (32). Critically-ill patients were not included in order to have a homogenous population, as well as to have a controlled number of variables to be adjusted for. Therefore, the results obtained could not be extrapolated to this group of patients. Finally, other PN safety variables, such as catheter-related infections, acid-base disturbances, metabolic bone disease, and other alterations were not assessed. We assessed the most prevalent adverse effects related to PN in hospitalized patients, since for less prevalent events a larger cohort would be needed.

In conclusion, non-critically ill inpatients of ≥ 65 years receiving PN had the same incidence of hyperglycemia, hypertriglyceridemia, and LFT alterations as younger patients when administered a caloric intake adapted to their cREE. In addition, the older age group may have a trend to a lower prevalence of LFT alterations related to PN.

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Trabajo Original

Nutrición artificial

Incidents and adverse events in enteral feeding tube users: warnings based on a cohort study

Incidentes y eventos adversos en usuarios de sonda enteral: alerta a partir de una cohorte

Franciele Anziliero and Mariur Gomes Beghetto

School of Nursing, Federal University of Rio Grande do Sul (UFRGS), Rio Branco, Porto Alegre

Abstract

Introduction: few studies clearly describe incidents or adverse events that occur during the enteral nutrition process, which hinders the identification of critical points.

Objective: to describe breaches of protocol, incidents and adverse events, during the period beginning with indications until the use of enteral feeding tube in an Emergency Department.

Method: trained nurses prospectively monitored a cohort of adults in a Brazilian Emergency Department where use of enteral feeding tube was indicated and up to their use. The study sought to identify breaches of protocol, such as verbal orders to insert feeding tubes, or authorization of their use without X-rays to confirm the position of the feeding tubes. Incidents were characterized as events that could have caused harm to patients, while adverse events were those that did actually cause harm. The study was approved by the institution's Research Ethics Committee.

Results: in 150 feeding tube insertions, there were 169 breaches of protocol: verbal orders for feeding tube insertion ($n = 59$); no X-rays taken ($n = 11$); and no examination of the X-rays by physicians ($n = 12$). There were 30 incidents: unintentional removal of the feeding tube ($n = 23$); and administration of enteral nutrition after breach of preventive barriers. There was one adverse event: aspiration of enteral nutrition.

Conclusion: there was a high frequency of breaches of safety protocols; many developed into incidents, and one resulted in an adverse event.

Key words:

Enteral nutrition.
Emergency
Department. Hospital.
Patient safety.

Resumen

Introducción: pocos estudios describen claramente los incidentes o eventos adversos que suceden durante el proceso de nutrición enteral, dificultando la identificación de puntos críticos.

Objetivo: describir las rupturas de protocolo, los incidentes y los eventos adversos de la indicación para uso de sondas nasogástricas en un Servicio de Urgencias.

Método: enfermeras capacitadas siguieron prospectivamente a una cohorte de adultos de un Servicio de Urgencias brasileño, con indicación de uso de sonda enteral. Se buscó identificar las rupturas de protocolo, descritas como: "orden verbal" para inserción de la sonda o para aprobar su uso; y no realización de radiografía confirmatoria del posicionamiento de la sonda. Los incidentes fueron considerados eventos que podrían haber provocado daños al paciente, mientras que los eventos adversos, como incidentes que efectivamente los provocaron. Este proyecto fue aprobado por el Comité de Ética en Investigación de la institución.

Resultados: en 150 inserciones de sonda hubo 169 rupturas de protocolo: orden verbal para inserción de sonda ($n = 59$), no realización de radiografía ($n = 11$) y radiografía no evaluada por médico ($n = 12$). Ocurrieron 30 incidentes: retiro inadvertido de sonda ($n = 23$) y administración de dieta en vigencia de ruptura de barreras ($n = 7$). Hubo un evento adverso grave (aspiración de dieta).

Conclusión: hubo elevada frecuencia de ruptura de protocolo de seguridad; muchas evolucionaron a incidentes y uno de ellos resultó evento adverso.

Palabras clave:

Nutrición enteral.
Servicio de
Urgencias. Hospital.
Seguridad del
paciente.

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Correspondence:

Franciele Anziliero, School of Nursing, Federal University of Rio Grande do Sul (UFRGS), Room 220, Rua São Manoel, 963. 90620-110 Rio Branco, Porto Alegre - RS
e-mail: francieleanziliero@gmail.com

INTRODUCTION

Despite being frequent in Brazilian hospitals and other centers, the insertion, maintenance and administration of enteral feeding tube (EFT) are procedures with risks. Errors in the position of the distal tip of the feeding tube can result in serious complications (1), such as aspiration or infusion of enteral nutrition or medication in the respiratory tract (1,2). In a study (2) prompted by the occurrence of two events, 2,079 feeding tube insertions were reviewed. X-ray reports between 2001 and 2004 were examined, looking for combinations of feeding tube, lung, pneumothorax and bronchus. In 1.3% ($n = 50$) of the patients, the X-ray reports showed that the distal tip of the feeding tube was located in the bronchi or lung. Among these 50 patients, 10% developed pneumonia, 16% experienced a pneumothorax, and two deaths were directly associated with incorrect anatomical positioning of the feeding tube. These findings show that the frequency of serious adverse events (permanent damage or death) is low, albeit of high clinical relevance, which justifies the adoption of strategies to minimize such risks.

Since incidents can occur at different times throughout the process in the period between indication and clinical use of EFT, the Brazilian Ministry of Health has established rules for the care of patients on enteral nutrition (EN) (3). The proposed actions are based on national (4) and international (5) guidelines and require the implementation of preventive measures when administering EN. These measures include confirming the prescription information on the enteral nutrition label, correct patient identification and composition of the therapy, and checking the entire access line to the gastrointestinal tract, with special attention to the anatomical position of the distal tip of the feeding tube, confirmed through X-rays (3-5).

In certain situations, the risk of incidents and adverse events can be even greater, such as in Emergency Departments, since they are characterized by overcrowding, high circulation of professionals, complex work processes and miscommunication, which can contribute to mistakes during the provision of care, such as in the EN process (6-8). Furthermore, most feeding tube insertions in hospitals are indicated in Emergency Departments (9). Especially in the Brazilian Health System, this data is corroborated by the fact that almost all hospital admissions take place through Emergency Departments. It is also worth noting that, in Brazil, short-term devices (Levin tube - Dobhoff type) are widely used for long periods, when long-term devices are indicated (10,11). The use of long-term devices for EN is still not a reality in Brazil.

Therefore, given the shortage of publications describing incidents or adverse events that occur during the enteral nutrition process, which hinders identifying critical points, especially in Emergency Departments, the objective of the present study was to describe breaches of protocol, incidents and adverse events related to the insertion and maintenance of EFT in an Emergency Department.

METHODS

In the first half of 2015, a cohort of adults (> 18) who needed the placement of enteral feeding tubes to administer therapy

(nutrition, water and/or medication) was prospectively monitored during the care they received in an Emergency Department. This Emergency Department is part of a 795-bed tertiary university hospital which is a reference for clinical patients in the south of Brazil. The institution where the study was conducted is certified by the Joint Commission International (JCI) and has a protocol that outlines the EN process: a) the physician prescribes the placement of the feeding tube and informs the nurse responsible for the patient; b) the nurse blindly inserts the EFT at the bedside, performing clinical tests, such as auscultation; c) the patient must be X-rayed to determine the position of the distal tip of the feeding tube; d) the attending physician examines the X-ray image and expresses an opinion on the patient's medical record, authorizing use of the feeding tube for administration of therapy, or requesting that the feeding tube be repositioned; and e) administration of therapy via the feeding tube, which should only be done after completing all the previous steps.

The selection of patients was based on a list generated when physicians prescribed feeding tubes. The sample was consecutive, by convenience. Patients whose EFT were inserted using endoscopy or during surgery; who had previously undergone gastrointestinal tract surgery or surgery in the region of the head and neck; or for whom there were contraindications for blind insertion of EFT were not included. It is worth noting that all patients used the same type of radiopaque feeding tube, with a tungsten distal tip and 10 Fr steel guidewire.

Previously trained nurses monitored the patients during every stage of the EN protocol (from indication to actual use of EFT), every day of the week, 24 hours a day, using a standardized instrument for data collection. Clinical data, as well as data on the patients' treatment and data related to the work process, were examined. The electronic patient records were also consulted daily in search of additional data.

Failures to comply with any of the steps of the institution's protocol were considered as breaches of protocol, including verbal orders to insert enteral feedings tube or authorize their use, considering that EN is not an emergency procedure. A guideline from the Brazilian Ministry of Health was used (12), based on definitions from the World Health Organization (13) that defines incidents as events or circumstances that could have resulted in unnecessary harm to patients, such as: unintentional removal of the EFT; obstruction of the feeding tube; administration of therapy/EN without having taken an X-ray; administration of therapy/EN without medical authorization to use the feeding tube; and administration of therapy with the EFT in a risk position for aspiration. In the same reference, adverse events are deemed to be any incidents that result in harm to patients.

The data was assessed according to its characteristics and distribution. When possible, associations between the categorical variables were tested using the Chi-squared test or Fisher's exact test. For all the analyses, the Statistical Package for the Social Sciences (SPSS) Version 20.0 was used.

All the outcomes were witnessed by the researchers during the monitoring of the cohort and communicated to the care team so that the applicable care and administrative measures could be

carried out. The methodological and ethical aspects of the study were approved by the institution's Ethics Committee for Research (protocol no. 150028).

RESULTS

A total of 150 EFT placement procedures were monitored. There was a high number of breaches of protocol ($n = 169$) and incidents ($n = 30$) during one or more steps of the process (from indication of the EFT to its actual use). There was one serious adverse event. The characteristics of the patients who used an EFT are described in table I.

Among the breaches of protocol, verbal orders, rather than written, for insertion (39.3%) and authorization to use feeding tubes (58%) were the most frequent. In 7.3% of the placements X-rays were not performed or the attending physicians failed to issue written or verbal opinions on the position of the EFT after the X-rays (8%).

As for incidents, there was a large number of cases where feedings tubes were accidentally displaced (traction) or unintentionally removed by patients (15.3%), resulting in another insertion procedure. In some patients, the procedure (feeding tube reinsertion) needed to be repeated twice (16.2%) or three times (5.6%). When the association between the condition of patients at the time of feeding tube insertion and the proportion of unintentional removals was examined, it was noted that those who were alert or agitated removed the device the most (78.3% *versus* 50.4%; $p = 0.014$). There were no cases of obstructions of feeding tubes (Table II).

Among the eleven insertions where X-rays were not taken, there was direct administration of enteral nutrition via feeding tubes in three. In addition, among the 12 insertions where there was no record of medical authorization to use feeding tubes, administration of nutrition occurred in two. In one case, the three first steps of the protocol were performed (written prescription for the

Table I. Characteristics of the patients who used an enteral feeding tube at an Emergency Department in the south of Brazil

Characteristics	n (%)
Age ($\pm$ SD)	65 $\pm$ 17.2
Male gender	60 (52.7)
<i>Reason for admission to the ED</i>	
Neurological problems	56 (48.7)
Respiratory problems	26 (22.6)
Gastrointestinal problems	22 (19.1)
Other	11 (9.6)
<i>Reason for indication of EFT*</i>	
Lower sensory functions	60 (40)
Lack of appetite or dysphagia	57 (38)
Invasive or noninvasive mechanical ventilation	22 (14.7)
Malnutrition	6 (4)
Other	5 (3.3)
<i>Previous diseases</i>	
Stroke (ischemic or hemorrhagic)	19 (16.5)
Parkinson or Alzheimer	14 (12.2)
Cerebral palsy or epilepsy	12 (10.4)
Systemic arterial hypertension	59 (51.3)

Source: research data, 2017. *The reasons for indication of the enteral tube were calculated using the total number of insertions ($n = 150$), since some patients who needed reinsertion had, as described in their charts, different reasons from the initial indication. The other values refer to the number of patients ($n=115$), since some patients required reinsertion of the enteral tube. ED: Emergency Department; EFT: enteral feeding tube.

Table II. Breaches of protocol, incidents and adverse events related to the insertion, maintenance and administration of therapy by EFT in an Emergency Department. The data is presented in absolute numbers and proportions

Outcome	Risk condition	n (%)
Breaches of protocol	Prescription to insert tube only by verbal order	59 (39.3)
	Authorization to use tube only by verbal order	87 (58)
	No X-ray taken	11 (7.3)
	No record of medical authorization to use the tube	12 (8)
Incidents	Accidental removal of the EFT	23 (15.3)
	Obstruction of the EFT	0 (0)
	Administration of therapy without an X-ray	3 (2)
	Administration of therapy with no record of medical authorization to use the tube	2 (1.3)
	Administration of therapy with the EFT in a bronchoaspiration risk position	2 (1.3)
Adverse event	Bronchoaspiration	1 (0.6)

Source: research data, 2017.

feeding tube placement, insertion of the feeding tube by the nurse, and taking of the X-ray). However, one patient received enteral nutrition before the X-ray had been checked by the attending physician. In this particular case, the X-ray showed that the tip of the EFT was inserted in the distal third of the esophagus. This patient suffered bronchoaspiration of the enteral nutrition and the feeding tube was removed. The same patient required the feeding tube to be reinserted, due to needing intensive care. During the reinsertion, the X-ray indicated that it was in the middle third of the esophagus. Once again, the patient received nutrition via the feeding tube in a risk position.

DISCUSSION

This is the first study that prospectively evaluated incidents and adverse events related to EN in an Emergency Department. There was a large number of breaches of protocol throughout the EN process (from indication to actual use of feeding tubes) and, despite the low number of monitored enteral feeding tube placements, there was one adverse event.

There are strikingly high numbers of verbal orders for EFT insertions and authorizations for their use. Although verbal orders are accepted in Emergency Departments, they should be restricted to clearly urgent situations (14), where there are specific routines to repeat them, since verbal orders have the potential to lead to incidents or adverse events (14,15). Despite these warnings, verbal orders to modify enteral nutrition, request tests, infuse blood components or administer medication, among others, were frequently documented in care practices, even outside Emergency Departments (15).

Less frequent, but equally alarming, were situations where patients were not X-rayed to check the anatomical position of EFT. There were also cases where X-rays were taken but there were no opinions from physicians on the position of feeding tubes or authorizations for their use. It bears noting that X-rays were first suggested as a test to confirm the anatomical location of feeding tubes in the 1940s (16). This is currently the standard test for checking the anatomical position of the distal tip of EFT (inserted blindly), and is indicated for all insertions or reinsertions (3,5).

In fact, the entire process, from indication to use of feeding tubes, should be documented in patient medical records, so that the information can be safely utilized by members of care teams (5). Although there appear to be well-established routines for EFT insertion and maintenance in the institution of the present study, it is possible that overcrowding in the Emergency Department, miscommunication, and non-prioritization of therapies such as enteral nutrition may account for these findings. For this reason, compliance with institutional protocols or checklists (17) has proven to be effective in ensuring that all the steps of a procedure are performed, thereby avoiding forgetting or failing to comply with steps or preventive safety measures.

To minimize risks related to the steps of the EN process, the Brazilian Society of Parenteral and Enteral Nutrition (BRASPEN/SBNPE) (4), based on international guidelines (5), has recom-

mended the adoption of indicators such as rates of tube obstruction, unintentional feeding tube removal, differences between the volume of nutrition prescribed and administered, and the percentage of patients where nutritional assessment was performed within the first 24 hours of admission, among others (4). In the current study, the percentage of unintentional tube removal was high (15.3%) compared to another university hospital, also in the south of Brazil, which examined the incidence of unintentional tube removal or obstruction and the difference between the volume of nutrition prescribed and administered to inpatients (18).

In that study (18), among the 46 patients monitored, unintentional removal was observed in 4.6%. However, the study assessed intensive care patients and those from another inpatient unit, environments where the variables related to overcrowding and the bustling atmosphere of Emergency Departments are not present.

More unintentional removals of care devices, including EFT, were identified in a study that assessed 49 intensive care units in 39 different hospitals in the United States. The records of 49,482 patients per day were observed, indicating 1,097 cases of removal, where the frequency of patient-initiated tube removal was 28.9%. In around two-thirds of the patients who removed their feeding tubes, there were indications for reinsertion of the devices (19). Differences in design, number of observations and profile of critical patients, where more than one-half (58%) of those who removed care devices were agitated or anxious at the time of the incident and 27% were lethargic, according to the definitions of the study (19), may explain the higher rates of feeding tube removal than those found in the current study.

The presence of agitation at the time of feeding tube insertion was associated with its removal by patients in the present study. Therefore, agitation at the time of insertion should serve as a warning of increased risk of removal of the device, since this condition is characterized as a risk for unintentional removal of care devices (5,20,21). The high incidence of accidental removal of devices is worth noting, since the need for reinsertion increases the risk of incidents and adverse events, in addition to treatment-related costs (5).

Other incidents, such as administration of therapy via feeding tubes without all the steps of the protocol having been completed, demonstrate the weaknesses in this work procedure. Problems in care processes have been studied, and theories about their causes, trajectories and results seek to shed light on this complex theme (22,23). In their review of care safety and quality (23), Reis et al. point out that conditions related to the infrastructure or work environment, education/training and supervision, work overload, communication failures, and process failures are the main causes of breaches of protocol that result in incidents and adverse events in hospitals. In this context, incidents and adverse events would be the result of multiple factors.

In the present study, one serious adverse event was documented, resulting from aspiration of enteral nutrition due to the position of the feeding tube, even though the X-ray had indicated this problem. From a clinical point of view, esophageal topography

of the tip of the feeding tube stimulates gastroesophageal reflux, increasing the chances of reflux of gastric content and consequent aspiration (24). Aspiration pneumonia is considered as the main consequence of improper positioning of the EFT (25).

The frequency of incidents and adverse events, as determined in this study, is difficult to ascertain, primarily due to non-disclosure of data. The literature is limited to reports (26,27) or case studies (28) that describe serious adverse events in general, retrospective studies (25), or studies that assess the topography of the distal tip of the feeding tube and the relationship with bronchoaspiration (29). There appears to be an incorrect assumption that the problem is of low relevance, due to the apparent small number of people affected. However, given the potential harm, in terms of morbidity and mortality, it is worth the effort to alert professionals to the risks related to the EN process, so that safety measures can be adopted.

In regard to this theme, it is very difficult to make comparisons between the findings of the present study and others. As previously mentioned, the literature lacks studies with more comprehensive design, apart from the fact that the culture of reporting incidents and adverse events is still not well-established, not only in Brazil, but also elsewhere. Reporting enables cases to be studied and represents an important strategy for creating mechanisms to prevent further events (30,31). In a Portuguese study (31), the author asserts: "That which is not recorded, does not exist." Without reporting, it is impossible to identify the frequency of incidents and adverse events and the factors that contribute to their occurrence. In addition, the culture of recording through reporting helps debunk the punitive tradition that underlies the safety culture (30,32).

Thus, the main result to pursue involves researching actions that improve patient safety, with respect to procedures such as feeding tube insertion and maintenance. Knowing, through indicators, the frequency of incidents or adverse events and their characteristics, as well as systematically studying cases and identifying their determinants, apart from building an historical record, also enables earlier adoption of corrective actions, in order to reduce the risk of new cases. Initiatives such as these have already been undertaken in other categories of events, such as patient falls, medication errors, healthcare-associated infections and pressure sores (33).

Finally, the results of the present study prompted immediate changes in the Emergency Department in question. A panel composed of professionals from the institution working in care, nutritional therapy process management and safety, in addition to the Ethics Committee, formulated an improvement plan. In the area of research, researchers became responsible for reporting incidents or adverse events identified during the conducting of observational studies, along the lines of experimental studies.

The small number of insertions and the fact that the observations occurred in only one center may limit generalization of the results. However, the lack of studies aimed at investigating breaches of protocol, incidents and adverse events, at every stage (from indication to use of EFT) justifies the dissemination of these findings.

CONCLUSION

Breaches of protocol and incidents were frequent in the process for indication and use of EFT. Adverse events were less frequent, but with major clinical impact. The measurement of care quality indicators and the recording of near misses, incidents and adverse events enable early identification of unexpected deviations, investigation of root causes and, especially, ways to ensure safe practices, particularly in complex environments, such as Emergency Departments. Further research is needed to demonstrate the implications and negative effects of incidents involving the insertion of EFT, the administration of enteral nutrition, and its potential harm.

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Trabajo Original

Pediatría

Nutritional outcomes in children with epidermolysis bullosa: long-term follow-up *Resultados nutricionales en niños con epidermólisis bullosa: seguimiento a largo plazo*

Ana Paula Caio Zidório¹, Dryelle Oliveira Dias Leão², Kênia Mara Baiocchi de Carvalho¹ and Eliane Said Dutra¹

¹Graduate Program in Human Nutrition. School of Health Sciences. University of Brasília. Brasília, Brazil. ²Undergraduate Program in Nutrition. School of Health Sciences. University of Brasília. Brasília, Brazil

Abstract

Background: some types of epidermolysis bullosa (EB) have extracutaneous manifestations. Manifestations that limit food intake and absorption may compromise nutritional status and increasing nutritional requirements.

Objectives: to investigate the following nutritional status indicators: exclusive breastfeeding duration, problems caused by the introduction of complementary foods, birth weight and length, and growth curves of children with EB.

Methods: assessment was based on the World Health Organization (WHO) growth charts. The anthropometric data were stored in the WHO's programs Anthro and Anthro Plus.

Results: three and seven of the ten study children had EB simplex (EBS) and recessive dystrophic EB (RDEB), respectively. Four of the children with RDEB had problems when complementary foods were introduced. The difference between the chronological age and age-for-height at the 25th (A/H 25th) percentile (p) varied from four months to four years and two months. Most children with RDEB (85%) had weight-for-age (W/A) curve below p3 and low height-for-age (H/A), starting before age four years. One child with EBS had excess weight.

Conclusions: anthropometric birth data, exclusive breastfeeding duration, and problems caused by the introduction of complementary foods are useful information for establishing the nutritional profile of children with EB. Supposedly, breastfeeding and no complementary feeding problems were not enough to prevent inadequate nutritional status, observed in the majority of the study children. The original presentation of the growth curves of children with EB may help to determine nutritional involvement and to establish how these children grow. The evaluation of growth curves with WHO as a standard suggests the need to establish growth curves adapted to the most serious type of EB and the need for permanent nutritional monitoring.

Key words:

Epidermolysis bullosa.
Nutritional outcomes.
Child. Growth chart.

Resumen

Introducción: algunos tipos de epidermólisis ampollosa (EB) presentan manifestaciones extracutáneas. Las manifestaciones que limitan la ingesta y absorción de alimentos pueden comprometer el estado nutricional y aumentar las necesidades nutricionales.

Objetivos: investigar los siguientes indicadores de estado nutricional: duración exclusiva de la lactancia, problemas causados por la introducción de alimentos complementarios, peso y longitud al nacer y curvas de crecimiento de los niños con EB.

Métodos: la evaluación se basó en los gráficos de crecimiento de la Organización Mundial de la Salud (OMS). Los datos antropométricos se almacenaron en los programas de la OMS Anthro y Anthro Plus.

Resultados: tres y siete de los diez niños del estudio tenían EB simplex (EBS) y EB distrófica recesiva (RDEB), respectivamente. Cuatro de los niños con RDEB tuvieron problemas cuando se introdujeron alimentos complementarios. La diferencia entre la edad cronológica y la edad para la talla en el percentil 25 (A/H 25) (p) varió de cuatro meses a cuatro años y dos meses. La mayoría de los niños con RDEB (85%) tenían una curva de peso por edad (W/A) por debajo de p3 y baja altura por edad (H/A), comenzando antes de los cuatro años de edad. Un niño con EBS tenía exceso de peso.

Conclusiones: los datos antropométricos de nacimiento, la duración de la lactancia exclusiva y los problemas causados por la introducción de alimentos complementarios son información útil para establecer el perfil nutricional de los niños con EB. La presentación original de las curvas de crecimiento de los niños con EB puede ayudar a determinar la implicación nutricional y establecer cómo estos niños crecen. La evaluación de las curvas de crecimiento con la OMS como patrón sugiere la necesidad de establecer curvas de crecimiento adaptadas al tipo más grave de EB y la necesidad de un seguimiento nutricional permanente.

Palabras clave:

Epidermólisis
ampollosa. Estado
nutricional. Niño.
Gráficos de
crecimiento.

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Correspondence:

Ana Paula Caio Zidório. School of Health Sciences.
Graduate Program in Human Nutrition. University of
Brasília. University Campus Darcy Ribeiro. 70910-900
Brasília/DF, Brazil
e-mail: anacaio@unb.br

INTRODUCTION

The term epidermolysis bullosa (EB), introduced in 1886, refers to a group of hereditary blistering diseases characterized by blistering on the skin and mucosa caused by minimum mechanical trauma (1,2). EB is associated with protein changes that cause defective adherence between skin structures, leading to blistering (3). Traditionally, four main types of EB have been identified based on distinct differences at the ultrastructural level where the blisters develop: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and a mixed type EB called Kindler syndrome (KS) (1,2).

EB severity varies from mild to severe, and skin involvement may be localized or generalized. Skin findings may include blisters, scars, changes in pigmentation, alopecia, absent or dystrophic nails, and hand or foot deformities (4,5). Some types of EB may also cause extracutaneous manifestations. Nutritional status may be compromised by clinical oral, pharyngeal, esophageal, and gastrointestinal manifestations that limit food intake and absorption. Hypermetabolism resulting from skin lesion inflammation may also occur (6). Nutritional involvement in EB is directly related to the severity of the associated clinical complications (6).

Since complications vary in number and intensity over time, it is very difficult to assess whether EB individuals have adequate growth and nutritional status. Weight and growth rate monitoring is a recognized way to verify the growth adequacy of healthy children, but comparison of healthy children's growth rates with those of children with EB has limited value (7). Despite knowledge of the nutritional risk of EB individuals, no assessment parameters exist, and growth charts for healthy children continue to be used (8).

This study investigated the following nutritional status indicators in children with EB: exclusive breastfeeding duration, problems caused by introduction of complementary foods, birth weight and length, and growth curves of children with EB.

MATERIALS AND METHODS

The present descriptive, retrospective clinical cohort study was approved by the Research Ethics Committee of the School of Health Sciences of the University of Brasilia under protocol number 120/12. All subjects provided informed consent. The study included all confirmed cases of EB aged less than 19 years, treated at the Pediatric Nutrition outpatient clinic of the University Hospital of Brasilia, a reference public service opened in 1998. The clinic employs a multidisciplinary team who has assisted roughly 20 patients and currently follows ten patients. Some patient data were collected from the medical records, such as the information registered between August 1998 and May 2013, which included sociodemographic characteristics, age at diagnosis, birth conditions, and anthropometric measurements collected during the entire follow-up period. Given the skin fragility of these patients, anthropometric assessment consisted only of weight and height measurement. Skinfold thicknesses and perimeters were not measured because the instruments needed for these measurements would press or pinch the skin.

Weight and height as a function of age and gender were presented in growth curves by percentile (p). The WHO growth curves height-for-age (H/A), weight-for-age (W/A), and body mass index (BMI)-for-age (BMI/A) were used (9). Since the W/A growth curve only assesses W/A until age ten years, the children's curves were limited to this age or to the nearest age with recorded weight.

The WHO programs Anthro and Anthro Plus (10) produced graphs of individual anthropometric measurements over time. The following variables were assessed during the interview, when the informed consent form was signed: exclusive breastfeeding duration, problems caused by the introduction of complementary foods, age at diagnosis, and birth length and weight. Chronological age on the last assessment was compared with the age that corresponded to height at p25 (A/H25th). This comparison was done because the equation that estimates the energy requirement of EB patients (6) uses p25 as reference of adequacy. The data were presented as years of difference between the chronological age and A/H25th.

RESULTS

Ten cases of EB were studied, seven of the recessive dystrophic EB (RDEB) type and three of the EB simplex (EBS) type. The mean age was ten years, ranging from one to 18 years. Age at diagnosis varied from the first day of life until after the first year of life. All patients were born at term, and nine cases had birth weight of 2,500 grams or more. The child with low birth weight had RDEB.

Nine children were breastfed. One child with RDEB was not breastfed because of the clinical manifestations of the disease. Three of the breastfed children were exclusively breastfed for six months. One child was exclusively breastfed for 18 months, also because of the clinical manifestations of the disease, which prevented the child from accepting complementary foods. Problems related to the clinical manifestations of the disease caused by the introduction of complementary foods (Table I) did not occur in children with EBS, but they occurred in four children with RDEB. No patterns were found regarding the type of problem the children experienced.

Nine patients had birth H/A higher than height at p3. This comparison could not be done for one patient because his birth length had not been recorded in the medical record.

The percent adequacy of the chronological age with respect to A/H25th was $\geq 100\%$ for all children with EBS, but children with RDEB had percent adequacy $< 90\%$, confirming growth impairment. The difference between chronological age and A/H25th varied from four months in the youngest patients to five years and ten months for the oldest patient. When sex was considered, the biggest difference was found in a female patient. The last anthropometric assessment included in this study found that all RDEB patients were underweight and stunted. One EBS patient presented excess weight (Table II).

The growth curves based on data from the first to the last assessment show that all EBS patients had ascending W/A curves, and their results were equal to or above those at p3 (Fig. 1).

Table I. Characterization of the cases, exclusive breastfeeding duration, and problems occurred during the introduction of complementary foods

Sex	Patient identification	Age	Type of epidermolysis bullosa	Exclusive breastfeeding duration	Problems occurred during the introduction of complementary foods
Female	F01	15 y 6 m	Recessive dystrophic	1 month	Difficulty chewing and swallowing
Female	F02	03 y 10 m	Recessive dystrophic	1 year and 6 months	Bloody vomits
Female	F03	12 y 10 m	Recessive dystrophic	3 months	No
Female	F04	09 y 4 m	Recessive dystrophic	1 month	No
Female	F05	10 y 5 m	Simplex	6 months	No
Female	F06	1 y 3 m	Recessive dystrophic	No exclusive breastfeeding	Difficulty in the evolution of food consistency
Male	M01	12 y	Recessive dystrophic	1 month	Difficulty chewing
Male	M02	18 y 11 m	Recessive dystrophic	6 months	No
Male	M03	10 y	Simplex	6 months	No
Male	M04	8 y 3 m	Simplex	2 months	No

y: years; m: months.

Table II. Anthropometric data at birth, difference between the chronological age and age corresponding to height at the 25th percentile, and current nutritional diagnosis, according to growth curves

Patient identification	EB type	Birth weight (g)	Birth length (cm)	Birth p H/A	Chronological age	A/H25 th age	Difference between chronological age and A/H25 th	Current nutritional diagnosis
F01	RDEB	2,520	46	3°-5°	15 y 6 m	9 y 8 m	5 y 10m	Inadequate*
F02	RDEB	2,700	SD	ND	3 y 10 m	2 y 7 m	1 y 3 m	Inadequate†
F03	RDEB	3,000	46	3°-5°	12 y 10 m	10 y 1 m	1 y 11 m	Inadequate‡
F04	RDEB	2,900	49	25°-50°	9 y 4 m	7 y 6 m	1 y 10 m	Inadequate§
F05	EBS	3,515	55	≥ 90°	10 y 5 m	10 y 5 m	0	Inadequate¶
F06	RDEB	2,062	47	10°-15°	01 y 3 m	11 m	4 m	Inadequate¶
M01	RDEB	3,020	50	50°-75°	12 y	10 y 8 m	1 y 4 m	Inadequate¶
M02	RDEB	3,050	50	50°-75°	18 y 11 m	14 y 9 m	4 y 2 m	Inadequate**
M03	EBS	3,835	52	≥ 85°	10 y	13 y 3 m	0	Adequate††
M04	EBS	3,650	50	≥ 85°	8 y 3 m	12 y 4 m	0	Adequate††

EB: epidermolysis bullosa; RDEB: recessive dystrophic epidermolysis bullosa; EBS: epidermolysis bullosa simplex; cm: centimeters; g: grams; p: percentile; H/A: height-for-age; ND: no data; y: years; m: months; A/H25th: age corresponding to height at the 25th percentile. *Very low weight-for-age. †Low weight and height-for-age.

‡Very low weight and height-for-age. §Very low height-for-age. ¶Obese child, appropriate height-for-age. ¶Low weight and appropriate height-for-age. **Appropriate height-for-age. ††Appropriate weight and height-for-age, eutrophic child.

One patient had W/A equal to or above p85, and after age six years, it increased to p97. Six of the seven patients with RDEB had W/A growth curves below that for p3 in the first visit, during the entire follow-up period, and in the last assessment conducted by this study. One patient had W/A growth curve equal to or above that for p3 between the second and third year of life, but after the third year of life until the last assessment, his curve remained in the same pattern as those of other children with RDEB, that is, below the curve for p3. The H/A and BMI/A growth curves could

not be constructed for one patient because of severe lower limb contractures, difficulty to maintain the back and neck straight, and fused feet and ankles.

Three of the seven patients with RDEB had H/A growth curves below that for p3 from the first assessment, which occurred between ages 24 and 48 months. EBS patients did not have impaired growth.

The BMI/A curve of the RDEB children confirmed the underweight of four patients, but the curves of two patients were equal to or above that for p3.

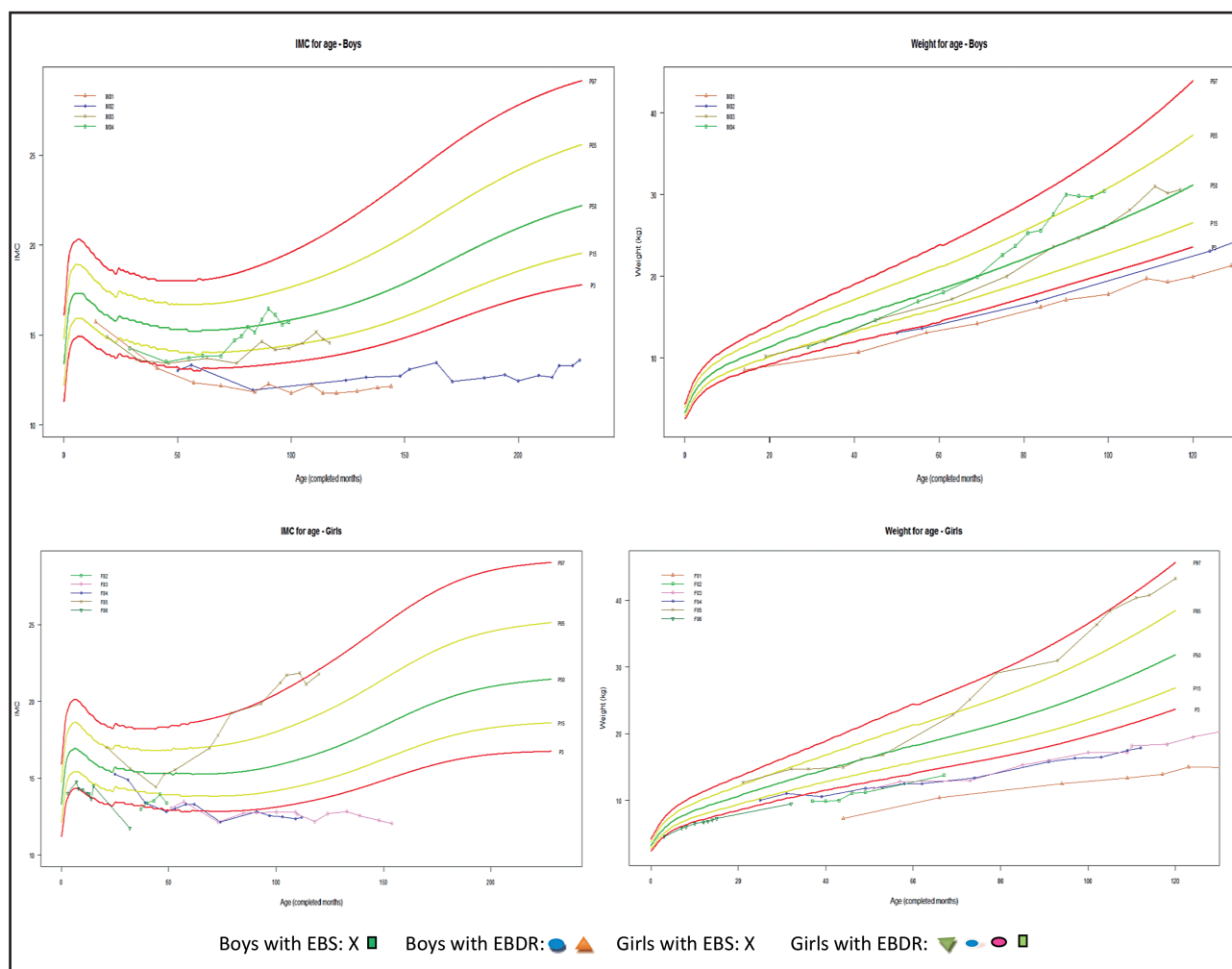


Figure 1.

Regarding the difference in years between the chronological age and the age corrected according to current height for the p25 growth curve, RDEB patients differed from EBS patients. Although age at EB diagnosis varied, all RDEB children had W/A curves below that for p3, from the first to the last assessment, or during most of the outpatient follow-up period.

DISCUSSION

To the best of our knowledge, this is the first study to investigate nutritional involvement, exclusive breastfeeding duration, and problems caused by the introduction of complementary foods in EB children conducted in University Hospital of Brasília. We hope this information will contribute to the establishment of the nutritional profile of EB individuals, especially in the first year of life.

EB children may be born with normal weight, but in some cases low weight may begin in the uterus. Fox, Alderdice, and Ather-

ton (11) found that English RDEB children had significantly lower birth weights than their healthy counterparts. On the other hand, the present and other studies (12,13) found that term children generally born with normal weight- and length-for-age stopped growing and gaining weight properly after the clinical manifestations of the disease appeared, as they compromised food intake and increased nutritional requirements. These divergent results indicate the need of more studies that thoroughly investigate birth conditions and short-, medium-, and long-term nutritional involvement.

This study was not able to assess whether nutritional deficits were associated with late disease diagnosis. Nevertheless, in the same way that prognosis is related to EB type (14), it is plausible that worse nutritional status is present in the severe EB types. Other studies may be able to clarify whether early EB diagnosis, especially in the more severe cases, results in better growth.

The WHO recommends exclusive breastfeeding for six months and complemented breastfeeding for two years or more. This practice efficiently promotes proper growth, avoids infant death,

diarrhea, and respiratory infections, and reduces the risk of allergies and obesity, among many other benefits (15,16). Literature data on the breastfeeding duration of EB children were not found, but the onset of manifestations may significantly affect the exclusive breastfeeding duration.

According to the WHO, the foods introduced after age six months should complement the numerous qualities and functions of breastmilk. In addition to meeting nutritional requirements, the introduction of complementary foods helps the child to progressively acquire the caregiver's food habits. Moreover, entering a new life stage, where children are exposed to new tastes, colors, aromas, textures, and knowledge, requires an adaptive effort (15). Similar to the present study, Birge (12) found that EB manifestations compromise food intake. Haynes (17) states that the critical interference on food intake begins during dentition and diseases that occur in the first year of life.

The study findings regarding the weight and height of EB children are similar to those in the literature. Birge (12) used growth curves from the National Center for Health Statistics to assess 60 patients with EBS, JEB, and RDEB aged two weeks to 18 years and found that 77% of the 35 RDEB patients had weight-for-age below p5, and 60% had height-for-age below p5. Barbosa et al. (18) assessed gastrointestinal signs and symptoms and nutritional aspects of children with different types of EB and found that the weight and height of 63.1% of their sample were below p2.5. Colomb et al. (19) found that RDEB children start to show delayed growth at a mean age of 4.9 years. The present study could not find length data before age 24 months, so it was not possible to determine when delayed growth began, but it may have been between the first year of life and the age at the first visit since all patients had normal birth length.

Regarding BMI, other studies have also found low BMI in a high percentage of individuals with the more severe types of EB. Barbosa (18) determined nutritional risk by assessing the growth parameters of children with EBS, JEB, and RDEB, and found that 22%, 57%, and 77%, respectively, were at risk of malnutrition. Stunting, which is normally attributed to chronic energy-protein malnutrition, was found in 11% of EBS children, 29% of JEB children, and 60% of RDEB children (18). The high percentage of malnourished RDEB children is also evidenced by the nutritional status diagnosis of the study sample. Generally, although RDEB is a severe disease subtype, the study RDEB patients did not have the same growth pattern, and some were more malnourished than others. Yet, they were all malnourished and grew less than EBS patients, whose growths were within the WHO curve. Martínez (20) suggests that most RDEB patients have delayed growth, which worsens over time, a finding confirmed by the present study: as age increases, the differences between the patient's weight and height and the reference weight and height increase.

EB children and adolescents have higher energy and nutrient requirements because of the constant blister healing process, skin losses, skin heat loss, and inflammatory and infectious processes that may affect the lesions (7). The association between low food intake and higher nutrient requirements compromises nutritional status and consequently, leads to malnutrition (21).

Therefore, weight and height should be measured in short intervals to allow an appropriate and timely intervention.

The study limitations include its retrospective character, the lack of complete weight and height information in the patients' medical records, and the possible measurement errors. Although measuring weight and height is a simple procedure, doing so in children with pain, infected blisters, difficulty to extend the lower or upper limbs, and restricted ability to maintain the back and neck straight constrains the use of standard measuring procedures.

The great advantage of the present study is that it brought to light information about the nutritional aspects of EB children as it is in this age group that it is possible to minimize nutritional sequelae, promote growth, development, and better quality of life, and optimize the appropriate interventions. Supposedly, breastfeeding and no complementary feeding problems were not enough to prevent inadequate nutritional status, observed in the majority of the study children. The original presentation of the growth curves of children with EB may help to determine nutritional involvement and to establish how these children grow. Nonetheless, more studies, especially prospective cohort studies about growth and feeding in the first year of life, with well-defined methodologies, are needed to better understand and contextualize these data for later use by services that treat this population. Future studies should also assess the need of creating specific growth curves for children with the more severe types of EB.

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Trabajo Original

Pediatría

Poor breastfeeding, complementary feeding and dietary diversity in children and their relationship with stunting in rural communities

Pobre lactancia materna, alimentación complementaria y diversidad de la dieta, y su relación con la baja talla en comunidades rurales

Jessica Zaragoza-Cortes, Luis Eduardo Trejo-Osti, Moisés Ocampo-Torres, Laura Maldonado-Vargas and Alicia Arminda Ortiz-Gress

Investigación en Nutrición. Coordinación de Investigación en Salud. Servicios de Salud de Hidalgo. Pachuca de Soto, Hidalgo. Mexico

Abstract

Introduction: stunted growth is the most common manifestation of malnutrition in México. Breastfeeding, adequate introduction of complementary feeding and dietary diversity can avoid this.

Objective: to characterize the feeding practices in children 1-24 months of age in rural communities of Hidalgo and define their relationship with stunting.

Methods: a 24-hour recall was used to obtain information. Z-scores for length-for-age (ZLA), complementary feeding (CF) and minimal dietary diversity (MDD) were determined. The sample was divided into breastfed and not breastfed children

Results: one hundred eighty nine mother-child dyads were evaluated; 59.3% were breastfed and 40.7% were not. Stunting was found in 10.1% and was identified starting at the fourth month of life. This was accompanied by early CF close to the third month (57.0%) and by a reduction in exclusive breastfeeding during the second month of life to only 30%. The proportion of not breastfed children with stunting (27.5%) was almost twice that of breastfed children (12.0%) ($p < 0.03$). By age, mean ZLA was different with a trend towards stunting increasing with age ($p < 0.05$): 1-6 months -0.463 ± 1.445 ; 7-12 months -0.669 ± 1.225 ; and 13-24 months -0.985 ± 0.917 . MDD was greater in not breastfed children (69.7%) ($p < 0.04$) and by age greater in children 13-24 months (69.7%) ($p < 0.02$).

Conclusions: the feeding practices of most mothers did not meet WHO recommendations. It is necessary to carry out nutrition education interventions aimed at mothers in rural population.

Key words:

Feeding practices.
Breastfeeding.
Complementary feeding.

Resumen

Introducción: el retraso en el crecimiento es la forma más común de desnutrición en México. La lactancia materna, la introducción adecuada de alimentos complementarios y la diversidad en la dieta pueden evitarla.

Objetivo: caracterizar las prácticas de alimentación de niños de 1-24 meses de comunidades rurales de Hidalgo y determinar su relación con baja talla.

Métodos: se aplicó un recordatorio de 24 horas para obtener la información. Se determinó la puntuación Z longitud para la edad (ZLE), alimentación complementaria (AC) y diversidad alimentaria mínima (DAM). La muestra fue dividida en niños amamantados y no amamantados.

Resultados: se evaluaron 189 diadas madre-hijo, 59.3% fueron amamantados y 40.7% no lo fueron. La baja talla fue del 10.1%, identificada a partir del cuarto mes, acompañada de AC precoz cerca del tercer mes (57.0%) y la disminución de la lactancia materna exclusiva durante el segundo mes de edad a solo 30%. La proporción de niños no amamantados con baja talla (27.5%) fue más del doble que los niños amamantados (12.0%) ($p < 0.03$). Por edad, las medias de ZLE fueron diferentes con tendencia hacia la baja talla, aumentando con la edad ($p < 0.05$): 1-6 meses, -0.463 ± 1.445 ; 7-12 meses, -0.669 ± 1.225 ; y 13-24 meses, -0.985 ± 0.917 . La DAM fue mayor en los niños no amamantados (69.7%) ($p < 0.04$) y, por edad, mayor en niños de 13-24 meses (69.7%) ($p < 0.02$).

Conclusión: las prácticas de alimentación en la mayoría de las madres evaluadas no cumplen con las recomendaciones de la WHO. Se recomienda realizar intervenciones educativas nutricionales dirigidas a las madres.

Palabras clave:

Prácticas de alimentación.
Lactancia materna.
Alimentación complementaria.

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Correspondence:

Jessica Zaragoza Cortes. Investigación en Nutrición. Coordinación de Investigación en Salud. Servicios de Salud de Hidalgo. Av. México, 300. Colonia Villa Aquiles Serdán. 42039 Pachuca de Soto, Hidalgo. Mexico
e-mail: jskzara@hotmail.com

INTRODUCTION

Childhood food practices directly impact a child's nutritional status and health. If they are adequate, the child's growth will be healthy; if they are not, it will hinder growth and the consequences will extend into adult life (1). The multiple benefits that breastfeeding (BF) provides to the mother and child affect the immune nutritional, body, and psychological status of the child, and has economic advantages also (2).

The World Health Organization (WHO) recommends exclusive breastfeeding (EBF) up to six months of age followed by the introduction of safe and appropriate foods for this age, maintaining BF for two years or beyond (3). In Mexico, according to the National Survey of Health and Nutrition 2012 (ENSANUT 2012), the percentage of EBF in children less than six months of age has declined to 14.4% in comparison to 22.3% reported in 2006 (4). As has been reported, the lack of EBF in the first months of life increases the probability of introducing foods prematurely, increasing the risk of allergies and infectious diseases (5). It has also been associated with chronic diseases such as diabetes, cardiovascular disease, and obesity in childhood (1). Furthermore, the absence of EBF, especially in low-income families, impacts the family's economy due to the need to buy maternal milk substitutes (6).

The age when complementary feeding (CF) is introduced is a particularly important moment in the child's development (7). The way the mother starts CF will determine the contribution of energy and nutrients to the child's growth and development without weaning, a situation that can prevent or favor iron and zinc deficiency, foment or not the inherent ability of the child to control food intake as well as determine the pleasure or displeasure for different food flavors, smells, and textures (8). Likewise, the introduction of foods will influence the acquisition of abilities that facilitate a smooth transition from total dependence on the parents to self-feeding, such as chewing, using a spoon and cup, etc. As shown, this period represents a key moment in the establishment of eating patterns. These are crucial moments in which there could be a stunting because of an inadequate nutritional intake or the development of overweight due to an excessive or hypercaloric intake (9). Mexico ranks first in childhood obesity (10), a situation that occurs at a young age and is associated with short stature, a hypothesis that has been tested in several studies (11).

Introducing children to the family diet is recommended at 12 months of age when the development of the nervous, digestive and renal system is similar to that of the adult (12); in other words, when the child is capable of consuming something from most food groups. Ideally, the child should have access to a diverse diet. According to the Food and Agriculture Organization (FAO) of the United Nations and the WHO, dietary diversity is a qualitative measure of food consumption that reflects household access to food and is a key factor for ensuring adequate consumption of nutrients and health promotion (13). Scientific evidence considers it a factor that protects against growth failure, a frequent nutritional problem in the country. It has been associated with nutritional adaptation, availability of foods in the home, and better food habits in adults (14).

In Mexico, less than 60% of children between six and eight months of age in rural communities consume a diet that meets nutritional recommendations (15). In Hidalgo, 78.3% of children under five years of age receive only the minimum recommended food diversity (16). The promotion of EBF and adequate CF as well as the maintenance of a diversified diet are fundamental for reducing child mortality and the burden of disease associated with nutrition in Mexico. The aim of this study is to characterize feeding practices in children under two years of age in rural communities of Hidalgo and determine their relationship with stunting. The findings can be used to identify and show the problems of nutrition and dietary patterns in infancy, and provide opportunities for designing and implementing programs for improving the diets and health of infants, in order to avoid the consequences in growth and short and long-term health.

MATERIAL AND METHODS

STUDY POPULATION

This was a descriptive cross-sectional study of a convenience sample of 189 mother-child dyads in children 1-24 months of age. The rural communities selected and evaluated during the national vaccination campaign were: Yolotepec, Patria Nueva, Ojo de Agua, San José Tepenené, La Estancia, and Dextho de Victoria, all within the Health Jurisdiction of Actopan, in the state of Hidalgo. Exclusion criteria were diseases requiring a special diet, not being a resident of the aforementioned communities, and not being the child's caretaker. Mothers and tutors provided written informed consent. The study was previously approved by the Ethics and Research Committees of the Health Services of Hidalgo.

CHILD NUTRITION

A 24-hour recall was applied to determine CF and minimum dietary diversity (MDD) in children six to 24 months of age. The latter was defined as the diet that includes at least four of the following seven food groups: a) cereals/tubers; b) legumes/oleaginous foods; c) milk derivatives (cheese, yogurt or milk substitutes); d) animal products (red meats, fish, chicken, viscera); e) eggs; f) fruits/vegetables rich in vitamin A; and g) other fruits and vegetables (17). The total group of children was divided into: a) breastfed children; and b) not breastfed children the day before, day or night. In breastfed children less than six months of age, maternal milk is exclusive when no other food or drink (including water) is offered. It is predominant (PBF) when infant formulas are used, and complementary (CF), when foods other than maternal milk are offered (18). Women who did not breastfeed their child or combined it with formula were asked why. A questionnaire to obtain the mother's (age, education, occupation) and the child's (sex, birth date, and if they were born by cesarean section) socio-demographic data was applied.

ANTHROPOMETRIC MEASURES

Children were weighed and measured using standardized methods by trained personnel. A SECA® model 874 scale (Seca GmbH & Co. KG, Hamburg, Germany) with a mother-baby function was used, together with a SECA® 217 stadiometer. Length-for-age was determined with WHO Anthro version 3.2.2.

DATA ANALYSIS

Collected data were captured and analyzed with IBM SPSS for Windows version 23.0. Student's t-test and one-way ANOVA were applied with 95% confidence intervals. For qualitative variables, the Chi-squared test was used ($p < 0.05$).

RESULTS

A total of 189 mother-child dyads were evaluated. Mean age in months was 10.5 ± 0.46 ; 59% were girls and 40% were boys. Classified by age groups, 33.3% were between 1-6 months, 31.7% between 7-12 months, and 34.9% between 13-24 months. Mean age of the mothers was 25.5 ± 5.6 years. Regarding occupation, 82.5% were housewives, 13.2% worked, and 4.2% were students. Mean years of education was calculated as 10.3 ± 2.6 years. In relation to births, 44.1% were primiparous, and according to type of delivery, 48.1% were vaginal and 51.9% were by cesarean section. Additionally, 92.6% of children were breastfed during the first two weeks after birth; 14.6% said they did not know the advantages to breastfeeding. In relation to advice about breastfeeding, 26.8% said they received no advice, 68.7% were counseled by healthcare personnel, and 4.5% received advice from their mother or mother-in-law.

An overview of feeding practices by age groups is shown in figure 1. As shown in this figure, 37% of children 1-6 months old were EBF, and the mean number of times children were breastfed per day was 6.4 ± 3.9 , 95% CI: 0.5-7.3; 16.0% were PBF, 6.0% were fed with infant formula, and 33.0% had begun CF and were breastfed. Eight percent were not being breastfed but were consuming other foods. All of the children in the 7-12 month age group had started CF; however, 63% were still breastfed and 37% were not; the mean number of times children were breastfed per day was 2.6 ± 2.4 times (95% CI: 1.9-3.2). In the 13-24 months group, 29% were breastfed and the mean number of times children were breastfed per day was 0.98 ± 1.6 times (95% CI: 0.57-1.4), while 71.0% were not consuming maternal milk anymore.

The trend followed by food practices is shown in figure 2. Regarding EBF, 73% of the children one month of age had received it. Nevertheless, when EBF in children two months of age was analyzed, there was a drastic decline, since only 30% were receiving it. Children three and four months of age had a similar percentage (43% and 40%, respectively) and those five months of age, 29%. Nine percent of children six months of age were EBF. Continuous breastfeeding counted from the sixth month was

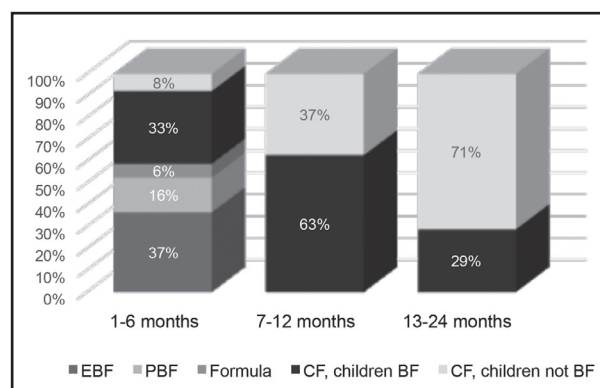


Figure 1.

Characteristics of food practices in the study population by age groups (%). CF: complementary foods; BF: breastfed; PBF: predominantly breastfed; EBF: exclusively breastfed.

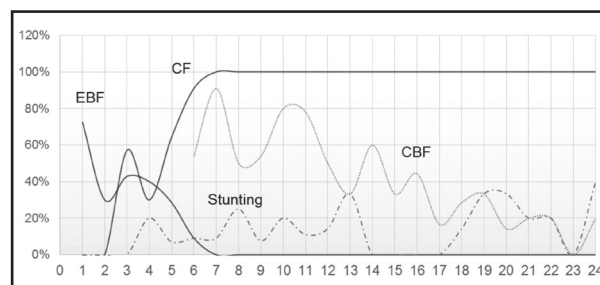


Figure 2.

Percentage of exclusively breastfed (EBF), continuously breastfed (CBF), complementary foods (CF) and short stature in children 1-24 months of age.

54.0% for children six months of age and 91.0% for those seven months of age. In the eighth and ninth months, a decline of 50.0% and 54%, respectively, was seen. However, the trend increased again in children ten and eleven months of age (80% and 78%, respectively). After 12 months of age, continuous breastfeeding declined considerably.

CF were present starting at the third month of age in 57% of children, in 33% at four months, in 63% at five months, and in 90% at six months. Regarding stunting included in this figure, our study reported 10.1% in the total sample, excluding the risk of short stature classification (31.9%).

Mean ZLA were different by age group. Younger children (1-6 months) showed a score of -0.463 ± 1.445 , and the values closest to low height were in the 7-12 month group (-0.669 ± 1.225). This was even greater in those 13-24 months of age (-0.985 ± 0.917 ; $p < 0.05$) (Table I). This trend is better seen in figure 3, where, notwithstanding, the three means are negative values; in other words, they tend towards low height.

The study population according to type of breastfeeding is described in table II. Of the total sample, 40.7% were not breastfed the day before and 59.3% were.

Table I. Z-score means of the growth indicators length for age and weight for age in children aged 1-24 months by age and by type of lactation

Age group	Length for age Z-score		
	n	Mean	95% CI
1-6 months	63	-0.4632 ± 1.445	-0.820, -0.106
7-12 months	60	-0.6692 ± 1.225	-0.989, -0.359
13-24 months	66	-0.9857 ± 0.917	-1.208, -0.762
*p-value		< 0.05	
Not breastfed	76	-0.992 ± 1.11	-0.0513, 0.375
Breastfed	111	-0.5179 ± 1.26	-0.190, 0.251
†p-value		< 0.009	

*ANOVA; †Student's t-test.

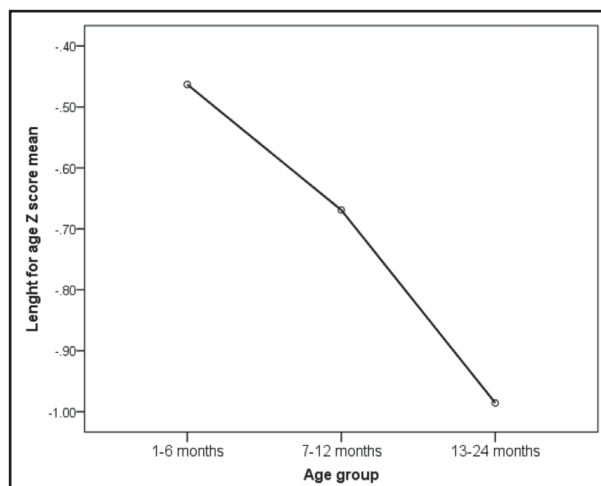


Figure 3.

Length for age Z-score mean of the study population by age group.

Table II. Study population according to type of breastfeeding

Variable	Total %	Breast-fed yesterday		p value
		No % n = 77	Yes % n = 122	
Sex (n = 189)				
Women	59.3	62.3	57.1	0.28
Men	40.7	37.7	42.9	
*Age of child (n = 189)				
1-6 months	33.3	11.7	48.2	0.00
7-12 months	31.7	27.3	34.8	
13-24 months	34.9	61.0	17.0	
Age of the mother				
≤ 20 years	23.9	24.7	23.4	0.48
> 20 years	76.1	75.3	76.6	
Mother's occupation				
Home	82.5	77.9	85.7	0.12
Works or studies	17.5	22.1	14.3	
Mother's education				
≤ 9 years	61.1	64.0	59.1	0.30
> 9 years	38.9	36.0	40.9	
Primiparous women (n = 189)				
Yes	44.1	48.7	40.9	0.18
No	55.9	51.3	59.1	
*Type of birth (n = 189)				
Vaginal	48.1	55.8	42.9	0.05
Cesarean section	51.9	44.2	57.1	
*Breast-fed first 2 weeks after birth				
Yes	92.6	84.2	98.2	0.00
No	7.4	15.8	1.8	

(Continue in the next page)

Table II (Cont.). Study population according to type of breastfeeding

Variable	Total %	Breast-fed yesterday		p value
		No % n = 77	Yes % n = 122	
Received counselling about breast-feeding (n = 189)				
No	26.8	23.6	29	0.30
Healthcare provider	68.7	70.8	67.3	
Mother/mother-in-law	4.5	5.6	29	
Knew about advantages of breast-feeding (n = 189)				
Yes	85.2	88.3	83.0	0.22
No	14.8	11.7	17.0	
Reasons for not breast-feeding† (n = 57)	%	n = 17	n = 21	
Disease	14.0	22.9	0.0	0.04
Child did not want it	8.8	14.3	0.0	
Did not have milk	22.8	22.9	22.7	
Child was not satisfied	12.3	5.7	22.7	
Studied	8.8	8.6	9.1	
Worked	12.2	11.4	13.6	
Other	21.1	14.3	31.8	
Dietary diversity in children 6-24 months (n = 136)	%	n = 73	n = 63	
Not diversified	44.1	32.9	57.1	0.04
Diversified	55.9	67.1	42.9	
*Length for age (n = 126)	%	n = 51	n = 75	
Short stature + severe short stature	18.3	27.5	12.0	0.03
Adequate length	81.7	72.5	88.0	

*Differences between breast-fed and not breast-fed children $p < 0.05$. †Exclusive breast-feeding.

In those 1-6 months, the proportion of children who were not breastfed (11.7%) was lower than that of those who were (48.2%), while in the 7-12 month group the proportions were similar (27.3% and 34.8%, respectively). In those older than 12 months, the number of children who were not breastfed was greater (61.0%; $p < 0.000$).

With regard to the type of birth, the high number of cesarean sections is notable (51.9%). Of those born by cesarean section, 44% were not breastfed and 57.1% were. Of the children born by vaginal delivery, a greater number were not breastfed (55.8%), against 42.9% who were ($p < 0.05$). On the other hand, the mothers of 1.8% of the group of children who were not breastfed the day before the survey indicated that they did not do it in the first two weeks, which means that they resumed the practice later. In the group of children who were not breastfed, there was a large percentage that was breastfed in the first days of life (84.2%). The rest (15.8%) were not breastfed at any time regardless of their age ($p < 0.000$).

When the mothers were asked why they fed their children formula or alternated breast milk and formula during the first six months of life, 38.6% of those who breastfed the previous

day stated that they did not have enough milk (22.7%); they had a feeling that the child was not satiated (22.7%); they studied (9.1%) or worked (13.6%); and others (31.8%) complained of weakness, a cesarean birth, pregnancy, lactose intolerance, and advice of a healthcare provider or use of contraceptives. Of the women who did not breastfeed, 22.9% answered that they were sick, 14.3% that the child did not want it, 22.8% that did not have milk, 5.7% said that their child was not satiated, 8.6% argued that they studied and 11.4%, that they worked ($p < 0.04$).

Stunting was also related to the absence or presence of BF. Regarding this relationship, it is notable that children who were not breastfed had a greater proportion of short stature (27.5%) than those who were breastfed (12.0%).

Finally, and according to the results of MDD in children six to 24 months, 55.9% received a diverse diet that included at least four of the seven food groups described in the methodology. In relation to not breastfed (67.1%) and breastfed (42.9%) children, it was found that the former had a higher proportion of MDD ($p < 0.04$). On the other hand, when this variable was compared, it was found that less than half of the children six to 12 months of age did not reach DMM (42.9%) and that those 13 to 24 months

Table III. Relationship of dietary diversity in the study population by age groups

Dietary diversity	Age in months*		
	(n = 136) %	6-12 months (n = 70) %	13-24 months (n = 66) %
Not diversified	44.1	57.1	30.3
Diversified	55.9	42.9	69.7
Odds ratio	1.6 (1.2-2.3), $p < 0.02$		

Values are percentages. *Differences by age group, $p < 0.05$.

represented a greater proportion (69.7%) ($p < 0.02$) (Table III). It is important to point out that this difference could be influenced by inadequate introduction of CF in the first group.

DISCUSSION

The percentage of EBF found in our study was 22.3%, in contrast with the results of the last state report in rural population, which was 18.5% (18). A good precedent is that more than 90% of the mothers exclusively breastfed their baby at least during the first two weeks after birth. At one month of age, the percentage was still high (73.0%); however, after this month the decline is drastic, since only 30% provided EBF. A study carried out in a low-income population in South America found a similar trend: 95.4% of children began with EBF, followed by a gradual decline (19). Another study carried out in the rural area of Gambia, where children have a high risk of malnutrition, reported that the mean interruption of EBF was 5.2 months and that the decline in growth began at 3.5 months of age (20). This study was able to identify that stunting becomes evident in the fourth month of age, a problem that in our study corresponded graphically to the month of decline of EBF and the early introduction of CF in the third month of age. It is important to point out that the problem with introducing foods at an early age (under four months) is that it favors a reduction in maternal milk consumption. With food, a child becomes satiated more quickly, which impedes reaching nutritional goals. In addition, there is a tendency to offer watery porridges, and a low energy density food, such as fruits and vegetables, which favors the risk of undernourishment (21); or overfeeding, which leads to overweightness (22).

The ENSANUT 2012 reported that 75% of children consumed fruits and vegetables before six months of age (4). Nevertheless, the recommendation is to begin CF at six months (23), considering that the signs that indicate that the infant is capable of receiving solid foods, such as axial tone and head control, motor coordination between the eyes, hands and mouth as well as the disappearance of the extrusion reflex, are present. It is also known that taste buds reach their maximum development at six months (24).

Stunting in this study population was determined as 10.1%; however, the high percentage of children classified at risk of short stature (31.9%) is noteworthy. Likewise, children who were not breastfed had a higher proportion of stunting than children who were breastfed, a finding that confirms the nutritional relevance of maternal milk during this stage.

Chronic malnutrition occurs because of a constant and inefficient consumption of energy and nutrients in the first years of life; this is the most common nutritional deficit in Mexico. Chronic malnutrition first affects weight and later, lineal growth. In Hidalgo, stunting was estimated in 2012 as 12.9% in children under five years of age, a figure similar to the estimated prevalence in Latin America in 2015 (11.6%, 5.9 million children) (25). Nevertheless, when the urban setting (9.6%) is separated from the rural setting in Hidalgo, it is seen that the latter is more affected (16%) (16). The delay in growth increases the risk of mortality from infectious diseases during infancy and deteriorates cognitive development. It is also associated with low financial resources and a low education in adolescents and adults (26). There is evidence that children who do not reach their development in height or muscle mass require less energy to gain weight in comparison with those who did because of changes in hormone response due to abnormal deceleration of lineal growth, an event that increases the risk of obesity (11).

In addition to EBF in the first six months of life, the WHO recommends that maternal milk be continued until two years of age or more if the child and the mother are willing (3). In our work, the decline in breastfeeding occurred starting at the 13th month (with 30% of children being breastfed, and the mean number of times children were breastfed being 2.6 times per day, 95% CI: 1.9-3.2); this was not greater after this age. Several studies have reported that long-lasting breastfeeding has a protective effect against obesity in childhood; however, this practice is rapidly disappearing (1,27).

In the past several years, a decline in the provision of maternal milk has been reported in groups with greater social vulnerability, such as those who live in rural communities, those with a low income, those who do not have health services and mothers who do not have a paying job (28). It is important to mention that maternal milk has also been related to economical convenience related to family savings associated with the purchase of formula and accessories as well as a smaller number of medical consultations and drug purchases (29); however, the abandonment of maternal milk is still notable. Scientific evidence suggests that the incorporation of women in the workplace could also be a factor for premature abandonment (30); however, most women in the evaluated study population were housewives (82.5%).

Although there were no significant differences with regard to knowledge and lack of knowledge of mothers regarding the advantages of breastfeeding and the fact that they did or did not receive counseling, the proportion of women who said that

they did not receive counseling (26%) or who did not know the advantages of breastfeeding (15%) was noteworthy. Some advantages for infants are protection from diarrhea and other infections, protection against obesity and chronic diseases in adulthood, and healthy growth; in women, breastfeeding delays fertility, helps them lose the weight gained during pregnancy, decreases the risk of cancer (breast and ovarian) and improves the relationship between the mother and baby (1). On the other hand, 35% of women who did not breastfeed said that "the child was not satisfied" or that "she had no milk." Scientific evidence suggests that regardless of maternal body mass index, lactating women are able to produce sufficient volume and macronutrient concentrations to support the child's needs, but tests are limited regarding micronutrient concentrations over a long period of time in those who experience nutritional vulnerability (31). This is why we believe that the nutritional status of the mother should be assessed in later studies with the aim of identifying if it is a mother's perception or a physiological cause (32). Nevertheless, the decision to breastfeed is strongly influenced by the information that mothers receive through physical, psychological, and social support provided during pregnancy, birth, and puerperium, and family, medical, and cultural attitudes, which can favor or hinder breastfeeding (33). A lack of counseling and a fear of breastfeeding can also possibly influence the decision to carry it out. A study performed in low-income African-Americans identified that the difference between women who breastfed for long periods and those who did it for a short period of time or did not do it at all was related to a clear intention of breastfeeding with positive experiences in hospital nutrition programs and with feeling more comfortable breastfeeding in public (34).

Also, the industry has been responsible for low breastfeeding rates and its consequences, with aggressive practices of commercialization of food for infants, such as the distribution of misleading information on food for infants with maternal milk substitutes, the distribution of free samples to mothers, and the direct and indirect publicity about the feeding of infants with maternal milk substitutes (35).

Regarding the quality of CF, Mexico has registered positive changes in recent years (16). In this study, the significant difference observed between the 6 to 12-month age group and the 12 to 24-month age group suggests a low level of knowledge about when, how, and what foods to introduce correctly. According to current recommendations, the group of meats, cereals, vegetables and fruits should be introduced starting at the sixth month of life, beginning each separately, observing their tolerance, and with an appropriate consistency; legumes should be started at seven to eight months of age; and milk derivatives, egg and fish, at eight to 12 months of age. The recommendation of meat at six months of age has to do, first, with avoiding iron deficiency since body iron reserves are depleted at that age, and second, with the high biological value proteins that meat provides (23). It is important to mention that the mother's fear regarding the ability of the child to eat these foods reduces the opportunity to offer them; (36) this should also be considered, together with the low availability and accessibility characteristic of this food group in rural communities.

In Mexico, a nationally-representative sample of infants showed that the alarming dietary problems arise before 12 months of age. They develop quickly during the second year of life and persist during the first few years of life, emphasizing the low prevalence of the consumption of meats and iron-fortified cereals for infants, in the second half of their infancy, especially children from 6-8,9 months of age (37). On the other hand, MDD in children 6-24 months was 55.9% (a diverse diet includes at least four of the seven food groups). In Hidalgo, this percentage was 78.3% of children under five years. Nevertheless, it calls our attention that children that were breastfed the day before (42.9%) had lower proportions of MDD than those who had not been breastfed (67.1%) ($p < 0.04$). It is important to remember that, in this period, a high or low consumption of calories and nutrients from foods rapidly affects the increase or loss of weight in children (38). In this work, the difference in the means of the ZLA indicator evidenced the progression of the risk of short stature in relation to age.

Maternal education on breastfeeding and CF as well as improvements in childhood dietary diversity have been found to be a major factor in reducing stunting, according to a study carried out in children at risk of malnutrition, which reported a total indicator change of up to 20 percent (39). Accordingly, the evident decline of breastfeeding makes it necessary to propose and perfect strategies that aim at increasing its prevalence among women, both in rural and urban environments (40). Likewise, the inappropriate promotion of formulas must be eliminated, and support during pregnancy and planned breastfeeding should be promoted. Finally, the introduction of complementary foods represents a critical period in which basic questions regarding when, what, and how they should be started and established with the correct feeding pattern should be answered. The evidence that this project presents suggests that there is a low level of knowledge about this topic, which is why we propose approaching this with nutritional counseling.

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Trabajo Original

Pediatría

Reduced serotonin levels after a lifestyle intervention in obese children: association with glucose and anthropometric measurements

Disminución de los niveles de serotonina tras una intervención de estilo de vida en niños obesos: asociación con glucosa y medidas antropométricas

Ana Ojeda-Rodríguez^{1,2}, Lydia Morell-Azanza^{1,2}, María Cristina Azcona-Sanjulián^{2,3}, J. Alfredo Martínez^{1,2,4,5,6}, María J. Ramírez⁷, Amelia Martí^{1,2,4}; and GENOI members*

Departments of ¹Food Science and Physiology and ²Pharmacology and Toxicology, University of Navarra, Pamplona, Spain. ³IdiSNA, Instituto de Investigación Sanitaria de Navarra, Pamplona, Spain. ⁴Pediatric Endocrinology Unit, Department of Pediatrics, Clínica Universidad de Navarra, Pamplona, Spain. ⁵CIBERobn, Centro de Investigación Biomédica en Red, Fisiopatología de la obesidad y nutrición, Carlos III Health Institute, Madrid, Spain. ⁶Center for Nutrition Research, University of Navarra, Pamplona, Spain. ⁷Madrid Institute of Advanced Science (IMDEA Food), Madrid, Spain

Abstract

Background: serotonin signaling participates in body weight regulation and glucose metabolism. However, little information is available on circulating serotonin levels in obese subjects after a weight loss program. We aimed to assess the effect of a lifestyle intervention on serotonin levels in obese children and possible associations with anthropometric and blood glucose measurements.

Methods: forty-four obese children were enrolled in a ten-week lifestyle intervention consisting of a moderate caloric restriction diet, nutritional education and familial involvement. They were distributed according to the weight loss response. Subjects who lost > 0.5 BMI-SDS were considered as high responders (HR; n = 22) and those who lost ≤ 0.5 BMI-SDS, as low responders (LR; n = 22). Anthropometric, biochemical parameters and plasma serotonin levels were measured as pre and post-intervention values.

Results: obese children (HR and LR groups) were able to reduce anthropometric indices and to improve glucose profile after the intervention. Interestingly, plasma serotonin levels were significantly ($p < 0.05$) reduced in all subjects (-35.14 nmol/l HR group and -30.63 nmol/l LR group). Moreover, multiple-adjusted regression models showed a significant association between pre-intervention ($R^2 = 0.224$, $B = 0.047$; $p = 0.004$) and post-intervention ($R^2 = 0.140$; $B = 0.055$; $p = 0.042$) plasma serotonin and glucose levels. In addition, in HR subjects changes in plasma serotonin were associated with changes in glucose levels ($R^2 = 0.292$; $b = 0.04$; $p = 0.045$). Interestingly, pre and post-intervention plasma serotonin levels were inversely associated ($p < 0.05$) with anthropometric measures.

Conclusions: serotonin levels were reduced after a lifestyle intervention independently of the program response. Moreover, plasma serotonin levels were associated with glucose and anthropometric measures in obese children.

Key words:

Serotonin. Lifestyle. Intervention. Obese. Children.

Resumen

Introducción: la señalización de la serotonina está involucrada en la regulación del peso corporal y el metabolismo de la glucosa. Sin embargo, existe poca información disponible sobre los niveles de serotonina circulantes en sujetos obesos tras un programa de pérdida de peso. Nuestro objetivo fue evaluar el efecto de una intervención de estilo de vida en los niveles plasmáticos de serotonina en niños obesos y su posible asociación con medidas antropométricas y de glucosa en sangre.

Métodos: cuarenta y cuatro niños obesos participaron en una intervención de estilo de vida durante diez semanas consistente en una dieta con restricción calórica moderada, educación nutricional y participación familiar. Los sujetos que perdieron > 0,5 z-IMC fueron considerados como altos respondedores (AR; n = 22) y aquellos que perdieron ≤ 0,5 z-IMC, como bajos respondedores (BR; n = 22). Los parámetros antropométricos y bioquímicos y los niveles plasmáticos de serotonina se midieron antes y después de la intervención.

Resultados: los niños obesos (grupos AR y BR) pudieron reducir los índices antropométricos y mejorar el perfil lipídico y glucémico tras la intervención. Los niveles plasmáticos de serotonina fueron significativamente ($p < 0,05$) reducidos en todos los sujetos (-35,14 nmol/l grupo de AR y -30,63 nmol/l grupo de BR). Por otra parte, los modelos de regresión múltiple ajustada mostraron una asociación significativa entre los niveles plasmáticos de serotonina y glucosa previos a la intervención ($R^2 = 0,224$; $B = 0,047$; $p = 0,004$) y tras la intervención ($R^2 = 0,140$; $B = 0,055$; $p = 0,042$). Además, en los sujetos AR los cambios en la serotonina plasmática se asociaron con cambios en los niveles de glucosa ($R^2 = 0,292$; $b = 0,04$; $p = 0,045$). Los niveles de serotonina plasmática antes y después de la intervención se asociaron inversamente ($p < 0,05$) con índices antropométricos.

Conclusiones: los niveles plasmáticos de serotonina se redujeron tras una intervención de estilo de vida en todos los grupos. Además, los niveles plasmáticos de serotonina se asociaron con niveles de glucosa e índices antropométricos en niños obesos.

Palabras clave:

Serotonina. Estilo de vida. Intervención. Obesos. Niños.

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Correspondence:

Amelia Martí del Moral. Department of Food Science and Physiology. University of Navarra. C/ Irunlarrea. Pamplona, Navarra. Spain
e-mail: amarti@unav.es

INTRODUCTION

Serotonin (5-hydroxytryptamine or 5-HT) is a biogenic amine, synthesized from the essential amino acid L-tryptophan, involved in the regulation of energy balance for its actions in both central nervous system (CNS) and peripheral tissues (1). Central serotonin (5%) suppresses appetite and decreases food intake (2) and hence it influences indirectly body fat, which is an important determinant of insulin resistance and glucose levels (3). However, most of the serotonin (95%) is released into the bloodstream, mainly by intestinal cells, but also by pancreatic β -cells, adipocytes and osteoclasts (4,5). Recent works indicate that peripheral serotonin serves as a secreted hormone to regulate metabolic function in multiple tissues (6-8). Specifically, peripheral serotonin modifies glucose metabolism, participating in both glucose homeostasis and hepatic gluconeogenesis in cellular and animal studies (9-13). These effects of peripheral serotonin in metabolism have driven a renewed interest in the study of serotonin, even as a therapeutic molecule for obesity and diabetes treatment (6-8).

Childhood obesity is a major public health problem worldwide, with an alarming trend in Europe and in Spain (14). A number of comorbidities are associated with obesity in pediatric population increasing cardiovascular risk (15). However, lifestyle interventions are able to reduce cardiovascular risk factors in obese children (16-20), but there is little information on the role of peripheral serotonin in weight loss interventions. Therefore, our aim was to evaluate plasma serotonin levels after a lifestyle intervention in obese children and its possible association with changes in glucose and adiposity measurements.

METHODS

The NUGENOI study (nutrigenomics and childhood obesity) was conducted by members of the GENOI group (Navarra Study Group of Childhood Obesity) in 2009. NUGENOI, an uncontrolled clinical trial (NCT01329367), is a ten-week intervention study involving 54 obese children and adolescents from Navarra. The weight loss program is based on a moderate caloric restriction together with nutritional education and familial involvement. Children and their parents received personal training in nutritional and physical education throughout the ten-week intervention period (17-20).

The study followed the ethical standards recognized in the Declaration of Helsinki (Brazil, October 2013), the Rules of Good Clinical Practice (EEC 111/3976/88 July 1990) and the current legislation responsible for regulating clinical research in humans (Royal Decree 561/1993). The project was approved and supervised by the Ethics Committee on Human Research of the University of Navarra (42/2005).

SUBJECTS

In the study, 71 overweight or obese children and adolescents (7-15 years) were recruited at the Pediatric Endocrinology Unit of

the Clínica Universidad de Navarra and the Pediatric Department of the Complejo Hospitalario de Navarra, according to the criteria of Cole et al. (21). All of them were Spanish or schooling foreigners for at least one year in Spain. Participants with a major psychiatric illness, significant neurological disease, bulimia nervosa, familial hyperlipidemia or any sort of either major cardiovascular or respiratory complication were excluded.

Fifty-four subjects agreed to participate in the study and signed the informed consent, but only 44 subjects (22 boys and 22 girls) completed the dietary intervention (drop-out rate 18.5%) during two different periods (April-June and September-December, 2010) in order to ease follow-up. They were distributed according to the response based on change in "Standard Deviation Score for Body Mass Index" (BMI-SDS, median equal to 0.5). Thus, the subjects who lost > 0.5 BMI-SDS were considered as high responders (HR; $n = 22$) and those who lost ≤ 0.5 BMI-SDS, as low responders (LR; $n = 22$).

DIETARY INTERVENTION

The child accompanied by his/her parent or tutor underwent ten weekly follow-up dietetic consultations for diet monitoring, weight control and nutritional education (17-20). The adherence to ten weekly individual sessions was 93% in the total population.

The dietary intervention was carried out by a registered dietitian with the support of pediatricians. On the first visit, participants were prescribed an energy restriction dietary program in a range from 10% to 40% depending on the degree of obesity presented (22). Firstly, energy expenditure of the participants was calculated according to the Scholfield equation (23) adapted to age and sex. Nevertheless, diets with an energy intake less than 1,300 kcal/day or greater than 2,200 kcal/day were not prescribed.

The distribution of the energy intake along the day was 20% at breakfast, 5-10% at morning snack, 30-35% at lunch, 10-15% at afternoon snack, and 20-25% at dinner. Daily macronutrient intake was distributed in the following corresponding nutrient-caloric percentages (24): 55% carbohydrates, 30% fat and 15% protein. A semi-quantitative Food Frequency Questionnaire (FFQ) previously validated in Spain (25) containing 132 food items was filled out to evaluate the dietary patterns of the participants. The adherence to the fixed full day dietary plan (five meals) was weekly evaluated during the personal interviews with the registered dietitian.

ANTHROPOMETRIC AND CLINICAL MEASUREMENTS

Anthropometric measurements (body weight, height, BMI, BMI-SDS, fat mass, waist circumference, hip circumference and waist-to-hip ratio) were performed by trained personnel with previously calibrated equipment. Triplicate measures were performed and average was taken as the final value. Subjects were in a large room, barefoot, in his/her underwear and wore an exploration gown.

Body weight was determined using a digital scale (TBF-410, Tanita®, Tokyo, Japan). Height was measured using a stadiometer (Seca® 220, Vogel & Halke, Germany). BMI was calculated from weight and height measurements. BMI in childhood is a determinant of BMI in adulthood, and it allows monitoring of overweight or obesity of the child from childhood to adulthood (26). In addition, in pediatric population BMI should be referred to sex and age of each participant, by calculating BMI-standard deviation score (SDS). For each subject, BMI-SDS derives from the difference between his/her own BMI values, age and sex specific cut-points taken from Spanish reference growth charts (27). Waist circumference (WC) and hip circumference (HC) were measured using a non-stretchable measuring tape (type SECA® 200). WC was measured as the smallest horizontal girth between the costal margins and the iliac crests at minimal respiration. HC was taken as the greatest circumference at the level of the greater trochanter (the widest portion of the hip) on both sides. Pubertal developmental stage was determined according Tanner stage (28). In addition, the children's body composition was measured using bioelectrical impedance analysis equipment (TBF-410, Tanita®, Tokyo, Japan).

Measurements were taken before and after the follow-up intervention at the same time of the day, except for the weight and height, which were measured weekly in order to have a rigorous control of weight loss.

BIOCHEMICAL MEASUREMENTS

Blood draws were performed before and after the study. Blood extraction was performed by specialized nurses through a BD Vacutainer® system (Becton Dickinson, GB), after overnight fasting. Venous blood samples were obtained on ethylenediaminetetraacetic acid (EDTA) tubes, which were separated in plasma and serum aliquots by centrifugation (3,500 rpm, 4 °C, 15 min). After centrifugation, plasma (10 ml) and serum (5 ml) were stored in three tubes each and frozen at -80 °C. Triglycerides, total cholesterol, cholesterol linked to high-density lipoproteins (HDL-cholesterol), glucose and insulin were determined by enzymatic colorimetric using the Hitachi 911 analyzer (Roche Diagnostics, Basel, Switzerland). The fraction of cholesterol linked to low-density lipoproteins (LDL-cholesterol) was calculated with the Friedewald formula (29). Insulin resistance and insulin sensitivity were calculated according to the homeostasis model assessment of insulin resistance ($HOMA-IR = [\text{insulin levels} \times \text{glucose levels}] / 405$) and quantitative insulin sensitivity check index ($QUICKI = 1 / [\text{logarithm of insulin levels} + \text{logarithm of glucose levels}]$), respectively.

Determination of serotonin and its metabolite 5-HIAA from plasma was performed by adding 50 µl of 0.4 N perchloric acid containing 0.1% metabisulfite and 1 nM EDTA per 50 µL sample. Then, the sample was centrifuged (13,000 rpm, 2 min) in order to discard the pellet; 75 µl of the supernatant were removed, and perchloric acid (75 µl) was added. After a second centrifugation (13,000 rpm, 2 min), the resulting supernatant were used for determination of serotonin and 5-HIAA.

For serotonin analysis, high performance liquid chromatography (HPLC) was used. The mobile phase consisted of 16% methanol and 80% aqueous solution, containing 0.05 M potassium phosphate monobasic (KH₂PO₄), 0.16 nM octanesulfonic acid (SOS) and 0.1 mM EDTA, and was injected at a flow rate of 1 ml/min and at pH value of 3. Serotonin and 5-HIAA were detected through a Waters® 717 plus Autosampler injector (Waters, USA) that injected 40 µl of sample in a reverse-phase column Spherisorb® ODS-2 (5 µm, 15 x 0.46 cm, Waters) connected to an amperometric detector DECADE® (Antec Leyden, Zoeterwoude, the Netherlands) with a range of 20 amps. In order to quantify both compounds, a specific program for HPLC was used (Empower 2.1.5.4, Waters®, USA), which compared the area generated by the peak with the standard-reference area (serotonin: 1,000 pg; 5-HIAA: 500 pg).

STATISTICAL ANALYSES

Stata 12.0 for Windows (version 12.0 Texas, USA) was used for statistical analyses. Plasma serotonin levels were log transformed to follow a normal distribution. Paired t tests were used to assess pre and post-intervention variables in participants.

Multiple linear regression analyses were fitted to estimate associations between plasma serotonin levels and blood glucose or anthropometric measures after adjustment for potential confounders (age and sex, or pre-intervention variables).

Values are shown as arithmetic mean (standard deviation/95% confidence interval). The level of statistical significance was $p < 0.05$.

RESULTS

Forty-four obese children (50% males, aged 7-15 years old) accomplished the ten-week lifestyle intervention. Anthropometric and biochemical variables from obese children (HR and LR groups) are indicated in table I; HR and LR subjects had similar pre-intervention measurements.

All obese children (HR and LR groups) showed a significant decrease in adiposity ($p < 0.05$) after the intervention. Specifically, HR subjects significantly reduced BMI-SDS (19%, $p < 0.001$), total cholesterol (12%, $p < 0.001$), LDL cholesterol (12%, $p < 0.001$), insulin levels (25%, $p = 0.010$) and HOMA-IR (30%, $p = 0.003$). Moreover, all subjects (HR and LR groups) had significantly lower BMI-SDS, fat mass, waist circumference and blood glucose levels after the intervention ($p < 0.05$).

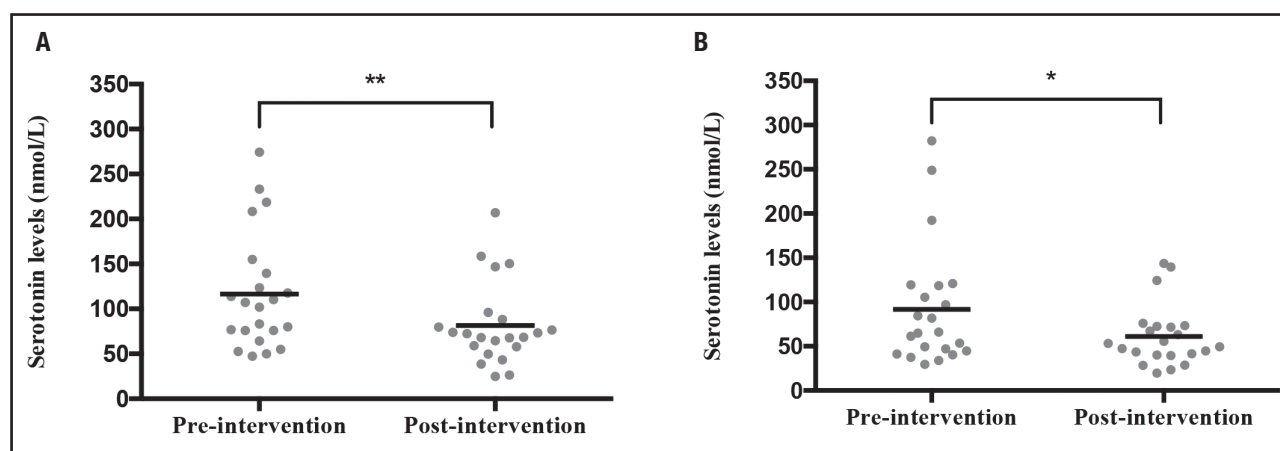
Interestingly, plasma serotonin levels were significantly diminished in both the HR (30% nmol/l, $p = 0.002$) and LR group (33%, $p = 0.026$) after the ten-week lifestyle intervention (Fig. 1).

Moreover, a significant association between pre-intervention serotonin and glucose levels was found in HR and LR subjects (Fig. 2). Curiously, 22% of the variability in baseline glucose levels is explained by its linear dependence on plasma serotonin. Thus, an increase of 0.05 mg/dl of glucose levels was explained by

Table I. Anthropometric and biochemical variables pre and post lifestyle intervention in obese children according to the response

	High responders (n = 22)			Low responders (n = 22)			
	Pre-intervention	Post-intervention	p*	Pre-intervention	Post-intervention	p*	p†
Sex (M/W)	14/8			8/14			0.073
Tanner (I/II/III)	7/12/3			4/16/2			0.618
Age (years)	11.23 (2.78)			11.82 (2.44)			0.458
Body weight (kg)	68.16 (17.17)	64.43 (16.78)	< 0.001	77.11 (22.83)	76.46 (23.29)	0.074	0.149
Height (m)	1.51 (0.13)	1.52 (0.13)	< 0.001	1.56 (0.12)	1.56 (0.12)	0.001	0.252
BMI (kg/m ²)	29.33 (4.00)	27.33 (4.04)	< 0.001	31.18 (5.73)	30.60 (5.91)	< 0.001	0.221
BMI-SDS	4.01 (1.84)	3.23 (1.67)	< 0.001	3.99 (2.28)	3.79 (2.36)	< 0.001	0.975
Fat mass (%)	35.59 (8.28)	32.64 (7.27)	< 0.001	39.00 (7.40)	38.21 (7.14)	0.024	0.157
Waist circumference (cm)	89.89 (9.89)	84.49 (9.40)	< 0.001	92.34 (9.20)	90.06 (10.03)	0.006	0.400
Hip circumference (cm)	98.50 (10.44)	95.23 (10.44)	< 0.001	104.58 (13.74)	103.72 (15.05)	0.205	0.106
Waist-to-hip ratio	0.91 (0.05)	0.89 (0.040)	< 0.001	0.89 (0.68)	0.87 (0.68)	0.053	0.175
Triglycerides (mg/dl)	88.04 (36.83)	71.23 (34.64)	0.050	109.91 (65.93)	110.05 (73.29)	0.991	0.184
Total cholesterol (mg/dl)	179.77 (36.79)	158.82 (32.34)	< 0.001	169.45 (27.64)	168.95 (35.59)	0.898	0.299
HDL-cholesterol (mg/dl)	51.95 (13.37)	47.19 (10.78)	0.001	48.18 (11.37)	45.09 (9.24)	0.005	0.415
LDL-cholesterol (mg/dl)	106.38 (29.04)	93.14 (29.04)	0.003	98.04 (21.60)	98.95 (30.19)	0.798	0.329
Glucose (mg/dl)	93.00 (8.16)	87.00 (8.02)	< 0.001	91.50 (4.87)	85.68 (7.59)	0.003	0.464
Insulin (μU/ml)	17.92 (7.67)	13.39 (6.38)	0.010	17.95 (9.99)	18.57 (12.81)	0.649	0.992
HOMA-IR	4.13 (1.76)	2.90 (1.45)	0.003	4.07 (2.31)	3.99 (2.80)	0.822	0.929
QUICKI	0.32 (0.02)	0.33 (0.02)	0.003	0.32 (0.03)	0.33 (0.04)	0.275	0.770
5-HIAA (nmol/l)	29.70 (3.83)	27.77 (6.25)	0.263	27.29 (5.48)	27.71 (6.16)	0.619	0.711

Values are expressed as mean (SD). Tanner I: infant; Tanner II: puberty; Tanner III: adult; BMI: body mass index; BMI-SDS: standard deviation score for BMI; HOMA-IR: homeostasis model assessment for insulin resistance; QUICKI: quantitative insulin sensitivity check index; 5-HIAA: 5-hydroxyindoleacetic acid; p*: p values for the comparison between pre and post-intervention variables in obese children distributed by the response; p†: p values for the comparison of pre-intervention variables between high and low responders.

**Figure 1.**

Plasma serotonin levels pre and post-lifestyle intervention in obese children from high (A) and low (B) responder groups. Each dot represents the plasma serotonin level in a subject. The solid horizontal lines indicate the mean values of plasma serotonin pre and post-intervention, respectively. *p < 0.05; **p < 0.01.

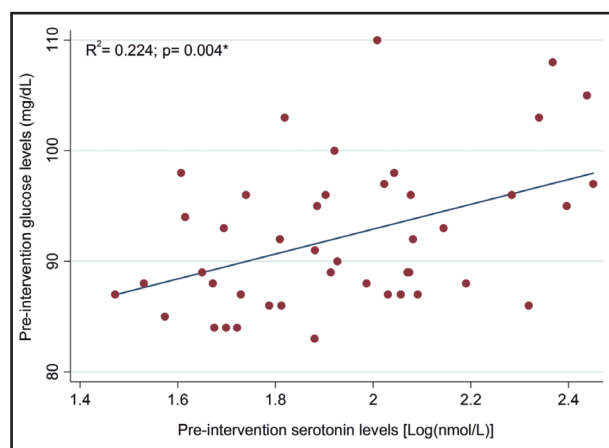


Figure 2.

Association between pre-intervention serotonin and glucose levels in an obese children population ($n = 44$). *Multiple linear regression analyses after adjustment for baseline BMI-SDS and age.

the increase in one unit of serotonin (nmol/l), after adjusting for potential confounders. The change in plasma serotonin significantly ($p < 0.05$) predicted the 29% of the variance in changes in glucose levels in the HR group (Fig. 3) in a multiple linear regression after adjustment for baseline glucose levels and age. Post-intervention serotonin and glucose levels were significantly associated in HR and LR subjects ($R^2 = 0.140$, $B = 0.055$, $p = 0.042$, data not shown).

Finally, multiple regression models were fitted in order to assess the association between pre and post-intervention serotonin levels and anthropometric measures in the total population (HR and LR groups). Notably, significant associations were found between serotonin levels and body weight (pre-intervention, $R^2 = 0.452$, $B = -0.109$, $p = 0.044$; post-intervention, $R^2 = 0.384$, $B = -0.174$,

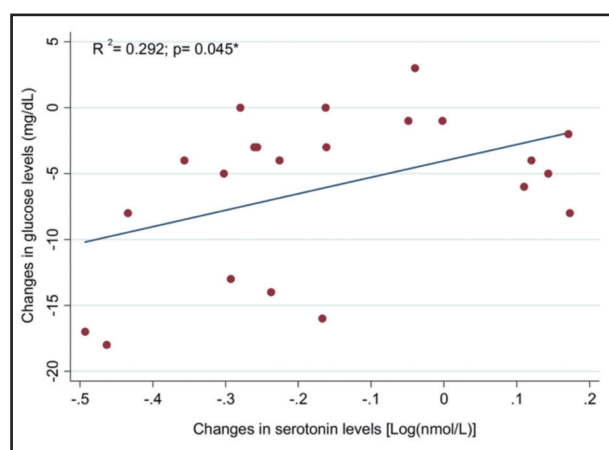


Figure 3.

Association between changes in serotonin and glucose levels after a ten-week lifestyle intervention in the HR group ($n = 22$). *Multiple linear regression adjusted for baseline glucose and age.

$p = 0.013$), BMI (post-intervention, $R^2 = 0.290$, $B = -0.048$, $p = 0.013$) and BMI-SDS (pre-intervention, $R^2 = 0.194$, $B = -0.026$, $p = 0.006$) (Table II).

DISCUSSION

In the present study a ten-week lifestyle intervention was conducted in obese children and adolescents based on a moderate caloric restriction diet, not to compromise growth and development of the population. Our intervention was able to reduce adiposity indices and some biochemical markers, thus lowering cardiometabolic risk. It is worth mentioning that, from a pediatrician's perspective, it is favorable to have no increase in body weight when treating obese children (30).

Furthermore, Reinehr et al. indicated that an improvement in body composition and cardiometabolic risk can be seen with a 0.2 decrease in BMI-SDS, while greater benefits occurs when losing at least 0.5 BMI-SDS (31). Indeed, in our study, a 0.49 BMI-SDS reduction was obtained together with an improvement in lipid and glucose profiles. We and other researchers have conducted successful programs for childhood obesity including lifestyle modification, moderate caloric reduced diet, nutritional education and family implication (22,32).

The novelty of this study is that plasma serotonin levels were notably decreased after a ten-week lifestyle intervention and they were associated with anthropometric and glucose measurements. Little research work focused on the relationship between serotonin and weight status in human subjects is found in the literature. In normal weight, anorexia nervosa and obese adult subjects, plasma tryptophan levels are diminished after dietary restriction, suggesting that serotonin synthesis could also be reduced (33-38). In a similar way, our results indicate that serotonin levels were reduced in obese children following a moderate calorie restricted diet.

Concerning the potential involvement of serotonin levels in glucose metabolism, we observed that plasma serotonin levels were significantly associated with blood glucose in our obese children population. Peripheral serotonin appears to exert its action on different tissues, metabolic pathways and endocrine organs involved in glucose homeostasis, which may explain the contradictory effects reported in the literature (39,40). In healthy subjects, a positive correlation between platelet serotonin and glucose levels was observed before and after an oral load glucose test (41). Furthermore, it has been observed that plasma 5-HIAA was associated with fasting plasma glucose in patients with metabolic syndrome (42,43) and diabetes (44).

As mentioned before, few studies in humans show a relationship between peripheral serotonin and glucose metabolism. However, in animals it is reported that glucose is a stimulator for the release of serotonin into blood in pancreatic β -cells (9,11) and enterochromaffin cells (12). Moreover, in animal hepatocytes, serotonin promotes hepatic gluconeogenesis and decreases glucose uptake, which would result in higher circulating glucose levels (10,13). These preliminary results in animal studies could help to understand the association between circulating serotonin and glucose levels.

Table II. Association between pre and post-intervention serotonin levels and anthropometric measurements in an obese children population (n = 44)

	Serotonin (Log[nmol/l])								
	Body weight (kg)			BMI (kg/m ²)			BMI-SDS		
	R ²	B (95% CI)	p	R ²	B (95% CI)	p	R ²	B (95% CI)	p
Pre-intervention	0.452	-0.109 (-0.212, -0.005)	0.044	0.320	-0.025 (-0.055, 0.006)	0.110	0.194	-0.026 (-0.054, 0.001)	0.006
Post-intervention	0.384	-0.174 (-0.370, 0.022)	0.013	0.290	-0.048 (-0.104, 0.008)	0.013	0.148	-0.013 (-0.029, 0.004)	0.131

Multiple linear regression adjusted for baseline sex and age. BMI: body mass index; BMI-SDS: standard deviation score for BMI.

The strengths of this study include: first, measurements in young subjects not confounded by chronic obesity-related disorders; second, the overweight/obese subjects achieved weight loss in a short term dietary intervention; and third, a standardized intervention with similar lifestyle recommendations given to a relatively homogenous group. On the other hand, weaknesses of the study are: first, the absence of a normal weight children group; second, the reduced sample size of our population and also that there was no sample available for tryptophan measurement; and third, the different pubertal stage of participants, with an intense growth and endocrine changes which may influence our results. To make this effect lower, each statistical model was adjusted for age and sex.

In summary, we have shown for the first time that plasma serotonin levels were decreased after a lifestyle intervention in obese children, and that they were associated with anthropometric indices (body weight, BMI, BMI-SDS) and blood glucose levels. Nevertheless, further studies are needed to confirm the findings in a larger population, and also to characterize the underlying mechanisms that link serotonin with body weight regulation and energy homeostasis.

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Trabajo Original

Pediatría

Socio-demographic variables and underlying pathologies associated to nutritional status of hospitalized children in a secondary-tertiary level hospital

Variables sociodemográficas y patologías asociadas al estado nutricional de niños hospitalizados en una unidad de segundo-tercer nivel

Nelly Carolina Muñoz Esparza¹, Edgar Manuel Vásquez-Garibay^{1,2}, Alfredo-Larrosa-Haro¹ and Enrique Romero-Velarde^{1,2}

¹Instituto de Nutrición Humana. Universidad de Guadalajara. Guadalajara, Mexico. ²Hospital Civil de Guadalajara "Dr. Juan I. Menchaca". Guadalajara, Mexico

Abstract

Objective: the purpose was to evaluate the nutritional status in hospitalized children according to their socio-demographic variables, underlying pathology and based on hospital length of stay.

Methods: seven-hundred and sixty-three hospitalized patients of the Civil Hospital of Guadalajara Dr. Juan I. Menchaca were included in a cross-sectional study. The following anthropometric indices were taken: weight/length, weight/height, weight/age, length/age, height/age, head circumference/age and BMI/age. Data of socio-demographic variables and underlying pathology were also obtained. Student's t-test, Chi-squared test, ANOVA with post-hoc tests and logistic regression were used to identify the likelihood of risk of malnutrition.

Results: subjects were divided according to their hospital length of stay in lower than seven days and seven days or more. At the time of admission, children with stay of seven days or more showed a greater deficit in the height/age index (OR = 1.77 [95% CI 1.16-2.7], p = 0.007), head circumference (OR = 2.68 [95% CI 1.5-4.7], p ≤ 0.001) and BMI (OR = 2.9 [95% CI 1.9-4.4], p ≤ 0.001). Males had higher risk of moderate/severe malnutrition (OR = 1.87 [95% CI 1.22-2.85], p = 0.003) and higher deficit in head circumference (OR = 1.89 [95% CI 1.06-3.37], p = 0.029). Infants with gastrointestinal and respiratory problems had higher frequency of malnutrition at the time of admission than did those with other pathologies (p < 0.001).

Conclusion: the pathological disease at time of admission and longer hospital length of stay increased the likelihood of malnutrition in male infants and preschool-aged children. There were demographic and educational risk factors in the home environment that could influence acute and chronic malnutrition.

Key words:

Malnutrition.
Hospitalization.
Socio-demographic
variables. Diagnosis.

Resumen

Objetivo: el propósito fue evaluar el estado nutricional en niños hospitalizados de acuerdo a variables sociodemográficas, patología de ingreso y días de estancia hospitalaria.

Métodos: en estudio transversal analítico se incluyeron 763 pacientes hospitalizados en el Hospital Civil de Guadalajara Dr. Juan I. Menchaca. Se estimaron los índices: peso/edad, longitud/edad, estatura/edad, peso/talla, IMC y circunferencia cefálica/edad. Se obtuvieron variables sociodemográficas y el diagnóstico de ingreso. Se utilizaron las pruebas t de Student, Chi-cuadrado, ANOVA y post-hoc y regresión logística para identificar la probabilidad de riesgo de mala nutrición.

Resultados: los participantes se dividieron de acuerdo a la duración de la estancia hospitalaria en menor de siete días e igual o mayor a siete días. Al ingreso, los niños con estancia de siete días o mayor mostraron déficit de los índices talla/edad (RM = 1.77 [IC 95% 1.16-2.7], p = 0.007), circunferencia cefálica (RM = 2.68 [IC 95% 1.5-4.7], p ≤ 0.001) e IMC (RM = 2.9 [IC 95% 1.9-4.4], p ≤ 0.001). Los varones mostraron mayor riesgo de desnutrición moderada o grave (RM = 1.87 [IC 95% 1.22-2.85], p = 0.003) y déficit en circunferencia cefálica (RM = 1.89 [IC 95% 1.06-3.37], p = 0.029). Los lactantes con problemas gastrointestinales y respiratorios tuvieron mayor frecuencia de desnutrición al ingreso hospitalario que aquellos con otras patologías (p < 0.001).

Conclusión: la patología al momento del ingreso hospitalario y la estancia más prolongada aumentaron la probabilidad de desnutrición en lactantes varones y en preescolares. Hay factores de riesgo demográfico y educacional en la familia que podrían influir en la frecuencia de desnutrición aguda y/o crónica.

Palabras clave:

Malnutrición.
Hospitalización.
Variables
sociodemográficas.
Diagnóstico.

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Correspondence:

Edgar M. Vásquez-Garibay. Instituto de Nutrición Humana. Centro Universitario de Ciencias de la Salud. Universidad de Guadalajara. Nuevo Hospital Civil de Guadalajara Salvador Quevedo y Zubieta, 750. Sector Libertad. 44240 Guadalajara Jalisco, México
e-mail: vasquez.garibay@gmail.com

INTRODUCTION

Malnutrition in children is a global public health concern because they have a higher risk of dying from infectious diseases (1). It is estimated that malnutrition is the underlying cause of 45% of global deaths in children under five years of age (2-4). In children, malnutrition syndromes are responsible for 3.1 million deaths each year (5). Childhood is characterized by a high demand for nutrients to support growth and development (6); therefore, any nutritional insult caused by a disease, infection or fever can have a high metabolic cost that could impair nutritional status and increase morbidity and mortality from other causes, usually infectious diseases (4,5).

While the prevalence of protein-energy malnutrition (PEM) in Mexican children under five years of age has decreased in the last decade (7,8), malnutrition secondary to an underlying pathology has not been widely studied (9). It has been shown that the worldwide prevalence of malnutrition in hospitalized children ranges widely between 6% and 50% (10-15). This rate is higher in public hospitals in Latin America, where the prevalence of malnutrition ranges from 7% to 90% (16,17). A percentage of these malnourished patients has been known to deteriorate while in the hospital (10) and on other occasions, patients enter and leave the hospital without undergoing any adequate nutritional assessment (1). One highly specialized Mexican pediatric hospital (9) found that at the time of hospital admission, 17% of children had chronic malnutrition and 8% had acute malnutrition. However, currently there is little information on malnutrition in hospitalized children. Therefore, the purpose of this study was to evaluate the nutritional status in hospitalized children according to their socio-demographic variables, underlying pathology and based on hospital length of stay.

METHODS

In a 2014 cross-sectional study, a convenience sample was collected over nine months consisting of 763 patients admitted to different departments of the Division of Pediatrics, of the Civil Hospital of Guadalajara, Dr. Juan I. Menchaca (18). All patients were admitted Monday through Friday into areas of the Pediatrics Division. Patients who spent less than 72 hours in the Emergency Room and were subsequently admitted in a hospital ward and whose parents or legal guardian signed the informed consent were accepted into the study. Patients hospitalized in the Intensive Care Unit, those with severe burns, and patients with end-stage-kidney-disease (on hemodialysis or peritoneal dialysis) were not included due to technical difficulties in measuring, or to the presence of chronic malnutrition (stunting) of months or years of evolution. Additionally, those children with cerebral palsy, those who could not provide anthropometric measurements or those who were hospitalized more than once in less than a three-month period were not included. Two patients with incomplete files or data were excluded from the analyses. For each participant or

family, a questionnaire was administered to the family member or legal guardian that included general identification data and socio-demographic information.

ANTHROPOMETRIC MEASUREMENTS

Two researchers who had been previously standardized in the Habitch method (19) took anthropometric measurements at the time of hospital admission. The weight of children under 24 months was measured without clothes, on a 5 g to 20 kg scale (Seca-354; Seca®, Hamburg, Germany); children over 24 months were weighed in light clothes or a robe on a scale with a minimum reading of 100 g (Tanita® UM-081, Tokyo, Japan). Length of infants and toddlers less than 24 months of age was obtained without clothes in a Seca infantometer-416 mark (Seca®, Hamburg, Germany). Height of children over 24 months of age was measured using a graduated scale dry-214 mark (Hamburg, Germany) without shoes, with the heels together and the tips of the feet slightly apart and with the head, shoulders, buttocks and heels vertically aligned.

Head circumference was measured in children under three years of age using a metal tape measure (Rosscraft®, USA). The tape was firmly applied around the head in the supraciliary region, so that it aligned with the most prominent parts of the frontal area and occipital protuberance. Mid-upper-arm circumference (MUAC) was obtained in the middle of the left arm with the same metal tape measure. A tricipital skinfold measurement was taken on the midpoint of the inner, rear face of the previously marked arm; a subscapular skinfold measurement was taken at the lower edge of the scapula. Both measurements were performed on the left side using a Lange skinfold caliper (Michigan, USA).

The Z-scores for the following indices were calculated: weight/length, weight/height, weight/age, length/age, height/age, head circumference/age and BMI/age using the programs WHO Anthro version 3.2.2 and Anthro Plus version 1.0.4 (20,21). Reference limits were set as ± 2 SD (z-score), as defined by the World Health Organization (WHO); however, in children under five years of age, overweight and obesity were defined as > 2 SD and > 3 SD, respectively. Additionally, in children over five years of age, overweight and obesity were defined as > 1 SD and > 2 SD, respectively. Body fat percentage was estimated using the triceps and subscapular fold measurements and the Slaughter equation (22).

STATISTICAL ANALYSES

Student's t tests and Chi-squared tests were used to analyze parametric variables in independent samples and non-parametric variables, respectively. ANOVA with post-hoc tests (T3 of Dunnett) were also conducted and odds ratios were estimated with multivariate binary regression logistic models to identify the probability of deficit on the anthropometric indicators. SPSS version 20 software was used for all analyses.

ETHICAL CONSIDERATIONS

The research protocol was reviewed and approved by the Bioethics and Research Committees of the Civil Hospital of Guadalajara. The registration number in the Secretary of Health of the Jalisco State is 1342-1314.

RESULTS

Seven hundred and sixty-one patients were included in the final study analyses. The population was 53% male, 31% infants, 29% toddlers and preschoolers, 23% school children and 17% adolescents. In 25.9% of cases, pathologies with pneumological origins were observed. In the remaining subject population, 20.1% of cases were admitted with internal medicine diseases, 11% with cancer, 10.2% for surgery, 9.9% with neurological issues, 7.9% with infectious diseases, 5.9% with gastrointestinal diseases, and 9.1% of whom there was not a definite diagnosis.

Forty percent of patients' parents were married by civil and religious laws or by civil laws alone, 36% were cohabiting as couple and 10% were single mothers. Sixty percent of the families were nuclear and 29% were extended. The average ages of the father and the mother were 33 ± 9.2 and 30 ± 8.3 , respectively. Among parents, 12.6% were illiterate or had incomplete elementary schooling, 22% had completed elementary school, 39.5% had completed junior high school, 19.5% had completed senior high school, and 6.3% had a college degree or higher.

In the total population, it was observed that at the time of hospital admission, 33.4% of subjects had some degree of malnutrition according to their BMI (Table I). When examining the study population, based on hospital length of stay, those with hospital stay of seven days or more (sub-acute and/or chronic evolution) (12.2 ± 7.3) showed a significantly greater deficit in height/age (-0.55 vs -1.07) and BMI/age (-0.24 vs -0.94) than those patients with hospital stay less than seven days (acute evolution) (3.5 ± 1.8), $p < 0.001$.

When comparing the nutritional status of children with hospital stay less than seven days vs hospital stay of seven days or more,

severe malnutrition was observed in 4% vs 14.1% and moderate malnutrition was observed in 6.3% vs 11.2%, respectively (Table II). The risk of having deficient anthropometric indices at admission was higher in children with hospital stay of seven days or more than in children with hospital stay less than seven days for the several indices. Weight/height index was deficient in 23.3% of children with hospital stay of seven days or more vs 9.6% of children with hospital stay less than seven days (OR = 2.9 [95% CI 1.6-5.07], $p < 0.001$). The height/age index was deficient in children with hospital stay of seven days or more (20.3%) vs 12.4% of children with hospital stay less than seven days (OR = 1.77 [95% CI 1.16- 2.7], $p = 0.007$). Head circumference was undersize in 32% of children with hospital stay of seven days or more vs 14.9% of children with hospital stay less than seven days (OR = 2.68 [95% CI 1.5-4.7], $p < 0.001$). Finally, BMI was lower in children with hospital stay of seven days or more (25.2%) vs. 10.5% of children with hospital stay less than seven days (OR = 2.9 [95% CI 1.9,-4.4], $p < 0.001$).

When comparing the nutritional status of subjects according to sex for the weight for age, head circumference and BMI indicators, a significantly greater deficit was observed in males than in females ($p < 0.05$) (Table III). Regarding BMI, a higher risk of moderate/severe malnutrition in males (18%) than in females (10.5%) was observed (OR = 1.87 [95% CI 1.22-2.85], $p = 0.003$); there was also greater deficit in head circumference in males (24.6%) than in females (14.7%) (OR = 1.89 [95% CI 1.06-3.37], $p = 0.029$) and in the weight/age index in males (23.7%) compared to females (16.2%) (OR = 1.61 [95% CI 1.06-2.46], $p = 0.024$). Table IV shows that infants were the most affected age group at the time of hospital admission ($p < 0.001$) compared to the preschooler, schoolchildren and adolescent age groups. This trend occurred in both indicators of acute deficit (weight/height and BMI) as well as indicators of chronic deficit (height/age index and head circumference).

It was observed that infants had acute malnutrition (moderate and severe) when using BMI cutoffs (27.3%), whereas chronic malnutrition occurred in 28.5% when using the height/age index. In preschool children, acute malnutrition (moderate and severe)

Table I. Percentage of anthropometric indexes (Z score) in total population (n = 761)*

Z-score	Weight/height n (%)	Weight/age n (%)	Height/age n (%)	Head circumference n (%)	BMI/age n (%)
< -3	22 (5.2)	56 (9.6)	49 (6.4)	27 (8.5)	52 (6.8)
≥ -3 to < -2	35 (8.3)	62 (10.7)	63 (8.3)	37 (11.6)	58 (7.6)
≥ -2 to < -1	79 (18.8)	117 (20.1)	157 (20.6)	75 (23.6)	144 (18.9)
≥ -1 to < 1	236 (56.1)	290 (49.8)	440 (57.8)	158 (49.7)	371 (48.8)
> 1 to < 2	41 (9.7)	45 (7.7)	44 (5.8)	16 (5)	99 (13)
≥ 2 to < 3	5 (1.2)	9 (1.5)	8 (1.1)	5 (1.6)	30 (3.9)
≥ 3	3 (0.7)	3 (0.5)	-	-	7 (0.9)
Total	421 (100)	582 (100)	761 (100)	318 (100)	761 (100)

*Some values are missing for unnecessary and/or lack of measurements.

Table II. Percentage of anthropometric indexes (Z score) according to hospital stay: < 7 days vs. ≥ 7 days (n = 761)

Z-score	Weight/height* n (%)	Weight/age† n (%)	Height/age‡ n (%)	Head circumference§ n (%)	BMI/age¶ n (%)
< 7 days (n = 555)					
< -3	10 (3.3)	28 (6.5)	23 (4)	12 (5.4)	23 (4)
≥ -3 to < -2	19 (6.3)	36 (8.4)	47 (8.5)	21 (9.5)	35 (6.3)
≥ -2 to < -1	52 (17.3)	83 (19.4)	106 (19)	53 (24)	101 (18.2)
≥ -1 to < 1	181 (60)	234 (54.7)	338 (61)	118 (53.4)	289 (52)
> 1 to < 2	32 (10.6)	36 (8.4)	34 (6)	13 (5.9)	77 (14)
≥ 2 to < 3	4 (1.3)	8 (1.9)	7 (1.5)	4 (1.8)	23 (4)
≥ 3	3 (1)	3 (0.7)	-	-	7 (1.5)
Total	301 (100)	428 (100)	555 (100)	221 (100)	555(100)
≥ 7 days (n = 206)					
< -3	12 (10)	28 (18.2)	26 (12.6)	15 (15.5)	29 (14.1)
≥ -3 to < -2	16 (13.3)	26 (16.9)	16 (7.8)	16 (16.5)	23 (11.2)
≥ -2 to < -1	27 (22.5)	34 (22.1)	51 (24.8)	22 (22.7)	43 (20.9)
> -1 to < 1	55 (45.8)	56 (36.4)	102 (49.5)	40 (41.2)	82 (39.8)
≥ 1 to < 2	9 (7.5)	9 (5.8)	10 (4.9)	3 (3.1)	22 (10.7)
≥ 2 to < 3	1 (0.8)	1 (0.6)	1 (0.5)	1 (1)	7 (3.4)
≥ 3	-	-	-	-	-
Total	120 (100)	154 (100)	206 (100)	97 (100%)	206 (100)

Chi-squared test (stratification ± 2 Z score); < 7 days vs ≥ 7 days: *weight/height, $p = 0.005$; †weight/age, $p < 0.001$; ‡height/age, $p < 0.001$; §head circumference, $p = 0.017$; ¶BMI/age, $p < 0.001$. Some missing values for unnecessary and/or lack of measurements.

Table III. Anthropometric indices according to sex

Indexes	Females			Males		
	n	Mean	SD	n	Mean	SD
	(n = 361)			(n = 400)		
Weight/height	187	-0.46	1.3	234	-0.57	1.7
Weight/age*	266	-0.72	1.5	316	-0.98	1.8
Height/age	361	-0.62	1.3	400	-0.76	1.5
Head circumference†	143	-0.75	1.3	175	-1.2	1.7
BMI/age‡	361	-0.31	1.5	400	-0.54	1.8

Student's t test for independent samples (two tails) * $p = 0.058$; † $p = 0.010$; ‡ $p = 0.058$. Some missing values for unnecessary and/or lack of measurements.

occurred in 6.2% when using BMI cutoffs and chronic malnutrition occurred in 12.7% when using the height/age index. In schoolchildren, there was acute malnutrition in 9.6% of the population when using BMI cutoffs and linear growth retardation (stunting) in 4.2% when using the height/age index. In adolescents, acute malnutrition occurred in 12.2% of the population when using BMI cutoffs and stunting, in 6.9% when using the height/age index. Overweight/obesity was observed in 27.6% of schoolchildren and 25.9% of adolescents, while in infants and preschool children, overweight and obesity were rare (Table V). Infants risk of defi-

cit in BMI was 27.3%, compared to 6.2% in preschool children (OR = 5.7 [95% CI 3.1-10], $p < 0.001$), 9.6% in schoolchildren (OR = 3.5 [95% CI 1.95-6.37], $p < 0.001$) and 12.2% in adolescents (OR = 2.6 [95% CI 1.48-4.89], $p < 0.001$). With the height/age index, a higher risk of deficiency was observed in infants (30.5%) than in preschool children (12.7%) (OR = 2.74 [95% CI 1.69-4.43], $p < 0.001$), school children (4.2%) (OR = 9.1 [95% CI 4.06-20.45], $p < 0.001$), and adolescents (6.9%) (OR = 5.41 [95% CI 2.60-11.26], $p < 0.001$). Additionally, a higher rate of deficiency in the height/age index was also observed in

Table IV. Anthropometric indexes (Z score) by age group. Mean and standard deviation (n = 761)

Indexes	Infants (n = 238)			Preschoolers (n = 218)			Schoolchildren (n = 175)			Adolescents (n = 130)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Weight/height	237	-0.80	1.5	181	-0.17	1.4	3	-0.63	0.88	-	-	-
Weight/age	238	-1.56	1.8	218	-0.45	1.4	126	-0.26	1.34	-	-	-
Height/age ^{*,†,‡,§}	238	-1.39	1.7	218	-0.61	1.2	175	-0.06	1.03	130	-0.40	1.1
Head circumference	231	-1.25	1.6	87	-0.30	1.3	-	-	-	-	-	-
BMI/age ^{§, ,¶}	238	-1.15	1.7	218	-0.10	1.5	175	-0.09	1.56	130	-0.15	1.6

One-way ANOVA (post-hoc T3 of Dunnett); height/age: *Infants vs preschoolers, $p < 0.001$; †Infants vs schoolchildren, $p < 0.001$; ‡Infants vs adolescents, $p < 0.001$; §Preschoolers vs schoolchildren, $p < 0.001$. BMI: §Infants vs preschoolers, $p < 0.001$; †Infants vs schoolchildren, $p < 0.001$; ‡Infants vs adolescents, $p < 0.001$. Some missing values for unnecessary and/or lack of measurements.

Table V. Frequency and percentage (%) of anthropometric indexes (Z-score) by age group, n = 761

Indexes	n	< -3	≥ -3 to ≤ -2	≥ -2 to ≤ -1	≥ -1 to ≤ 1	> 1 to ≤ 2	> 2 to ≤ 3	> 3
Infants								
Weight/height*	237	17 (7.2)	26 (11)	51 (21.5)	120 (50.6)	20 (8.4)	2 (0.8)	1 (0.4)
Weight/age [†]	238	48 (20.2)	39 (16.4)	44 (18.5)	99 (41.6)	7 (2.9)	1 (0.4)	-
Height/age [‡]	238	37 (15.5)	30 (12.6)	62 (26.1)	102 (42.9)	6 (2.5)	1 (0.4)	-
Head circumference [§]	231	26 (11.3)	29 (12.6)	64 (27.7)	103 (44.6)	8 (3.5)	1 (0.4)	-
BMI/age	238	34 (14.3)	30 (12.6)	46 (19.3)	108 (45.4)	18 (7.6)	1 (0.4)	1 (0.4)
Preschooler								
Weight/height*	181	5 (2.8)	9 (5)	26 (14.4)	115 (63.5)	21 (11.6)	3 (1.7)	2 (1.1)
Weight/age [†]	218	7 (3.2)	13 (6)	51 (23.4)	125 (57.3)	18 (8.3)	2 (0.9)	2 (0.9)
Height/age [‡]	218	8 (3.7)	22 (10.1)	42 (19.3)	129 (59.2)	16 (7.3)	1 (0.5)	-
Head circumference [§]	87	1 (1.1)	8 (9.2)	11 (12.6)	55 (63.2)	8 (9.2)	4 (4.6)	-
BMI/age	218	4 (1.8)	10 (4.6)	37 (17)	132 (60.6)	28 (12.8)	5 (2.3)	2 (0.9)
Schoolchildren								
Weight/height	3	-	-	2 (66.7)	1 (33.3)	-	-	-
Weight/age [†]	126	1 (0.8)	10 (7.9)	22 (17.5)	66 (52.4)	20 (15.9)	6 (4.8)	1 (0.8)
Height/age [‡]	175	1 (0.6)	5 (2.9)	26 (14.9)	127 (72.6)	11 (6.3)	5 (2.9)	-
BMI/age	175	6 (3.4)	10 (5.7)	39 (22.3)	72 (41.1)	31 (17.7)	15 (8.6)	2 (1.1)
Adolescents								
Height/age [‡]	130	3 (2.3)	6 (4.6)	27 (20.8)	82 (63.1)	11 (8.5)	1 (0.8)	-
BMI/age	130	8 (6.2)	8 (6.2)	22 (16.9)	59 (45.4)	22 (16.9)	9 (6.9)	2 (1.5)

Chi-squared test: *weight/height, $p = 0.004$; †weight/age, $p < 0.001$; ‡height/age, $p < 0.001$; §head circumference, $p < 0.001$. Some missing values for unnecessary and/or lack of measurements.

the preschool aged subjects (12.7%) than in the schoolchildren (4.2%) (OR = 3.33 [95% CI 1.42-7.80], $p = 0.006$).

When examined according to BMI, the prevalence of acute malnutrition (moderate/severe) was more frequent in pathologies of gastroenterological origin (26.7%), internal medicine (19.7%), pneumology diseases (15.2%), those without clear diagnosis (15.9%)

and to a lesser extent, surgical (12.8%), infectious (8.3%), neurological (8%) and oncological (7.2%) pathologies. Additionally, low BMI was more frequent in patients with gastrointestinal diseases than in those with oncological ($p = 0.011$) or neurological diseases ($p = 0.033$). Deficit in the height/age index was higher in patients with pneumological diseases than surgical pathologies ($p = 0.016$).

Table VI. Logistic binary regression models with BMI (z) and height/length for age (z) as dependent variables and socio-demographic and educational data as covariates in the whole population, n = 761

Model	Dependent variable	Independent variables	Unadjusted analysis		Adjusted analysis	
			OR	95% IC	OR	95% IC
1	Low BMI for age < -2 (z-score)	Hospitalization				
		> 7 days	3	1.9-4.5	3.1	2-4.7
		≤ 7 days				
		Gender				
		Males Females	1.8	1.2-2.7	1.9	1.3-3
		Age group				
	< 6 years ≥ 6 years	1.8	1.1-2.7	1.7	1.1-2.6	
2	Low BMI for age < -2 (z-score)	Marital status				
		Other*	2.2	1.4-3.6	2	1.2-3.5
		Civil and/or religious marriage				
		Mother's age				
		< 23 years	2.1	1.3-3.2	1.2	1.1-2.8
		≥ 23 years				
		Father's education				
		Elementary	1.6	1.1-2.5	1.6	1-2.5
High school or higher						
3	Low length or height < -2 (z-score)	Age group				
		< 6 years	5	2.8-8.8	4.1	2.1-7.4
		≥ 6 years				
		Mothers' education				
		Elementary	1.8	1.1-3.1	2.2	1.2-4
		High school or higher				
		Hospitalization				
		> 7 days	1.8	1.2-2.7	1.7	1.1-2.6
		≤ 7 days				
		Type of family				
		Other†	1.8	1.2-2.8	1.6	1.1-2.4
Nuclear						
4	Low length or height < -2 (z-score)	Father's age				
		< 20 years	3.2	1.6-6.3	2.3	1.1-4.8
		≥ 20 years				
		Mother's age				
		< 23 years	2.1	1.3-3.2	1.7	1-2.9
		≥ 23 years				
		Mother's education				
		Elementary	1.8	1.1-3.1	1.7	1-3
High school or higher						

OR: odds ratio; CI: confidence interval. *Single, cohabiting with a partner, widow. †Extensive or composite families or single parents. BMI: father's age < 20 years (OR = 3.5, CI 95% 1.8-6.7, $p < 0.001$) and mother's elementary education (OR = 2.2, CI 95% 1.4-3.6) were independently associated with < -2 SD z-score for BMI but could not be included in either of the two logistic regression models. Length- or height-for-age: marital status was independently associated (OR = 1.5, CI 95% 1-2.4, $p = 0.05$) but could not be included in either of the two logistic binary regression models.

Table VI shows four logistic binary regression models with BMI and height/age index (low vs normal) that included personal, demographic and education variables of families that predict the risk of malnutrition.

DISCUSSION

This study included 761 patients, of whom infants were the predominant age group, as is common in other studies (11,23). Most parents were cohabiting couples, though a small percentage were married by civil and religious laws, or civil laws alone, which is increasingly happening in Mexico (24). These data confirm that a major fraction of the Guadalajara metropolitan population has significantly changed their lifestyle and way of living as a couple compared to what was occurring some years ago (9,25). Approximately 60% of families included in the study were nuclear and the remaining families were extended or composite, consistent with other findings made in the Guadalajara metropolitan area (Strategic Plan of the Metropolitan Area of Guadalajara, 2010). It is likely that the economic situation of young families today influences the observed family structures. For example, the monthly family income was 2.4 ± 0.22 minimum wages (MW \$ 70.10 per day), equivalent to \$ 3.9 USA dollar per day (in 2014, average annual peso: dollar ratio was 17.9:1).

By dividing the study population according to hospital length of stay (stays less than seven days and stays seven days or longer), it was observed that rates of both acute and chronic malnutrition were significantly higher in children with hospital stay of seven days or more. Especially infants were the most likely to have both acute and chronic malnutrition. In another study (10), similar results were observed, with 40% of infants showing some degree of malnutrition.

The pediatric population that was admitted to the hospital showed particular anthropometric characteristics. In infants, the prevalence of acute, moderate and severe malnutrition (BMI) was high (27.3%). Contrastingly, in preschool children the prevalence of acute, moderate and severe malnutrition was measured to be 7%. This prevalence increased to 9.6% in schoolchildren and 12% in adolescents. Moreover, chronic malnutrition is common in infants (28.5%), significantly lower in preschool children (13%) and lower still in schoolchildren (4.2%). An interesting finding was that between 26% and 28% of children and adolescents were overweight/obese. This high prevalence of overweight/obesity in hospitalized children reflects the nutrition transition and the high prevalence of overweight and obesity in children and adolescents in the general Guadalajara metropolitan area (8). It also reflects the nutrition transition happening in the Mexican population, with the simultaneous presence of acute and chronic malnutrition and obesity within the same community (9,23,26). This phenomenon has also been observed in hospitalized Canadian children (11), with a prevalence of 6.9% acute malnutrition, 13.4% chronic malnutrition and 30.8% overweight/obesity. Similarly, in Brazilian hospitalized children (17), 16.1% of the study population showed under nutrition and 19.17% had overweight/obesity.

It was observed that males had a higher frequency of acute and chronic malnutrition than females. This trend would explain the differences found in the anthropometric measurements, which would be a result of frequent infections in the "windows" of more active physical growth (27). It has been suggested that early life morbidity and mortality is more common in males than in females (26,28). However, this finding does not coincide with findings observed by other authors, who have shown that acute and chronic malnutrition is more common in girls than in boys (29), especially in extremely poor and/or indigenous populations.

The pathologies that led to hospitalization were varied, so it was difficult to interpret the potential impact of any particular pathology on nutritional status. However, both acute malnutrition and chronic malnutrition occurred in patients with pneumological, gastroenterological and internal medicine pathologies. One explanation for this could be that the gastroenterological and pneumological patients were generally infants and preschool children with relatively severe acute diseases as well as secondary insufficient feeding. It should be noted that in older children (school children and adolescents), the severity of the pathology at the time of admission significantly affected their nutritional status during their hospital stay.

The first binary logistic regression model presented, which used individual profiles of the participants, showed that when patients remained in the hospital for more than seven days, they were most likely to be male and under six years of age, and they had 2-3 times the probability of low BMI as an expression acute malnutrition. The second binary logistic regression model showed that participants whose parents were not united by civil and/or religious laws, with a maternal age less than 23 years and with only basic paternal education, had a 1.2-2 times higher probability of having a low BMI. The third binary logistic regression model showed that the odds of a deficit in the height/age index were 1.6-4.1 times higher in children under six years of age, whose mothers received only basic education, who were hospitalized for more than seven days and who came from non-nuclear families. Finally, the last binary logistic regression model showed that the odds of deficit in the height/age index were 1.7 to 2.3 times higher in patients whose fathers were under 20 years of age and whose mothers were under 23 years of age and had only an elementary education.

One strength of this study is its duration (nine continuous months between April and December), which limits seasonal biases. Additionally, the sample size was quite large and included virtually all children who were hospitalized during the study duration. A potential limitation of the study was that children admitted for severe malnutrition or severe burns, children admitted directly to the Intensive Care Unit, patients with chronic renal disease and replacement therapy (hemodialysis and/or peritoneal dialysis) and children with cerebral palsy were not included. We believe that such patients require very special and selective assessment of the nutritional status and a specific dietary management.

In conclusion, it should be emphasized that nutritional status assessment upon admission to the hospital is very important because if there is some degree of malnutrition, it is likely that it

will be exacerbated during hospitalization and could thus increase the risk of complications or even death. It is also important to consider that the type of pathology prompting hospital admission as well as the hospital length of stay can expose pediatric patients to greater risk for worsened nutritional status, particularly if they are infants, toddlers or, as shown in this study, males. Additionally, it was clear that regardless of the characteristics of the patients and their pathologies, there were social, demographic and educational family risk factors that also potentially influence both acute and chronic malnutrition.

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Trabajo Original

Nutrición en el anciano

Prevalence of metabolic syndrome and its determinants in older Mexican non-diabetic adults

Prevalencia de síndrome metabólico y sus determinantes en adultos mayores mexicanos sin diabetes

Heliodoro Alemán-Mateo¹, Miriam T. López Teros², Rene Urquidez-Romero³ and Luis Huesca⁴

¹Department of Nutrition and Metabolism. Coordination of Nutrition. Centro de Investigación en Alimentación y Desarrollo (CIAD), A. C. Hermosillo, Sonora. México. ²Health Department. Universidad Iberoamericana, Ciudad de México. Ciudad de México, México. ³Department of Health Science. Biomedical Science Institute. Universidad Autónoma de Ciudad Juárez, Chihuahua. México. ⁴Department of Economics. Coordination of Regional Development. Centro de Investigación en Alimentación y Desarrollo (CIAD), A. C. Hermosillo, Sonora. México

Abstract

Introduction: the prevalence of metabolic syndrome (MetS) is high in older people, and several factors have been explored as main determinants. However, few data exist for older people from low- and middle-income countries. Therefore, our objective was to estimate the prevalence of MetS. Secondly, to explore which of the cardio-metabolic, body composition, inflammatory and demographic risk factors were associated with the prevalence of MetS in a population of older Mexican adults.

Methods: data for this analysis were collected in subjects over 60 years of age from northwest Mexico. Fasting and two-hour glucose, fasting insulin, homeostasis model assessment of insulin resistance, lipid profiles, markers of adiposity and inflammation, and blood pressure were assessed. In addition, anthropometry and body composition data, levels of physical activity and demographic variables were also considered. MetS was diagnosed by three different criteria.

Results: total sample size was 369 subjects. The prevalence of MetS varied widely, from 36% to 52% depending on the criteria applied, but regardless of the criteria, all subjects with MetS were heavier and more overweight, and had higher triglyceride values and lower values of total HDL-cholesterol compared to those without MetS ($p < 0.0001$). Final models adjusted for age showed that, regardless of the diagnostic criteria applied, fat mass, the homeostasis model assessment and some demographic variables were main determinants of MetS in this sample of older people without diabetes.

Conclusions: the prevalence of MetS is relatively high in non-diabetic older adults and it was associated with some biological and demographic factors as the main determinants.

Key words:

Demographic status. Inflammation markers. Insulin resistance. Metabolic syndrome. Older people. Risk factors.

Resumen

Introducción: la prevalencia de síndrome metabólico (SMet) es alta en los adultos mayores y se han explorado diversos factores como los principales determinantes. Sin embargo, existen pocos datos para los adultos mayores de países de ingresos bajos y medios. Por lo tanto, nuestro objetivo fue estimar la prevalencia de SMet. Segundo, se exploraron cuáles de los factores cardiometabólicos, de composición corporal, inflamatorios y demográficos fueron los principales determinantes del SMet.

Métodos: se incluyeron 369 sujetos mayores de 60 años de edad del noroeste de México. Se determinaron la glucosa en ayuno y de dos horas y la insulina en ayuno, y se realizó la evaluación del modelo homeostático de resistencia a la insulina, perfil de lípidos, de los marcadores de adiposidad e inflamación y la presión sanguínea. También se consideraron los datos de antropometría y composición corporal, la actividad física y las variables demográficas. El SMet se diagnosticó por tres diferentes criterios.

Resultados: la prevalencia de SMet varió ampliamente de 36 a 52% y fue dependiente del criterio aplicado. Independientemente del criterio, todos los sujetos con SMet presentaron sobrepeso y tenían valores más altos de triglicéridos y valores más bajos de colesterol HDL comparados con aquellos sin SMet ($p < 0.0001$). La masa grasa, el modelo de determinación de la homeostasis y algunas variables demográficas fueron los principales determinantes del SMet en esta muestra de adultos mayores sin diabetes.

Conclusiones: la prevalencia de SMet es relativamente alta en adultos mayores no diabéticos y se asoció con algunos factores biológicos y demográficos como los principales determinantes.

Palabras clave:

Factores demográficos. Marcadores de inflamación. Resistencia a la insulina. Síndrome metabólico. Adultos mayores. Factores de riesgo.

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Correspondence:

Heliodoro Alemán Mateo. Department of Nutrition and Metabolism. Centro de Investigación en Alimentación y Desarrollo (CIAD), A. C. Carretera a La Victoria, km 0.6. 83304. Hermosillo, Sonora. México. Apartado postal 1735. C. P. 83304
e-mail: helio@ciad.mx

INTRODUCTION

Metabolic syndrome (MetS) is characterized by a cluster of cardio-metabolic risk factors that includes abdominal obesity, high blood pressure, increased glucose concentrations, and dyslipidemia (1,2). MetS is highly-prevalent in geriatric populations, where it varies from 11-43%, 23-55%, and 37-41.9%, according to the World Health Organization, the National Cholesterol Education Program-Third Adult Treatment Panel (ATP III), and the International Diabetes Federation (IDF), respectively (3-7). The clinical impact of MetS in older adult populations consists in its association with cardiovascular morbidity (4,7-10) and mortality (11-13).

The underlying causes of MetS are still being studied. Though insulin resistance and central obesity are currently considered as the most significant factors (1), other important contributing factors include inflammation, endothelial, renal and hepatic dysfunction, and oxidative stress (14). Also, recent studies had reported an association of MetS with such gender-specific risk factors as demographic variables (socioeconomic status, educational level and marital status, among others) in adult (15,16) and older adult subjects (17-21). To our knowledge, there are few specific studies of the association between socioeconomic status and MetS in older people, and even fewer of older people in developing countries. It is well-known that the prevalence of MetS increases with age, especially in individuals with high body-mass index (BMI) and low levels of physical activity (22).

In Mexico, the over-60 population has grown considerably. At the same time, obesity, central obesity, type 2 diabetes and hypertension, among other ailments, have become significant public health issues (23,24). In addition, an important segment of older Mexican people have low educational levels, a large proportion has neither formal jobs nor pensions, and others have extremely low incomes. Many are single; indeed, living alone is quite common in this age group (25). Unfortunately, few data exist on the prevalence and determinants of MetS in relation to cardio-metabolic, body composition and inflammatory profiles, or to associated demographic factors in older people from low- and middle-income countries. Therefore, the objective of the present study was to estimate the prevalence of MetS and, secondly, to explore which of the cardio-metabolic, body composition, inflammatory and demographic risk factors were associated with the prevalence of MetS in a population of older Mexican adults.

METHODS

A non-probabilistic, cross-sectional study was conducted with older people from the city of Hermosillo and some rural areas of Municipality of Hermosillo, Sonora, Mexico. During visits to homes and clubs, short interviews were conducted to invite older people to participate, in order to gather information on their health and nutritional status. All potential participants then underwent a comprehensive medical examination, an oral glucose tolerance test (OGTT) and other biochemical determinations. Anthropometric measurements were taken and body composition was assessed.

A series of demographic variables was also evaluated as part of the study protocols. The research protocol was carried out in the Laboratory of Body Composition and Functionality, Coordination of Nutrition, Research Center for Food and Development, and was approved by the Ethics Committee of CIAD, A.C. All volunteers were fully informed and signed the consent form before commencing the protocol.

STUDY POPULATION

The total sample comprised 369 participants, and included 195 women and 174 men over 60 years old (range: 60-83 years) who were physically independent according to the Katz scale (26) and in free-living conditions. Participants underwent a general medical examination and urine analyses and an oral glucose tolerance tests (OGTT). Subjects were free of type 2 diabetes as determined by the OGTT and the 1997 ADA criteria (27) and were also free of other major chronic diseases, according to their clinical histories. Controlled hypertensive subjects and those with controlled endocrine disorders such as hypothyroidism were included.

MEASURES

Anthropometry and body composition assessment

Body weight and standing height were recorded, and BMI (kg/m^2) was determined and used as indirect marker of adiposity (overweight and obesity) (28). Waist circumference (WC) was measured to the nearest 0.1 cm at the umbilicus level using a fiberglass measuring tape. Body composition including fat-free mass (FFM), total appendicular skeletal muscle mass (TASM) and fat mass (FM) was measured by DXA using DPX-MD+™ (GE Lunar Madison, WI, USA), as previously published (29). Fat mass index (FMI), kg/m^2 was obtained and considering the FMI values and the classification proposed by Kelly et al. (2009), three categories were formed (30). Both, FM and FMI were used as direct marker of adiposity.

Cardio-metabolic and inflammatory biochemical determinations

After an 8-12 h overnight fast, whole blood samples (20 ml) were collected. Glucose levels were measured using the glucose oxidase method, while serum insulin was analyzed by radio-immunoassay (Iso Data, IL, USA) following the Coat-A-Count® procedure (Coat-A-Count, DPC) and by enzyme-linked immunosorbent assay (DRG Instruments GmbH, Marburg, Germany), using ALPCO™ (cat. EIA2935 DRG). The homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR) was calculated using the Matthews' equation (31) and insulin resistance was defined based on percentile distribution using the 75th per-

centile (HOMA-IR = 2.43). Lipid profile was calculated by the enzymatic-colorimetric method and, more recently, by RX monza (Randox Laboratories Ltd; Crumlin, UK). Serum interleukin 6 (IL-6) and C-reactive protein (CRP) concentrations were measured by ELISA High Sensitivity HS600 Quantikine® kit (R&D Systems Inc., Minneapolis, MN, USA).

Blood pressure measurements

Blood pressure (BP) was measured with a mercury column sphygmomanometer (Graham-Field™ Inc., NY, USA). The values reported are the mean of two measurements. In relation to the application of the MetS criteria, subjects with a systolic BP > 130 or diastolic BP > 85 mmHg, or who were taking medications for previously-diagnosed hypertension were registered as hypertensive (ATP III and AHA/NHLBI), while for the 2009 IDF standards, systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg, or treatment of previously-diagnosed hypertension were the parameters used.

Assessment of demographic variables

In the study protocol, age and gender were recorded. Family income was ascertained from the amount estimated by subjects considering all household members who contributed to total monthly family income. Classification of socioeconomic status followed the procedure in Esteban et al. (2007) obtaining three socioeconomic (SES) groups (Low SES group: 38.7%; medium: 46.7%; high: 14.6%) (32). The estimates in this study for the low SES group (the poor) comprised 52%, in line with those shown in official poverty figures from CONEVAL (2015) (33). In addition, educational level was classified in accordance with Mexico's educational system. Technical careers were also considered when classifying educational levels. Marital status, toxicities (smoking and alcoholism) and employment status were identified.

Physical activity level

Physical activity levels (PAL) were estimated by predictive equations that estimate total energy expenditure and resting metabolic rate in older people (34). PAL was classified as sedentary, moderately active, vigorously active, and extremely active (28).

Diagnoses of MetS

We applied three sets of criteria to diagnose MetS: ATP III (35), ATP III modified by the AHA/NHLBI in 2005 (AHA/NHLBI) (1), and the 2009 IDF classification (36). For the 2009 IDF criteria (36), the cut-off points for WC recommended for Asian populations were used.

Statistical analysis

Student's t-tests or Chi-squared tests were used to compare several characteristic of the subjects with and without MetS. The main associated factors of the MetS were explored by multiple logistic regression, both univariate analysis and multivariate stepwise regression methods. It is important to specify that models were constructed separately for MetS as diagnosed by the ATP III, AHA/NHLBI, and 2009 IDF criteria. Models were evaluated for logistic regression assumptions (*i.e.*, lack of strongly-influential outliers) and interactions of all variables in the model with gender were tested at $p \leq 0.1$. All analyses were performed using STATA (version 11.0; Stata Corp, College Station, TX, USA).

RESULTS

The mean age of the total sample was 68.9 ± 6.5 years, and they had a mean BMI of 27.3 ± 3.9 kg/m². Women represented 53% of the total sample. Overall prevalence of MetS was 36% and 45% according to ATP III and AHA/NHLBI, respectively, increasing to 52% with the 2009 IDF criteria.

Table I shows the behavior of several cardio-metabolic, marker of adiposity, inflammatory and demographic variables according to the different criteria used. Subjects with MetS were heavier and had greater BMI, FM, FMI, and WC. Overweight and obesity were more prevalent in subjects with MetS, regardless of the criteria applied ($p < 0.0001$). Additionally, they had higher values of triglycerides and lower values of total HDL-cholesterol compared to those without MetS ($p < 0.0001$). Fasting glucose, insulin and HOMA were significantly higher in the MetS group diagnosed by AHA/NHLBI and 2009 IDF criteria. Also, an effect of gender and hypothyroidism was found. MetS was also more prevalent in older subjects with educational levels of high school or less, single or widower or divorce, low socioeconomic status, and those who were sedentary or had low physical activity levels, regardless of the criteria applied.

Table II shows the potential predictors of MetS. Waist circumference, BMI, FM, FMI, fasting glucose and insulin, HDL-cholesterol, triglycerides, gender, educational level, alcohol consumption, PAL, BMI, overweight and obesity by BMI classification and hypertension, all proved to be predictors of MetS defined by all three sets of criteria ($p \leq 0.2$). Other variables were selected as predictors of MetS, but for only one or two criteria, such as residence (rural and urban), marital status, socioeconomic status, obesity by FMI classification and HOMA and insulin resistance.

Tables III, IV and V show the final separate models, and in which the components of each of the three criteria used for MetS were not included. These models were adjusted for age, and shows that both, biological and demographic variables such as fat mass and HOMA, and schooling, socioeconomic status, and physical activity level, respectively were the best predictors of MetS defined by the ATP III, AHA/NHLBI and IDF criteria. The OR for each predictor of the different criteria is depicted in the tables III, IV and V.

Table I. Behavior of several cardio-metabolic, body composition compartments, inflammatory and demographic variables according to MetS status as defined by three different sets of criteria

Variables	MetS								
	2001 NECP ATP III			2005 AHA/NHLBI			2009 IDF		
	Without	With	p-value	Without	With	p-value	Without	With	p-value
Age, years	69.2 ± 6.6	68.4 ± 6.3	0.2440	69.2 ± 6.7	68.5 ± 6.4	0.3297	69.1 ± 6.3	68.8 ± 6.7	0.5174
Body weight, kg	69.6 ± 11.6	74.3 ± 12.3	0.0003	67.9 ± 10.8	75.5 ± 12.1	0.0000	67.5 ± 10.6	75.0 ± 12.2	0.0000
Height, m	1.67 ± 0.09	1.60 ± 0.09	0.0103	1.62 ± 0.09	1.60 ± 0.08	0.1742	1.62 ± 0.08	1.61 ± 0.09	0.2196
BMI, kg/m ²	26.34 ± 3.7	28.9 ± 3.7	0.0000	25.8 ± 3.7	29.1 ± 3.5	0.0000	25.7 ± 3.8	28.7 ± 3.5	0.0000
Waist circumference, cm	94.5 ± 10.8	103.1 ± 9.9	0.0000	92.3 ± 10.0	103.6 ± 9.7	0.0000	92.7 ± 10.3	102.4 ± 10.1	0.0000
Fat-free mass, kg	44.3 ± 9.0	43.2 ± 9.4	0.2563	43.8 ± 8.9	43.9 ± 9.6	0.9097	43.5 ± 8.6	44.2 ± 9.7	0.4759
TASM, kg	18.5 ± 4.2	17.9 ± 4.4	0.2494	41.4 ± 8.5	41.5 ± 9.2	0.9136	41.1 ± 8.2	41.7 ± 9.3	0.4654
Fat mass, kg	24.1 ± 8.7	29.5 ± 7.7	0.0000	22.9 ± 8.5	29.8 ± 7.4	0.0000	22.9 ± 8.8	29.1 ± 7.5	0.0000
Fat mass index, kg/m ²	9.3 ± 2.6	10.6 ± 2.5	0.0000	9.0 ± 2.6	10.7 ± 2.3	0.0000	9.0 ± 2.7	10.5 ± 2.3	0.0000
Fasting glucose (mg/dl)	94.7 ± 8.5	96.4 ± 10.5	0.0941	93.2 ± 8.1	97.9 ± 9.9	0.0000	93.2 ± 8.0	97.4 ± 9.9	0.0000
Fasting insulin, U/ml	9.2 ± 4.4	9.9 ± 7.1	0.4213	8.9 ± 4.0	10.0 ± 6.9	0.0524	8.6 ± 3.2	10.2 ± 7.0	0.0057
HOMA	2.19 ± 1.08	2.33 ± 1.76	0.3220	2.07 ± 0.94	2.45 ± 1.73	0.0072	1.99 ± 0.79	2.47 ± 1.70	0.0006
Insulin resistance, %									
Yes	65.9	34.0	0.5957	56.3	43.7	0.3726	51.2	48.8	0.2000
No	62.9	37.0		51.0	49.0		43.6	56.4	
Total cholesterol, mg/dl	207.4 ± 38.2	205.9 ± 41.2	0.7457	207.7 ± 3.2	205. ± 41.2	0.6387	208.0 ± 36.6	205.7 ± 41.7	0.5806
HDL-cholesterol, mg/dl	54.1 ± 15.1	39.0 ± 9.1	0.0000	54.6 ± 15.8	41.3 ± 10.4	0.0000	55.6 ± 15.8	41.8 ± 10.8	0.0000
Triglycerides, mg/dl	126.2 ± 66.8	177.5 ± 63.6	0.0000	124.3 ± 65.9	169.9 ± 66.9	0.0000	120.6 ± 65.5	168.4 ± 66.3	0.0000
LDL-cholesterol, mg/dl	128.3 ± 33.1	131.9 ± 35.1	0.3211	128.5 ± 32.2	131.9 ± 35.8	0.4495	128.4 ± 31.5	130.9 ± 36.0	0.4751
CRP, log natural (mg/l)	0.87 ± 0.83	1.0 ± 0.63	0.3257	0.77 ± 0.81	1.0 ± 0.67	0.0298	0.82 ± 0.75	1.0 ± 0.76	0.1689
IL-6 log natural (pg/ml)	0.67 ± 0.95	0.81 ± 0.65	0.3076	0.58 ± 0.98	0.86 ± 0.67	0.0579	0.57 ± 1.0	0.84 ± 0.66	0.0651
Gender, % women	54.9	45.1	0.0002	47.7	52.3	0.0028	43.6	56.4	0.0197
Residence, %									
Rural	52.0	48.0		41.6	58.4		41.7	58.3	
Urban	65.4	34.6	0.0731	57.0	43.0	0.0463	50.5	49.5	0.2553
Schooling, %									
High school,	80.2	19.8		71.4	28.6		62.6	37.4	
High school or less	58.4	41.6	0.0002	49.6	50.4	0.0003	45.2	54.8	0.0041
Marital status, %									
Married or common-law	65.1	34.9		60.9	39.1		50.7	49.3	
Single or widowed or divorced	58.8	41.2	0.2514	44.6	55.4	0.0026	44.7	55.3	0.3026

(Continue in the next page)

Table I (Cont.). Table I. Behavior of several cardio-metabolic, body composition compartments, inflammatory and demographic variables according to MetS status as defined by three different sets of criteria

Variables	MetS							
	2001 NECP ATP III			2005 AHA/NHLBI			2009 IDF	
	Without	With	p-value	Without	With	p-value	Without	With
Employment status, %								
Manual and non-manual	67.6	32.4		57.6	42.4		54.0	56.0
None	62.3	37.7	0.3433	54.8	45.4	0.6179	47.7	52.3
								0.2685
Smoking, %								
No	63.2	36.8		53.9	46.1		48.8	51.2
At least 100 cigarettes	66.6	33.4	0.6909	63.6	36.4	0.2833	51.5	48.5
								0.7622
Alcohol consumption, %								
No	59.3	40.7		51.2	48.8		45.3	54.7
Yes	74.3	25.7	0.0148	60.9	39.1	0.1289	54.9	45.1
								0.1363
Chronic disease, %								
No	64.6	35.4		55.5	44.5		49.4	50.6
Yes	58.6	41.6	0.5175	51.7	48.3	0.6961	48.3	51.7
								0.9084
Hypertension, %								
No	63.8	36.2		55.2	44.8		49.3	50.6
Yes	64.8	35.2	0.8879	53.7	46.3	0.8319	48.1	51.9
								0.8715
Body mass index, %								
Normal	81.8	18.2		80.9	19.1		76.4	23.6
Overweight	60.3	39.7		51.1	48.9		43.1	56.9
Obese	47.0	53.0	0.0000	29.4	70.6	0.0000	27.0	73.0
								0.0000
SES, %								
High	13.5	6.1		13.5	7.4		13.8	8.0
Medium	53.9	43.1		53.7	44.4		50.9	48.1
Low	33.6	50.4	0.0030	32.8	48.2	0.0080	35.3	43.9
								0.1070
PAL, %								
Active or moderately active	96.1	3.9		96.1	3.9		92.3	7.7
Sedentary or light	61.2	38.8	0.0004	51.9	48.1	0.0000	46.0	54.0
								0.0000
Heart disease, %								
No	63.7	36.3		55.1	44.9		49.1	50.9
Yes	71.4	28.6	0.6740	42.8	58	0.5178	42.8	57.2
								0.7419
Hypothyroidism, %								
No	62.8	37.2		53.4	46.6		47.2	52.8
Yes	93.3	6.7	0.0157	93.3	6.7	0.0023	93.3	6.7
								0.0005

BMI: body mass index; HOMA: homeostasis model assessment; TASM: total appendicular skeletal muscle; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CRP: C-reactive protein; IL-6: interleukin 6; SES: socioeconomic status; PAL: physical activity level. A Student's t-test was used for continuous variables and Chi-squared test for categorical variables.

Table II. Univariate associations of potential predictors of MetS as defined by three different sets of criteria

Variables	MetS											
	2001 NECP ATP III				2005 AHA/NHLBI				2009 IDF			
	OR	SE	p	OR	SE	p	OR	SE	OR	SE	p	p
Age, years	0.98	0.02	0.244 [†]	0.98	0.02	0.329 [†]	0.99	0.02	0.99	0.02	0.362 [†]	0.362 [†]
Waist circumference, cm	1.08	0.01	0.000	1.12	0.02	0.000	1.09	0.01	1.09	0.01	0.000	0.000
BMI, kg/m ²	1.20	0.04	0.000	1.29	0.05	0.000	1.26	0.04	1.26	0.04	0.000	0.000
TASM, kg	0.97	0.03	0.247 [†]	1.00	0.02	0.941 [†]	1.03	0.03	1.03	0.03	0.304 [†]	0.304 [†]
Fat mass, kg	1.08	0.02	0.000	1.11	0.02	0.000	1.09	0.02	1.09	0.02	0.000	0.000
Fat mass index, kg/m ²	1.22	0.06	0.000	1.34	0.07	0.000	1.30	0.06	1.30	0.06	0.000	0.000
Fasting glucose, mg/dl	1.02	0.01	0.095	1.06	0.01	0.000	1.06	0.01	1.06	0.01	0.000	0.000
HOMA	1.08	0.09	0.339 [†]	1.34	0.15	0.009	1.60	0.21	1.60	0.21	0.000	0.000
Fasting insulin, U/ml	1.02	0.02	0.432	1.05	0.03	0.007	1.09	0.03	1.09	0.03	0.004	0.004
Total cholesterol, mg/dl	1.00	0.00	0.745 [†]	1.00	0.00	0.638 [†]	1.00	0.00	1.00	0.00	0.394 [†]	0.394 [†]
HDL-cholesterol, mg/dl	0.89	0.01	0.000	0.92	0.01	0.000	0.91	0.01	0.91	0.01	0.000	0.000
Triglycerides, mg/dl	1.01	0.00	0.000	1.01	0.00	0.000	1.01	0.00	1.01	0.00	0.000	0.000
LDL-cholesterol, mg/dl	1.00	0.00	0.320 [†]	1.00	0.00	0.448 [†]	1.00	0.00	1.00	0.00	0.610 [†]	0.610 [†]
C-reactive protein, mg/l*	1.26	0.29	0.324 [†]	1.67	0.40	0.033 [†]	1.22	0.29	1.22	0.29	0.382 [†]	0.382 [†]
Interleukin 6, pg/ml*	1.25	0.27	0.306 [†]	1.51	0.33	0.061 [†]	1.39	0.30	1.39	0.30	0.132 [†]	0.132 [†]
Gender, % women	2.29	0.51	0.000	1.89	0.40	0.003	1.42	0.30	1.42	0.30	0.095	0.095
Residence, %												
Rural	Ref.			Ref.			Ref.		Ref.			
Urban	0.57	0.18	0.076	0.54	0.17	0.049	0.76	0.24	0.76	0.24	0.371 [†]	0.371 [†]
Schooling, %												
High school	Ref.			Ref.			Ref.		Ref.			
High school or less	2.56	0.80	0.003	2.18	0.61	0.006	1.61	0.43	1.61	0.43	0.072	0.072
Marital status, %												
Married or common-law	Ref.			Ref.			Ref.		Ref.			
Single or widow/er or divorced	1.40	0.33	0.156	1.33	0.31	0.217 [†]	1.24	0.29	1.24	0.29	0.350 [†]	0.350 [†]
Employment status, %												
Manual and non-manual	Ref.			Ref.			Ref.		Ref.			
None	1.26	0.31	0.344 [†]	1.12	0.26	0.618 [†]	1.15	0.27	1.15	0.27	0.532 [†]	0.532 [†]
Smoking, %												
No	Ref.			Ref.			Ref.		Ref.			
At least 100 cigarettes	1.17	0.38	0.624 [†]	0.85	0.27	0.616 [†]	0.89	0.28	0.89	0.28	0.724 [†]	0.724 [†]

(Continue in the next page)

Table II (Cont.). Univariate associations of potential predictors of MetS as defined by three different sets of criteria

Variables	MetS									
	2001 NECP ATP III			2005 AHA/NHLBI			2009 IDF			
	OR	SE	p	OR	SE	p	OR	SE	p	
Alcohol consumption, %										
No	Ref.			Ref.			Ref.			
Yes	0.54	0.15	0.027	0.72	0.19	0.204	0.80	0.20	0.374†	
SES, %										
High	Ref.			Ref.			Ref.			
Medium	1.81	0.77	0.166	1.51	0.58	0.276†	1.62	0.59	0.184	
Low	3.30	1.43	0.006	2.68	1.04	0.011	2.13	0.80	0.043	
PAL, %										
Active or moderately-active	Ref.			Ref.			Ref.			
Sedentary or light	15.83	16.24	0.007	23.17	23.76	0.002	15.08	11.22	0.000	
Heart disease, %										
No	Ref.			Ref.						
Yes	0.70	0.59	0.676†	1.64	1.26	0.522†	1.20	0.93	0.811†	
BMI classification, %										
Normal	Ref.			Ref.			Ref.			
Overweight	2.96	0.86	0.000	4.05	1.16	0.000	3.69	0.97	0.000	
Obesity	5.06	1.67	0.000	10.17	3.46	0.000	7.19	2.33	0.000	
FMI classification, %										
Normal	Ref.			Ref.			Ref.			
Excess fat	1.07	0.31	0.821†	1.38	0.40	0.269†	1.47	0.41	0.167	
Obesity	1.49	0.45	0.188	2.57	0.77	0.002	2.96	0.88	0.000	
Hypertension, %										
No	Ref.			Ref.			Ref.			
Yes	3.38	0.76	0.000	3.44	0.76	0.000	4.05	0.91	0.000	
Insulin resistance, %										
No	Ref.			Ref.			Ref.			
Yes	0.88	0.22	0.596†	1.23	0.30	0.373†	1.48	0.36	0.103	
Chronic diseases, %										
No	Ref.			Ref.			Ref.			
Yes	1.29	0.51	0.518†	1.63	1.26	0.522†	1.20	0.93	0.811†	

BMI: body mass index; HOMA: homeostasis model assessment; TASMI: total appendicular skeletal muscle; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SES: socioeconomic status; PAL: physical activity level; FMI: fat mass index; Ref: reference. [†]Variables not selected for the multivariate analysis according to the criteria $p \leq 0.2$ and/or a reduced number of observations or categories. OR: odds ratio; SE: standard error.

Table III. Association between MetS defined by the 2001 NECP ATP III criteria as dependent variable and fat mass and demographic variables as risk factors

Independent variables	OR	SE	CI 95%	p-value
Fat mass, kg	1.08	0.02	1.05-1.12	0.000
Schooling, %				
High school	Ref			
High school or less	2.07	0.70	1.07-4.02	0.032
SES, %				
High	Ref			
Medium	1.72	0.79	0.70-4.22	0.235
Low	3.29	1.56	1.29-8.33	0.012

Stepwise backward using logistic regression analysis using MetS as the dependent variable. The model was age-adjusted. SES: socioeconomic status; OR: odds ratio; SE: standard error; CI: confidence intervals.

Table IV. Association between MetS defined by 2005 AHA/NHLBI criteria as dependent variable and fat mass and demographic variables as risk factors

Independent variables	OR	SE	CI 95%	p-value
Fat mass, kg	1.11	0.02	1.07-1.14	0.000
Schooling, %				
High school	Ref			
High school or less	1.87	0.61	0.99-3.54	0.054
PAL, %				
Active or moderately-active	Ref			
Sedentary or light	9.40	10.02	1.16-76.10	0.036
SES, %				
High	Ref			
Medium	1.51	0.64	0.66-3.46	0.325
Low	3.38	1.53	1.39-8.22	0.007

Stepwise backward by logistic regression analysis using MetS as the dependent variable. The model was age-adjusted. PAL: physical activity level; SES: socioeconomic status; OR: odds ratio; SE: standard error; CI: confidence intervals.

Table V. Association between MetS defined by 2009 IDF criteria as dependent variable and fat mass, HOMA and demographic variables as risk factors

Independent variables	OR	SE	CI 95%	p-value
Fat mass, kg	1.07	0.02	1.03-1.10	0.000
HOMA	1.60	0.25	1.18-2.18	0.002
PAL, %				
Active or moderately-active	Ref			
Sedentary or light	14.12	14.95	1.77-112.42	0.012
SES, %				
High	Ref			
Medium	2.65	1.11	1.16-6.00	0.021
Low	4.78	2.12	2.01-11.39	0.000

Stepwise backward by logistic regression analysis using MetS as the dependent variable. The model was age-adjusted. HOMA: homeostasis model assessment; PAL: physical activity level; SES: socio-economic status. OR: odds ratio; SE: standard error; CI: confidence intervals.

DISCUSSION

The prevalence of MetS in this Mexican aged group is high, and varies widely according to the diagnostic criteria used ($p = 0.0001$), with the 2009 IDF standards generating the highest prevalence. Similar findings have been reported by studies carried out in some Latin American countries with older people (5,6,21). This could be explained largely by the high proportion of obesity, especially central obesity, in this age group. In fact, recent evidence underscores that older obese people with MetS have more abdominal visceral fat, but less subcutaneous thigh fat than older obese people without this condition (37). To our knowledge, few studies have explored cardio-metabolic, body composition, inflammatory and demographic variables as the main determinants of MetS in older people in a developing country. Our results show that this high prevalence is strongly and consistently associated with fat mass as direct marker of adiposity in this age group. It is important to note that, aside from fat mass and HOMA, only some sociodemographic variables assessed in this study were found to be mainly determinants of the high prevalence of MetS. Therefore, our findings are important and may help define specific lifestyle and demographic strategies for preventing MetS in this vulnerable age group as evidence of the association between MetS and cardiovascular mortality in older adult population continues to accumulate (11-13).

At the national level, the prevalence of MetS in older people is relatively high in Mexico. The 2012 National Health and Nutrition Survey (2012 ENSANUT for its initials in Spanish) reported a prevalence of MetS of 56.3% using the ATP III criteria, 60.8% according to the AHA/NHLBI's definition, and 67.9% by the IDF criteria (24). The prevalence found in this non-representative sample is lower (36%, 45% and 52% according to the ATP III, AHA/NHLBI, and 2009 IDF criteria, respectively), perhaps because our study excluded subjects diagnosed with type 2 diabetes by the 1977 ADA criteria (28), while the ENSANUT report included them. However, independently of the inclusion of diabetics, prevalence in this non-representative sample is high, indicating that greater attention must be paid to preventing this condition. Overall, prevalence of MetS in this age group is within the range reported for other, non-Latin American populations (3,4,7). Thus, it seems that the presence of MetS in older adult populations is relatively high regardless of genetic background, environmental exposures and the diagnostic criteria used.

Central obesity, hypertension and low-HDL-cholesterol were the most frequent criteria components found in subjects with MetS, and similar results have been reported by other studies in adults and older people (12,38). Central obesity was consistently the most prevalent factor identified by each set of criteria (87%, 87% and 99% by the ATP III, AHA/NHLBI, and 2009 IDF, respectively), followed, in second place, by hypertension (84%, 81% and 79% by the ATP III, AHA/NHLBI and 2009 IDF criteria, respectively), and then low HDL-cholesterol (87%, 75% and 72%, respectively). It is interesting to note that low HDL-cholesterol was the most prevalent component of abnormality found in a study of young and middle-aged Korean men and women (39). In our sample, the prevalence of central obesity, hypertension and low HDL-cho-

lesterol were related to the increasing prevalence of MetS, which has been found to be relatively high among older age groups (40).

The regression analysis showed that most of the variables were determined to be significant predictors of MetS, but that some cardio-metabolic, body composition, inflammatory and demographic variables (including age, TASM, total cholesterol, LDL-cholesterol, CRP, interleukin-6, marital status, employment status, smoking, alcohol consumption, insulin resistance and chronic diseases) were not selected as predictors of MetS (Table II). It is important to note that several studies have shown a strong association between demographic variables and MetS in adult and fewer in older adult subjects (15-21). In fact, in this study we found a significant association between schooling or education level, socioeconomic status based on family income, and physical activity level with MetS, together with several biological factors as shown in table I and II. In addition, multiple logistic regression results presented in tables III, IV and V show that high school or less; low SES and sedentary or light activities, together with fat mass and HOMA as independent variables were main determinants, regardless of the criteria used. Therefore, our results do support that fat mass as direct marker of adiposity and HOMA, and some demographic variables as the main determinants of the high prevalence of MetS. Other studies have reported a significant association between such variables as gender, socioeconomic status, educational level and marital status, among others, with MetS in adults (15-16) and older adult subjects (17-21).

Importantly, there are few studies in older people and the results are controversial about the association between SES, schooling and MetS, and fewer on the association between PAL and MetS (17-21,41,42). These three factors are important indicators of social status. The role of education level in the development of MetS is unclear nowadays. However, it has been reported that SES or income and education level can influence health behaviors, psychological distress, neighborhood characteristics, and access to health care (42). Regarding to the association between fat mass and MetS, some studies have shown a significant association; however, this component no added value over other markers of adiposity such as WC and BMI (43,44). In the elderly, adiposity particularly peripheral subcutaneous fat and trunk subcutaneous fat are associated with insulin resistance and this last one is one of the markers of MetS (45).

In accordance with the results of our multiple logistic regression analysis, it is clear that in addition to fat mass and HOMA, some demographic variables were main determinants of MetS in older subjects who may, therefore, be at high risk of cardiovascular morbidity and mortality. Of the total mortality recorded in Mexico in 2014 (633,000 deaths), 63.9% corresponded to people aged ≥ 60 . Heart diseases (16.9%), cerebrovascular diseases (6.8%) and hypertension (4.7%) were the main contributing factors to all deaths that occurred in this population group (INEGI, 2014) (46). Therefore, we must give high priority to defining and implementing strategies to prevent MetS in this growing, older Mexican adult population.

The present study had some limitations. Firstly, all subjects included were free of type 2 diabetes, using the former criteria of

2 hour glucose value OGTT (fasting glucose ≥ 126 or ≥ 200 mg/dL at 2 h). Therefore, prevalence of MetS found is only valid for this particular sample. Second, HOMA to define insulin resistance and its associations could not be determined using the hyperinsulinemic-euglycemic clamp. However, it is well known that the method used in the present study correlated well with the hyperinsulinemic-euglycemic clamp. Additionally, the methods used for insulin determination in the three different mentioned studies varied in sensitivity. Third, this is a cross-sectional study, therefore only an association, not a causal relationship, is shown. Further studies in different settings are required to explore the effect of demographic variables as determinant of MetS in older people.

In conclusion, metabolic syndrome is highly prevalent in non-diabetic older adults and non-representative sample. In this study, the main determinants were fat mass and HOMA, and some demographic variables, mainly schooling, physical activity and SES. It is well-known that all these risk factors are potentially modifiable at general population. However, more research in other population on the interrelation between MetS and socioeconomic status and other demographic variables would provide additional evidence and allow us to identify other significant factors and to strength our results. At present, however, our findings support the importance of strengthening specific lifestyle strategies to prevent MetS in this vulnerable age group.

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Trabajo Original

Obesidad y síndrome metabólico

Impact of *APOE2* allele on lipid profile change after a weight loss program

Impacto del alelo APOE2 en el cambio del perfil lipídico después de un programa de pérdida de peso

Blanca Romero-Moraleda¹, Rocío Cupeiro Coto², Domingo González-Lamuño³, Teresa Amigo³, Barbara Szendrei², Miguel Ángel Rojo-Tirado², Francisco Javier Calderón² and Ana Belén Peinado²

¹Department of Physical Activity and Sport Sciences. Faculty of Health Sciences. Universidad Camilo José Cela. Villanueva de la Cañada, Madrid. Spain. ²Departamento de Salud y Rendimiento Humano. Facultad de Ciencias de la Actividad Física y del Deporte. Universidad Politécnica de Madrid. Madrid, Spain. ³Department of Medical and Surgery Sciences. Faculty of Medicine. Universidad de Cantabria -IDIVAL Marqués de Valdecilla Research Institute. Santander, Cantabria. Spain

Abstract

Background: apolipoprotein E (ApoE) polymorphism is a genetic determinant of lipid and lipoprotein levels and the risk for coronary heart disease.

Objective: to evaluate the impact of *ApoE2* allele in lipid plasma levels and the influence of a healthy hypocaloric diet plus a controlled physical activity on the lipid profile, we performed a study in a cohort of overweight and obese healthy subjects (Body Mass Index (BMI) between 25 and 34.9 kg·m⁻²).

Methods: one hundred eighty participants (96 women), aged 18-50 years participated in a 22 weeks weight loss intervention based on same dietary treatment and different controlled exercise programs. All subjects followed a hypocaloric diet (25-30% less energy intake than the daily energy expenditure). Blood samples were obtained for lipids measurements at the beginning and end of the study.

Results: after intervention, men of the E2 group showed the greatest decreases in low-density lipoprotein (LDL), triglycerides (TG) and total cholesterol (TC) values ($p = 0.039$; $p = 0.001$; $p = 0.001$; respectively). For high-density lipoprotein (HDL), E2 group had significant differences compared with E4 at pre- ($p = 0.020$) and post-intervention values ($p = 0.024$).

Conclusion: our results show great changes in men carrying *ApoE2*, mainly in TG and TC concentrations after treatment with hypocaloric diet and controlled exercise. Therefore, adding supervised training to nutritional intervention seems to be a good alternative for the reinforcement of the effect of the treatment.

Key words:

ApoE genotype.
Lipoprotein.
Overweight. Obese.
Weight loss program.

Resumen

Antecedentes: el polimorfismo de la apolipoproteína E (ApoE) es un determinante genético de los niveles de lípidos y lipoproteínas y el riesgo de enfermedad coronaria.

Objetivo: para evaluar el impacto del alelo ApoE2 en los niveles de lípidos plasmáticos y la influencia de una dieta hipocalórica sana más una actividad física controlada en el perfil lipídico, se realizó un estudio en una cohorte de sujetos sanos con sobrepeso y obesidad (índice de masa corporal entre 25-34,9 kg·m⁻²).

Métodos: ciento ochenta participantes (96 mujeres), de 18-50 años participaron en una intervención de pérdida de peso de 22 semanas basada en el mismo tratamiento dietético y diferentes programas de ejercicios controlados. Todos los sujetos siguieron una dieta hipocalórica (consumo de energía entre 25-30% inferior que el gasto energético total diario). Se obtuvieron muestras de sangre para las mediciones de lípidos al inicio y al final del estudio.

Resultados: después de la intervención, los hombres del grupo E2 mostraron las mayores disminuciones en los valores de lipoproteína de baja densidad (LDL), triglicéridos (TG) y colesterol total (TC) ($p = 0,039$; $p = 0,001$; $p = 0,001$). Para las lipoproteínas de alta densidad (HDL), el grupo E2 presentó diferencias significativas en comparación con E4 en los valores previos ($p = 0,020$) y postintervención ($p = 0,024$).

Conclusión: nuestros resultados muestran grandes cambios en los hombres que portan ApoE2, principalmente en las concentraciones de TG y TC después del tratamiento con dieta hipocalórica y ejercicio controlado. Por lo tanto, la adición de entrenamiento supervisado a la intervención nutricional parece ser una buena alternativa para el refuerzo del efecto del tratamiento.

Palabras clave:

Genotipo ApoE.
Lipoproteína.
Sobrepeso. Obesidad.
Programa de pérdida de peso.

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Correspondence:

Blanca Romero-Moraleda. Department of Physical Activity and Sport Sciences. Faculty of Health Sciences. Universidad Camilo José Cela. C/ Castillo de Alarcón, 49. Urb. Villafranca del Castillo. 28692 Villanueva de la Cañada, Madrid. Spain
e-mail: bromero@ucjc.edu

INTRODUCTION

Atherosclerosis is a multifactorial disease involving environmental and genetic factors and their interactions (1). The lipoprotein concentrations are modulated by different apolipoproteins, mainly by the multifunctional apolipoprotein E (ApoE), that plays a key role in the metabolism of cholesterol and triglycerides by binding to hepatic ApoE receptor or LDLR in the liver to help mediate clearance of chylomicrons and very low-density lipoproteins from the plasma (1-3). So, ApoE plays a crucial role in transport and redistribution of lipids in peripheral tissues such as brain peripheral nerves, and arterial wall (4). The phenotype of severe hyperlipidemia and spontaneous development of atherosclerosis in mice lacking ApoE clearly demonstrates the central role of ApoE in mammalian lipid metabolism (5,6).

The *ApoE* gene locus is polymorphic with 3 common alleles, designated as *ApoE2*, *ApoE3* and *ApoE4*. The corresponding protein isoform for each allele has different affinity for the cellular apolipoprotein receptor (7). Hence, the presence of at least one *ApoE4* allele is associated with lower plasma ApoE (8) and increased plasma cholesterol, LDL cholesterol, and ApoB levels (2). The presence of at least one copy of the *ApoE2* allele has been associated with higher plasma ApoE (8) and lower plasma cholesterol, LDL cholesterol, and ApoB levels (2) when compared with *ApoE3* homozygotes. The *ApoE2* allele is also associated with lower risk of coronary artery disease (9), except in 5-10% of *ApoE2* homozygotes who develop type III hyperlipoproteinemia and premature atherosclerosis (10). Under an obesogenic environment (sedentarism, hypercaloric and cholesterol-enriched diets), the presence of the *ApoE4* allele is associated with a significant risk of coronary artery disease (9), when compared with *ApoE3* homozygotes. Low-cholesterol diets normalize lipid profile and minimize cardiovascular risk in subjects with at least one *ApoE4* allele. In addition, clinical trials and longitudinal studies indicate that after supervised exercise carriers of the *ApoE2* allele and homozygotes for the *ApoE3* allele have greater improvements in plasma lipoprotein lipid than *ApoE4* carriers (11-13). However, the impact of a strict hypocaloric and equilibrated diet plus controlled physical activity program in *ApoE2* and *ApoE4* carriers it is less established.

Therefore, in order to investigate the impact of *ApoE2* allele in triglycerides plasma levels, and the influence of a healthy hypocaloric-diet plus a controlled physical activity program on lipid profile, we performed a study with overweight and obese healthy subjects in which the hyper caloric-sedentary conditions were presumed.

MATERIAL AND METHODS

DESIGN

The present RCT (ClinicalTrials.gov ID: NCT01116856) was conducted from January, 2010, through June, 2011, and fol-

lowed the ethical guidelines of the Declaration of Helsinki. The Institutional Review Board of the Hospital Universitario La Paz (PI-643) reviewed and approved the study design and research protocol. Details of the study's theoretical rationale, protocol, and intervention are described elsewhere (14).

PARTICIPANTS

Participants were sought via advertisements in newspapers and on the radio, internet and TV. The sample population consisted of 180 subjects (96 women and 84 men, weight: 80.44 ± 10.1 , 96.40 ± 9.43 kg; height: 1.63 ± 0.06 , 1.76 ± 0.07 m; BMI: 30.29 ± 1.22 , 38.01 ± 7.8 , 38.3 ± 8.01 years) overweight ($n = 84$, 48 women and 36 men; BMI 25-29.9 kg/m²) and obese participants ($n = 96$, 48 women and 48 men; BMI 30-34.9 kg/m²). All subjects were healthy, normoglycaemic, non-smokers, but led sedentary lifestyles. All female subjects had regular menstrual cycles. The exclusion criteria covered all physical and psychological diseases that may have precluded the performance of the requested strength or endurance training, and the taking of any medication known to influence physical performance or the interpretation of the results. Subjects with a background of systematic strength or endurance training (moderate to high intensity training more than once a week) in the year before the study started were also excluded. Before starting, all participants signed an institutionally approved document of informed consent.

PROCEDURES

A 6-months diet and exercise-based intervention, focusing on a behavior change. Participants entered into the study in two waves, one of overweight participants and the other of obese participants. Each wave was split into four randomly assigned groups, stratified by age and sex: strength group (S), endurance group (E), combined strength and endurance group (SE) and the control group, who follow the physical activity recommendations. The measurements took place in the first week (pre-intervention values) for all participants before starting and after 22 weeks of intervention, in week 24 (post-intervention values).

Before the intervention started, physical activity was assessed by a SenseWear Pro3 Armband™ accelerometer (Body Media, Pittsburgh, PA). Daily energy expenditure was calculated using the Body Media propriety algorithm (Interview Research Software Version 6.0). In addition, they were required to report the kind, duration, and intensity of any physical activity and the amount of any food undertaken during the intervention period, through a personal diary, to ensure compliance with the recommendations given.

At the beginning of the intervention, the negative energy balance was calculated taking into account the daily energy expenditure, and an estimated 3-day food record, in order to decrease the energy intake of the diet by a 25-30% during the intervention.

EXERCISE INTERVENTION

All exercise training groups (Strength, Endurance and Combined-SE groups) followed an individualized training program, which consisted on three times per week exercise sessions during 22 weeks, carefully supervised by certified personal trainers. Details of the different protocols developed by the groups are described elsewhere (14). An adherence to exercise of 80% was required.

CONTROL GROUP

Participants from the control group followed the dietary intervention and respected the recommendations about physical activity from the American College of Sport Medicine (ACSM) (15). Thus, the C subjects were advised to undertake at least 200-300 min of moderate-intensity physical activity per week (30-60 min on most, if not all, days of the week).

DIET INTERVENTION

All groups underwent an individualized and hypocaloric diet (between 1,200 and 3,000 kcal). The diet implied a 25% reduction from the total daily energy expenditure (TDEE) (16) measured using SenseWear Pro Armband™ data. Macronutrient distribution consisted of 29-34% of energy from fat, 12-18% from protein, and 50-55% from carbohydrates, according to recommendations (17). A dietician interviewed each participant at baseline, 3 months, and 6 months and reviewed a 3-day food record diary. An adherence to diet of 80% was elicited and was calculated with 72-hour recall (18).

OUTCOMES

Blood analysis

All blood samples were taken after 12 h fast between 7:00 and 9:00 a.m. at baseline and post-training intervention (week 1 and week 24). All post-training samples were obtained 72 hours after the last training day to avoid acute effects of training on blood lipids. All blood samples were drawn from the antecubital vein and handled according to standardized laboratory practice at Hospital Universitario La Paz. Serum biochemicals total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and TG (19) were determined using enzymatic methods with Olympus reagents by automated spectrophotometry performed on Olympus AU 5400 (Olympus Diagnostica, Hamburg, Germany). Menstrual cycle was controlled by diary to define the follicular and luteal phases when blood samples were taken (20).

Genotyping

Genomic DNA was extracted from peripheral blood using a QIAamp DNA Blood Mini kit (QIAGEN, Hilden, Germany). The *ApoE* genotypes for the *ApoE3*, *ApoE4* (rs7412) and *ApoE2* (rs429358) alleles were determined by polymerase chain reaction (PCR) and allele-specific restriction digestion of the amplified products with the restriction enzyme HhaI (21). Samples were analyzed in Metabolism, Genetics and Nutrition Research Group of the Universidad de Cantabria-IDIVAL. Subjects were typed at the *ApoE* locus as previously described (22). To analyse the association of the ApoE phenotype with lipid and apolipoprotein responses and lipoprotein fractions, subjects were grouped as E2 carriers (E2: E3/E2 subjects), E3 homozygotes (E3/E3 subjects) and E4 carriers (E4: E4/E4 and E4/E3 subjects). A single subject with ApoE4/2 phenotype was not included in the study sample.

Body composition

Body composition was assessed by Dual-energy X-ray Absorptiometry DXA (GE Lunar Prodigy; GE Healthcare, Madison, WI, GE Encore 2002, version 6.10.029 software) and was used to measure total body fat (%). Anthropometric measures included height (stadiometer SECA; range 80-200 cm), body mass (BC-420MA, Bio Lógica, Tecnología Médica S.L.) and body mass index (BMI) calculated as [body weight (kg)/(height (m))²].

Physical fitness

Peak oxygen uptake test ($\text{VO}_{2\text{peak}}$) was measured using the modified Bruce protocol used elsewhere with overweight and obese population (23,24). The test was conducted on an H/P/COSMOS 3P 4.0 computerised treadmill (H/P/Cosmos Sports & Medical, Nussdorf-Traunstein, Germany). The volume and composition of expired gas measure were measured using a Jaeger Oxycon Pro gas analyser (Erich Jaeger, Viasys Healthcare, Germany) and continuous 12-lead electrocardiographic monitoring. The exercise test was maintained until exhaustion. Peak oxygen uptake ($\text{VO}_{2\text{peak}}$) was taken to be the mean of the three largest measurements.

STATISTICAL ANALYSES

SPSS version 15.0 for Windows was used for statistical analyses (SPSS Inc., Chicago, Illinois, USA). Standard statistical methods were used for the calculation of the means and standard deviation (SD).

Three-way analysis of variance (ANOVA) for repeated measures was used to determine any differences between men and women and differences in baseline values and post-training values in each *ApoE* group assessed (E2, E3 and E4). Multivariate analysis of variance (MANOVA) was used to compare *ApoE* group and sex in differences in baseline and post-training values.

Bonferroni's *post-hoc* test was employed to locate specific differences. The delta percentage was calculated through the standard formula: change (%) = [(post-test score – pre-test score)/pre-test score] × 100. The significance level was set at $\alpha = 0.05$.

RESULTS

Due to alterations in data collection final analysed completers were $n = 173$ (94 women and 79 men). The *ApoE2*, *ApoE3*, and *ApoE4* alleles had frequencies of 0.04, 0.88, and 0.08, respectively. The distribution of the *ApoE* genotypes is E2/E3 7.5%; E2/E4 0.6%; E3/E3 76.4%; E3/E4 14.9%; and E4/E4 0.6%; and did not differ between males and females ($p = 0.961$). All the genotype frequencies of the analysed gene polymorphism were in agreement with the Hardy-Weinberg equilibrium (chi-square test = 1.60; $p = 0.660$). The genotype groups were initially similar in terms of age, body weight and composition, VO_{2peak} , and plasma lipoprotein lipid profiles. After the intervention, body composition and VO_{2peak} did not differ significantly among groups (Table I).

BLOOD LIPIDS AND LIPOPROTEINS

Table II shows the changes in plasma lipid and lipoprotein concentrations in three *APOE* (*APOE* gene) groups before and after the intervention period. At baseline, E2 group had a more adverse lipid profile for the atherogenic variables. Men of the E2 group had significantly higher TG levels compared to E3 and E4 groups (E3 $p = 0.001$; E4 $p = 0.018$). However, for HDL, E2 group had healthy values with significant differences with E3 ($p = 0.010$) and E4 ($p = 0.020$) groups. After intervention, the men of the E2 group achieved the greatest decrease in both TG ($p = 0.001$) and TC concentrations ($p = 0.001$). Furthermore, the E2 group maintained the HDL levels, being significantly higher than the E4 men ($p = 0.024$).

On the other hand, men of the E3 group decreased LDL, TG and TC concentrations ($p = 0.001$; $p = 0.012$; $p = 0.001$; respectively), and increased HDL levels ($p = 0.013$) after the intervention.

In contrast, E4 men obtained a reduction only in LDL ($p = 0.007$) and TC ($p = 0.006$) levels.

In the group of women who participated in our study no significant differences were observed among genotype groups either baseline or the post-training values. Only women of the E3 group showed a slight improvement in the lipid profile with a significant decrease in the levels of TC ($p = 0.008$) after the intervention, although their HDL levels also decreased ($p = 0.048$).

Figure 1 shows the percentage of change in blood lipid profile by *ApoE* and gender groups. There were significant differences between E2 men and E3 men for TG and TC concentrations ($p = 0.050$; $p = 0.022$, respectively).

DISCUSSION

The main finding of the present study was that the presence of the allele *ApoE2* in men beneficially affects TG and TC responses.

Table I. Body composition and peak oxygen uptake (VO_{2peak}) changes by *ApoE* groups and gender

	Men						Women					
	E2 carriers (n = 6)			E3 homozygotes (n = 62)			E3 homozygotes (n = 71)			E4 carriers (n = 15)		
	Baseline	Post-training	p-value	Baseline	Post-training	p-value	Baseline	Post-training	p-value	Baseline	Post-training	p-value
Age	43.5 ± 6.6	±		37.1 ± 7.9	±		38.31 ± 7.62			37.00 ± 9.12		
Weight (kg)	101.25 ± 7.77	90.47 ± 5.99	0.01*	95.27 ± 11.37	86.57 ± 11.47	0.01*	80.76 ± 10.24	73.86 ± 10.47	0.01*	79.21 ± 10.04	72.19 ± 10.26	0.01*
BMI (kg/m ²)	31.98 ± 4.21	27.63 ± 5.40	0.01*	30.98 ± 2.68	28.21 ± 2.96	0.01*	31.56 ± 9.14	28.07 ± 3.13	0.01*	30.97 ± 3.14	28.44 ± 3.29	0.19
Body fat (%)	34.48 ± 5.76	28.97 ± 6.87	0.01*	36.87 ± 4.90	31.01 ± 5.87	0.01*	44.92 ± 4.31	40.39 ± 5.19	0.01*	46.19 ± 3.31	40.81 ± 5.08	0.01*
VO_{2peak} rel (mL/kg/min)	34.96 ± 5.84	44.12 ± 5.89	0.01*	36.66 ± 5.88	43.75 ± 7.21	0.01*	28.16 ± 3.64	32.73 ± 5.05	0.01*	28.11 ± 3.47	31.77 ± 5.62	0.01*
Age	42.75 ± 7.67											
Weight (kg)	80.50 ± 10.00	73.76 ± 13.53	0.01*									
BMI (kg/m ²)	30.87 ± 3.03	28.45 ± 4.76	0.39									
Body fat (%)	44.43 ± 3.15	39.70 ± 5.53	0.01*									
VO_{2peak} rel (mL/kg/min)	26.28 ± 3.09	31.98 ± 6.26	0.01*									

Data are reported as mean ± SD. *Significantly different between baseline and post-training (all $p < 0.05$).

Table II. Changes in blood lipid profile by Apo E groups and gender

	Men						Women					
	E2 carriers (n = 6)			E3 homozygotes (n = 62)			E3 homozygotes (n = 71)			E4 carriers (n = 15)		
	Baseline	Post-training	p-value	Baseline	Post-training	p-value	Baseline	Post-training	p-value	Baseline	Post-training	p-value
HDL (mg/dL)	55.33 ± 18.79	56.67 ± 16.69	0.63	45.19 ± 7.26	47.35 ± 8.79	0.01*	55.3 ± 10.8	53.70 ± 11.00	0.05*	53.67 ± 10.9	52.60 ± 7.71	0.54
LDL (mg/dL)	145.00 ± 47.73	127.40 ± 53.29	0.04*	138.90 ± 29.59	121.95 ± 25.13	0.01*	124.3 ± 25.3	121.71 ± 23.00	0.25	133.73 ± 42.38	128.47 ± 37.83	0.28
TG (mg/dL)	206.33 ± 68.53	133.67 ± 63.50	0.01*	123.11 ± 61.25	109.15 ± 45.64	0.01*	102.03 ± 46.76	97.38 ± 47.45	0.37	106.53 ± 35.35	99.33 ± 36.50	0.52
TC (mg/dL)	235.00 ± 46.90	197.67 ± 67.05	0.01*	209.24 ± 36.08	190.31 ± 28.68	0.00*	201.00 ± 33.55	193.37 ± 30.47	0.01*	208.33 ± 42.53	200.93 ± 38.96	0.23

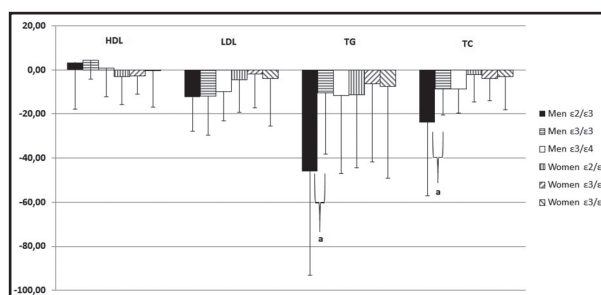
Data are reported as mean ± SD. *Significantly different between baseline and post-training; ^aSignificantly different from E2 carriers (all $p < 0.05$).

Figure 1.

Percentage of change (%) in blood lipid profile by ApoE group and gender (^aSignificantly different from E2 carriers. ^bSignificantly different from E3 homozygotes).

Several studies have demonstrated an association between the ApoE phenotype and lipid levels. This work, to our knowledge, is the first well controlled clinical trial (14) to examine the effects of *ApoE* genotype on the response to a weight loss program with diet combining exercise.

Based on the review of Hagberg et al. (12) low-fat diet interventions tend to reduce plasma lipoprotein levels more in *ApoE4* carriers than in either *ApoE2* carriers or *ApoE3* homozygotes. Interventions with dietary fat content similarly to our study showed the greatest TC and LDL responses in *ApoE4* carriers (25-27). However, in our results we observed that E4 group had low influence on the change in lipid profile after a treatment combining diet and exercise. These differences could be due to the pre-intervention healthy status (no clinical relevant dyslipemia) of participants required in our intervention, as well as the type of diet (well balanced and hypocaloric maintaining 29-34% energy intake of lipids).

On the other hand, different studies (28,29) showed evidence that plasma lipoprotein-lipid responses to exercise training might be influenced by the *ApoE* genotype. These authors reported that physical activity levels did not affect plasma lipoprotein-lipid levels in E4 men. Furthermore, and in accordance with our results, the E2 men group showed the greatest responses after the exercise intervention program (13,28,29). According to our results, Hagberg et al. found that middle-aged and older *ApoE2* genotype men had larger overall plasma lipoprotein-lipid profile improvements with prolonged endurance exercise training than *ApoE3* homozygotes and *E4* carriers men (22). Therefore, the best treatment to improve lipid profile for the E2 carriers seems to be an exercise program, since diet intervention studies showed no improvements in lipid profile for E2 carriers (25,30).

The most favourable response in all lipid profile variables for men in the E2 group (decrease LDL, TG and TC and increase HDL) can be due to the increase in physical activity through our intervention, since regular exercise is known to increase the amount of lipoprotein lipase (LPL) in adipose and muscle tissue. This may reduce TG concentrations adding the decreased fat intake. However, this better response of the E2 group could be due to the higher initial levels, which can be considered as high values (31). These elevated initial levels of TG in E2 subjects are consistent

with impaired clearance of remnant particles containing ApoE2, presumably due to defective receptor recognition of ApoE2 containing particles (32). The work of Taimela et al. (13) found a stronger effect of physical activity on TC in men carrying the E2 allele. The authors of these study (13,22) concluded that plasma lipoprotein profiles of E2 individuals appear to be especially affected by increased physical fitness.

In E3 men, our results showed a greater increase in HDL. This may be related to increased adherence to the HDL particle. HDL is cholesterol enriched in part by the LPL (lipoprotein lipase) mediated transfer of cholesterol from VLDL, and this is one of the postulated mechanisms by which exercise training increases HDL (33).

On the other hand, LDL decreased significantly to values considered as no atherogenic for all *ApoE* groups without differences among groups in men. These results are consistent with other interventions to improve dyslipidemia (33,34). This result suggests that our intervention is appropriate to reduce cardiovascular risk even in men with borderline atherogenic values (31). On the other hand, for the women of our study we observed no significant differences between baseline and final lipid profile levels except for TC in E3 group. The work by Leon et al. (28) reported more favourable changes in TG concentrations for E4/E4 women.

In our study, pre-treatment lipids levels for the *ApoE* genotypes showed values close to non-atherogenic concentrations especially in women. This was due to the inclusion criteria of our study, since all the participants were healthy overweight and obese people. However, it is important to emphasize that the BMI of the participants increased the risk of having metabolism lipid alterations. A point of interest of the present study was to include the randomized-controlled design, the long-supervised training period and the lifestyle changes. Another strength was that it is the first, which combines diet and exercise and includes normoglycemic and borderline or no atherogenic lipid profile according to the guidelines published by the expert panel report (31), young to middle-aged men and women. Furthermore, our participants achieved healthy or non-atherogenic values. In contrast, a limitation of this study is that sample size could be too small to detect significant differences among *ApoE* groups. Another limitation could be that not all the participants followed the same exercise program although the different protocols had the same volume and intensity and they did not show significant differences between intervention groups for lipid profile changes (35,36).

Summarizing, this article explains what type of training is the most appropriate according to the polymorphism of ApoE that the subject has. In conclusion, we observed greater improvements in lipid profile in men carrying the *ApoE2* allele after a highly-controlled diet and exercise program, mainly due to decreases in TG and TC concentrations. Future research is required in order to confirm this finding and, if confirmed, to define the mechanism for this effect.

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Trabajo Original

Obesidad y síndrome metabólico

Cardiorespiratory fitness and fat oxidation during exercise as protective factors for insulin resistance in sedentary women with overweight or obesity

Fitness cardiorrespiratorio y oxidación de grasas durante el ejercicio como factores protectores de resistencia a la insulina en mujeres sedentarias con sobrepeso u obesidad

Javiera Cancino-Ramírez^{1,2}, Johana Soto-Sánchez³, Hermann Zbinden-Foncea⁴, Manuel Moreno González⁵, Bárbara Leyton-Dinamarca⁶ and Luis González-Rojas^{2,4}

¹Magíster de Fisiología Clínica del Ejercicio. Facultad de Medicina. Universidad Mayor. Santiago, Chile. ²Centro de Tratamiento de la Obesidad. Pontificia Universidad Católica de Chile. Santiago, Chile. ³Facultad de Ciencias de la Actividad Física del Deporte y Recreación. Departamento de Educación Física. Universidad de Playa Ancha. Valparaíso, Chile. ⁴Laboratorio de Ciencias del Ejercicio. Escuela de Kinesiología. Facultad de Medicina. Universidad Finis Terrae. Santiago, Chile. ⁵Departamento de Nutrición, Diabetes y Metabolismo. Facultad de Medicina. Pontificia Universidad Católica de Chile. Santiago, Chile. ⁶Instituto de Nutrición y Tecnología de los Alimentos Doctor Fernando Monckeberg Barros. Universidad de Chile. Santiago, Chile

Abstract

Introduction: obesity is a global pandemic and it is the biggest risk factor for death worldwide nowadays. Studies suggest that both cardiorespiratory fitness and fat oxidation in exercise are related to insulin resistance and type 2 diabetes mellitus, and they could be used as metabolic fitness markers.

Objectives: the aim of this study is to determine if cardiorespiratory fitness ($\dot{V}O_2$) and fat oxidation during exercise are protective factors of insulin resistance (IR) in sedentary women with obesity or overweight.

Methods: sixty women were selected for fat oxidation analysis and 55 for cardiorespiratory fitness analysis that fitted the inclusion and exclusion criteria. $\dot{V}O_{2\max}$, maximal fat oxidation (MFO) and the intensity where MFO is reached (FATmax) were determined through an incremental test on a cycle ergometer with gas analysis. The subjects with a Homeostatic model assessment of IR index greater or equal to 2.5 were considered as insulin-resistant. Participants were divided into 2 groups, IR group (n = 38) and Non-IR group (n = 22).

Results: $\dot{V}O_{2(2\%)}$ and MFO were lower in the IR group (76.1% vs. 83.2%; p = 0.015 and 1.08 mg × kg⁻¹ × min⁻¹ vs. 1.62 mg × kg⁻¹ × min⁻¹; p = 0.044, respectively) compared to the Non-IR group. There was an association between $\dot{V}O_{2(2\%)}$ and IR (OR = 0.92, p = 0.017) and between MFO and IR (OR = 0.52, p = 0.035), both models adjusted for age and body mass index.

Conclusions: $\dot{V}O_{2(2\%)}$ and MFO are independent protective factors for IR. No association was found between FATmax and IR.

Key words:

Cardiorespiratory fitness. Lipid metabolism. Insulin resistance. Cardiopulmonary exercise test. Oxygen consumption.

Resumen

Introducción: la obesidad es una pandemia global y actualmente es el mayor factor de riesgo de muerte a nivel mundial. Estudios sugieren que tanto el *fitness* cardiorrespiratorio ($\dot{V}O_2$) como la oxidación de grasas durante el ejercicio podrían ser utilizados como marcadores del *fitness* metabólico.

Objetivos: el objetivo de este estudio es determinar si el $\dot{V}O_2$ y la oxidación de grasas durante el ejercicio son factores protectores de resistencia a la insulina en mujeres sedentarias con obesidad o sobrepeso.

Métodos: fueron seleccionadas 60 mujeres para análisis de oxidación de grasas y 55 para análisis de $\dot{V}O_2$ que cumplieran con los criterios de inclusión y exclusión. El $\dot{V}O_{2\max}$, la máxima oxidación de grasas (MFO) y la intensidad donde se alcanza el MFO (FATmax) fueron determinados mediante un test incremental en cicloergómetro con análisis de gases. Los sujetos con un índice HOMA-IR mayor o igual a 2,5 fueron considerados con resistencia a la insulina. Los participantes fueron divididos en dos grupos, IR (n = 38) y No-IR (n = 22).

Resultados: el $\dot{V}O_{2(2\%)}$ y la MFO fueron menores en el grupo IR en comparación al grupo No-IR (76,1% *versus* 83,2%; p = 0,015 y 1,08 mg × kg⁻¹ × min⁻¹ *versus* 1,62 mg × kg⁻¹ × min⁻¹; p = 0,044, respectivamente). Mediante el análisis de regresión logística se encontró una asociación entre $\dot{V}O_{2(2\%)}$ e IR (OR = 0,92; p = 0,017) y entre MFO e IR (OR = 0,52; p = 0,035), ambos modelos ajustados por edad e índice de masa corporal.

Conclusión: el $\dot{V}O_{2(2\%)}$ y la MFO son factores protectores independientes de IR. No se encontró asociación entre el FATmax y la IR.

Palabras clave:

Fitness cardiorrespiratorio. Metabolismo de lípidos. Resistencia a la insulina. Prueba de esfuerzo cardiopulmonar. Consumo de oxígeno.

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Correspondence:

Luis González Rojas. Laboratorio de Ciencias del Ejercicio. Escuela de Kinesiología. Facultad de Medicina. Universidad Finis Terrae. Av. Pedro de Valdivia 1509, Santiago, Chile
e-mail: rojas.gonzalez.luis@gmail.com

INTRODUCTION

Many studies suggest that a lipids oversupply in peripheral tissues could contribute to insulin resistance (IR) development (1). Subjects with IR frequently show an abnormal lipids metabolism including an increase of free fatty acids, an elevated content of intramyocellular lipids, and an impaired mitochondrial fatty acid oxidation (1-3).

On the other hand, multiples studies have related IR with mitochondrial oxidative capacity, which, in effect, is strictly related to fat oxidation and total body oxidative capacity (4). Oxygen consumption (VO_2) is a reflex of this oxidative capacity and many authors suggest that higher values of VO_2 substantially reduce the adverse effects of obesity on morbidity and mortality (5), and that lower levels of VO_2 predispose to metabolic conditions such as IR and type 2 diabetes mellitus (6).

Just as VO_2 , maximal fat oxidation during exercise reflects mitochondrial respiration and, since their changes are related to mitochondrial fat oxidation capacity, it could be used as metabolic fitness markers (7,8).

Physical training is one of the non-pharmacological actions most used in the prevention and treatment of IR, and diverse studies have related physical fitness with insulin sensitivity (9). Nevertheless, there are no studies that determine the protective role of aerobic capacity and fat oxidation on IR. The aim of this study is to determine the protective role of cardiorespiratory fitness and fat oxidation during exercise on IR in sedentary women with obesity or overweight.

MATERIALS AND METHODS

STUDY DESIGN

This study was conducted in accordance with the Declaration of Helsinki and was approved by Ethics Committee with a waiver of the need to obtain informed consent (register 15-267). All participants' data were obtained from our retrospective database at Obesity Treatment Center according to inclusion/exclusion criteria.

PATIENTS

We identified 60 women who met the criteria shown in Figure 1 that were selected in a non-probabilistic way.

Body composition

Height was measured with a stadimeter (0.5 cm precision) and weight with a SECA digital scale (0.1 kg precision). Both assessments were performed without shoes and in light clothing. Body mass index (BMI) was calculated as $\text{weight} \times \text{height}^{-2}$ ($\text{kg} \times \text{m}^{-2}$). Lean and fat mass was assessed by octopolar multifrequency

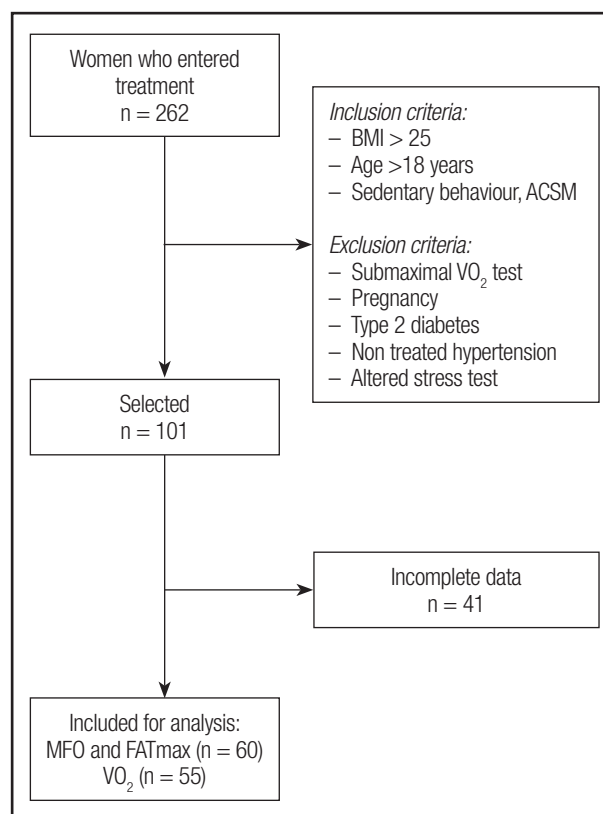


Figure 1.

Sample's selection flow chart (BMI: body mass index; ACSM: American College of Sports Medicine; VO_2 : maximal oxygen consumption; MFO: maximal fat oxidation; FATmax: intensity were MFO is reached).

bioimpedance (10) in 4 hours fasting state, without menstruation and with at least 12 hours free of exercise.

Cardiorespiratory fitness

An incremental cycle ergometer test was performed with gas analysis (Metalyzer 3B-R2, Cortex). The patients were free of exercise, alcohol, coffee, drugs or other stimulants consumption in the previous 24 hours and in a 6 hours fasting condition. Theoretical maximal load (W_t) was estimated by Jones equation in Watts (11). Protocol consisted in a 3-minutes rest period, then a 3-minutes warm up at 20% of W_t followed by 6 minutes stages at 30, 40, 50 and 60% of W_t until a respiratory exchange ratio (RER) ≥ 1 was reached. Then 1-minute stages were performed with increases of 10% of W_t until exhaustion. Verbal stimuli were allowed. The test was considered as maximal if a RER ≥ 1.1 was reached and/or if the maximal heart rate (HR_{max}) was greater or equal to the theoretical maximum predicted by Morris equation for ergometer cycle test (12). This protocol was adapted from the one proposed by Brun, Romain and Mercier (7). The next variables were calculated from the average of the final 30 seconds from the last completed stage (breath by breath): HR_{max} in $\text{beats} \times \text{min}^{-1}$, maximal load

in Watts ($W_{\max}$), maximal load expressed as a percentage of W_t ($W_{\max(\%)}$) and relative to body weight in watts $\times$ kg ($W_{\max \text{ rel}}$).

The same methodology was used for determining cardiorespiratory fitness from the measurements of maximal oxygen consumption. This was expressed as an absolute value in $L \times \text{min}^{-1}$ ($VO_{2\max}$) and as a percentage of the maximum estimated ($VO_{2\max(\%)}$) according to the Wasserman and Hansen weight algorithm (13).

Fat oxidation

Frays equations were used (14) with the average value of oxygen and carbon dioxide volumes of the last 2 minutes of every completed stage of 6 minutes. Was calculated: a) maximal fat oxidation rate (MFO), that is the maximum fat amount used during an incremental workload exercise and is expressed as an absolute value ($g \times \text{hour}^{-1}$) and relative to body weight and to fat free mass ($mg \times \text{kg}^{-1} \times \text{min}^{-1}$); and b) the intensity or workload where MFO is reached (FATmax), expressed as percentage of W_t (FATmaxW) and as a percentage of theoretical maximum oxygen consumption (FATmax VO_2) (13).

Insulin resistance

The homeostatic model assessment of insulin resistance (HOMA-IR) proposed by Mathews et al. (15) was used. Patients were considered with insulin resistance if they had a HOMA-IR value greater or equal to 2.5 according to the existent literature (16).

STATISTICAL ANALYSIS

The sample was categorized into two groups according to the presence of IR. Distribution of the variables was assessed

with Kolmogorov-Smirnov test. Variables with normal distribution are presented as mean and standard deviation and those without normal distribution are shown as a median and in the 25-75 percentile. For comparing means between both groups a Student's t-test for independent samples was used for variables with normal distribution and a Wilcoxon test for non-normally distributed variables. For association of IR with cardiorespiratory fitness and exercise fat oxidation a stepwise logistic regression analysis was performed, adjusting by age and BMI. Data are presented as *odds ratio* and confidence interval of 95%. The goodness of fit was evaluated with a Hosmer-Lemeshow test.

For all the analysis a p-value < 0.05 was considered significant. A sample size analysis revealed that a 42 subjects sample is enough to obtain statistical power with a power of 0.8 and an alpha of 0.05 (17). Statistical analysis was performed with the computational statistics program STATA 12 (Stata Corp, College Station, TX).

RESULTS

General characteristics of the subjects are shown in table I. IR group presents a higher weight, BMI, fat mass and body fat percent in contrast to Non-IR group, whereas this last one presents a greater amount of fat-free mass.

Table II shows the differences in cardiorespiratory fitness and fat oxidation between both groups. $VO_{2\max(\%)}$ and MFO were lower in the IR group in a 7.1% and 33.3%, respectively.

Table III shows logistic regression models for the association of IR with $VO_{2\max(\%)}$, MFO and FATmax, adjusted by age and BMI. Models a) and b) were statistically significant and both are valid according to the Hosmer-Lemeshow goodness of fit test ($p = 0.056$ and $p = 0.309$, respectively).

Table I. General characteristics

	No-IR (n = 22)	IR (n = 38)	p-value
Age ¹ (years)	35.4 $\pm$ 10.2	30.6 $\pm$ 8.5	0.028*
Weight ² (kg)	74.7 (69.6-81.0)	81.8 (79.1-88.8)	0.007 [†]
Height ¹ (cm)	161.9 $\pm$ 8.1	159.3 $\pm$ 5.7	0.054
BMI ² ($\text{kg} \times \text{m}^{-2}$)	29.4 (28.1-31.8)	32.8 (30.6-35.9)	0.001 [†]
FFM ¹ (kg)	42.2 $\pm$ 5.8	42.4 $\pm$ 4.9	0.445
FFM ² (%)	53.2 (51.5-57.1)	50.1 (46.9-53.1)	0.006 [†]
FM ² (kg)	33.6 (26.6-41.3)	38.8 (35.1-42.8)	0.016 [†]
FM ¹ (%)	43.3 $\pm$ 8.4	46.8 $\pm$ 4.8	0.023*
Fasting glycemia ($\text{mg} \times \text{dL}^{-1}$)	84.8 $\pm$ 5.3	89.3 $\pm$ 8.0	0.022*
Fasting insulinemia ($\text{mg} \times \text{dL}^{-1}$)	10.1 (8.7-11.8)	19.3 (15.4-28.9)	0.000 [†]
HOMA-IR	2.1 (2.0-2.5)	4.2 (3.4- 5.8)	0.000 [†]

BMI: body mass index; FFM: fat free mass; FM: fat mass; HOMA-IR: homeostatic model assessment.

¹ Values are expressed as mean ($\pm$) standard deviation; ²Values are expressed as median (p25-75).

*Student's t test for independent samples: $p < 0.05$. [†]Wilcoxon test for independent samples: $p < 0.05$.

Table II. Cardiorespiratory fitness and fat oxidation

	No-IR (n = 22)	IR (n = 38)	p-value
VO _{2max} (L × min ⁻¹)	1.53 ± 0.27 ^b	1.51 ± 0.28 ^c	0.386
VO _{2maxrel} (mL × kg ⁻¹ × min ⁻¹)	24.3 ± 3.1 ^b	23.9 ± 3.2 ^c	0.321
VO _{2max} (%)	83.2 ± 10.2 ^b	76.1 ± 11.9 ^c	0.015*
Maximal load (W _{max})	108.3 ± 27.0 ^b	110.8 ± 24.1 ^c	0.360
Maximal load (W _{max} (%))	88.1 ± 24.8 ^b	88.6 ± 17.7 ^c	0.460
MFO (g × h ⁻¹)	7.63 ± 6.6	5.4 ± 5.0	0.076
MFO (mg × kg ⁻¹ × min ⁻¹)	1.62 ± 1.37	1.08 ± 1.01	0.044*
MFO ^a (mg × kg ⁻¹ × min ⁻¹)	3.0 ± 2.6	2.2 ± 2.0	0.073
FATmax W (%)	33.4 ± 5.7	32.1 ± 5.5	0.198
FATmax VO ₂ (%)	46.1 ± 9.0	45.3 ± 8.5	0.358

VO_{2max}: maximal oxygen consumption; MFO: maximal fat oxidation rate.

Values are expressed as mean (±) standard deviation.

^akg of fat free mass; ^bn = 20; ^cn = 35. *Student's t test for independent samples: p < 0.05

Table III. Logistic regression for association of IR with VO_{2max} and fat oxidation

Model**	OR	95% CI	p-value
a) VO _{2max} (%)	0.92	0.87-0.97	0.017*
b) MFO (mg × kg ⁻¹ × min ⁻¹)	0.52	0.28-0.96	0.035*
c) FATmax (%)	0.99	0.92-1.06	0.774

OR: odds ratio; 95% CI: confidence interval of 95%; VO_{2max}: maximal oxygen consumption; MFO: maximal fat oxidation rate.

*p-value < 0.05. **Model adjusted by age and BMI.

DISCUSSION

The goal of the present study was to determine the protector role of cardiorespiratory fitness and exercise fat oxidation on IR in women with obesity or overweight. Statistically significant differences were found between both groups in VO_{2max}(%), which was lower in IR group (76.1% versus 83.2%; p = 0.015). At the same time, an association between VO_{2max}(%) and IR was found, which could indicate a possible protective role against the condition. It was determined that the increase in one unit of VO_{2max}(%) reduces the probability of presenting IR in an 8%. Although there are no studies that associate VO_{2max} with IR, the results are consistent with previous studies that describe VO_{2max} as a strong independent predictor of insulin sensitivity in non-diabetic subjects (18). In turn, this has been associated with glucose tolerance and HOMA2-IS in sedentary women with obesity (19) and with the presence of metabolic syndrome in overweight subjects (20). This has also been evidenced in adolescents with obesity, where a low VO_{2max} was related to higher insulin indexes (HOMA-IR and insulin secretion in oral glucose tolerance test) (21). Similarly, Haufe et al. (22) found that in healthy subjects with obesity, those that had a greater VO_{2max} were more sensitive to insulin, similar to that described by

Messier et al. (23) and by Morris et al. (24) in postmenopausal women with obesity and in healthy subjects, respectively.

In regard to fat oxidation, no differences in FATmax were found between both groups, similar to the findings of Mogensen et al. (25) and Larsen et al. (26) in subjects with obesity with and without type 2 diabetes mellitus, and by Croci et al. in trained normal weight and overweight subjects (27). However it was observed that the IR group had a lower MFO than the Non-IR group (1.08 mg × kg⁻¹ × min⁻¹ versus 1.62 mg × kg⁻¹ × min⁻¹; p = 0.044). In turn, an association between MFO and IR was found that also could indicate a possible protective role against the condition.

As in the previous case, there are no studies that associate IR with MFO and they principally focus on the study of insulin sensitivity. In congruence with the results previously shown, Robinson et al. found a positive correlation between plasma insulin (28) and insulin sensitivity (29) with MFO in healthy young men.

Fat oxidation is strictly linked to mitochondrial oxidative capacity (30,31). At the same time, the mitochondrial metabolism has been related to IR (4,32). If we consider that VO_{2max} and MFO are indirect and systemic clinical manifestations of muscular mitochondrial metabolism, it could be hypothesized that the present results might be due to a relation between mitochondrial metabolism and IR. It is necessary to mention the existence of some studies that have not found that relationship (33,34), including Lalia et al. (18) who showed a strong association between VO_{2max} and IR, without finding an association between this last one and mitochondrial metabolism. Nevertheless, a correlation between VO_{2max} and mitochondrial enzymatic content (35) and cytochrome c oxidase activity (36) has been described, which suggests a possible relation of the total quantity of mitochondrial respiration enzymes with oxidative muscular capacity and thus with total body oxidative capacity.

Previous researchers have evidenced an increase in MFO and VO_{2max} through different types of training in subjects with IR and obesity (37). Studies related to the limitations of fatty acid utiliza-

tion in skeletal muscle during exercise are controversial, attributing it to enzymes and/or transporters involved in the translation of intermediate metabolites and to beta oxidation (38). Training has shown improvements in the function of all components involved in healthy subjects (38,39). Therefore, physical training has risen as one of the fundamental tools in the treatment of IR (40), but it is still not possible to determine which of the many parameters modified through exercise would have a greater impact on IR.

Currently, there is much divergence in the objectives and strategies of treatment in this patients profile, so the results of the present study could be useful in trying to define more accurate strategies on IR treatment. Future studies must evaluate the variation of VO_{2max} and MFO and its impact in the improvements in insulin sensitivity and IR.

The principal limitation of this study is the utilization of HOMA-IR instead of hyperinsulinemic euglycemic clamp, which is considered the gold standard for the determination of IR. Another limitation of the study is the lack of a normal weight control group for contrasting the obtained results.

CONCLUSION

This study demonstrated that $VO_{2max(\%)}$ and MFO present a protective role against IR. An increase of 1% in $VO_{2max(\%)}$ reduces the risk of IR in an 8%, whereas an increase of $1 \text{ mg} \times \text{kg}^{-1} \times \text{min}^{-1}$ in MFO reduces the risk of IR in a 48% in sedentary women with overweight or obesity. No association between FATmax and IR was found. Future studies should explain the mechanism by which an increase of VO_{2max} and of MFO can improve insulin sensitivity (considering fatty acid transporters, enzymes and metabolic variables) and how these improvements could favor the treatment of IR.

ETHICAL APPROVAL

This study was approved by the Scientific Ethics Committee (register 15-267). All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

A waiver of the need to obtain informed consent was obtained from Scientific Ethics Committee.

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Nutrición Hospitalaria



Trabajo Original

Obesidad y síndrome metabólico

Açaí improves non-alcoholic fatty liver disease (NAFLD) induced by fructose *El açaí mejora la enfermedad de hígado graso no alcohólico (NAFLD) inducida por la fructosa*

Mayara Medeiros de Freitas Carvalho^{1,2}, Larissa Lélis Teixeira Reis², Juliana Márcia Macedo Lopes², Nara Nunes Lage², Joyce Ferreira da Costa Guerra³, Helena Porto Zago⁴, Larissa de Freitas Bonomo⁵, Renata Rebeca Pereira^{2,6}, Wanderson Geraldo de Lima^{1,2,6}, Marcelo Eustáquio Silva^{1,2,7} and Maria Lucia Pedrosa^{1,2,6}

¹Program in Health and Nutrition. Federal University of Ouro Preto. Ouro Preto, MG, Brazil. ²Research Center in Biological Sciences. Federal University of Ouro Preto. Ouro Preto, MG, Brazil. ³Institute of Genetics and Biochemistry. Federal University of Uberlândia. Patos de Minas Campus. Patos de Minas, MG, Brazil. ⁴School of Nutrition. Federal University of Ouro Preto. Ouro Preto, MG, Brazil. ⁵Department of Pharmacy. Federal University of Juiz de Fora. Governador Valadares Campus. Governador Valadares, MG, Brazil. ⁶Department of Biological Sciences. Federal University of Ouro Preto. Ouro Preto, MG, Brazil. ⁷Department of Foods. Federal University of Ouro Preto. Ouro Preto, Minas Gerais, Brazil

Abstract

Introduction: the excessive consumption of fructose can cause liver damage, characteristic of non-alcoholic fatty liver disease (NAFLD) associated with changes in lipid metabolism and antioxidant defenses. Açaí, the fruit of *Euterpe oleracea* Mart., has demonstrated numerous biological activities, including anti-inflammatory, antioxidant, and lipid metabolism modulating action.

Objective: we evaluated the benefits of açaí supplementation on liver damage caused by replacing starch with fructose in rats.

Methods: thirty male *Fischer* rats were divided into two groups, the control group (C, 10 animals), which consumed a standard diet (AIN-93M), and the fructose (F, 20 animals) group, which consumed a diet containing 60% of fructose. After eight weeks, 10 animals from the fructose group received 2% of lyophilized açaí, and were called the açaí fructose group (FA). The animals were fed *ad libitum* with these diets for another ten weeks. Serum, hepatic and fecal lipid profile, antioxidant enzymes and carbonylated protein were assessed and histopathological characterization of the liver was performed.

Results: açaí promoted the reduction of ALT activity in relation to the fructose group (F), reduced alkaline phosphatase to a level similar to that of the control group (C) in relation to the fructose group (F), and reduced catalase activity. The fruit also increased the ratio of total/oxidized glutathione (GSH/GSSG) and reduced the degree of macrovesicular steatosis and the number of inflammatory cells.

Conclusion: the replacement of starch by fructose during this period was effective in promoting NAFLD. Açaí showed attenuating effects on some markers of hepatic steatosis and inflammation.

Key words:

Euterpe oleracea Mart. Fructose-diet. Hepatic steatosis. Antioxidant enzymes. Inflammation.

Resumen

Introducción: el consumo excesivo de fructosa puede causar daño hepático, característico de la enfermedad hepática grasa no alcohólica (EHGNA), asociada con cambios en el metabolismo de los lípidos y defensas antioxidantes. El açaí, fruto del *Euterpe oleracea* Mart., ha demostrado desempeñar numerosas actividades biológicas, incluidas acciones antiinflamatorias, antioxidantes y moduladoras del metabolismo lipídico.

Objetivo: se evaluaron los beneficios de la suplementación con açaí en el daño hepático causado por la sustitución del almidón por fructosa en ratas.

Métodos: se distribuyeron 30 ratas Fischer macho en dos grupos: 10 ratas en el grupo control (C), que consumía una dieta estándar (AIN-93M), y 20 ratas en el grupo fructosa (F), que consumía una dieta que contenía un 60% de fructosa. Después de ocho semanas, diez animales del grupo fructosa recibieron un 2% de açaí liofilizado, por lo que pasaron a integrar el grupo açaí fructosa (FA). Los animales fueron alimentados *ad libitum* con estas dietas durante otras diez semanas. Se analizaron el perfil lipídico hepático y fecal, las enzimas antioxidantes y la proteína carbonilada, y se realizó la caracterización histopatológica del hígado.

Resultados: el açaí promovió la reducción de la actividad de ALT en relación al grupo de fructosa (F) y la reducción de la fosfatasa alcalina a niveles similares a los hallados en el grupo control (C) en relación con el grupo de fructosa (F). El fruto también aumentó la proporción de glutatión total/oxidado (GSH/GSSG) y redujo el grado de esteatosis macrovesicular y el número de células inflamatorias.

Conclusión: la sustitución de almidón por fructosa durante este periodo fue eficaz en la promoción de NAFLD. El açaí mostró efectos atenuantes en algunos marcadores de esteatosis hepática y de inflamación.

Palabras clave:

Euterpe oleracea Mart. Dieta rica en fructosa. Esteatosis hepática. Enzimas antioxidantes. Inflamación.

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Correspondence:

M. L. Pedrosa. Biological Research Center. Federal University of Ouro Preto. Ouro Preto, MG, Brazil
e-mail: mlpedrosa@gmail.com

INTRODUCTION

The non-alcoholic fatty liver disease (NAFLD) includes isolated hepatic steatosis and non-alcoholic steatohepatitis (NASH) and their prevalence has doubled in the last 20 years. It has been considered as the primary cause of liver disease (1). The prevalence of this disease is estimated to be 20-30% of the general population in Europe and the USA (2). NAFLD was confirmed as the etiology that most involves hepatocellular carcinoma in the United States (3). Mechanisms involved in NAFLD pathogenesis have been elucidated and it is known that dietary components may aggravate or reduce the risk of development of steatosis. Insulin resistance and obesity increase caloric intake, *de novo* lipogenesis (DNL) and free fatty acid (FFA) flux from adipose tissue to the liver, and impaired VLDL secretion leads to fat accumulation in the liver. The accumulation of lipids and multiple hits are involved in the development of NASH, including mitochondrial impairment, the role of microbiota, iron accumulation, genetic factors, and the release of reactive oxygen species (4).

Fructose has been a key player in the development of NAFLD; its hepatic extraction and metabolism are especially high, as compared to glucose. This happens because of the extensive amount of fructokinase that phosphorylates fructose to fructose 1-phosphate in the liver and to the subsequent metabolism of fructose 1-phosphate at the triose phosphate level, which bypass flux control at phosphofructokinase (5).

The high intake of fructose results in substrate for *de novo* lipogenesis, the FFA are incorporated into triacylglycerols (TAG) or other lipids are connected with increased VLDL synthesis, which has a player in non-alcoholic fatty liver disease. Whenever hepatic DNL is induced, new lipids are synthesized, nonesterified FA are re-esterified, and hepatic lipid oxidation is downregulated. These facts cause an imbalance between hepatic lipids, induce intra-hepatic fat accumulation (4,6).

Excessive accumulation and deposition of fat in the liver predisposes for the development of NASH, increasing the vulnerability for cirrhosis and hepatocellular carcinoma. The presence of oxidative stress and proinflammatory mediators accelerates the deterioration of the liver, because of reactive oxygen species (ROS) overproduction and excessive fatty acids oxidation, which increases lipid peroxides. The presence of toxic metabolites activates the lysosomal cell death pathway and it results in cytotoxicity, collaborating with hepatic inflammation, ROS and the possibility of hepatic fibrosis and cirrhosis by activating hepatic stellate cells. However, these indications can be relieved as activating hepatic antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase and antioxidants compounds (4,7).

Antioxidant therapy for the treatment of NAFLD, and also including NASH, has the potential to alleviate oxidative stress and cell death, which promote diseases (8). Anthocyanins have shown beneficial effects in reducing steatosis and liver damage (9).

The *Euterpe oleracea* Mart., popularly known as açai, is native to Brazilian Amazon, and has gained new markets by the presence of beneficial antioxidants which are beneficial to health, such as

phenolic compounds, mainly anthocyanins and vitamin E (10). *In vivo* studies demonstrate the action of açai in improving the lipid profile, different parameters related to oxidative stress, antioxidant enzymes and the reduction of non-alcoholic liver steatosis (11-14). In addition to acting as an antioxidant, anthocyanins also regulate the lipid metabolism, and we have previously shown that açai attenuates the development of hepatic steatosis in mice on a high-fat diet, downregulating the expression of genes involved in lipogenesis (15).

In this context, this study aimed to evaluate the effect of açai consumption on the metabolism of rats under NAFLD induced by the isocaloric replacement of starch by fructose. In this study, the administration of lyophilized açai improved liver function and antioxidant enzymes, increased the ratio of the total glutathione per oxidized (GSH/GSSG), and reduced the degree of macrovesicular steatosis and inflammation. The clarification of the protective effects of açai may expand the range of dietary options in the treatment and prevention of this disease, and contributes to the hypothesis that adding bioactive compounds sources to the diet can alleviate NAFLD progression (8). We expect our results may subsidize future efforts researching açai and other potential sources to be used in the NAFLD treatment.

MATERIALS AND METHODS

LYOPHILIZED AÇAÍ PURCHASE AND COMPOSITION

Lyophilized açai pulp was kindly provided by the Company Liotécnica Tecnologia em Alimentos (São Paulo-SP/Brazil). Each 100 g of freeze-dried açai contained had 541 kcal, 5 g of total carbohydrate, 9.8 g of protein, 54 g of total fat and 27 g of dietary fiber, according to the provider.

The Folin-Ciocalteu method was used to determine total phenolic content, as described by Georgé et al. (16). The total amount of phenolic compounds was expressed in milligrams of gallic acid equivalents (GAE) per 100 g of açai.

The antioxidant capacity was determined by the modified 2,2-diphenyl-1-picrylhydrazyl (DPPH) method (17), which is based on the quantification of free radical-scavenging. A methanol solution containing DPPH was prepared, and an aliquot of açai was added, homogenized and kept in the dark for 30 min at room temperature. Antioxidant activity was determined by the reduction in absorbance of the DPPH radical at 515 nm. Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid) was used as an antioxidant standard and the results were expressed as trolox equivalent antioxidant capacity (TEAC) per 100 g of açai.

ANIMALS AND EXPERIMENTAL DESIGN

Eleven-week-old male Fischer rats weighing approximately 200 g were obtained from the Laboratory of Experimental Nutrition at the School of Nutrition of the Federal University of Ouro Preto (UFOP).

The Ethics Committee in Animal Research of the UFOP (protocol no. 2013/46) approved animal procedures. The rats were housed individually under a 12-h light/12-h dark cycle and temperature-controlled conditions, with food and water *ad libitum*.

Initially, 30 rats were distributed into two experimental groups: 10 animals in the control (C) group were fed the AIN-93 M standard diet (18), and 20 animals in the fructose (F) group received a fructose-rich diet (containing 60% fructose) (19,20). The composition of these experimental diets is described in table I. After eight weeks, group F was further divided and ten animals started receiving the same diet but now containing 2% of lyophilized açai, and was called the group FA (fructose açai). Rats were fed these diets *ad libitum* for ten weeks. After all 18 weeks, the rats were euthanized by total blood collection from adjacent vessels to the brachial plexus under isoflurane anesthesia. Blood was collected in polypropylene tubes and centrifuged at 3,000×g for 15 min. Serum was then removed and stored at -80 °C. The liver was collected and weighed during the experiment, and body weight and food intake were weekly monitored.

LIPIDS EXTRACTION AND SERUM ANALYSIS

The lipid extraction of the liver was performed according to the method described by Folch et al. (21) and the total hepatic lipids obtained by solvent evaporation. These lipids were dissolved in 1 ml of isopropanol, and triglycerides were measured using Labtest® kits (Lagoa Santa, MG, Brazil). In serum, the activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, as well as cholesterol, triglycerides, high density lipoprotein (HDL), and glucose were measured using Labtest® (Lagoa Santa, MG, Brazil) kits. Measurements were performed according to the manufacturer's instructions.

ANTIOXIDANT PROFILE AND PROTEIN CARBONYL LEVEL

Superoxide dismutase (SOD) was assayed using Superoxide Dismutase Assay Kit (Cayman Chemical Company, no. 706002; lot 0450282). This assay utilizes tetrazolium salt for the detection of superoxide radicals generated by xanthine oxidase and hypoxanthine. One unit of SOD was defined as the amount of enzyme needed to cause 50% dismutation of the superoxide radical; only Cu/Zn-SOD is measured.

Catalase (CAT) activity was determined according to Aebi (22), a method that is based on the enzymatic decomposition of H₂O₂ observed spectrophotometrically at 240 nm for 3 min, using 50 mM phosphate buffer, pH 7.0, containing 5 mM H₂O₂. Hydrogen peroxide decomposition was calculated using the molar absorption coefficient 0.0394 l/mmol/l/cm of peroxide. One unit of CAT is equivalent to the hydrolysis of 1 µmol of H₂O₂ per min and the results were expressed as activity per milligram of protein.

The total glutathione content was determined by a kinetic assay which utilizes a method based on the reduction of DTNB (5,5'-dithio-bis [2-nitrobenzoic] acid) in TNB (5-thio-2-nitrobenzoic acid) proposed by Griffith (23), which can be detected spectrophotometrically at 412 nm. Oxidized glutathione (GSSG) was determined after derivatization of total GSH with 2-vinylpyridine. Oxidative stress index was calculated from the GSH/GSSG ratio.

The activity of glutathione peroxidase (GPx) was determined according to the method proposed by Paglia and Valentine (24) with modifications. The method is based on the oxidation of reduced glutathione (GSH), catalyzed by glutathione peroxidase, coupled to the recycling of GSSG through the reaction catalyzed by the enzyme glutathione reductase that uses NADPH as cofactor. The decrease in absorbance measured at 340 nm during the oxidation of NADPH is indicative of the activity of glutathione

Table I. Composition of experimental diets

Components	Control (g/kg)	Fructose (g/kg)	Fructose açai (g/kg)
Choline	2.5	2.5	2.5
Methionine	2.5	2.5	2.5
Vitamins mixture	10.0	10.0	10.0
Mineral mixture	35.0	35.0	35.0
Cellulose	50.0	50.0	50.0
Sucrose	100.0	100.0	100.0
Soybean oil	40.0	40.0	40.0
Casein	140.0	140.0	140.0
Corn starch	620.0	20.0	0.0
Fructose*	0.0	600.0	600.0
Lyophilized açai†	0.0	0.0	20.0

Vitamin mixture (IU or g/kg of mixture): retinol acetate, 2 000 000 IU; cholecalciferol, 200,000 IU; p-aminobenzoic acid, 10.00; inositol, 10.00; niacin, 4.00; calcium pantothenate, 4.00; riboflavin, 0.80; thiamin HCl, 0.50; pyridoxine HCl, 0.50; folic acid, 0.20; biotin, 0.04; vitamin B12, 0.003; sucrose, quantity sufficient to 1 kg; choline, 200.0; α-tocopherol, 10,000 IU (AOAC, 1980). Salt mixture (g/kg of mixture): NaCl, 139.3; KCl, 0.79; MgSO₄·7H₂O, 57.3; aCO₃, 381.4; MnSO₄·H₂O, 4.01; FeSO₄·7H₂O, 0.548; CuSO₄·5H₂O, 0.477; CoCl₂·6H₂O, 0.023; KH₂PO₄, 389.0. (AOAC, 1980). *Fructose (Sythn); †Lyophilized açai (Liotécnica/Brazil).

peroxidase. The determination of the enzymatic activity of glutathione reductase (GR) was performed according to the method proposed by Carlberg and Mannervik (25). The assay is based on the reduction of glutathione oxidized by NADPH in the presence of glutathione reductase. The decrease in absorbance measured at 340 nm during the oxidation of NADPH is indicative of the activity of glutathione reductase.

Carbonyl protein (PC) levels were determined according to the method described by Levine et al. (26). Each sample was precipitated with 10% (w/v) TCA (trichloroacetic acid). After centrifugation, the precipitate was treated with 10 mmol of DNPH in 2N HCl, incubated in the dark for 30 min and then treated with 10% TCA. After centrifuging, the precipitate was washed twice with ethanol/ethyl acetate (1:1) and dissolved in 6% SDS. Absorbance was determined at 370 nm. The results were expressed in nmol of DNPH incorporated/mg of protein. The content of DNPH incorporated was calculated using the molar absorption coefficient of DNPH ($22,000 \text{ M}^{-1}\text{cm}^{-1}$).

Total protein content was determined according to the method described by Lowry et al. (27) using bovine serum albumin (BSA) as the standard. This test was used only for correction of previous trials, such as SOD, CAT, PC, glutathione peroxidase and reductase.

HEPATIC HISTOLOGY

Livers were removed at the end of the experiment and fixed in 10% buffered formalin, subsequently embedded in paraffin, for cutting in sections of about 4 μm in a semi-automatic microtome, mounted and stained by hematoxylin and eosin (H&E). Photomicrographs were taken on a Leica DM5000 microscope coupled to a digital camera at 400 $\times$ magnification. A semiquantitative scoring system was used to assess the severity of hepatic steatosis in ten microscopic fields examined as described previously (28). In brief, macrovesicular steatosis was graded from 1 to 3 depending on the percentage of hepatocytes that contained fat; grade 1 was assigned if < 33% of hepatocytes contained fat; grade 2, if 33-66% contained fat; and grade 3, if > 66% contained fat.

Inflammation was assessed with the Leica QWin software (Leica Microsystems, Germany) using 15 images of randomly-selected fields (total area $1.15 \times 106 \mu\text{m}^2$) of tissue sections for a single slide per animal. The inflammatory process was determined by the difference ($p < 0.05$) between the number of inflammatory cells present in the liver of the animals.

STATISTICAL ANALYSIS

Data were subjected to the Kolmogorov-Smirnov test for normality, expressed as mean $\pm$ standard deviation (SD) in cases of normal distribution, and expressed as median and interquartile ranges in cases of non-parametric distribution. The data were analyzed by one-way analysis of variance (ANOVA), followed by Tukey's *post hoc* test, for parametric data or the Kruskal-Wallis test followed by Dunn post-test for non-parametric data. Differ-

ences were considered as significant when $p < 0.05$. All analyses were conducted using the software GraphPad Prism version 6.00 for Windows (San Diego, CA).

RESULTS

ANALYSIS OF LYOPHILIZED AÇAÍ

Freeze-dried açai showed a high content of total polyphenols (1,619.03 mg GAE/g) and antioxidant capacity (104.80 $\mu\text{MTEAC/g}$).

EFFECTS ON BODY MASS AND FOOD INTAKE

At the end of the experimental period there was no difference between groups with respect to food intake, weight gain, feed efficiency coefficient and fecal excretion (Table II).

EFFECTS ON BLOOD GLUCOSE AND LIPID PROFILE IN SERUM AND THE LIVER

The fructose-rich diet promoted changes in the lipid profile of the animals, increasing serum and liver TAG levels. The administration of açai did not change these parameters. The other serum fractions, total cholesterol, HDL cholesterol and non-HDL showed no significant differences between groups (Table III).

EFFECTS ON ANTIOXIDANT ENZYMES

Superoxide dismutase (SOD) showed reduced activity in the F and FA groups. On the other hand, catalase activity (CAT) was higher in group F and the group FA showed a partial reduction of this activity when compared to group F.

The concentration of GSSG in group F was not changed and treatment with açai reduced this parameter compared to controls. The ratio between reduced and oxidized glutathione (GSH/GSSG)

Table II. Food intake, weight gain and fecal excretion in rats fed a control diet or a fructose rich-diet supplemented (FA) or not (F) with açai

Parameter	Experimental groups		
	C	F	FA
Food intake (g/day)	19.8 $\pm$ 1.2	19.5 $\pm$ 0.8	19.3 $\pm$ 0.9
Weight gain (g)	171.3 $\pm$ 30.1	153.5 $\pm$ 19.5	157.4 $\pm$ 31.4
Fecal excretion (g/week) ¹	5.1/4.2-6.3	5.0/4.1-6.6	5.7/4.5-5.8

Values are expressed as the mean $\pm$ SD or ¹median and interquartile ranges ($n = 10$).

Table III. Serum lipid profile and liver triacylglycerols of rats fed a control diet or a fructose rich-diet supplemented (FA) or not (F) with açai

Parameter	Experimental groups		
	C	F	FA
Glucose (mg/dL)	96.9 ± 15.6 [‡]	137.1 ± 29.2 [†]	138.8 ± 13.9 [†]
TAG (mg/dL)	116.6 ± 34.5 [‡]	180.4 ± 36.1 [†]	185.8 ± 50.0 [†]
CT (mg/dL)	115.0 ± 17.6	103.4 ± 14.9	104.4 ± 16.7
HDL (mg/dL)	79.9 ± 13.9	70.3 ± 10.6	69.7 ± 12.6
Non-HDL (mg/dL)	35.0 ± 7.2	33.0 ± 6.6	34.8 ± 6.5
TAG (mg/g of liver) *	8.5/7.4-10.7 [‡]	16.0/11.9-29.4 [†]	14.8/8.9-31.4 [†]

TAG: triacylglycerols; CT: total cholesterol; Non-HDL: VLDL + LDL. Values are expressed as the mean ± SD or *median and interquartile ranges (n = 10). Within a row, significantly different values are marked with different superscript signs.

was higher in group FA. Total glutathione, reduced glutathione, GR and GPx showed no statistical difference between the experimental groups. There were no statistical differences in the PC level (Table IV).

EFFECTS ON STEATOSIS AND LIVER INJURY

As shown in table V, the fructose-rich diet increased liver weight and glucose levels as compared to group C. ALT and alkaline

Table IV. Antioxidant enzymes and protein carbonyl levels in the liver of rats fed a control diet or a fructose rich-diet supplemented (FA) or not (F) with açai

Parameter	Experimental groups		
	C	F	FA
SOD (U/mg protein)	0.11 ± 0.03 [‡]	0.06 ± 0.03 [‡]	0.08 ± 0.03 [‡]
CAT (U/mg protein)	83.2 ± 11.0 [‡]	99.6 ± 16.5 [†]	85.1 ± 13.6 ^{†,‡}
Total glutathione (nmoles/mL)	69.2 ± 27.2	68.9 ± 32.5	94.0 ± 15.3
GSSG* (nmoles/mL)	5.5/4.2-8.4 [†]	7.01/5.1-7.7 [†]	4.5/3.2-5.4 [‡]
GSH (nmoles/mL)	63.1 ± 27.6	62.6 ± 31.0	98.2 ± 14.8
GSH/GSSG ratio	10.9 ± 6.1 [‡]	9.6 ± 4.9 [‡]	19.7 ± 5.1 [†]
GPx (U/mg protein)	0.02 ± 0.00	0.01 ± 0.00	0.01 ± 0.00
GR (U/mg protein)	0.08 ± 0.02	0.08 ± 0.01	0.08 ± 0.02
PC (nmoles/ mg protein)	1.8 ± 0.5	1.9 ± 0.4	1.9 ± 0.3

SOD: superoxide dismutase; CAT: catalase; PC: protein carbonyl; GSSG: oxidized glutathione; GSH: reduced glutathione; GSH/GSSG: ratio of reduced glutathione and oxidized glutathione; GPx: glutathione peroxidase; GR: glutathione reductase. Values are expressed as the mean ± SD or *median and interquartile ranges (n = 10). Within a row, significantly different values are marked with different superscript signs.

phosphatase activities in group F were increased, as compared to the other groups. The group FA showed reduction in ALT and alkaline phosphatase activity to similar levels as the control group. There was no difference in AST activity between the experimental groups (Table V).

According to histological analyses after processing and staining with H&E, we observed the high presence of macrovesicular steatosis and the number of inflammatory cells (Fig. 1A-C). The addition of açai reduced the degree of steatosis, since 90% of the animals were classified as grade 1 steatosis (Fig. 1D) and reduced the number of inflammatory cells to intermediate levels (Fig. 1E).

DISCUSSION

We examined whether açai improves liver damage, antioxidant enzymes and inflammation in fructose rich diet-induced NAFLD in rats. Although there are other reports on positive effects of açai on steatosis induced by a high-fat diet as well as its antioxidant capacity (11-15), studies using açai on steatosis induced by fructose were not found. We provide evidence that the açai fruit reduced lipid accumulation, inflammation and oxidative stress in rats with NAFLD induced by a fructose-rich diet.

The lyophilized açai used in this study showed a total phenolic content of 1,619.03 mg GAE/g. This value is higher than that in commercial açai pulps, ranging between 182.95 and 598.55 mg GAE/g (29) and a fresh fruit extract, which had 31.20 mg GAE/g of polyphenols (30). In the present study, the antioxidant capacity (TEAC) of lyophilized açai was 104.80 µM/g, which corresponds to higher values of commercial pulp studies which presented between 10.21 and 52.47 µM/g (29). The addition of 2% lyophilized açai to the fructose-rich diet corresponded to an increase of 28.3 kcal/kg, which did not alter significantly the calorie content; previous studies using 2% pulp açai showed protective effect against metabolic disorders (12,14).

In the present study, increased food consumption, body weight gain and fecal excretion in group F is in accordance with findings of previous studies, in which a fructose-rich diet was used (31-33).

Table V. Relative weight of the liver and enzyme activity in serum of rats fed a control diet or a fructose rich-diet supplemented (FA) or not (F) with açai

Parameter	Experimental groups		
	C	F	FA
Liver (%)	2.3 ± 1.1 [‡]	3.05 ± 0.3 [†]	3.10 ± 0.2 [†]
AST (U/mL)	52.9 ± 9.9	54.4 ± 12.1	54.3 ± 12.7
ALT (U/mL)	16.9 ± 2.7 ^{†,‡}	20.1 ± 5.4 [†]	15.7 ± 1.9 [‡]
Alkaline phosphatase (U/L)	79.3 ± 19.0 [‡]	107.2 ± 18.9 [†]	98.9 ± 22.9 ^{†,‡}

AST: aspartate-aminotransferase; ALT: alanine-aminotransferase. Values are expressed as the mean ± SD (n = 10). Within a row, significantly different values are marked with different superscript signs.

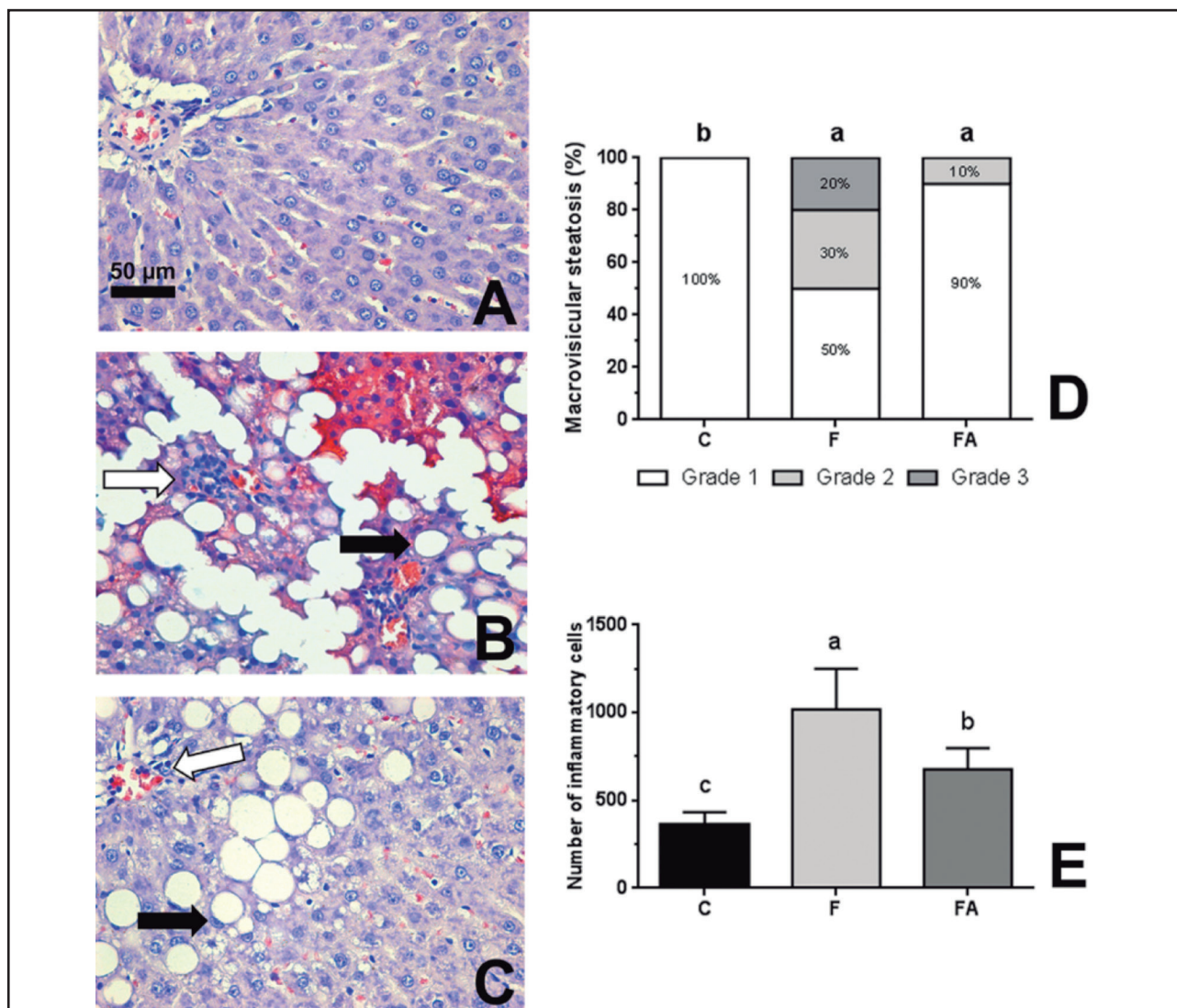


Figure 1.

Histological micrographs of liver tissue stained with H&E. A. Group C presenting normal histological picture. B. Group F presenting intense macrovesicular steatosis (black arrow). C. Group FA presenting mild macrovesicular steatosis (black arrow). D. Classification of the degree of macrovesicular steatosis. E. Number of inflammatory cells between experimental groups. The white arrow in panels B and C indicates inflammatory cells. Steatosis rating: grade 1, < 33%; grade 2, 33-66%; and grade 3, more than 66%. Different letters represent statistical differences using the Kruskal-Wallis test followed by Dunn's post-test test. Bar = 50 μ m. Images were shot with 400x magnification.

The presence of açai in the FA group did not change body weight gain and fecal excretion; the same behavior was observed in studies using açai in high-fat model (11,15). In addition, the açai treatment did not modify food consumption.

Fructose is primarily metabolized in the liver and its hepatic load increases gluconeogenesis and reduces the ability of insulin to suppress glucose production. In addition, enhanced lipogenesis and decreased peripheral lipid catabolism play a role in hyperinsulinemia, hypertriglyceridemia and insulin resistance induced by fructose-rich diet, as demonstrated in studies using rat models (32,33). Here, we reinforce the previous findings, but in a model that may best portray the pathogenesis of NAFLD in humans, since it has been previously observed that fructose supplemen-

tation also induces hyperinsulinemia, hypertension, hypertriglyceridemia and insulin resistance (34), characteristics associated with NAFLD and findings observed in the present report. The administration of açai did not change glucose and TAG in serum and the liver. Previously, Guerra et al. (15) observed reduced hepatic lipid content and downregulation in the expression of genes involved in lipogenesis. This may be due to the different models of NAFLD induction, and therefore, different metabolic pathways are involved in the accumulation of TAG, suggesting that the pathways involved in the accumulation of TAG from fructose were not influenced by açai components.

NAFLD pathogenesis involves multiple *hits*, and oxidative stress plays a central role and correlates with severity and disease states

such as cell death and tissue damage. We investigated antioxidant defense and oxidative damage to macromolecules. Oxidative damage was evaluated using protein carbonyls, a generic marker of protein oxidation for examining the extent of protein oxidation *in vivo* (35). No differences were found amongst the experimental groups regarding these analyses in our study, possibly the longest experimental period, as compared to other studies in the literature (36,37).

However, fructose addition effectively improved the GSH/GSSG ratio. Glutathione is synthesized in the liver and is the first line of defense against oxidative stress (38). The addition of açai promoted a reduction in the levels of GSSG and an increase in GSH/GSSG ratio, showing its beneficial action on the main antioxidant system. Chronic insults increased the GSSG levels and the application of the GSH/GSSG ratio is used to measure the oxidative status (39). In fact, the formation and accumulation of GSSG were effectively inhibited by açai feeding under the present experimental conditions, and it suggests that the endogenous glutathione pool slowly shifted toward the reduced state in the açai group when compared to the fructose group, developing an antioxidative *status* in the açai-fed rats.

The results obtained in this study suggest that açai may improve oxidative stress and NAFLD by regulating glutathione metabolism. Similar results were observed in other models with different polyphenols (13,36,37). This suggests that polyphenols and other nutrient fractions in açai pulp could function to reduce the stressful environment caused by the fructose-rich diet.

Similar to the antioxidant defense system GSH/GSSG, an improvement in the activity of CAT was observed. CAT is an important enzyme which is responsible for the removal of H_2O_2 produced under various stress conditions, while SOD plays an important role in protecting against the toxic effects of superoxide radicals by catalyzing radical dismutation reactions, protecting cells from oxidative-stress-related damage. In view of these findings, it was observed that CAT activity was partially reduced in the açai-fed group, what can be justified by the fact that flavonoids reduce the activity of antioxidant enzymes, particularly CAT, due to an improvement in the redox state.

The administration of a fructose-rich diet resulted in a higher relative mass of the liver in the animals and this can be explained by the fact that the monosaccharide is primarily metabolized in the liver, resulting in increased *de novo* lipogenesis, lipogenic enzymes and gluconeogenesis (31-33). The presence of açai in this model reduced the liver mass and the number of inflammatory cells, and improved ALT activity; in line with this, serum alanine and aspartate aminotransferase (ALT and AST) activities have been associated with the improvement of hepatic steatosis, and lobular inflammation, so their serum activity has been used as a biomarker of liver damage and/or treatment benefits (4).

The liver changes found in our study and described to date were confirmed by histological analysis, since there was a prevalence of fatty macrovesicles in the model group, which are characteristic of NAFLD, as demonstrated elsewhere (31-33,40). The addition of açai also reduced the macrovesicular steatosis levels resulting in the presence of 90% of steatosis grade 1, against 50% in the

presence of açai. This improvement in the severity of macrovesicular steatosis stages was also observed in NAFLD induced by a high-fat diet (14).

Taken together, our results showed that an isocaloric substitution of fructose for starch in rats causes steatosis and inflammation and reduces antioxidant systems in the liver. The açai treatment attenuated the degree of steatosis and inflammation, and improved the response to oxidative stress by increasing the activity of catalase and the GSH/GSSG ratio. Therefore, the present study adds knowledge about açai feasible therapeutic strategy for prevention of NAFLD induced by a fructose-rich diet.

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Trabajo Original

Obesidad y síndrome metabólico

Visceral adiposity index associated with behavioral and inflammatory parameters in adults: a population based study

Índice de adiposidad visceral asociado con parámetros inflamatorios y del comportamiento: estudio transversal de población

Fabírcia Geralda Ferreira^{1,3}, Wellington Segheto², Danielle Cristina Guimarães da Silva³, Patricia Feliciano Pereira³ and Giana Zarbato Longo³

¹Escola Preparatória de Cadetes do Ar- EPCAr. Barbacena, Minas Gerais. Brazil. ²Faculdade Governador Ozanan Coelho – FAGOC. Ubá, Minas Gerais. Brazil. ³Universidade Federal de Viçosa – UFV. Viçosa, Minas Gerais. Brazil

Abstract

Introduction: the visceral adiposity index (VAI) is an indicator of fat distribution and function which is considered a predictor of cardiometabolic risk.

Objective: analyze the factors associated with VAI in Brazilian adults.

Methods: a cross-sectional population-based study was conducted with 854 adults, in Viçosa, MG, Brazil. A questionnaire was applied and anthropometric measurements, body composition and biochemical data were collected. Ordinal logistic regression was used to evaluate the factors associated with VAI.

Results: the increase in percentage of fat, uric acid concentration and ultra-sensitive C reactive protein in the blood was positively associated with VAI in males. The level of physical activity in leisure was negatively associated. Among women, the increase in age, neck circumference, sitting time of more than 300 minutes, increased serum uric acid concentration and ultra-sensitive C reactive protein were associated with VAI.

Conclusion: except for age, all other factors associated with VAI are modifiable, suggesting that adopting early intervention measures that promote changes in habits and alter the risk of increased visceral adiposity and consequently the appearance of comorbidities should be encouraged.

Key words:

Adipose tissue.
Investigation.
Anthropometry.
Comorbidities.

Resumen

Introducción: el índice de adiposidad visceral (VAI) es un indicador de distribución y función de la grasa que se considera un predictor del riesgo cardiometabólico.

Objetivo: analizar los factores asociados con el VAI en adultos brasileños.

Métodos: se realizó un estudio transversal de población con 854 adultos, en Viçosa, MG, Brasil. Se aplicó un cuestionario y se analizaron las medidas antropométricas, la composición corporal y los datos bioquímicos. La regresión logística ordinal se utilizó para evaluar los factores asociados con VAI.

Resultados: el aumento en el porcentaje de grasa, la concentración de ácido úrico y la proteína C reactiva ultrasensible en la sangre se asoció positivamente con VAI en varones. El nivel de actividad física en el ocio se asoció negativamente. Entre las mujeres, el aumento de la edad, la circunferencia del cuello, el tiempo en sedestación de más de 300 minutos, el aumento de la concentración sérica de ácido úrico y la proteína C reactiva ultrasensible se asociaron con VAI.

Conclusión: con excepción de la edad, todos los otros factores asociados con el VAI son modificables, lo que sugiere que debe fomentarse la adopción de medidas de intervención temprana que promuevan cambios en los hábitos y alteren el riesgo de aumento de la adiposidad visceral y, consecuentemente, la aparición de comorbididades.

Palabras clave:

Tejido adiposo.
Investigación.
Antropometría.
Comorbididades.

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Correspondence:

Fabírcia Geralda Ferreira. Departamento de Nutrição e Saúde / CCBII. Av. P.H. Rolfs, s/n. Campus Universitário, 36570-000. Viçosa, MG. Brazil
e-mail: fagefe@yahoo.com.br

INTRODUCTION

The visceral fat component is the adipose tissue compartment most strongly associated with cardiometabolic complications (1-3), but its precise quantification requires high cost imaging studies, making its use in population studies and clinical practice unfeasible. For this reason, there is an increasing search for a simple, inexpensive, and easy-to-apply tool to assess visceral adiposity.

Because excess visceral fat is an independent risk factor for the development of cardiovascular diseases and is related to associated with dyslipidemia, systemic arterial hypertension, insulin resistance, and subclinical inflammation (4,5), the formulation of an indicator that can be routinely applicable is of importance to evaluate this fat as it would allow its wide use.

Recently, the visceral adiposity index (VAI) has been proposed as an indicator of fat distribution and function (6) and considered as a predictor of cardiometabolic risk (7). VAI is gender-specific and takes up simple anthropometric parameters such as waist circumference (WC) and body mass index (BMI), as well as the metabolic parameters triglyceride (TG) and high-density lipoprotein (HDL-c). VAI showed a high correlation with the visceral fat measured by magnetic resonance (6), in addition to association with cardiometabolic risk (8), metabolic syndrome (9), diabetes (10), and hypertension (11).

Population-based studies have not yet been conducted to determine which factors are associated with VAI in the Brazilian adult population and how this occurs, with his gap remaining unexplained. Therefore, the objective of this study was to analyze the association of socioeconomic, demographic, anthropometric, body composition, behavioral and biochemical factors with VAI in Brazilian adults.

MATERIALS AND METHODS

STUDY DESIGN AND SAMPLE CALCULATION

The current research was conducted as a cross-sectional, population-based study from 2012 to 2014. Data were obtained from a research that aimed to evaluate the health conditions of the adult population of Viçosa, Minas Gerais, Brazil. The study was approved by the Ethics Committee in Research of the Federal University of Viçosa (Regulation 02/2013 / CEP / 07.12.13) and its procedures are described in Segheto et al. (12).

Study sample consisted of adult individuals aged 20 to 59 years, of both sexes and living in the urban area of the municipality. For the sample calculation of this outcome, 43,431 individuals were considered as reference population (13), confidence level of 95.0%, expected prevalence of 50%, predicted sample error of 4.5 percentage points, and a design effect of 1.5. The obtained value was added with 10% of losses and refusals and 10% more to control confounding factors, requiring a minimum sample of 844 individuals. As this study is part of a survey that aims to evaluate different outcomes, 854 individuals were included who

had the complete data for the calculation of VAI and $TG \leq 279$ mg/dL and $BMI \leq 40$ kg/m² (14). The sampling process was probabilistic, without replacement, and used a two-stage conglomerate sampling (census and domicile).

DATA COLLECTION

Data collection was carried out in two stages: the first stage was conducted in the domiciles, by applying a structured questionnaire, while the second stage was carried out in the university's premises, using the anthropometric evaluations body composition and biochemical parameters. Initially, a total of 30 census tracts were selected among the 99 existing in the urban area of the municipality, then, the blocks and the starting corner of the data collection were randomly chosen. After identification of the households, all the adults residing in them were invited to participate in the study, considering as criteria for non-inclusion the pregnant women, individuals who were bedridden or unable to undergo anthropometric measurements and those unable to answer the questionnaires.

STUDY VARIABLES

VAI was considered the dependent variable and was calculated from the equations described below (6) and analyzed in tertile.

$$\text{Men: } \left(\frac{WC}{39.68 + (1.88 \cdot BMI)} \right) * \left(\frac{TG}{1.03} \right) * \left(\frac{1.31}{HDL} \right)$$

$$\text{Women: } \left(\frac{WC}{36.58 + (1.89 \cdot BMI)} \right) * \left(\frac{TG}{0.81} \right) * \left(\frac{1.52}{HDL} \right)$$

The socioeconomic, demographic, behavioral, anthropometric, body composition and biochemical characteristics were investigated as independent variables.

The socioeconomic and demographic variables included sex, age group in years, skin color categorized as white and non-white; schooling categorized into 0-4 years, 5-8 years, 9-11 years and ≥ 12 years, marital status categorized as with and without partner, and socioeconomic status grouped into higher (A + B), intermediate (C) and lower (D + E).

The variables related to the behavior were leisure-time physical activity (LTPA) and sedentary behavior. LTPA was evaluated by the International Physical Activity Questionnaire (IPAQ), long form, using the fourth domain. The LTPA was calculated by adding the time spent with moderate physical activities plus twice the time with vigorous activities, within the categories insufficiently active (< 150 minutes of activities in the week) or physically active (≥ 150 minutes of activities) (15). The sedentary behavior was evaluated by the sitting time (ST) calculated by the average of time (minutes) spent sitting on weekdays. TS was categorized into ≤ 300 minutes and > 300 minutes per day.

The anthropometric variables measured were BMI, WC and neck circumference (NC), all in triplicate, using the average. The criteria proposed by the World Health Organization (WHO) (16) were used for BMI. Normal-weight individuals were grouped into the normal weight category. WC and NC were measured respectively at the midpoint between the last rib and the iliac crest and below the laryngeal prominence.

The female body composition was estimated by the triceps, abdominal, and thigh skinfolds, and male body composition by triceps, pectoral and subscapular skinfolds. Skinfold data were used in sex-specific equation to calculate body density (17,18), then the fat percentage was estimated by the Siri equation (19). The skinfolds were measured using a Lange caliper (Cambridge Scientific Industries, Inc., Cambridge, MD), 1 mm precision.

The biochemical variables measured were HDL-c, TG, uric acid (UA) and ultra-sensitive C-reactive protein (us-CRP). Blood samples were collected for dosages after a 12-hour fast by venipuncture using a vacutainer system (Becton Dickinson, UK). HDL-c was measured by the enzymatic colorimetric method, TG and UA with commercial kits and us-CRP by the immunoturbidimetric assay.

STATISTICAL ANALYSIS

Data analysis was conducted using the statistical program Stata (Version 13.1, StataCorp, College Station, Texas). Considering

the complex nature of the sample, the command set “svy” was used, with sample weights assigned to the variables sex, age and schooling (13).

A descriptive analysis was carried out and association was found between the VAI and the independent variables by the ordinal logistic regression. After analyzing the independent variables in the multiple regression model, the variables that were associated with the outcome with $p < 0.05$ were maintained in the final model.

RESULTS

We evaluated 854 individuals, 392 males and 462 females. Regardless of sex, most individuals evaluated were not white (men 57.81% CI 95% 48.01-67.03 and women 60.60% CI 95% 51.83-68.73), had 12 or more years of schooling (men 55.20% CI 95% 40.11-69.38% and women 45.60% CI 95% 33.98-57.70), and were defined as intermediate socioeconomic status (men 63.42% CI95% 56.35-69.95 and women 68.44% CI95% 61.69-74.48) (Table I).

Except for LTPA in the female sex and ST in both sexes, all other parameters evaluated showed a significant difference between the third and the first VAI tertiles (Table II).

The percentage of fat, uric acid and C-reactive protein concentration in the blood were positively and independently associated

Table I. Demographic and socioeconomic characteristics of adults assessed by sex, Viçosa, MG, Brazil, 2012-2014 (n = 854)

Variable	Males		Females	
	Proportion (%)	CI (95%)	Proportion (%)	CI (95%)
Age group (years)				
20-29	39.91	(28.12-52.99)	26.65	(19.47-35.31)
30-39	26.30	(19.70-34.16)	27.24	(23.02-31.92)
40-49	16.99	(11.80-23.85)	27.28	(19.80-36.30)
50-59	16.80	(12.28-22.55)	18.83	(13.73-25.27)
Skin color				
White	42.19	(32.96-51.99)	39.40	(31.27-48.16)
Not white	57.81	(48.01-67.03)	60.60	(51.83-68.73)
Schooling (years)				
0-4	12.27	(5.91-23.73)	19.18	(11.56-30.11)
5-8	13.62	(8.56-20.99)	14.50	(10.76-19.27)
9-11	18.91	(13.41-25.98)	20.72	(17.14-24.82)
≥ 12	55.20	(40.11-69.38)	45.60	(33.98-57.70)
Marital status				
Without partner	50.03	(36.50-63.53)	48.80	(39.14-58.55)
With partner	49.97	(36.46-63.49)	51.20	(41.45-60.85)
Socioeconomic status				
Higher	31.53	(24.60-39.39)	22.51	(16.31-30.21)
Intermediate	63.42	(56.35-69.95)	68.44	(61.69-74.48)
Lower	5.05	(2.26-10.87)	9.05	(5.13-15.47)

CI: confidence interval; ≥ greater than or equal to.

Table II. Distribution (mean $\pm$ SE and 95% confidence interval) of the anthropometric variables, body composition, biochemical and behavioral variables, according to VAI tertiles in adults. Viçosa, MG, Brazil, 2012/2014 (n = 854)

Variable	Tertile 1 of VAI	Tertile 2 of VAI	Tertile 3 of VAI
<i>Age (years)</i>			
Men	31.07 $\pm$ 1.16 (28.69-33.45) ^a	34.53 $\pm$ 1.83 (30.79-38.27) ^{ab}	38.67 $\pm$ 1.68 (35.23-42.12) ^b
Women	34.16 $\pm$ 1.13 (31.84-36.49) ^a	37.43 $\pm$ 1.21 (34.94-39.91) ^{ab}	41.85 $\pm$ 1.36 (39.06-44.64) ^b
<i>NC (cm)</i>			
Men	37.18 $\pm$ 0.22 (36.73-37.61) ^a	38.53 $\pm$ 0.27 (37.98-39.08) ^b	39.08 $\pm$ 0.22 (38.64-39.53) ^b
Women	31.84 $\pm$ 0.14 (31.55-32.12) ^a	32.44 $\pm$ 0.22 (31.98-32.89) ^a	33.85 $\pm$ 0.22 (33.39-34.31) ^b
<i>% Fat</i>			
Men	15.73 $\pm$ 0.74 (14.20-17.25) ^a	20.50 $\pm$ 0.63 (19.21-21.80) ^b	23.22 $\pm$ 0.42 (22.35-24.08) ^c
Women	29.90 $\pm$ 0.58 (28.71-31.08) ^a	32.01 $\pm$ 0.54 (30.90-33.12) ^{ab}	34.23 $\pm$ 0.58 (33.04-35.43) ^b
<i>UA (mg/dL)</i>			
Men	4.35 $\pm$ 0.12 (4.11-4.60) ^a	4.52 $\pm$ 0.11 (4.30-4.74) ^a	4.99 $\pm$ 0.09 (4.80-5.18) ^b
Women	3.03 $\pm$ 0.08 (2.87-3.19) ^a	3.18 $\pm$ 0.07 (3.04-3.33) ^a	3.79 $\pm$ 0.16 (3.48-4.12) ^b
<i>us-CRP (mg/L)</i>			
Men	1.05 $\pm$ 0.13 (0.79-1.31) ^a	1.32 $\pm$ 0.14 (1.02-1.61) ^{ab}	1.64 $\pm$ 0.13 (1.37-1.91) ^b
Women	1.58 $\pm$ 0.16 (1.25-1.91) ^a	1.82 $\pm$ 0.16 (1.49-2.14) ^a	2.58 $\pm$ 0.16 (2.25-2.92) ^b
<i>LTPA (min)</i>			
Men	194.90 $\pm$ 30.29(132.85-256.96) ^a	175.05 $\pm$ 39.06 (95.03-255.07) ^{ab}	82.71 $\pm$ 19.73 (42.29-123.13) ^b
Women	75.33 $\pm$ 15.88 (42.79-107.87)	113.55 $\pm$ 21.26 (70.00-157.10)	69.90 $\pm$ 15.95 (37.23-102.56)
<i>ST (min)</i>			
Men	344.35 $\pm$ 33.68 (275.36-413.33)	334.88 $\pm$ 23.68 (286.36-383.39)	329.31 $\pm$ 12.07 (304.59-354.04)
Women	299.06 $\pm$ 20.27 (257.53-340.59)	274.39 $\pm$ 23.27 (226.52-322.26)	277.58 $\pm$ 23.07 (230.32-324.85)

SE: standard error; VAI: visceral adiposity index - VAI Tertile of men (tertile 1: 0.211-0.889; tertile 2: 0.891-1.667; tertile 3: 1.676-7.840) - VAI Tertile of women (tertile 1: 0.309-1.049; tertile 2: 1.059-1.667; 1.059-1.667; tertile 3: 1.673-1750); NC: neck circumference; %: Percentage; UA: uric acid; us-CRP: ultra-sensitive c-reactive protein; LTPA: leisure-time physical activity; ST: sitting time. Bold numbers and different letters indicate statistical difference.

with VAI in the male sex, while the leisure-time physical activity level was independent and negatively associated with VAI. A positive and independent association was found in females for increase in age, neck circumference, sitting time over 300 minutes, increased uric acid concentration and C-reactive protein in blood (Table III).

DISCUSSION

This is the first study evaluating the association of socioeconomic, demographic, anthropometric, body composition, behavioral and biochemical factors with VAI in Brazilian adults and may serve as a basis for conducting longitudinal studies aimed to assess the risk of increase in VAI and its association with comorbidities.

We found a positive and independent association between VAI and increase in age for women (OR 1.04 CI 95% 1.01-1.07), with a significant increase in age between the third (41.85 $\pm$ 1.361 CI 95% 39.06-44.64) and the first tertiles (34.16 $\pm$ 1.135 95% CI 31.84-36.49) of VAI in both sexes.

Previous studies (20,21) have shown that advancing age leads to an increase in visceral adiposity, reinforcing the need to evaluate this adiposity in different age groups. Possible explanations for this association in women are changes in lifestyle that promote decreased levels of physical activity and consequently change in basal metabolism, as well as changes in hormone levels in particular after menopause (21).

The increase in the percentage of total fat was positively associated in men (OR 1.14 95% CI 1.09-1.18), indicating that an increase in overall adiposity in this group also leads to an increase in visceral adiposity, which may compromise health (22,23).

We found that increase in NC was also positively associated with VAI independently in women (OR 1.28 95% CI 1.15-1.44). NC is a simple marker of upper body adiposity, and a synergistic effect between this measure and visceral adipose tissue with cardiometabolic risk factors was observed in the Framingham Heart Study (24). It is worth noting that fat located in the upper part of the body can cause metabolic abnormalities, increasing circulating free fatty acids, which can lead to insulin resistance (25,26).

Table III. Final model of the ordinal logistic regression for factors associated with the visceral adiposity index in adults. Viçosa, MG, Brazil, 2012-2014 (n = 854)

Variable	Males			Females		
	OR	CI 95%	p	OR	CI 95%	p
Age (years)	—	—		1.04	1.01-1.07	0.003
% fat	1.14	1.09-1.18	< 0.001	—	—	
NC (cm)	—	—		1.28	1.15-1.44	< 0.001
LTPA (min)			0.007			
Inactive	1.00	—		—	—	
Active	0.54	0.35-0.83		—	—	
ST (min)						0.023
≤ 300	—	—		1.00	—	
> 300	—	—		2.10	1.11-3.97	
UA (mg/dL)	1.42	1.14-1.78	0.003	1.50	1.14-1.98	0.006
us-CRP (mg/L)	1.19	1.05-1.35	0.008	1.19	1.06-1.33	0.005

OR: odds ratio; CI: confidence interval; %: Percentage; NC: neck circumference; LTPA: leisure-time physical activity; ST: sitting time; UA: uric acid; us-CRP: ultra-sensitive C-reactive protein.

In our study, we found that being active contributed to a 46% reduction in the chance of increased visceral adiposity among men (OR: 0.54 95% CI 0.35-0.83), constituting a protective factor. LTPA was statistically lower in men who had higher VAIs (82.71 ± 19.73 CI 95% 42.29-123.13) than in those with lower VAI (194.90 ± 30.29 CI 95% 132.85-256.96). Inverse association between LTPA and obesity has previously been demonstrated (27), reinforcing the benefits of an active life in body composition.

Our results also showed that sedentary behavior time > 300 minutes in women was independently and positively associated with VAI (OR 2.10 95% CI 1.11-3.97). Previous studies have shown association between greater time spent in sedentary behavior and greater waist circumference (1.89 95% CI 0.94-2.83 cm) (28), as well as higher risk of overweight and obesity (OR 1.38 95% CI 1.26-1.52) (29). The physiological effect of sedentary behavior promoting unhealthiness may result from the absence of muscle contraction that leads to an increase in triglycerides, plasma glucose and a reduction in lipoprotein lipase activity, which is an enzyme related to the regulation of triglyceride absorption and the production of HDL-c in skeletal muscles (30).

Identifying differences between the sexes in the association of LTPA and sedentary behavior with VAI is important for proposing specific intervention strategies for this adult population. This study suggests that physical activity should be encouraged for men to reduce the chance of increasing VAI, while for women the greatest encouragement should be to decrease sitting time as this more than doubles the chance of increasing VAI.

We observed that in both sexes the increase in UA concentration was positively associated (OR: 1.42 CI 95% 1.14-1.78 in men; OR: 1.50 CI 95% 1.14-1.98 in women). The association between high concentration of UA with factors such as obesity, hypertriglyceridemia, hypertension, diabetes and consequently metabolic syndrome has been demonstrated in the Brazilian adult population (31), as well as a correlation between VAI and UA (9)

in adult Chinese, suggesting the possibility of using VAI to predict inflammation. Recently, an association between increased UA and visceral and subcutaneous adipose tissue was described, but the association was lost when the effect of visceral adipose tissue was controlled (32).

Increase in us-CRP concentration was also positively associated in both sexes (OR: 1.19 95% CI 1.05-1.35 in men; OR: 1.19 CI 95% 1.06-1.33 in women). As us-CRP is a marker for low-grade inflammation, its association with IAV suggests that it may also indicate inflammation. Recent research on the impact of the number of risk factors for metabolic syndrome on the serum concentration of us-CRP in women and men has shown that even in absence of evident disease and pharmacological treatment, individuals with risk factors for metabolic syndrome already have an increased concentration of us-CRP (33). Correlation between VAI and us-CRP in women ($0.19 p < 0.005$) has been previously demonstrated (34), corroborating with our study, as well as the increase observed in us-CRP as the tertile value of VAI increases both in pre-diabetes (OR 2.17 CI 95% 1.40-3.37) and type 2 diabetes (OR 1.17 95% CI 1.16-2.71) (35).

Some limitations of this study are that the transversal design does not allow us to establish a temporal relation between the exposure and the outcome, but this was not the objective of our study. The proportion of selected individuals had no correspondence to data referring to the Viçosa population for sex, schooling, and age, which was corrected by weighing the sample means. Finally, a questionnaire was used to estimate LTPA and quantification of sitting time as an indicator of sedentary behavior was memory dependent. However, we believe that when we evaluated LTPA with a validated questionnaire and took only the last week for the sitting time we were able to minimize these limitations.

Considering the data from this study, we conclude that there is a positive and independent association in men between VAI and the increase in fat percentage, in the concentration of UA

and us-CRP in the blood, whereas a negative association was observed with LTPA. In women, the increase in age and NC, sitting time greater than 300 minutes, increase in AU concentration and us-CRP were the independent factors and positively associated with VAI. With the exception of age, the other factors are modifiable, suggesting that the adoption of early intervention measures that lead to changes in habits may alter the risk of increased visceral adiposity and, consequently, the appearance of comorbidities. However, more research on this topic needs to be undertaken to investigate the factors associated with VAI in different populations.

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Nutrición Hospitalaria



Trabajo Original

Valoración nutricional

¿Puede el índice de masa corporal pregestacional relacionarse con el estado psicológico y físico de la madre durante todo el embarazo?

May pregestational body mass index be related to mother's psychological and physical condition during pregnancy?

Borja Romero-González¹, Rafael A. Caparrós-González^{1,3}, Helen Strivens Vílchez², María Isabel Peralta-Ramírez^{1,4}

¹Centro de Investigación Mente, Cerebro y Comportamiento (CIMCYC). Facultad de Psicología. Universidad de Granada. Granada. ²Departamento de Matronas. Centro de Salud Góngora. Granada. ³Departamento de Ginecología y Obstetricia. Hospital de Poniente. El Ejido, Almería. ⁴Departamento de Personalidad, Evaluación y Tratamiento Psicológico. Facultad de Psicología. Universidad de Granada. Granada

Resumen

Introducción: el índice de masa corporal (IMC) pregestacional afecta a la salud de la madre durante y después del embarazo, y se relaciona con un aumento del riesgo a sufrir diabetes gestacional, preeclampsia o muerte fetal. Además, el IMC pregestacional elevado aumenta los niveles de ansiedad, estrés y depresión, lo que conlleva al aumento de riesgo de aborto, bajo peso al nacer y prematuridad.

Objetivos: comprobar si existen diferencias en estrés, síntomas psicopatológicos y variables fisiológicas durante el embarazo, entre embarazadas con IMC pregestacional normal e IMC pregestacional elevado.

Métodos: han participado 156 mujeres embarazadas evaluadas longitudinalmente durante los tres trimestres de embarazo divididas en dos grupos: grupo con IMC pregestacional normal ($n = 115$) y grupo con IMC pregestacional elevado ($n = 41$). Se midieron niveles de estrés, síntomas psicopatológicos, hipertensión y glucosa.

Resultados: los resultados mostraron que existían diferencias estadísticamente significativas entre los dos grupos en estrés específico del embarazo y en las subescalas del SCL-90-R: depresión, ideación paranoide y la escala de síntomas generales en el primer trimestre; en el segundo trimestre, en estrés específico del embarazo y subescalas (somatizaciones, obsesión compulsión, sensibilidad interpersonal, depresión, ansiedad, ideación paranoide y en las escalas generales; y en estrés percibido) y las subescalas somatizaciones, ansiedad y en la escala SP en el tercer trimestre. También se encontraron diferencias entre ambos grupos en tensión arterial diastólica en el primer trimestre, y en tensión arterial sistólica y diastólica en el tercer trimestre.

Conclusiones: el IMC pregestacional elevado se relaciona con mayor estrés psicológico y con síntomas psicopatológicos y fisiológicos durante el embarazo.

Palabras clave:

Índice de masa corporal. Embarazo. Estrés psicológico. Psicopatología. Ansiedad. Depresión.

Abstract

Introduction: pregestational Body Mass Index (BMI) affects mother's health during and after pregnancy and is related to negative outcomes such as low birth weight and preterm birth. Higher pregestational BMI may increase anxiety, stress and depression.

Objectives: to assess potential differences on stress, psychopathological symptoms and physiological variables during pregnancy, among pregnant women with normal pregestational BMI rates and high pregestational BMI rates.

Methods: a sample of 156 pregnant women were longitudinally assessed during the three trimesters of pregnancy. They were divided into two groups: a group with normal pregestational BMI rates ($n = 115$) and a group with high pregestational BMI rates ($n = 41$). Stress levels, psychopathological symptoms, blood pressure and glucose blood levels were assessed.

Results: in the first trimester, significant differences were found between groups regarding pregnancy-specific stress and some of the SCL-90-R subscales (depression, paranoid ideation and global wellness index). In the second trimester, there were differences regarding pregnancy-specific stress and some of the SCL-90-R subscales (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, paranoid ideation and the general scales, global wellness index and symptoms free). In the third trimester, there were differences between groups regarding perceived stress and some of the SCL-90-R subscales (somatization, anxiety and the general scale symptoms free). Significant differences were found between groups on diastolic blood-pressure in the first trimester, and systolic and diastolic blood-pressure in the third trimester.

Conclusions: higher pregestational BMI is related to higher psychological stress, higher psychopathological symptoms and elevated blood-pressure during pregnancy.

Key words:

Body Mass Index. Pregnancy. Psychological stress. Psychopathology. Anxiety. Depression.

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Correspondencia:

Rafael A. Caparrós-González y Borja Romero-González. Centro de Investigación Mente, Cerebro y Comportamiento. Facultad de Psicología. Universidad de Granada. Campus Universitario de Cartuja s/n. 18071 Granada
e-mail: rcg477@correo.ugr.es; borjaps@correo.ugr.es

INTRODUCCIÓN

El sobrepeso y la obesidad son problemas de creciente preocupación entre la población mundial y española, relacionados con enfermedades cardiovasculares, diabetes mellitus, cáncer y un mayor riesgo de fallecimiento (1). La prevalencia de mujeres españolas con sobrepeso es del 54,6%, con una media de índice de masa corporal (IMC) de 25,8 kg/m² (2,3). Durante el embarazo, aumenta el riesgo de la mujer a sufrir sobrepeso y obesidad, lo cual conlleva un importante riesgo para la salud materna, fetal e infantil (4,5).

Por una parte, la obesidad y el sobrepeso pregestacional aumentan el riesgo de sufrir diabetes gestacional, preeclampsia, hipertensión, nacimiento por cesárea urgente, mayor peso del bebé al nacer, e incluso aumenta el riesgo de muerte fetal (6-8). Por otro lado, el embarazo es un proceso estresante que conlleva importantes cambios en la mujer (9). En este sentido, altos niveles de estrés, así como síntomas de depresión y ansiedad durante el embarazo se han relacionado con un aumento del riesgo de aborto, nacimiento pretérmino y bajo peso fetal. Además, se relaciona con menor neurodesarrollo motor y cognitivo en bebés a los 8 y 12 meses de edad, respectivamente (10-13). De esta forma, conocer la salud psicológica de la embarazada durante todo el embarazo puede favorecer la aplicación de medidas preventivas y mejorar su bienestar (14,15). Por otro lado, niveles elevados de IMC pregestacional se han relacionado con mayores niveles de estrés, depresión y ansiedad durante el embarazo (16-18), así como con un aumento de probabilidad de desarrollar depresión postparto (19). Además, a largo plazo, un IMC superior a 24,9 kg/m² antes del embarazo se ha relacionado con un desarrollo cognitivo menor en el bebé, puntuaciones más bajas en inteligencia a la edad de 6 años y un mayor riesgo de desarrollar trastorno por déficit de atención e hiperactividad (20-22).

Si atendemos a las consecuencias negativas que tiene la obesidad y el sobrepeso pregestacional sobre el embarazo, es necesario investigar qué áreas psicológicas se ven afectadas cuando el IMC pregestacional es superior a 24,9 kg/m² (23-25). Por todo esto, el objetivo de este estudio fue comprobar si existían diferencias en los niveles de estrés psicológico, síntomas psicopatológicos y variables fisiológicas a lo largo del embarazo, en un grupo de participantes con IMC pregestacional normal *versus* un grupo de gestantes con IMC pregestacional superior a la norma.

MÉTODOS

PARTICIPANTES

Un total de 170 mujeres embarazadas dieron su consentimiento para participar en este estudio. Tres tuvieron un aborto espontáneo y 11 manifestaron su deseo de abandonar su participación en el estudio, alegando falta de tiempo. Finalmente, 156 mujeres embarazadas con edades comprendidas entre 21 y 44 años (*media* [*M*] = 32,44; *desviación típica* [*DT*] = 4,95) fueron evaluadas longitudinalmente durante el primer trimestre (*M* =

11,90 semanas de gestación; *DT* = 3,65), segundo trimestre (*M* = 25,16 semanas de gestación; *DT* = 3,34) y tercer trimestre de embarazo (*M* = 34,87 semanas de gestación; *DT* = 3,34). Las participantes pertenecían al Centro de Salud Góngora, del Servicio Andaluz de Salud de Granada.

Los criterios de inclusión fueron: ser mayor de 18 años, dominio del idioma castellano (escrito, hablado, comprensión oral y escrita) y llevar un seguimiento del embarazo en la sanidad pública. Como criterio de exclusión se encontraba tener un IMC inferior a 18,5 kg/m² antes del embarazo, debido a los objetivos de la investigación.

Las participantes fueron divididas en dos grupos: un grupo con IMC pregestacional elevado (superior a 24,9 kg/m²) y otro grupo con IMC pregestacional normal (inferior a 24,9 kg/m²).

Las embarazadas que estaban interesadas en participar leyeron la hoja de información del estudio y firmaron un documento de consentimiento informado. El estudio se rigió por las normas éticas según la Declaración de Helsinki (revisada en Fortaleza, Brasil, 2013), y fue revisado y aprobado por el comité de ética para la investigación humana de la Universidad de Granada (referencia 881) y el Comité de ética de investigación del área sanitaria pública de Granada.

INSTRUMENTOS

Se recogió información acerca de variables sociodemográficas y obstétricas del Documento de Salud de la Embarazada (26), el cual contiene información acerca del embarazo y ofrece una valoración del riesgo obstétrico, antecedentes médicos, historia obstétrica, gestación actual, diagnóstico prenatal, visitas tanto concertadas como urgentes, visita puerperal e información fetal por medio de diagnóstico ecográfico. Además, se llevó a cabo una evaluación psicológica, los siguientes instrumentos:

– *Cuestionario de preocupaciones prenatales*, PDQ (27,28).

Este instrumento evalúa el estrés específico del embarazo mediante preguntas relacionadas con preocupaciones de la madre, en relación con su embarazo, problemas médicos, síntomas físicos, cambios corporales, crianza de los hijos, parto y nacimiento, relaciones interpersonales y salud del bebé. Está compuesto de 12 ítems de respuesta tipo Likert, que varían desde 0 (en absoluto) a 4 (en extremo). El coeficiente de fiabilidad alfa de Cronbach de la versión española es de $\alpha = 0,71$ (28).

– *Cuestionario de 90 síntomas*, SCL-90-R (29,30). Mediante 90 ítems, que se responden en una escala Likert de cinco opciones, donde 1 es nada y 5 es mucho, evalúa el malestar subjetivo percibido por la persona. El cuestionario aporta información de nueve dimensiones primarias (somatizaciones, obsesión compulsión, sensibilidad interpersonal, depresión, ansiedad, hostilidad, ansiedad fóbica, ideación paranoide y psicoticismo). Además, el cuestionario incluye tres índices globales de malestar psicológico: índice global de sintomatología general (IGS), total de síntomas positivos (SP) e índice de malestar positivo (PSDI). Las nueve dimensiones muestran

una fiabilidad adecuada, con una consistencia interna en el alfa de Cronbach de entre 0,81 y 0,90 (30).

- *Escala de estrés percibido*, EEP-14 (31,32). Evalúa el grado en que diferentes situaciones de la vida se perciben como estresantes, a través de 14 ítems a responder en una escala Likert. Permite cinco opciones de respuesta (0: nunca; 4: muy a menudo) y la puntuación total oscila entre 0 y 56, donde a mayor puntuación, mayor nivel de estrés percibido. La escala ha demostrado una fiabilidad adecuada, con una alta consistencia interna (alfa de Cronbach = 0,81) (32).
- *Tensión arterial*. Se evalúa mediante manguitos de tensión tanto la tensión arterial sistólica como la diastólica.
- *Prueba O'Sullivan*. Prueba de glucosa en sangre que sirve de cribado para la diabetes mellitus gestacional. Se realiza en el segundo trimestre de embarazo.

PROCEDIMIENTO

Las participantes eran captadas cuando atendían a su primera visita de control de embarazo con su matrona, correspondiente al primer trimestre de su embarazo. En este momento, se les informaba del estudio y se les hacía entrega de la hoja de información. Aquellas que manifestaron su deseo de participar leían y firmaban el documento de consentimiento informado. Además, ofrecieron información acerca de su peso antes de quedarse embarazadas y de su talla, se registró en el Documento de Salud de la Embarazada (26) y esto sirvió para calcular el IMC pregestacional de cada participante.

Durante cada visita trimestral, la matrona les hacía entrega de los instrumentos psicológicos (PDQ, SCL-90R, PSS). Dicha batería se aplicaba tres veces durante todo el embarazo, coincidiendo con su revisión trimestral. Los datos médicos se registraron igualmente en el Documento de Salud de la Embarazada (26), del cual se tomaron los correspondientes a tensión arterial y niveles de glucosa en sangre para su posterior análisis.

ANÁLISIS DE DATOS

Con el objetivo de comprobar si los grupos estaban igualados en las principales variables sociodemográficas y obstétricas, se realizó la prueba *t* de *Student* para muestras independientes en el caso de variables continuas. En el caso de variables categóricas, se utilizó la prueba Chi cuadrado para muestras independientes. Las variables dependientes fueron las variables sociodemográficas, obstétricas, fisiológicas y las puntuaciones en cada uno de los cuestionarios psicológicos (PDQ; SCL-90-R; PSS) en los tres trimestres de gestación; la variable independiente fue el IMC previo al embarazo, con dos niveles (IMC pregestacional normal e IMC pregestacional elevado).

Para comprobar si existían diferencias entre los dos grupos (normopeso *versus* sobrepeso) respecto a las diferentes puntuaciones en los cuestionarios psicológicos utilizados, se llevaron a cabo diferentes *t* de *Student*.

Finalmente, se realizaron distintas pruebas *t* de *Student* para comprobar si existían diferencias entre ambos grupos en algunas variables médicas, como hipertensión o glucosa en sangre.

Todos los análisis estadísticos se realizaron con *Statistical Package for Social Sciences* versión 20.0 para Mac (SPSS, Armonk, New York).

RESULTADOS

DESCRIPCIÓN DE LA MUESTRA

La muestra incluida en el estudio fue de 156 participantes, que se dividieron en dos grupos: uno con IMC pregestacional normal ($M = 21,22 \text{ kg/m}^2$; $DT = 2,04$), compuesto por 115 participantes; y otro grupo con IMC pregestacional elevado ($M = 26,31 \text{ kg/m}^2$; $DT = 1,65$), formado por 41 participantes. En la tabla I se muestran las puntuaciones de IMC pregestacional, primer trimestre, segundo trimestre y tercer trimestre de embarazo, además de los datos sociodemográficos y de historia obstétrica de ambos grupos. Habría que destacar que existieron diferencias estadísticamente significativas entre los dos grupos en la puntuación IMC durante todo el embarazo: pregestacional ($t = -8,64$; $p \leq 0,02$) y en las puntuaciones IMC del primer trimestre ($t = -8,81$; $p \leq 0,02$), segundo trimestre ($t = -4,08$; $p \leq 0,02$), y tercer trimestre ($t = -3,89$; $p \leq 0,02$). Ambos grupos estaban igualados en las principales variables sociodemográficas y obstétricas evaluadas (Tabla I).

RELACIÓN DEL ÍNDICE DE MASA CORPORAL PREGESTACIONAL CON ESTRÉS A LO LARGO DEL EMBARAZO

Con respecto a las puntuaciones medias en estrés percibido en relación con el IMC pregestacional, aunque las puntuaciones en estrés fueron mayores en el grupo con IMC pregestacional elevado durante los tres trimestres de embarazo, solo se encontraron diferencias estadísticamente significativas en el tercer trimestre de embarazo ($t = -3,83$; $p \leq 0,02$). Del mismo modo, las puntuaciones obtenidas en el instrumento de estrés específico del embarazo son mayores en el grupo IMC pregestacional elevado frente a las de IMC pregestacional normal a lo largo de todo el embarazo, y son estadísticamente significativas en primer trimestre ($t = -2,33$; $p \leq 0,02$) y segundo trimestre ($t = -2,32$; $p \leq 0,02$) (Tabla II).

RELACIÓN DEL ÍNDICE DE MASA CORPORAL PREGESTACIONAL CON SÍNTOMAS PSICOPATOLÓGICOS A LO LARGO DEL EMBARAZO

En la fig. 1 se representa el perfil psicopatológico en las distintas subescalas y escalas generales del SCL-90-R durante los tres trimestres de embarazo. En el primer trimestre, las puntuaciones

Tabla I. Diferencias en puntuaciones de IMC, variables sociodemográficas e historia obstétrica entre mujeres con IMC pregestacional normal e IMC pregestacional elevado

		IMC normal X (DT)/%	IMC elevado X (DT)/%	Test de contraste*	p
Puntuaciones de IMC					
Pregestacional		21,22 (2,04)	26,31 (1,65)	-8,64	0,00
Primer trimestre		22,99 (2,44)	26,85 (1,21)	-8,81	0,00
Segundo trimestre		23,40 (1,31)	27,40 (0,43)	-4,08	0,00
Tercer trimestre		24,50 (1,43)	28,79 (1,33)	-3,89	0,00
Variables sociodemográficas					
Edad		32,31 (4,74)	32,80 (5,54)	-0,54	0,58
Nacionalidad	Española	95 (75,40%)	31 (24,60%)	7,29	0,39
	Inmigrante	20 (66,70%)	10 (33,30%)		
Estado civil	Soltera/separada/viuda	3 (50%)	3 (50%)	5,40	0,14
	Casada/en pareja	112 (74,70%)	38 (25,30%)		
Situación laboral	Trabajando	88 (75,90%)	28 (24,10%)	4,52	0,34
	Desempleada	27 (63,90%)	13 (36,10%)		
Nivel educativo	Primario	2 (25%)	6 (75%)	12,19	0,34
	Secundario	30 (68,20%)	14 (31,80%)		
	Universitario	83 (79,80%)	21 (20,20%)		
	Sin estudios	0 (0%)	0 (0%)		
Deporte	Sí	61 (77,20%)	18 (22,80%)	1,01	0,36
	No	54 (70,10%)	23 (29,90%)		
Tabaco	Sí	8 (53,30%)	7 (46,70%)	3,55	0,07
	No	107 (75,90%)	34 (24,10%)		
Alcohol	Sí	2 (50%)	2 (50%)	1,19	0,28
	No	113 (74,30%)	39 (25,70%)		
Historia obstétrica*					
Número de hijos	0	76 (82,60%)	16 (17,40%)	-0,92	0,58
	1 o más	39 (60,90%)	25 (39,10%)		
Embarazo deseado	Sí	105 (74,30%)	36 (25,70%)	0,42	0,51
	No	10 (66,70%)	5 (33,30%)		
Método de embarazo	Natural	103 (75,20%)	34 (24,80%)	3,12	0,21
	Artificial	12 (63,20%)	7 (36,80%)		
Abortos previos	0	84 (77,80%)	24 (22,20%)	-1,67	0,10
	1 o más	31 (64,60%)	17 (35,40%)		

Nivel de significación $p \leq 0,02$. *Los estadísticos reflejan t de Student para variables cuantitativas y test Chi cuadrado para variables categóricas.

medias del grupo con IMC pregestacional elevado son mayores en todas las subescalas y escalas generales. Sin embargo, solo se encontraron diferencias estadísticamente significativas entre grupos en las subescalas de depresión ($t = -2,35$; $p \leq 0,02$), ideación paranoide ($t = -2,00$; $p \leq 0,05$), y la escala general PSDI ($t = -2,75$; $p \leq 0,02$).

En el segundo trimestre, las mujeres con IMC pregestacional elevado mostraron mayores puntuaciones medias en todas las

subescalas y escalas generales del SCL-90-R. De igual forma, se hallaron diferencias estadísticamente significativas entre grupos, en las subescalas de somatizaciones ($t = -2,30$; $p \leq 0,02$), obsesión compulsión ($t = -2,14$; $p \leq 0,05$), sensibilidad interpersonal ($t = -2,06$; $p \leq 0,05$), depresión ($t = -2,05$; $p \leq 0,05$), ansiedad ($t = -2,02$; $p \leq 0,05$), ideación paranoide ($t = -2,94$; $p \leq 0,02$), y en las escalas generales IGS ($t = -2,38$; $p \leq 0,02$) y SP ($t = -2,37$; $p \leq 0,02$).

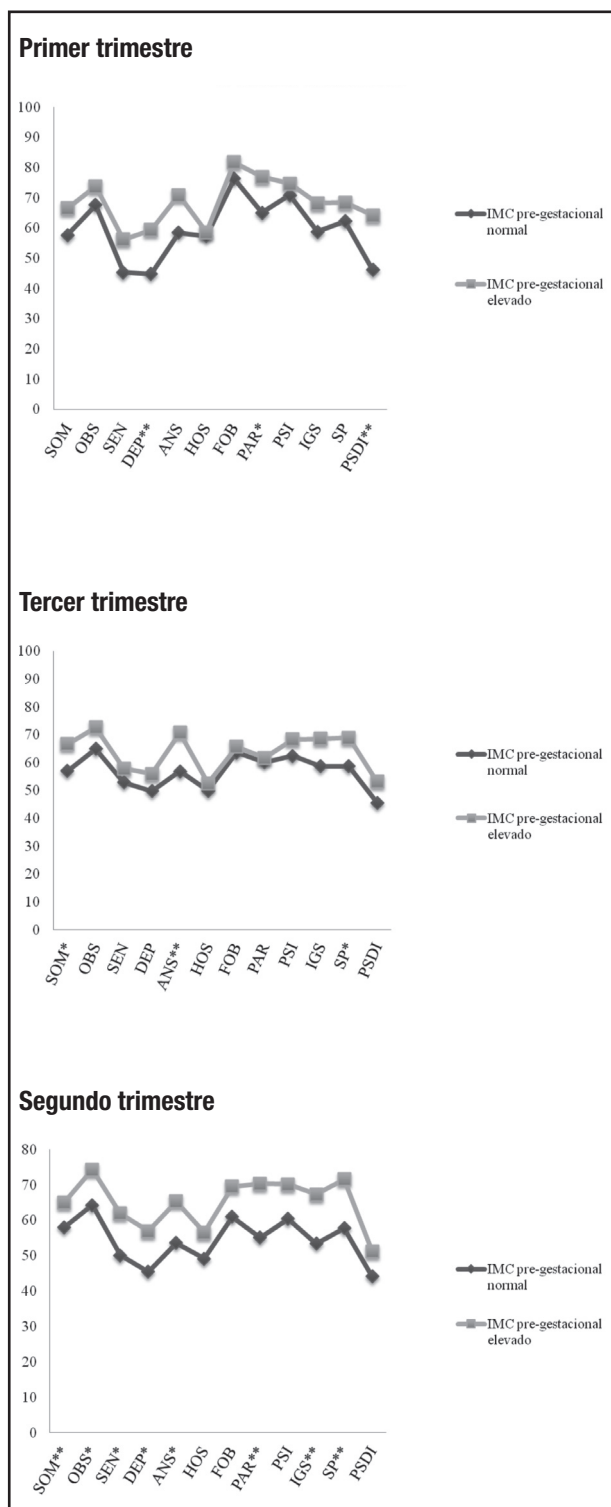


Figura 1.

Perfil psicopatológico del SCL-90-R de embarazadas en primer, segundo y tercer trimestre, según IMC pregestacional normal o elevado (*Nivel de significación $p \leq 0,05$; ** $p \leq 0,02$; ***SOM = somatizaciones; OBS = obsesión compulsión; SEN = sensibilidad interpersonal; DEP = depresión; ANS = ansiedad; HOS = hostilidad; FOB = ansiedad fóbica; PAR = ideación paranoide; PSI = psicoticismo; IGS = índice de sintomatología general; SP = índice total de síntomas positivos; PSDI = índice de malestar positivo).

De igual modo, en el tercer trimestre, las puntuaciones medias en las subescalas del SCL-90-R son mayores en el grupo con IMC pregestacional elevado con respecto al grupo IMC pregestacional normal. Estas diferencias son estadísticamente significativas en las subescalas de somatizaciones ($t = -2,08$; $p \leq 0,05$), ansiedad ($t = -2,96$; $p \leq 0,02$) y en la escala general SP ($t = -2,00$; $p \leq 0,05$).

RELACIÓN DEL ÍNDICE DE MASA CORPORAL PREGESTACIONAL CON TENSIÓN ARTERIAL Y NIVELES DE GLUCOSA

Las pruebas realizadas a lo largo del embarazo muestran mayores niveles de tensión arterial sistólica (TAS) y tensión arterial diastólica (TAD) en el grupo de IMC pregestacional elevado, siendo estas diferencias estadísticamente significativas en los niveles de TAD en el primer trimestre ($t = -2,27$; $p \leq 0,02$), en TAS ($t = -2,08$; $p \leq 0,05$) y en TAD ($t = -2,43$; $p \leq 0,02$) en el tercer trimestre. No se encontraron diferencias entre ambos grupos en el nivel de glucosa medido en el segundo trimestre. Estos resultados se muestran en la tabla III.

DISCUSIÓN

Dada la demostrada importancia del IMC de la embarazada por sus implicaciones en el proceso de embarazo, el objetivo de este estudio fue profundar sobre la relación de este con variables psicológicas; en concreto, conocer si existen diferencias en los niveles de estrés y síntomas psicopatológicos entre las mujeres que presentan un IMC pregestacional superior y las que tienen un IMC normal antes del embarazo. Los resultados han mostrado que existen diferencias en los niveles de estrés específico del embarazo entre ambos grupos en el primer y segundo trimestre, además de diferencias en los niveles de estrés percibido en el tercer trimestre.

En lo que respecta a los síntomas psicopatológicos, ambos grupos muestran diferentes puntuaciones en las subescalas a través de todo el embarazo. En concreto, encontramos diferencias en depresión, ideación paranoide y escala general PSDI en el primer trimestre. Aumentan las diferencias entre los dos grupos en el segundo trimestre de embarazo, donde encontramos diferencias en somatizaciones, obsesión compulsión, sensibilidad interpersonal, depresión, ansiedad, ideación paranoide y las escalas generales IGS y SP. En el tercer trimestre, ambos grupos se igualan más, al mostrar mayores puntuaciones únicamente en las subescalas de somatización, ansiedad y la escala general SP. Habría que añadir que en lo que respecta a variables fisiológicas, se encontraron mayores niveles de tensión arterial diastólica en el primer trimestre, y mayor tensión arterial sistólica y diastólica en el tercer trimestre en el grupo de mayor IMC pregestacional.

En primer lugar, en relación con las diferencias encontradas en los niveles de estrés percibido y estrés específico del embarazo, estos datos están en concordancia con los encontrados por Laraia y cols. (16) en su estudio transversal, donde muestran que

Tabla II. Diferencias en estrés percibido y estrés específico del embarazo entre mujeres con IMC pregestacional normal e IMC pregestacional elevado

Trimestres	Cuestionarios	IMC normal X (DT)	IMC elevado X (DT)	t	*
Trimestre 1	EEP	26,93 (2,16)	27,56 (1,80)	-1,30	0,19
	PDQ	14,60 (5,72)	18,48 (7,64)	-2,33	0,02**
Trimestre 2	EEP	26,81 (1,61)	27,14 (1,62)	-1,06	0,19
	PDQ	13,10 (5,29)	15,53 (6,30)	-2,32	0,02**
Trimestre 3	EEP	26,66 (1,55)	27,88 (2,22)	-3,83	0,00**
	PDQ	14,31 (5,78)	16,05 (5,94)	-1,66	0,09

*Nivel de significación $p \leq 0,05$; ** $p \leq 0,02$; ***EEP = escala de estrés percibido; PDQ = cuestionario de preocupaciones prenatales.

Tabla III. Diferencias en tensión arterial y glucosa entre mujeres con IMC pregestacional normal e IMC pregestacional elevado

Trimestres	Pruebas	IMC normal X (DT)	IMC elevado X (DT)	t	*
Trimestre 1	TAS	108,09 (11)	112,14 (12,02)	-1,40	0,16
	TAD	64,62 (10,32)	70,29 (7,81)	-2,27	0,02**
Trimestre 2	TAS	107,15 (14,04)	109,56 (10,80)	-,62	0,53
	TAD	64,38 (9,67)	67,19 (6,91)	-1,72	0,28
	Glucosa	106,98 (30,06)	114,31 (26,40)	-,79	0,43
Trimestre 3	TAS	108,88 (10,81)	113,80 (12,20)	-2,08	0,03*
	TAD	65,63 (11,08)	71,34 (10,67)	-2,43	0,01**

*Nivel de significación $p \leq 0,05$; ** $p \leq 0,02$; ***TAS = tensión arterial sistólica; TAD = tensión arterial diastólica. Glucosa expresada en mg/dL.

los niveles de estrés percibido, medidos antes de la semana 20 de gestación, son mayores en mujeres con un alto IMC previo al embarazo. Sin embargo, este estudio no permite conocer los niveles de estrés percibido de manera longitudinal a lo largo del embarazo, por lo que nuestro estudio da un paso más y nos permite conocer qué trimestre es en el que esta población puede ser especialmente vulnerable. Además, nuestro estudio es el primero que muestra la relación entre el IMC pregestacional y el estrés específico del embarazo, y en el que se encuentra que las mujeres de un alto IMC pregestacional muestran mayores niveles de estrés en el primer y segundo trimestre. Sin embargo, hay que destacar que las diferencias que se han encontrado entre ambos instrumentos de estrés no concuerdan. Esto podría deberse al instrumento usado, ya que en el estrés específico del embarazo se evalúan preocupaciones de la madre directamente relacionadas con el embarazo, mientras que en el cuestionario de estrés percibido, el nivel de estrés evaluado es general y no específico de esta población. Es importante destacar que existe aval científico de que el estrés específico del embarazo está relacionado de manera más potente con resultados negativos, como el aumento de riesgo de aborto, nacimiento pretérmino y bajo peso fetal que el propio estrés general (10); por lo que cabe esperar que usando este tipo

de instrumentos la información recogida sea más adecuada a la población que se está evaluando. Esto es, usar un instrumento para medir estrés específico del embarazo puede detectar estos niveles de estrés, que no serían captados con instrumentos de estrés general.

En lo que respecta a los síntomas psicopatológicos, la tendencia general que se muestra en los tres trimestres es que las embarazadas con un IMC pregestacional elevado tienen un estado psicológico más afectado durante su embarazo, pues las puntuaciones son mayores durante todos los trimestres. Además, durante el segundo trimestre se encuentran más diferencias entre ambos grupos. El segundo trimestre es en el que la mujer embarazada se encuentra en el nivel más óptimo de su embarazo. Probablemente esta sea la razón por la que se encuentran dichas diferencias, ya que las mujeres que presentan un IMC pregestacional elevado muestran puntuaciones altas en psicopatología en numerosas subescalas, mientras que las mujeres con un IMC normal muestran unos síntomas psicopatológicos iguales a la media de la población.

En concordancia con nuestros hallazgos, estudios previos muestran un incremento durante la gestación en los niveles de ansiedad y depresión cuando la mujer tiene un IMC pregestacional

elevado (17,18,33). Sin embargo, estos estudios son transversales, y pierden por tanto información sobre la evolución de los síntomas psicopatológicos durante todo el embarazo, como es el caso de nuestra investigación. Nuestros resultados han mostrado una amplia variedad de síntomas psicopatológicos que se ven afectados durante el embarazo cuando el IMC pregestacional es elevado, que no se limitan exclusivamente a procesos de ansiedad y depresión. Por esto, es imprescindible prestar atención a estos síntomas psicopatológicos durante el embarazo, con el fin de prevenir consecuencias negativas.

Respecto a las complicaciones médicas asociadas al IMC pregestacional elevado, nuestros resultados concuerdan con los encontrados por Bodnar y cols. (34), pues se asocia un mayor IMC pregestacional con el aumento de la tensión arterial durante el embarazo. Por su parte, los niveles de glucosa en sangre no muestran diferencias estadísticamente significativas entre ambos grupos, a pesar de que otros autores sí muestran dicha relación (6). No obstante, son dos variables que deben ser controladas durante el embarazo para evitar consecuencias negativas.

A pesar de los resultados encontrados, y aunque el número de embarazadas incluidas en el estudio es alto, sería interesante haber incluido un número mayor de muestras con el fin de conseguir mayor número de mujeres en el grupo de IMC pregestacional elevado. Para futuras investigaciones sería interesante comprobar también cómo se relaciona el IMC de la madre con la evolución del bebé. En concreto, se podría realizar un seguimiento en el tiempo para comprobar si los hijos de mujeres con IMC pregestacional elevado tienen algunas áreas del desarrollo más pobremente desarrolladas, o si presentan dificultades del aprendizaje e incluso trastornos psicológicos. Además, podrían estudiarse las consecuencias psicológicas de un IMC pregestacional inferior a 18,5 kg/m².

Es de gran importancia conocer cómo afecta el IMC previo al embarazo a la mujer, pues estos resultados muestran que un IMC superior al normal conlleva en sí mismo un deterioro psicológico, no solo en términos de estrés percibido, ansiedad y depresión, sino también en estrés específico del embarazo y en un amplio rango de síntomas psicopatológicos, así como variables sanitarias. Dicho deterioro psicológico y de la salud puede provocar consecuencias negativas tanto para la mujer como para el feto, e incluso para el bebé a corto y largo plazo (10-13). Además, la condición psicológica de la mujer embarazada sana se ve alterada por cambios hormonales, debido a que esta etapa es una fuente de estrés y ansiedad (9). Por esto, en casos en los que está presente un IMC superior al normal, el bienestar psicológico se ve aún más afectado, que puede derivar en psicopatologías clínicas.

Los resultados de este estudio tienen importantes repercusiones a nivel clínico, en concreto en el ámbito de la prevención. De este modo, es necesario que la población sea sensible al papel del sobrepeso y su importancia en la evolución del embarazo tanto a nivel físico como a nivel psicológico en la mujer embarazada. Para ello es clave la sensibilización del personal sanitario, que proporcione información basada en consejos dietéticos acerca de su peso y sobre su alimentación, incluso elaborando una dieta personalizada durante su embarazo en los casos en que sea

necesario. De esta forma podrían reducirse las consecuencias negativas derivadas de tener un peso superior al normal (35,36). Es indispensable que tanto los profesionales de la salud como las propias mujeres adquieran conciencia de lo importante que es un peso adecuado antes de quedarse embarazadas, y de su control a lo largo del embarazo.

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Trabajo Original

Valoración nutricional

Dual energy X-ray absorptiometry (DXA) reliability and intraobserver reproducibility for segmental body composition measuring

Reproducibilidad de la absorciometría dual de rayos X (DXA) y la reproducibilidad intraobservador para la medición de la composición corporal segmentaria

Osvaldo Costa Moreira^{1,2}, Cláudia Eliza Patrocínio de Oliveira^{1,3} and José Antonio de Paz¹

¹Institute of Biomedicine (IBIOMED). Universidad de León. León, Spain. ²Institute of Biological Science and Health. Federal University of Viçosa. Campus Florestal. Florestal, Minas Gerais. Brazil. ³Department of Physical Education. Federal University of Viçosa. Viçosa, Minas Gerais. Brazil

Abstract

Background: the measurement precision of body composition can interfere on the diagnosis and prescription of diseases' treatment. Furthermore, with regard to dual energy X-rays absorptiometry (DXA), there may be important differences between the measures of regions of interest (ROI) automatically performed by DXA or manually by an evaluator, which can cause measurement error and influence the evaluation or diagnosis.

Aim: thus, this study aimed to evaluate the measurement reliability of body composition by DXA and intraobserver reproducibility for the ROI measurement.

Methods: a total of 15 young adults were subjected to two full-body scans by DXA, under the same conditions. The first scan of all volunteers was chosen and the extent of the ROI was performed, in two stages, separated by a period of 2 weeks, by a single trained evaluator. The coefficient of variation (CV) and intraclass correlation coefficient (ICC) were calculated with a significance level of $p < 0.05$.

Results: high-precision measurements of DXA for whole body mass (ICC = 0.999; CV = 2.3%), fat mass (ICC = 0.998; CV = 1.6%), lean mass (ICC = 0.995; CV = 0.3%) and bone mineral content (ICC = 0.996; CV < 0.1%) were obtained. Further, it was observed high intraobserver reproducibility for ROI measurement, with ICC values ranging between 0.952 and 0.999.

Conclusion: body composition measurement by DXA presents high reproducibility for whole body mass, fat mass, lean mass and bone mineral content and also high intraobserver reproducibility for the ROI measurement.

Key words:

Densitometry.
Reliability of results.
Reproducibility
of results. Body
composition. Bone
mineral density.

Resumen

Introducción: la precisión de las medidas de la composición corporal puede interferir en el diagnóstico y prescripción del tratamiento de las enfermedades. Además, con respecto a la absorciometría dual de rayos X (DXA), pueden existir diferencias importantes entre las medidas de regiones de interés (ROI) realizadas automáticamente por DXA o manualmente por un evaluador, lo que puede causar error de medición e influir en la evaluación o diagnóstico.

Objetivo: evaluar la reproducibilidad de la medida de la composición corporal por DXA y la reproducibilidad intraobservador para la medición de las ROI.

Métodos: quince adultos jóvenes fueron sometidos a dos exploraciones de cuerpo completo por DXA, en las mismas condiciones. Se escogió la primera exploración de los voluntarios y se realizó la extensión de las ROI en dos etapas, separadas por un periodo de 2 semanas, por un solo evaluador capacitado. El coeficiente de variación (CV) y el coeficiente de correlación intraclase (ICC) se calcularon con un nivel de significación de $p < 0,05$.

Resultados: la DXA presentó alta precisión para las medidas de la masa corporal total (ICC = 0.999, CV = 2.3%), masa grasa (ICC = 0.998, CV = 1.6%), masa magra (ICC = 0.995, CV = 0.3%) y hueso (ICC = 0.996, CV < 0,1%). Además, se observó una alta reproducibilidad intraobservador para la medida de las ROI, con valores de ICC entre 0,952 y 0,999.

Conclusión: la medida de la composición corporal por DXA presenta alta reproducibilidad para todos los componentes y también alta reproducibilidad intraobservador para la medida de las ROI.

Palabras clave:

Densitometría.
Fiabilidad de
los resultados.
Reproducibilidad
de los resultados.
Composición
corporal. Densidad
mineral ósea.

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Correspondence:

Osvaldo Costa Moreira. Institute of Biomedicine (IBIOMED). Universidad de León. Campus Universitario de Vegazana, 24071 León, Spain
e-mail: osvaldo.moreira@ufv.br

INTRODUCTION

Body composition, admittedly plays a key role in the health/disease process, since its components have, among others, metabolic functions that may be involved in the prevention or genesis of various diseases (1-5). In this sense, the precise measurement or monitoring of fat mass (FM), lean mass (LM) or bone mineral content (BMC) can have significant clinical application, once can interfere in the diagnosis and prescription of drug or non-drug treatment (6,7).

Based on this premise, a recent systematic review (8) indicates that the dual energy X-ray absorptiometry (DXA) is being considered the new gold standard for measuring body composition, due to its high correlation with the methods of the MRI and computed tomography and present better cost benefit compared to these methods. This is making to engage yourself in some studies to analyze the reliability of measurements of the apparatus for body composition assessment (9-14). However, these studies only analyze the data relating to measures total body and not providing accurate information about DXA to measure segmental body composition.

Segmental body composition is measured by DXA defining regions of interest (ROI) (15), which can be automatically set by the apparatus or manually by the observer. Both definitions can lead to errors which, in turn, can interfere with the measurement result. In this sense, none of the studies reviewed had dedicated to analyze if assessing the measurements of ROI made by the same evaluator are accurate or not.

Therefore, this study aimed to evaluate the reliability of the measurement of body composition by DXA and intraobserver reproducibility for the measurement of ROI.

METHODS

SAMPLE

The sample included 15 young adults, males, apparently healthy and physically active who volunteered for the study. None of the volunteers reported use of drugs or any substance that could interfere with the results of the measures.

Before any test, all volunteers were informed of the possible risks and objectives of the study and signed informed consent to partic-

ipate. All assessment procedures were done in the Exercise Physiology Laboratory of the Department of Biomedical Sciences at the University of León. The procedures used in this work were approved by the Ethics Committee of the University of León, in accordance with the ethical principles expressed in the Declaration of Helsinki.

PROCEDURES

To set the measurements precision, both the apparatus used and the evaluator who performed the measurements of the ROI, was conducted the design presented in figure 1.

To check the reproducibility of DXA to measure body composition, the volunteers were subjected to two full-body scans by DXA using a densitometer General Electric, model Lunar Prodigy and the software Encore 2009, version 13.0. Before conducting the exploration, the equipment has been calibrated.

The two scans of each volunteer were done after stand by for 30 minutes and under the same conditions. In the first whole body scan (S1) by DXA, the volunteer laid in supine position on the device, with upper limbs extended and parallel to the trunk, hands pronated and supported on the device. The lower limbs were also extended, with standard separation at hip width and secured by a tape that held his ankles. They were instructed to remain as still as possible for the duration of the scan (10,15,16). After the end of the first scan, it was requested to the volunteer stands up and lies down again on device, keeping the same body position of the first scan. From there, the second exploration proceeded with another whole body scan (S2) by DXA. Each scan took about seven minutes and from S1 and S2, an automatic calculation of DXA outcome parameters (TBM, FM, LM, BMC) was achieved. For each subject, the following outcome parameters were obtained: TBM_{S1} , FM_{S1} , LM_{S1} , BMC_{S1} , TBM_{S2} , FM_{S2} , LM_{S2} , BMC_{S2} . Using these outcome parameters, were calculated the coefficient of variation (CV), the interclass correlation coefficient (ICC) and its 95% confidence interval (CI95%).

To measure the intraobserver reproducibility for ROI measures, in two different days (D1 and D2, seven to twenty days between both readings), one expert manually defined ROIs on the S1. Then, the body was divided into 16 ROI, determined based in some anatomical points, as follows:

- *Foot*: it was considered as part of the bottom edge of the distal phalanx of the hallux to the line drawn on the medial

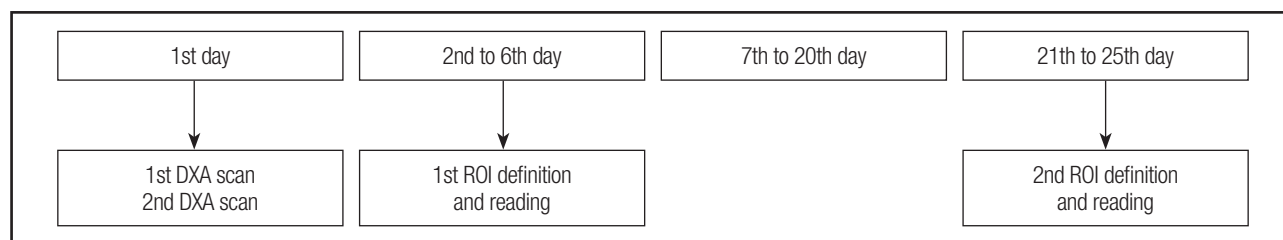


Figure 1.

Summary of the methodological design used in this study.

and lateral malleolus of tibiotalar joint. The medial and lateral boundaries of the ROI were made so that encompasses all soft tissue. The same points were considered for the right and left feet.

- *Leg*: it was measured starting from the line drawn on the medial and lateral malleolus of tibiotalar joint to the line drawn at the lower edge of the medial and lateral condyles of the knee joint. The medial and lateral boundaries of the ROI were made so that encompasses all soft tissue. The same points were considered for the right and left legs.
- *Thigh*: it was measured from the line drawn at the lower edge of the medial and lateral condyles of the knee joint to the lower edge of the ischium. The medial and lateral boundaries of the ROI were made so that encompasses all soft tissue. The same points were considered for the right and left thighs.
- *Pelvic area*: it was measured from the lower edge of the ischium to the posterior-superior border of the iliac crest. The medial boundary of the pelvic area was made by a line drawn from the midline of the pubic symphysis to the median line of the lumbar vertebra four (L4). The lateral boundary of the ROI was made so that encompasses all soft tissue. The same points were considered for the right half and the left half of the pelvic area.
- *Trunk*: it was measured from the posterior-superior edge of the iliac crest to the upper edge of the sternoclavicular joint. The lateral boundaries of the ROI (arm spacing) were made along the midline of the glenohumeral joint, right and left.
- *Hand*: it was measured starting from the lower edge of the distal phalanx of the middle finger to the line drawn on the lower edge of the medial and lateral styloid process of radiocarpal joint. The medial and lateral boundaries of the ROI were made so that encompasses all soft tissue. The same points were considered for the right and left hands.
- *Forearm*: it was measured from the line drawn on the lower edge of the medial and lateral styloid process of the radiocarpal joint to the line drawn on the medial and lateral epicondyles of the humerus. The medial and lateral boundaries of the ROI were made so that encompasses all soft tissue. The same points were considered for the right and left forearms.
- *Arm*: it was measured starting from the line drawn on the medial and lateral epicondyles of the humerus to the upper edge of the acromial extremity of the clavicle. The medial boundary of the ROI (separation of the trunk) was made in the midline of the glenohumeral joint and the lateral boundary was made so that all soft tissue was encompassed by the ROI. The same points were considered for the right and left arms.
- *Head*: it was measured from the upper edge of the sternoclavicular joint to the cranial vertex.

All ROI are illustrated in figure 2.

These ROI delineations were then used to compute the total mass of each body segment, for each subject. Using these outcome parameters, was computed the CV, the ICC and its CI95% to total mass of each body segment.

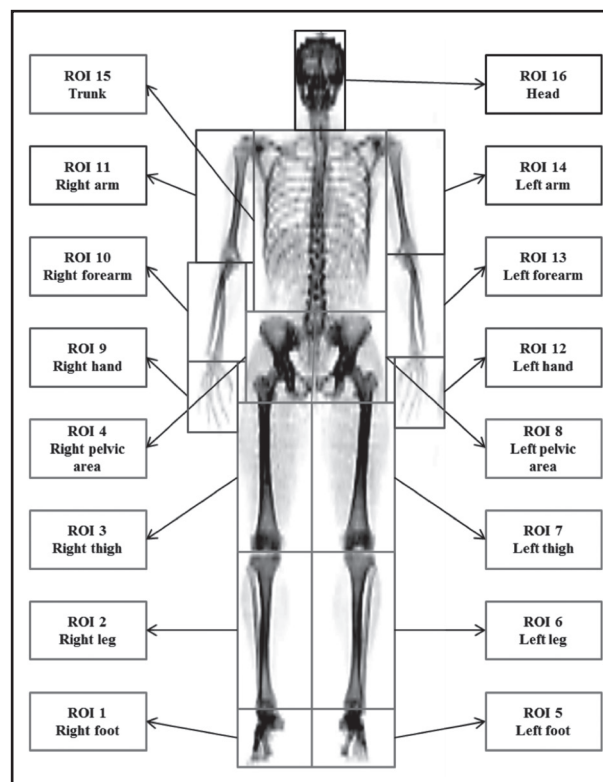


Figure 2.

Graphic representation of the 16 ROI analyzed.

STATISTICAL TREATMENT

All statistical analyzes were performed in SPSS for Windows, version 21 (IBM, Chicago, USA). Initially, the data were subjected to normality test of Shapiro-Wilk. After, the descriptive analysis of the data was done, through the mean and standard deviation (SD). The reliability of body composition measurements by DXA was determined by calculating the CV and the ICC. ICC was also used to verify the intraobserver reproducibility for the measurement of each one of the 16 ROI, with a CI95%. A level of statistical significance of $p < 0.05$ was established for all treatments.

RESULTS

The 15 volunteers tested had a mean age of 24.25 ± 5.52 years, with extremes ranging between 18.5 and 36 years; an mean height of 179.80 ± 7.23 cm, with extremes of 169 and 192 cm; an mean body mass of 78.15 ± 7.92 kg, with extreme values of 67 and 99 kg; and an mean BMI of 24.13 ± 1.34 kg/m², with extreme values ranging between 21.49 and 26.86 kg/m².

Regarding DXA reliability to measure the components of body composition, it may be seen in table I that for all components, a low CV and high internal consistency of measurement repeatability were found.

Table I. Results of DXA reliability to measure TBM, FM, LM and BMC

	Eval.	X	SD	CV	ICC (CI95%)	p-value
TBM	1 st	76.79	7.95	2.3%	0.999 (0.998-1.000)	< 0.001
	2 nd	76.57	7.69			
FM	1 st	12.09	4.90	1.6%	0.998 (0.992-0.999)	< 0.001
	2 nd	11.91	5.06			
LM	1 st	60.71	6.21	0.3%	0.997 (0.992-0.999)	< 0.001
	2 nd	60.79	6.03			
BMC	1 st	3.66	0.58	0.1%	0.998 (0.993-0.999)	< 0.001
	2 nd	3.66	0.60			

Eval.: evaluation; X: mean; SD: standard deviation; CV: coefficient of variation; ICC: intraclass correlation coefficient; IC95%: confidence interval of 95%; TBM: total body mass; FM: fat mass; LM: lean mass; BMC: bone mineral content.

The results of the intraobserver reproducibility for the measurement of the 16 ROI show a high consistency of the measures of the two assessments, with intraclass correlation values slightly lower in the feet, pelvic areas and trunk, as shown in the table II.

DISCUSSION

The reliability of results for DXA to measure the TBM, FM, LM and BMC, showed high levels of reproducibility for all components evaluated with lower CV (< 2.3%) and higher ICC (between 0.992 and 1.000).

Similar results were observed by Hind et al. (12), in a study that sought to assess DXA reliability *in vivo* (GE Lunar Prodigy) to measure body composition in 52 British adults. The authors found low CV for BMC (1.3%) and FM (2.5%). However, they did not describe the CV for LM and TBM. Similarly, Rothney et al. (14), in a study that aimed to characterize *in vivo* the reliability of total and regional body composition by DXA (GE Lunar iDXA) in a sample of obese American adults, found CV of 0.5% for BMC, 1% for FM and 0.5% for LM with the total body scanning.

In obese people, Carver et al. (11), who sought to evaluate DXA reliability (GE Lunar iDXA) to measure body composition and fat distribution, also observed low CV values for measures BMC (1.08%), FM (0.9%) and LM (0.94%). The authors also reported ICC values of 0.99 for the three components (BMC, FM and LM).

Based on the protocols, study objectives and characteristics such as quality control, reliability and valuation measures, the DXA may be considered as one of better methods to determining the values of FM, LM and BMC, and also one advanced and cost-effective technology that is useful for data acquisition of body composition in clinical trials of short to medium term, since its limitations are considered when planning the stages of an intervention (16,17).

Thus, regardless of the characteristics of the populations evaluated, DXA has shown good reliability, with high ICC and low CV (11,12,14), as observed in our study. These results allow us to consider the DXA as a method for assessing total body compo-

sition with precise and consistent results at different times of evaluation.

Little has been done to evaluate the intraobserver reproducibility of measurements of the ROI in DXA, especially since most studies assessing the reproducibility of this method were based in automatic measurements performed by the device. Thus, this study presents an unprecedented contribution to the scientific literature by evaluating the reproducibility of measurements intra analyzed for the 16 ROI, in which higher ICC values were obtained (between 0.952 and 0.999), indicating an excellent measurement reliability of this method for all body regions.

Similarly, the study by Buckinx et al. (10), which aimed to evaluate the correlation between the bioelectric impedance and DXA (Hologic QDR Discovery) for assessment of body composition in 138 Belgian adults, found an intraobserver reproducibility also high [ICC = 0.89 (0.86 to 0.92) for the total sample], although presented lower values than the ones of this study. However, Buckinx et al. (10) did not determine the reproducibility of measures for body segments; neither established which procedure used to define the ROI in the members.

The ICC is a statistical calculation that can be used to indicate reliability or reproducibility between two measurements for the same evaluator. The more ICC approaches 1, the higher the precision or reproducibility, thereby resulting in equal values of 0.90 or superior can be regarded as very high, values between 0.70 and 0.89, can be regarded as high and values between 0.50 and 0.69, as moderate (18). In this sense, the values found in this study indicate an intraobserver agreement very high for the definitions and readings of the measures, regardless of the region scanned and region size.

Thus, it is possible to consider that in measurements TBM, FM, LM and BMC, the DXA has very high reliability. In this study, for the 16 ROI analyzed, was also obtained a high intraobserver reproducibility, which indicates a high reliability for both measures, for the instrument and the observer.

This study presents a possible limitation for evaluating only a sample of men, once sex can influence body composition (19,20) and that the amount of fat may involve greater variations in mea-

Table II. Intraobserver reproducibility results for measuring of the 16 ROI of analyzed body segments

Body segments	Eval.	X	SD	ICC (CI95%)	p value
Right foot	1 st	1.02	0.08	0.955 (0.866-0.985)	< 0.001
	2 nd	1.03	0.08		
Left foot	1 st	1.03	0.09	0.952 (0.857-0.984)	< 0.001
	2 nd	1.05	0.10		
Right leg	1 st	3.45	0.51	0.998 (0.995-0.999)	< 0.001
	2 nd	3.43	0.50		
Left leg	1 st	3.41	0.49	0.998 (0.994-0.999)	< 0.001
	2 nd	3.40	0.48		
Right thigh	1 st	9.00	1.06	0.994 (0.982-0.998)	< 0.001
	2 nd	9.12	1.15		
Left thigh	1 st	8.73	0.99	0.996 (0.987-0.998)	< 0.001
	2 nd	8.82	1.07		
Right pelvic area	1 st	7.09	0.86	0.986 (0.959-0.995)	< 0.001
	2 nd	6.94	0.82		
Left pelvic area	1 st	7.07	0.95	0.989 (0.968-0.996)	< 0.001
	2 nd	6.93	0.84		
Trunk	1 st	24.21	2.39	0.983 (0.950-0.994)	< 0.001
	2 nd	24.18	2.29		
Right hand	1 st	0.34	0.08	0.994 (0.982-0.998)	< 0.001
	2 nd	0.34	0.08		
Left hand	1 st	0.32	0.10	0.996 (0.987-0.999)	< 0.001
	2 nd	0.32	0.10		
Right forearm	1 st	1.27	0.22	0.999 (0.998-1.000)	< 0.001
	2 nd	1.26	0.22		
Left forearm	1 st	1.21	0.20	0.995 (0.986-0.998)	< 0.001
	2 nd	1.21	0.20		
Right arm	1 st	2.81	0.47	0.992 (0.975-0.997)	< 0.001
	2 nd	2.78	0.48		
Left arm	1 st	2.79	0.42	0.993 (0.979-0.998)	< 0.001
	2 nd	2.76	0.45		
Head	1 st	5.78	0.41	0.995 (0.984-0.998)	< 0.001
	2 nd	5.81	0.41		

Eval.: evaluation; X: mean; SD: standard deviation; ICC: intraclass correlation coefficient; CI95%: confidence interval of 95%.

surements of DXA (Valentine et al., 2008). However, we opted for this strategy in order to minimize a possible influence of factors related to the female gender, as the menstrual cycle, in the body composition. Future researches should establish the possible differences in segmental body composition between genders.

Based on the results of this study, we can conclude that the calculations performed with DXA in young people show a high reproducibility for both, TBM and FM, LM and BMC. In addition, the definition of specific body segments, the ROI, performed by

a single observer, presents high reproducibility in both large and small segments.

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Nutrición Hospitalaria



Trabajo Original

Valoración nutricional

The BFMNU method as an alternative to the methods in use based on energy: study of the correlation between food energy and body mass

El método BFMNU como alternativa a los métodos en uso basados en energía: estudio de la correlación entre la energía alimentaria y la masa corporal

Greta Rondini¹, Beatrice Olearo¹, José Miguel Soriano del Castillo^{2,3} and Pietro Marco Boselli¹

¹Department of Biosciences. University of Milan. Milan, Italia. ²Mixed Unit for Research in Endocrinology, Nutrition and Clinical Dietetics. Universidad de Valencia - Instituto de Investigación Sanitaria La Fe. Valencia, Spain. ³Grupo de Ciencias de la Alimentación Basada en la Evidencia y Experimentación (CIAIBEx). Instituto de Ciencias de los Materiales. Universidad de Valencia. Paterna, Spain

Abstract

Introduction: to establish slimming guidelines and any other changing treatments is useful to know the individual's energy expenditure due to the fact that, nowadays, the incidence of many diseases related to the loss of lean mass and the accumulation of adipose tissue has increased. The dietary treatments are carried out on calculating the energy contained in food, and then put in relation to the total energy expended by the body in order to produce changes in body mass.

Objective: the aim of this study was to evaluate the correlation between the food energy and body mass of different subjects in various pathophysiological conditions.

Methods: one hundred and twenty subjects (male and female, aged 7-78 years old) were studied in various pathophysiological conditions and previously treated with the BFMNU (*Biología e Fisiología Modellistica della Nutrizione Umana*) method.

Results: a correlation coefficient R^2 of 0.1256 was found between food energy of the diet usually followed by the subjects and their body mass. The correlation between food energy and food mass was with R^2 of 0.211. The correlation between $\Delta\%$ of food energy and $\Delta\%$ of body mass of the subjects, obtained through dietary treatment with the BFMNU method, was 95.77 percent.

Conclusions: the correlation between food energy and body mass is not significant, being a critical point about the diets designed on an energy basis. However, the body mass of an individual is determined by mass balance, regulated by corresponding metabolic rate, calculated by the BFMNU method, thanks to which the macronutrients in the diet are absorbed, redistributed and eliminated. A significant correlation, although not straight, is demonstrated between $\Delta\%$ of food energy, supplied after processing through the dietary BFMNU method, and the $\Delta\%$ of body mass, obtained following the dietetic path.

Key words:

Human energy expenditure. Body mass changes. Energy intake. Food mass intake.

Resumen

Introducción: con el fin de establecer pautas de adelgazamiento es necesario conocer el gasto energético del individuo, sobre todo porque hoy en día la incidencia de muchas enfermedades relacionadas con la pérdida de masa magra y la acumulación de tejido adiposo ha aumentado. Por lo tanto, los tratamientos dietéticos se basan en el cálculo de la energía contenida en los alimentos y luego se ponen en relación con la energía total gastada por el cuerpo para producir cambios en la masa corporal.

Objetivo: el objetivo del estudio fue analizar la correlación entre la energía alimentaria y la masa corporal de diferentes sujetos en diversas condiciones fisiopatológicas.

Métodos: la muestra consistió en 120 sujetos, varones y mujeres, de 7 a 78 años de edad, en diversas condiciones fisiopatológicas, previamente tratados con el método BFMNU (*Biología e Fisiología Modellistica della Nutrizione Umana*).

Resultados: se encontró un coeficiente de correlación R^2 de 0,1256 entre la energía alimentaria de la dieta habitualmente seguida por los sujetos y su masa corporal. La correlación entre la energía alimentaria y la masa alimentaria fue de R^2 de 0,211. La correlación entre el $\Delta\%$ de la energía alimentaria y $\Delta\%$ de la masa corporal de los sujetos, obtenida con el tratamiento dietético por el método BFMNU, ascendió a 95,77%.

Conclusiones: la correlación no significativa entre la energía alimentaria y la masa corporal plantea una gran pregunta sobre las dietas diseñadas sobre una base energética. En su lugar, la masa corporal de un individuo está determinada por el balance de masa, regulado por la tasa metabólica correspondiente, calculado por el método BFMNU, gracias al cual los macronutrientes en la dieta son absorbidos, redistribuidos y eliminados. Se demuestra una correlación significativa, aunque no lineal, entre $\Delta\%$ de la energía alimentaria, suministrada después del procesamiento a través del método BFMNU de la dieta, y el $\Delta\%$ de la masa corporal, obtenido siguiendo la pauta dietética.

Palabras clave:

Gasto de energía humana. Cambios en la masa corporal. Consumo de energía. Ingestión de masa alimentaria.

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Correspondence:

José Miguel Soriano del Castillo. Instituto de Investigación Sanitaria La Fe. Avenida Fernando Abril Martorell, 106 Torre A, 7ª planta. 46026 Valencia, Spain
e-mail: jose.soriano@uv.es

INTRODUCTION

The worldwide prevalence of overweight and obesity has increased remarkably over the past decades (1,2), which is associated with attempting to lose weight. Nowadays, there are different dietary strategies to slimming and many of these lead to an initial weight loss from 5 to 9%, which seems stable over the first six months. In most cases, in fact, the real problem lies not in weight loss, but in the maintenance of long-term weight reached: a meta-analysis study on the body weight reduction showed that after 48 months half of the body weight lost is regained (3). In addition, the National Health and Nutrition Examination Survey (NHANES) has shown that 35% of people who have achieved a significant reduction in weight have regained it after one year. Even today it is believed that the principle which underpins the process concerning the change in body weight resides in the balance between the energy content of food eaten and the energy expended by the body to maintain vital functions and associated with physical exercise relationship (4). Since living organisms obey to the first principle of thermodynamics, the energy balance equation is used to predict changes in body weight as a result of a variation in energy intake or/and in energy expenditure. Despite the simplicity of this principle, the calculation of the energy balance change and the translation of this one in a change in body weight is not simple. Often, the static equation of energy balance is used improperly; in fact, energy intake is equal to energy expenditure only in a particular case: when body weight and body composition are maintained constant (5). It is not considered that the process is dynamic and that the variation of energy expenditure depends itself on the variation of body mass, due both to an increase and to a decrease of weight (6-8). The "rule of body weight loss" is derived from the estimation of the energy content of the lost weight, but ignores the dynamic physiological adaptations that arise during the change of weight, which lead to changes both in the basal metabolic rate and in energy expenditure for physical activity (9). Unfortunately, this static rule for weight loss continues to be used in prescriptions and advice geared to slimming, and at the population level it is applied to predict the effect on the prevalence of obesity and the effect of certain programs (10-13). These same concerns, together with the numerous contradictions emerged from a proportional and linear conception of the masses changing processes, as well as the use of static energy balance equation for predicting the resulting changes in body mass, contributed to design a new method abbreviated as BFMNU (*Biologia e Fisiologia Modellistica della Nutrizione Umana*) (14,15), according to which it was possible to predict the change in mass and body composition in response to a change in mass and food energy introduced.

The aim of the study was to evaluate the relationship between the energy contained in food from the diet (energy supply) and body mass, on a large and heterogeneous sample of 120 subjects in various pathophysiological conditions. In addition, other correlations were analyzed: between food energy and food mass, and between the $\Delta\%$ of body mass and the $\Delta\%$ energy food supplied after the elaboration of the diet.

METHODS

The study concerns the collection, from the database, of the data of 120 subjects in a variety of pathophysiological conditions, which had previously been followed in a dietetic path of annual duration (BFMNU method), for which all the information necessary for the research was available.

The BFMNU method was devised by Pietro Marco Boselli (18) in 1995 with the objective of proposing a new nutritional intervention method, different from the existing ones, which was able to systemically interpret the metabolic processes of mass and energy, and to overcome the many and obvious contradictions of the methods already in use. It is a phenomenologic-mathematical method applicable to any individual, at any physiopathological condition, whose primary objective is to determine the optimal diet that most of all is capable of producing a synergistic change in body mass, body composition and energy in order to improve the functionality of the body with the smallest possible variation in comparison to previous eating habits. In order to achieve this goal, and therefore provide an adequate diet, it is necessary to know the starting body composition: the method uses the measurement of lengths and circumferences to calculate volume (V), the surface area (S) and pseudo thickness (Sp), considering the body as a set of geometric solids; through these structural variables the body composition can be calculated as follows (14):

$$\begin{aligned} - M_w &= -3.2169 + 26.925 \cdot S \\ - M_p &= +0.2559 + 0.1179 \cdot V \\ - M_l &= +0.0194 \cdot Sp^{4.7355} \\ - M_g &= 0.003606 + 0.004539 \cdot M_t \end{aligned}$$

In this formulae, M_w , M_p , M_l , M_g and M_t are respectively the body masses of water, proteins, lipids, carbohydrates and total, expressed in kg, S is the body surface area in m^2 , V is the volume expressed in dm^3 and Sp is the pseudo thickness in cm. Through the use of the DIES4 software, specifically designed for the application of the BFMNU model and the facilitation of calculations, the constant rates related to each component can be determined:

$$\begin{aligned} - K_m [h^{-1}] &= - (1/24) \ln [(M_c - M_a)/M_c] \\ - K_E [h^{-1}] &= - (1/24) \ln [(E_c - E_a)/E_c] \\ - M_c &\text{ is the body mass and } M_a \text{ is the food mass (both expressed in kg), } E_c \text{ is the total energy contained in the body (kcal), corresponding to the sum of the body masses multiplied by the respective specific heat, and } E_a \text{ is the food energy (kcal) contained in the food introduced with the diet.} \end{aligned}$$

For this study, 120 subjects including men, women and children, aged 7 to 78 years, were randomly selected from a pool of subjects who followed the BFMNU diet for a period of one year, in years 2010-2015. For each subject data were collected, including age, body mass (M_c), initial body mass index ($M_{c,i}$) and the final body mass ($M_{c,f}$) corresponding to stable weight reached, the height (h) and the body mass index (BMI). There were also collected data about the diet normally followed before the BFMNU dietetic treatment, resulting from food consumption diaries filled in by them, such as food mass (M_a) and the daily food energy (E_a). The food consumption data were obtained using the protocol provided by the BFMNU method: this involves the compilation

by the subject of a diary of nutrition and excretion in which the subject for three days, including two weekdays and one during the weekend (not necessarily consecutive), must note the weight (g) of each food and/or drink consumed and the weight of urine and feces excreted. The diary must adhere to the representativeness and accuracy requirements, for which the individual must follow to write what normally is part of his current diet, and that has been part over a period of at least eight months prior to the compilation. The study was approved by the Ethical Committee of University of Milan (Italy).

RESULTS AND DISCUSSION

The correlation between M_{ci} of the subjects and E_a introduced was investigated, corresponding to the diet followed by the person before the dietetic treatment. The correlation index amounted to 12.5% and therefore, it is insufficient to justify a valid linear correlation between the two variables mentioned (Fig. 1). As shown in figure 1, the points on the graph, each representing a different subject, are randomly distributed and the regression applied is actually meaningless; it just puts in evidence the great dispersion of experimental points.

Figure 2 shows the distribution of the starting body mass (M_{ci}) and the food energy normalized on starting body mass (E_a/M_{ci}), whose correlation is equal to 29.2%. Despite being increased compared to that shown in figure 1, the correlation index is still insignificant: dietary energy justifies body mass only for a quarter of the subjects considered. Additionally, this distribution highlights another aspect: the basal metabolic rate changes with the body mass so greater than the extra basal metabolism, because it is connected to the evaporation rate (*perspiratio insensibilis*) and then to the body surface. Therefore, the increase of the index value of correlation shown in figure 2 is a consequence of the operation of normalization: the body mass is in fact more correlated with the ratio E_a/M_{ci} than with E_a .

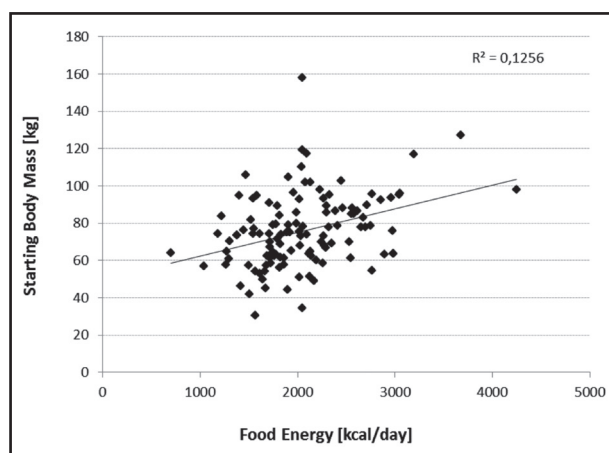


Figure 1.

Correlation between food energy (E_a) characteristic of the subjects' habitual diet subjects and starting body mass (M_{ci}).

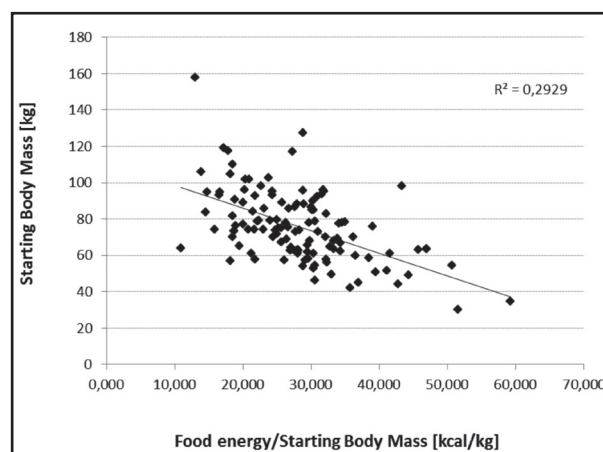


Figure 2.

Correlation between food energy (E_a) normalized on starting body mass (M_{ci}) and starting body mass.

Based on the results obtained, is it possible to change the body mass of an individual by changing the intake of food energy? Is it possible to predict changes in body composition by relying on the static equation of energy balance?

The fact that emerges, that is that there is no significant correlation between E_a and M_{ci} , questions the validity of all diets determined on an energy basis.

Actually, what correlates body mass with food mass (and also body energy with food energy) is the metabolism of the subject, characterized by the metabolic constant rates (k) that are specific of the individual himself. In fact, the metabolic rates explain how the outcome of body mass can be independent of the food energy introduced with the diet (15).

The correlation between food mass (M_a) and food energy (E_a) was also studied (Fig. 3) and, contrary to what might be expected,

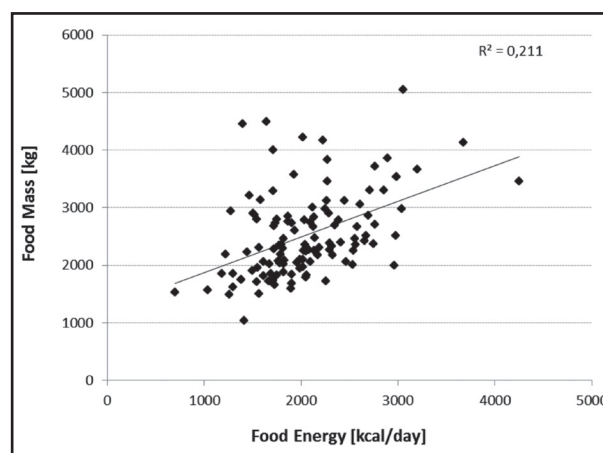


Figure 3.

Correlation between food energy (E_a) and food mass (M_a).

the correlation coefficient is equal to 0.211: with the same amount of food mass, the energy content varies depending on the composition of nutrition.

Finally, on the set of the collected data, we studied the relationship:

- $\Delta M_c \% = (\Delta E_1 \%^{1.777}) / \Delta E_2 \%$, proposed by P. M. Boselli (15), where
- $\Delta M_c \% = 100 * (\text{final body mass} - \text{initial body mass}) / \text{initial body mass}$
- $\Delta E_1 \% = 100 * ([\text{energy of the new diet} \pm \text{extra basal energy due to the variation of physical activity}] - \text{energy of the old diet}) / \text{energy of the old diet}$
- $\Delta E_2 \% = 100 * (\text{energy of the new diet} - \text{energy of the old diet}) / \text{energy of the old diet}$

The correlation is highly significant and shows that about 96% of the percentage changes of dietary energy justify the percentage change in body mass (Fig. 4). It should be considered that the percentage changes, both of the body mass and food energy, are dimensionless and without units of measurement. Therefore, the non-rectilinear correlation found only expresses the link between the numerical values: this, however, allows to predict the final body mass (M_{cf}) of the subject after the variation of food energy (E_a) caused by the new diet obtained through the solution of the system of metabolic balance.

The same correlation, applied to the food energy data suggested by diets formulated on an energy basis, produces a correlation index $R^2 = 0.3439$. This result shows the difference between the two different approaches, BFMNU and diets on an energy basis, and especially the inadequacy of the latter.

The results concerning the non-correlation between E_a and M_{ci} emerged in our study reflect and confirm the doubt which moti-

vated the initial choice to perform this type of analysis. As shown by Alpert (16), the commonly used energy balance equation is inadequate to predict changes in body mass consequent to different energy supplies. In addition, small increases in taking energy during long periods cannot lead to higher weight gains, as often claimed (16,17). The only exception is within the same individual under equilibrium conditions: with the same diet, metabolism, and pathophysiological conditions, in the same individual, the correlation between E_a and M_c is still valid, as motivated by the specific heat of macronutrients. Instead, the correlation between E_a and M_{ci} , applied in situations of imbalance, that is, in most cases, is not significant from the biological point of view; for this reason, it is necessary to consider the calculation of quantitative balances (mass - mass and energy - energy). It is therefore necessary to update the existing standard by which nutrition plans are prescribed for any changing and stabilization of body weight and statistical evaluations are made on the population scale. Being able to customize nutrition on the individual, on the basis of its metabolic speed, allows minimizing the experimental errors due to inference of the energy expenditure of the subject, as well as the maximization of the result on the progress and improvement of body composition (18).

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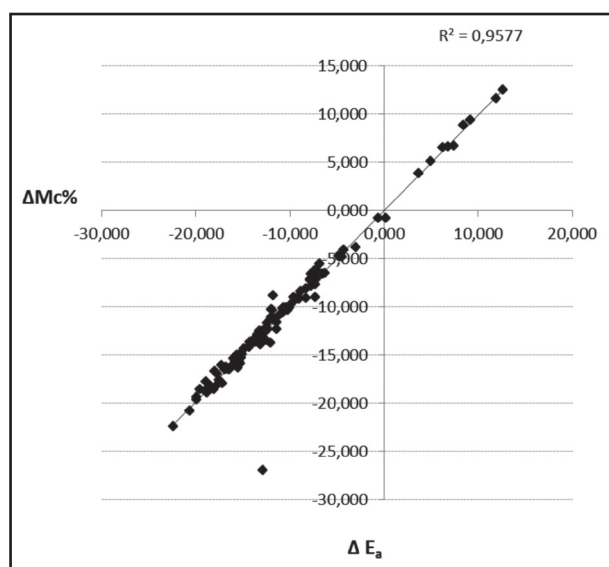


Figure 4.

Correlation between percentage changes of body mass and percentage changes of food energy.

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Nutrición Hospitalaria



Trabajo Original

Valoración nutricional

Validación del cribado nutricional Malnutrition Screening Tool comparado con la valoración nutricional completa y otros cribados en distintos ámbitos sociosanitarios *Validation of nutritional screening Malnutrition Screening Tool compared to other screening tools and the nutritional assessment in different social and health areas*

Iciar Castro-Vega¹, Silvia Veses Martín¹, Juana Cantero Llorca², Christian Salom Vendrell¹, Celia Bañuls¹ y Antonio Hernández-Mijares^{1,3}

¹Sección de Endocrinología y Nutrición. Hospital Universitario Dr Peset - Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana. Valencia. ²Dirección Médica de Atención Primaria. Departamento de Salud Dr Peset. Valencia. ³Departamento de Medicina. Universidad de Valencia. Valencia

Resumen

Introducción: los cribados son empleados para detectar el riesgo nutricional y permiten intervenir precozmente e influir en el pronóstico. La herramienta Malnutrition Screening Tool (MST) está validada en paciente hospitalizado y oncológico ambulatorio.

Objetivo: analizar por ámbitos sociosanitarios y grupos etarios los cribados MST, Malnutrition Universal Screening Tool (MUST) y Mini Nutritional Assessment-Short Form (MNA-sf) respecto a la valoración nutricional completa (VNC) como patrón de referencia, y evaluar la utilidad del MST en aquellos ámbitos donde no está validado.

Material y métodos: se han incluido 815 sujetos ambulatorios, hospitalizados e institucionalizados. Se les realizó el cribado MUST, MST y una VNC; con los ≥ 65 años también se llevó a cabo el MNA-sf. Se empleó el Consenso SENPE-SEDOM para el diagnóstico.

Resultados: en ambulatorios, los tres cribados presentan una validez AUC ROC $> 0,8$ respecto a la VNC. En los institucionalizados, el MNA-sf genera falsos positivos y el MUST presenta mayor validez que el MST (AUC ROC = 0,815 y 0,763 respectivamente). En hospitalizados, hay excelentes resultados con el MUST y el MST. En los tres ámbitos el MST obtiene mejor valor predictivo positivo. Por rango de edad, tanto el MUST como el MST son herramientas válidas.

Conclusiones: en nuestro estudio, el MST diagnostica correctamente a más del 80% de los pacientes (S = 69,4%, E = 94,2%), y posee buena concordancia y validez respecto a la VNC no solo en paciente hospitalizado y oncológico ambulatorio, donde ya había sido validado. En nuestra población, el MST es válido para ser aplicado en pacientes ambulatorios, institucionalizados y hospitalizados.

Palabras clave:

Riesgo nutricional.
Desnutrición establecida.
Valoración nutricional.
Cribado nutricional.
Validez. Fiabilidad.

Abstract

Introduction: nutritional screenings are used to detect nutritional risk, allow early intervention and influence the prognosis. The Malnutrition Screening Tool (MST) is only validated in hospitalized patients and oncology outpatients.

Objectives: to analyze the nutritional screening MST, Malnutrition Universal Screening Tool (MUST) and Mini Nutritional Assessment-Short Form (MNA-sf) compared to the nutritional assessment gold standard according to socio-sanitary areas and age groups; and to assess the utility of the MST in those areas where it has not been validated.

Material and methods: a total of 815 outpatient, hospitalized and institutionalized subjects were included in this study. MUST and MST screenings, and nutritional assessment were performed in all subjects. MNA-sf was also performed in subjects ≥ 65 years of age. Nutritional diagnosis was performed according to the SENPE-SEDOM consensus.

Results: in the outpatient cohort, three screenings have a validity (AUC ROC) greater than 0.8 compared to nutritional assessment. In the institutionalized, the MNA-sf generates false positives and the MUST is more valid than MST (AUC ROC = 0.815 and 0.763, respectively). In hospitalized patients, there are excellent results with MUST and MST. In all socio-sanitary areas the MST obtains a better positive predictive value. By age groups, MUST and MST are valid tools.

Conclusions: in our study, the MST correctly diagnoses more than 80% of the patients (S = 69.4%, E = 94.2%), and has a good reliability and validity with respect to nutritional assessment not only in hospitalized patients and oncology outpatients, where it has already been validated. In our population, the MST was found to be valid in outpatient, institutionalized and hospitalized subjects.

Key words:

Nutritional risk.
Malnutrition established.
Nutritional assessment.
Nutritional screening.
Validity. Reliability.

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Correspondencia:

Antonio Hernández-Mijares. Servicio de Endocrinología y Nutrición. Hospital Universitario Dr. Peset. Av. Gaspar Aguilar, 90. 46017 Valencia
e-mail: hernandez_antmij@gva.es

INTRODUCCIÓN

La desnutrición relacionada con la enfermedad (DRE) es el resultado de la compleja interacción entre enfermedad y nutrición. Tiene elevada prevalencia y, sin embargo, con frecuencia es ignorada e infratratada, lo que comporta importantes consecuencias clínicas y económicas (1). La detección temprana debe ser prioritaria en todos los ámbitos asistenciales, pero la realidad es que no existen suficientes recursos disponibles para ello y es indispensable el empleo de herramientas de cribado nutricional para la detección de la desnutrición o el riesgo de padecerla (2). Estas herramientas deben estar ligadas a un plan de acción con el fin de promover intervenciones costo-efectivas al seleccionar aquellos pacientes que se beneficiarían de una intervención dietética-nutricional (3,4).

Desde 1996, diferentes organizaciones profesionales recomiendan el uso sistemático de herramientas de cribado nutricional (3). El consenso multidisciplinar sobre el abordaje de la desnutrición hospitalaria en España indica (5) que se debe implementar el uso de un método de cribado del estado nutricional en los centros de Atención Primaria en cualquier paciente que presente criterios de sospecha clínica de desnutrición, en los centros geriátricos al ser institucionalizados cuando también presenten los criterios de sospecha y en pacientes hospitalizados en las primeras 24-48 horas de ingreso, con reevaluación semanal.

Hasta el momento se han desarrollado más de 70 herramientas distintas de cribado nutricional (6) y no existe ninguna considerada patrón de referencia para identificar la desnutrición o el riesgo nutricional. De los diversos estudios publicados se desprenden dos conclusiones: que la variabilidad en las cifras de prevalencia depende de la herramienta utilizada y que es necesario implementar un cribado en la valoración rutinaria del paciente. No obstante, diferentes trabajos postulan qué requisitos debe cumplir un cribado nutricional (1,3,7-10). En resumen, estos deben ser sencillos, válidos, fiables, reproducibles y estar conectados con protocolos específicos de actuación, que no sean fácilmente modificables por factores no nutricionales y que sean capaces de predecir el pronóstico del paciente al aplicar o no un soporte nutricional.

La European Society of Parenteral and Enteral Nutrition (ESPEN) (9) propone como métodos de cribado el Nutrition Risk Screening 2002 (NRS-2002), validado en hospitalización; el Malnutrition Universal Screening Tool (MUST), validado en adultos ambulatorios, hospitalizados e institucionalizados; y el Mini Nutritional Assessment (MNA), validado en población anciana. Con estas herramientas se hace hincapié en la condición nutricional actual del paciente y si esta ha permanecido estable en los últimos meses o puede empeorar en caso de que la ingesta sea insuficiente. La American Society for Parenteral and Enteral Nutrition (ASPEN) (11) añade el Malnutrition Screening Tool (MST), validado en paciente hospitalizado y en sujetos ambulatorios en tratamiento con radio o quimioterapia; y el Short Nutrition Assessment Questionnaire (SNAQ), validado en individuos hospitalizados, en ambulatorios > 65 años y en residencias de ancianos o aquellos con cuidados domiciliarios.

A pesar de la gran variedad de herramientas de cribado nutricional, ninguna ha sido validada de forma efectiva al no existir un patrón de referencia para el diagnóstico de la desnutrición. Numerosos estudios han analizado los diferentes cribados a través de comparaciones con herramientas de valoración preestablecidas (1,6,7,12) como la valoración global subjetiva (VGS), el MNA o el NRS-2002. También han sido analizados y comparados con una definición de malnutrición (13) o por bioimpedancia eléctrica (14) y, sin embargo, pocos son los trabajos que los analizan con parámetros antropométricos y bioquímicos (15), sin encontrar por el momento estudios que los comparen con una valoración nutricional completa (VNC) que incluya la historia médica, la historia dietética-nutricional, el tratamiento farmacológico, la exploración física, las medidas antropométricas y datos de laboratorio.

El objetivo de este trabajo es conocer la validez, el comportamiento y la concordancia del cribado nutricional MST respecto a la VNC, por grupos de edad y en diferentes ámbitos de estudio. Además, se compararán los resultados con los obtenidos por herramientas validadas (MNA-sf y MUST) para determinar si el cribado nutricional MST es una herramienta útil en pacientes institucionalizados y ambulatorios no oncológicos para los cuales no está validada por el momento.

MATERIAL Y MÉTODOS

Este trabajo es un subanálisis del estudio transversal y descriptivo sobre prevalencia de riesgo de desnutrición y desnutrición establecida en población ambulatoria, institucionalizada y hospitalizada en un departamento de salud (16). En él se detalla la metodología empleada para el reclutamiento de la muestra, el procedimiento seguido para el cribado, la valoración y el diagnóstico nutricional de los sujetos.

Para establecer el riesgo de desnutrición, se emplearon tres herramientas de cribado nutricional: las herramientas MUST y MST se realizaron a toda la muestra y el cribado MNA-sf, a pacientes ≥ 65 años. Para la valoración del estado nutricional, se realizó a todos los sujetos una VNC y el diagnóstico nutricional se llevó a cabo con las indicaciones del Consenso de la Sociedad Española de Nutrición Parenteral y Enteral (SENPE) y la Sociedad Española de Documentación Médica (SEDOM) (17).

El cribado nutricional MUST (1,7,18) incluye tres parámetros clínicos y los puntúa con 0, 1 o 2 puntos, como sigue: índice de masa corporal (IMC) $> 20 \text{ kg/m}^2 = 0$; $18,5\text{-}20 \text{ kg/m}^2 = 1$; $< 18,5 \text{ kg/m}^2 = 2$. Pérdida de peso $< 5\% = 0$; $5\text{-}10\% = 1$; $> 10\% = 2$. Enfermedad aguda y su relación con la ingesta en los próximos cinco días, ausencia = 0; presencia = 2. Tras la cumplimentación, el riesgo de desnutrición se establece como, bajo riesgo = 0 puntos; riesgo medio = 1 punto; y riesgo alto ≥ 2 puntos. Su gran validez se debe a que incluye guías de actuación para desarrollar el tratamiento nutricional y puede ser utilizado en comunidad, hospital y en pacientes institucionalizados.

La herramienta de cribado MST (1) incluye dos parámetros que valoran, por un lado, el apetito reciente (inapetencia = 1 punto; apetito conservado = 0 puntos; donde se ha tenido en cuenta

la disminución de la ingesta por cualquier motivo) y, por otro, la pérdida de peso (no pérdida de peso = 0 puntos; no sabe si hay pérdida de peso = 2 puntos; pérdida de peso 1-5 kg = 1 punto, 6-10 kg = 2 puntos, 11-15 kg = 3 puntos, > 15 kg = 4 puntos). Clasifica a los pacientes en dos grupos, riesgo nutricional si la puntuación obtenida es ≥ 2 puntos o sin riesgo de desnutrición si la puntuación es ≤ 1 . No requiere la realización de ningún cálculo y es rápido y fácil de llevar a cabo sin requerir personal entrenado para ello. Está validado en paciente hospitalizado (19,20) y ambulatorio con tratamiento radio (21) o quimioterápico (22).

El test de cribado MNA-sf (1,7,23-26) consta de seis preguntas a las que se les adjudica una puntuación de hasta 2-3 puntos y que responden a la ingesta (ha comido mucho menos = 0 puntos; ha comido menos = 1 punto; ha comido igual = 2 puntos), pérdida de peso en los últimos tres meses (> 3 kg = 0 puntos; no lo sabe = 1 punto; 1-3 kg = 2 puntos; sin pérdida de peso = 3 puntos), movilidad (de la cama al sillón = 0 puntos; autonomía en el interior = 1 punto; sale del domicilio = 2 puntos), ha tenido enfermedad aguda o situación de estrés psicológico en los últimos tres meses (sí = 0 puntos; no = 2 puntos), problemas neuropsicológicos (demencia o depresión grave = 0 puntos; demencia o depresión moderada = 1 punto; sin problemas neuropsicológicos = 2 puntos), e IMC (< 19 = 0 puntos; 19-20,9 = 1 punto; 21-22,9 = 2 puntos; ≥ 23 = 3 puntos). En caso de no estar disponible el IMC, se sustituiría por la circunferencia de la pantorrilla (< 31 cm = 0 puntos y ≥ 31 cm = 3 puntos). Clasifica a los pacientes en tres categorías (malnutrición ≤ 7 puntos; riesgo de malnutrición = 8-11 puntos; estado nutricional normal = 12-14 puntos). Es una herramienta de cribado rápida de realizar y creada específicamente para población anciana.

DISEÑO DEL ESTUDIO

El tamaño muestral se calculó con el programa estadístico Epidat 3.1. Según nuestros datos publicados, la prevalencia de desnutrición en nuestro medio es del 26,4% (16). En base a estos resultados, se estimó un tamaño muestral de 815 sujetos asumiendo que el cribado nutricional MST presenta como mínimo un 80% de sensibilidad y especificidad con un nivel de confianza del 95% y una precisión del 5%.

El estudio se llevó a cabo de acuerdo con las directrices establecidas por la Asociación Médica Mundial y la Declaración de Helsinki. Los procedimientos se aprobaron por el Comité Ético de Investigación Clínica (CEIC) del hospital y todos los sujetos incluidos o su representante legal firmaron el consentimiento informado.

Se realizó el análisis estadístico agrupando los resultados de los cribados en dos variables: *riesgo nutricional* (MUST: medio y alto riesgo; MST: riesgo nutricional; MNA-sf: malnutrido y riesgo de malnutrición) y *normonutrido* (MUST: bajo riesgo; MST: sin riesgo nutricional; MNA-sf: estado nutricional normal). La VNC se consideró el patrón de referencia para evaluar la sensibilidad, especificidad, valores predictivos, eficiencia, concordancia y validez de las herramientas en cada ámbito de estudio y por grupos

de edad. Para analizar por ámbitos de estudio, se generaron tres grupos: ambulatorios, hospitalizados e institucionalizados. Se consideraron pacientes institucionalizados los que residían en centros de tercera edad, en domicilio con un índice Barthel ≤ 60 puntos y los usuarios de centros de día por la similitud de su estado clínico. Para evaluar las herramientas de cribado nutricional frente a la VNC por edad, se clasificaron en tres grupos: de 30 a 64 años, 65 a 74 años y ≥ 75 años.

Tras el reclutamiento de la muestra y la recogida de las variables de interés, se realizó el análisis estadístico con el programa SPSS 17.0 software (SPSS Statistics Inc., Chicago, IL, USA). Para valorar la validez o exactitud de las pruebas diagnósticas se comparó cada cribado nutricional con la VNC. Se determinaron la capacidad y eficiencia de la prueba mediante los índices de sensibilidad (S) y especificidad (E), y se aceptó el resultado al alcanzar un 80% en cada caso. Mediante los valores predictivos se evaluó el comportamiento de las herramientas de cribado. Para conocer la fiabilidad, se estudió la concordancia encontrada con el *índice kappa ponderado* por tratarse de variables ordinales (< 0,2 = pobre; 0,2-0,4 = limitada; 0,41-0,6 = moderada; 0,61-0,8 = buena; > 0,8 = perfecta). La validez de los cribados nutricionales respecto a la VNC se analizó mediante el área bajo la curva ROC (AUC). La significación estadística se alcanzó cuando $p \leq 0,05$ para todas las herramientas de cribado analizadas.

RESULTADOS

PREVALENCIA DE RIESGO NUTRICIONAL Y DESNUTRICIÓN ESTABLECIDA

Se han utilizado tres herramientas de cribado nutricional para determinar la prevalencia de riesgo de desnutrición, según el ámbito y/o edad de los pacientes. La VNC se llevó a cabo en el 100% de los sujetos.

En las figuras 1 y 2 se muestran las prevalencias obtenidas con cada cribado nutricional empleado. Se hallaron diferencias estadísticamente significativas ($p < 0,001$) frente a la prevalencia encontrada con la VNC en cada ámbito de estudio y también por rango de edad. Dado el resultado, se procedió a evaluar cada herramienta de cribado nutricional respecto a la VNC para establecer de forma objetiva el comportamiento, la concordancia y la validez de cada una de ellas.

VALIDEZ, COMPORTAMIENTO Y CONCORDANCIA DE LOS CRIBADOS NUTRICIONALES

Muestra completa

Como hemos comentado previamente, las herramientas MUST y MST se emplearon en toda la muestra (815 pacientes). Como puede observarse en la tabla I, ambas herramientas, a pesar de obtener una S por debajo del 80% (79,4% y 69,4% respectiva-

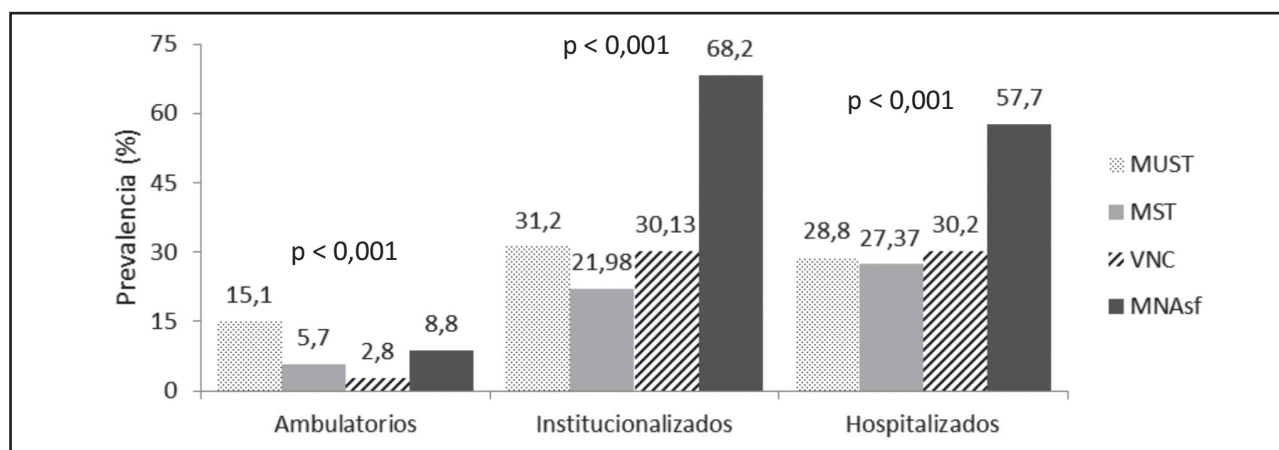


Figura 1.

Prevalencia del riesgo nutricional (MUST, MNA-sf, MST) y desnutrición establecida (VNC) en la población según el ámbito de estudio.

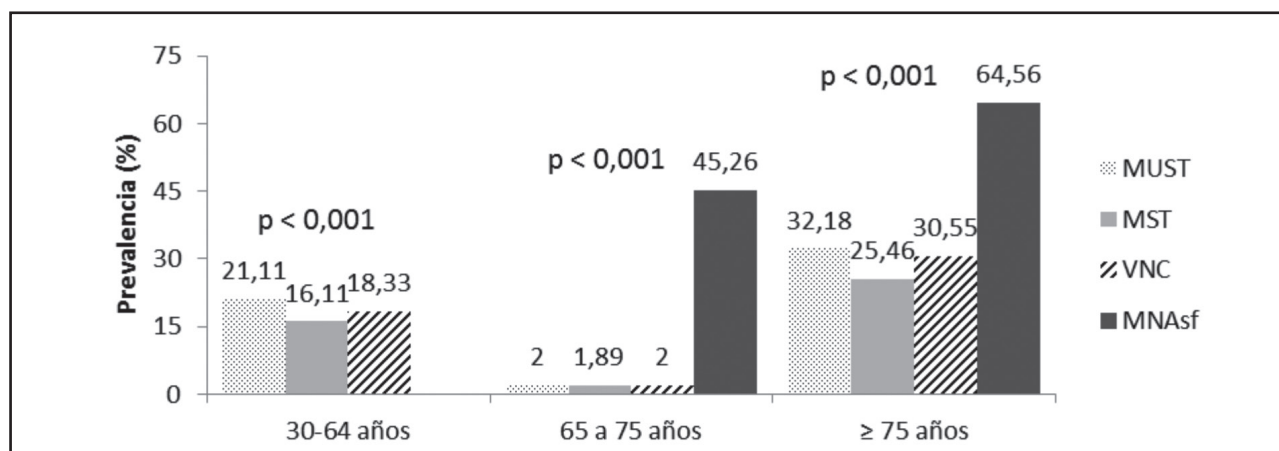


Figura 2.

Prevalencia del riesgo nutricional (MUST, MNA-sf, MST) y desnutrición establecida (VNC) en la población según el rango de edad.

mente), tienen una E elevada (89,1% y 94,2% respectivamente) y una eficiencia superior al 80%. Presentan un alto valor predictivo negativo (VPN) y, especialmente el MST, un valor predictivo positivo (VPP) superior al 80%. Adicionalmente, se analizó la concordancia respecto a la VNC, obteniendo un índice kappa del 0,673 y 0,669 en cada caso. En cuanto a la validez, se obtuvieron resultados muy similares con cada cribado (0,842 y 0,818, respectivamente).

ÁMBITO DE ESTUDIO

Ambulatorios

Se realizaron los cribados MUST y MST en toda la serie (155 sujetos, con una media de edad de $50,3 \pm 17,7$ años) y el MNA-sf en los sujetos con una edad ≥ 65 años (65 sujetos). En la

tabla I se muestran los resultados obtenidos. Se objetivó que las tres herramientas presentaron E, VPN y una eficiencia superior al 80%. Tanto la concordancia como la validez respecto a la VNC fueron similares y estadísticamente buenas en los tres casos. Destaca que el VPP fue notablemente superior para el MST en este ámbito de estudio.

Institucionalizados

Se realizaron los tres cribados en 375 sujetos; la media de edad en este ámbito fue de $84,2 \pm 7,5$ años. En la tabla I constan los resultados obtenidos respecto a la VNC. La S del MST y del MUST fueron más bajas en comparación con la del MNA-sf (69,4%, 75,2% y 97,3% respectivamente), mientras que la E se manifiesta a la inversa (93,4%, 87,8% y 44,6% en cada caso). El MST tuvo un VPP mayor (79,3%) y menor VPN (88,2%) que el MUST y el MNA-sf

Tabla I. Validez, comportamiento y concordancia de las herramientas de cribado nutricional frente a la VNC por ámbito de estudio

	S (%)		E (%)		VPP (%)		VPN (%)		Eficiencia (%)		Kappa		AUC ROC	
	MUST	MNA-sf	MST	MNA-sf	MST	MNA-sf	MST	MNA-sf	MST	MNA-sf	MST	MNA-sf	MST	MNA-sf
MC*	79,4	96,3	69,4	52	94,2	46,9	83,2	91,3	97	88,2	84,3	74,2	81,8	0,669
A*	89,7	95,7	76,9	81	94,8	73,3	83,3	96,1	97,1	92,4	87,1	88,6	85,9	0,736
I*	75,2	97,3	69,4	44,6	93,4	43,5	79,3	89,1	97,5	88,2	81,5	70,9	81,5	0,566
H*	80,2	94,3	75,6	57,4	95	47,6	86,7	91,6	96,1	90	86,9	75,9	85,3	0,732
														0,853

S: sensibilidad; E: especificidad; VPP: valor predictivo positivo; VPN: valor predictivo negativo; MUST: malnutrition universal screening tool; MNA-sf: mini nutritional assessment short form; MST: malnutrition screening tool; MC: muestra completa; A: ambulatorios; I: institucionalizados; H: hospitalizados. *p < 0,001 (significación estadística entre las herramientas de cribado y la VNC en la muestra completa y en cada ámbito de estudio).

(MUST: 72,6%, 89,1% y MNA-sf: 43,5%, 97,5%, en cada caso). En esta serie, tanto la concordancia como la validez respecto a la VNC fueron superiores con el MUST (k = 0,624, AUC ROC = 0,815), seguido del MST (k = 0,566, AUC ROC = 0,763) y, finalmente, el MNA-sf (k = 0,311, AUC ROC = 0,710).

Hospitalizados

Se evaluó a 285 individuos con las herramientas MUST y MST (con una media de edad de $64 \pm 16,2$ años); en aquellos ≥ 65 años también se realizó el MNA-sf (181 sujetos). En la tabla I se especifican los resultados obtenidos respecto a la VNC. En global, la S fue del 80,2% con el MUST, 94,3% con el MNA-sf y 75,6% con el MST; la E fue del 93,5%, 57,4% y 95% con MUST, MNA-sf y MST, respectivamente. El MST tuvo el mejor VPP y el MNA-sf, el mayor VPN. Tanto el MUST como el MST obtuvieron mejores resultados que el MNA-sf en eficiencia (86,9%, 85,3% y 75,9%, respectivamente), concordancia (k = 0,747, k = 0,732 y k = 0,401, respectivamente) y validez (AUC ROC = 0,868, 0,853 y 0,759).

RANGO DE EDAD

30 a 64 años

Se realizaron los cribados MUST y MST en toda la serie (198 sujetos), cuyos resultados se detallan en la tabla II. Ambas herramientas presentaron E, VPN y eficiencia superior al 80%. A pesar de que el MST tiene una S menor al MUST (69,4% y 83,7% respectivamente), tiene un VPP estadísticamente superior (97,1% y 77,4% en cada caso). Ambas herramientas presentan adecuada concordancia y validez frente a la VNC.

65 a 74 años

Se evaluó con los tres cribados nutricionales a 108 sujetos. En la tabla II constan los resultados obtenidos respecto a la VNC. Las S del MUST y del MNA-sf fueron más bajas en comparación con la del MST, aunque en todos los casos superiores al 80%. La E fue de 93,7%, 61,7% y 93,8% con MUST, MNA-sf y MST respectivamente. El VPN fue superior al 80% en cada caso, mientras que el VPP del MNA-sf era del 42,6% frente al 83,3% del MST y el 75,9% del MUST. Se obtuvo la mejor eficiencia, concordancia y validez para el MUST y MST, especialmente este último, que alcanzó una validez del 0,932 en este rango de edad.

≥ 75 años

Se realizaron los tres cribados a 509 sujetos. En la tabla II se describen los resultados obtenidos respecto a la VNC. Las S del MUST y del MUST fueron más bajas en comparación con la del

Tabla II. Validez, comportamiento y concordancia de las herramientas de cribado nutricional frente a la VNC por rangos de edad

	S (%)			E (%)			VPP (%)			VPN (%)			Eficiencia (%)			Kappa			AUC ROC		
	MUST	MNA-sf	MST	MUST	MNA-sf	MST	MUST	MNA-sf	MST	MUST	MNA-sf	MST	MUST	MNA-sf	MST	MUST	MNA-sf	MST	MUST	MNA-sf	MST
30-64*	83,7	-	69,4	91,9	-	99,3	77,4	-	97,1	94,5	-	90,7	87,8	-	84,4	0,736	-	0,760	0,878	-	0,844
65-74*	81,5	88,5	92,6	93,7	61,7	93,8	75,9	42,6	83,3	91,4	94,3	97,4	87,6	75,1	93,2	0,711	0,368	0,833	0,864	0,751	0,932
≥ 75*	77,8	97,5	65,4	87,3	49,6	92,2	74,1	47,4	79,4	82,6	97,7	85,2	82,1	73,6	78,8	0,643	0,368	0,604	0,825	0,735	0,788

S: sensibilidad; E: especificidad; VPP: valor predictivo positivo; VPN: valor predictivo negativo; MUST: malnutrition universal screening tool; MNA-sf: mini nutritional assessment short form; MST: malnutrition screening tool.
*p < 0,001 (significación estadística entre las herramientas de cribado y la VNC en cada rango de edad).

MNA-sf (65,4%, 77,8% y 97,5%, respectivamente), mientras que la E fue más elevada para estos dos cribados (93,8%, 93,7% y 61,7% en cada caso). El MST tuvo un VPP mayor (79,4%) que el MUST y el MNA-sf (74,1% y 47,4%, respectivamente). En esta serie, tanto la eficiencia como la concordancia y la validez respecto a la VNC fueron superiores con el MUST (82,1%, $k = 0,643$, AUC ROC = 0,825), seguido del MST (78,8%, $k = 0,604$, AUC ROC = 0,788) y finalmente, el MNA-sf (73,6%, $k = 0,368$, AUC ROC = 0,735).

DISCUSIÓN

Nuestros resultados establecen prevalencias de desnutrición muy dispares con los cribados nutricionales empleados y en comparación con la VNC. Los hallazgos con algunas de las herramientas empleadas presentan altas sensibilidades con bajos VPP que tienden a sobreestimar la prevalencia de DRE. Se objetivan diferencias en la validez y el comportamiento de las mismas, tal y como se describe en la literatura (3), lo que depende de la prevalencia de desnutrición en la muestra de estudio y de la herramienta elegida como patrón de referencia.

La mayor prevalencia de desnutrición establecida se encuentra en pacientes institucionalizados y hospitalizados (30,1% y 30,2%, respectivamente), donde la implantación de un cribado ligado a un plan de acción permitiría realizar la VNC en aquellos con riesgo nutricional. No obstante, se requiere el uso de herramientas de cribado validadas (10) con una S y E adecuadas para la detección de sujetos en riesgo nutricional y evitar a su vez falsos positivos que incrementarían de forma innecesaria los costes sanitarios.

En pacientes ambulatorios, tanto el MUST como el MST presentan una eficiencia y validez similares y estadísticamente muy buenas en toda la serie, al igual que los resultados observados en individuos ≥ 65 años con el MNA-sf. A pesar de que el MST tiene una S aceptable pero menor que el MUST (76,9% y 89,7%, respectivamente), su elevada E (94,8%) hace que tenga un VPP más elevado (83,3% y 66%, respectivamente); por ello es la herramienta que obtiene una prevalencia más aproximada a la hallada con la VNC y resulta un cribado útil con independencia de que los pacientes sean oncológicos o no.

En los pacientes institucionalizados, tanto el MUST como el MST presentan una eficiencia del 81,5%. En ambos casos la S es inferior a la del MNA-sf, sin embargo, presentan una E y VPP estadísticamente mayores a las halladas con el MNA-sf, por lo que la eficiencia de esta última está comprometida al generar falsos positivos. En el trabajo de Tarazona FJ y cols. (27) se analizó el MNA con marcadores bioquímicos (albúmina, colesterol), antropométricos (IMC y circunferencia braquial) y el índice de Barthel, existiendo una correlación significativa con esta escala ($r = 0,742$), ya que relaciona el riesgo nutricional con aquellos pacientes que presentan mayor deterioro funcional (dependencia y fragilidad) al incluir preguntas sobre movilidad y problemas neuropsicológicos. Así pues, el estado funcional y la calidad de vida podrían aumentar la S del cribado sin existir una desnutrición establecida, ocasionar el bajo VPP que hemos obtenido en nuestra

muestra (43,5%) y sobreestimar el riesgo nutricional (28). El MNA ha demostrado ser más útil para detectar pacientes ancianos en riesgo nutricional que para detectar la malnutrición establecida (8,9). La validez que presenta el MST en este ámbito, a pesar de ser discretamente inferior a la obtenida por el MUST (0,763 y 0,815 respectivamente), es una herramienta útil, tal y como indican otros autores al comparar dicho cribado con herramientas preestablecidas como la VGS (29,30), el MNA (30) o con parámetros más objetivos (28).

En pacientes hospitalizados, la mayor concordancia y validez con la VNC se encuentra con el MUST y el MST ($k = 0,747$ y $0,732$; $AUC = 0,868$ y $0,853$, respectivamente), dos herramientas ya validadas en este ámbito. Entre ellas, el MUST es el cribado con mejor sensibilidad, con una diferencia del 4,6% respecto a la S del MST. No obstante, hay que tener en cuenta que el primero precisa cálculos y personal entrenado para su cumplimentación, mientras que el MST no, y puede ser rellenado por personal sanitario, el propio paciente o un familiar, lo que supone una ventaja (4,31). En cuanto al MNA-sf, herramienta empleada en pacientes con edad ≥ 65 años, genera falsos positivos y presenta baja especificidad, por lo que solo en el 57,4% de los casos será capaz de establecer la ausencia de malnutrición en pacientes sanos y, en cierto modo, podría confundir sobre el estado nutricional real de los pacientes, como indican otros autores con resultados similares a los nuestros (7). Puede deberse a que incluye cuestiones sobre el estado funcional y referentes a la presencia de enfermedad aguda, que en pacientes hospitalizados directamente resta puntuación.

Cuando se analizan los cribados por rango de edad, el MST también obtiene buenos resultados. En la serie de 30 a 64 años, tanto el MUST como el MST presentan adecuada concordancia y validez frente a la VNC. En la serie de 65 a 74 años, el MST es el cribado que presenta mejor comportamiento, concordancia y validez. En los sujetos a partir de 75 años se obtienen unos resultados muy similares a los encontrados en pacientes institucionalizados, ya que en dicho ámbito se ubican los pacientes de mayor edad.

El riesgo nutricional debe valorarse y registrarse de forma rutinaria en todos los pacientes, de manera análoga a como se hace con la temperatura, la tensión arterial o la frecuencia cardiaca, con la implicación de las unidades asistenciales responsables de los pacientes (32). Algunos autores con experiencia en la implementación de cribados nutricionales (33) objetivan que hay un cambio de conocimiento respecto a la DRE en la mayoría de los profesionales sanitarios. No obstante, escoger la adecuada herramienta de cribado es importante por el impacto de sus resultados en la práctica clínica (9).

Este trabajo presenta limitaciones. La principal ha sido comparar nuestros resultados con los encontrados en la literatura, ya que el comportamiento, la concordancia y la validez de las herramientas de cribado dependen de la muestra del estudio, de la prevalencia de la enfermedad y del patrón con el que se hayan comparado (9). En este sentido, hemos empleado la VNC como patrón de referencia, mientras que en la literatura se emplean herramientas de cribado o de valoración estandarizadas que difi-

cultan la realización de una comparación efectiva. Otra limitación es que se analiza de forma global, por ámbito sanitario y por edad; sin embargo, los resultados podrían variar si se analizaran el comportamiento y la validez de estas herramientas por patologías. Por otro lado, consideramos una limitación la interpretación de los resultados del cribado MNA-sf, especialmente en hospitalizados e institucionalizados, donde el estado funcional de los pacientes puede aumentar la S pero con bajo VPP.

En resumen, se debe implementar un cribado nutricional para identificar a pacientes con DRE y adecuar los recursos disponibles en el abordaje de este problema. La herramienta seleccionada debe tener una buena validez en el ámbito socio sanitario en el que se vaya a instaurar. Podemos concluir con nuestros resultados que, tanto en la muestra completa como por ámbito de estudio, el MST es el cribado con menor S respecto a la VNC, aunque es el más específico y con mayor VPP tanto por ámbito como por rango de edad. Estas características del MST, unidas a su simplicidad y rapidez en la cumplimentación, hacen que sea una herramienta de cribado nutricional válida no solo en pacientes hospitalizados y ambulatorios oncológicos, sino también en pacientes institucionalizados, los dependientes en su domicilio y ambulatorios no oncológicos, en los cuales no estaba previamente validada.

DECLARACIONES ÉTICAS

Los autores declaran que los procedimientos seguidos cumplían los reglamentos del Comité Ético de Investigación Clínica responsable y de la Asociación Médica Mundial y la Declaración de Helsinki. Declaran que han cumplido los protocolos de su centro de trabajo para la publicación de datos de pacientes y que todos los pacientes incluidos en el estudio han recibido suficiente información y han dado su consentimiento informado por escrito para participar en él. Los autores declaran que en este artículo no aparecen datos de pacientes.

CONTRIBUCIÓN

ICV y AHM han contribuido al diseño del estudio. ICV, SVM, JCL y CSV han participado en el reclutamiento de los pacientes. ICV, SVM, CBM y AHM han realizado el análisis de los datos y la realización del manuscrito. Todos los autores han contribuido a la revisión crítica del contenido intelectual y han aprobado la versión definitiva.

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Trabajo Original

Epidemiología y dietética

Critical overview of current anthropometric methods in comparison with a new index to make early detection of overweight in Spanish university students: the normalized weight-adjusted index

Visión crítica de los métodos antropométricos actuales en comparación con un nuevo índice para la detección precoz de sobrepeso en estudiantes universitarios españoles: el índice normalizado ajustado al peso

Guillermo Doménech-Asensi¹, Carlos Gómez-Gallego^{1,2}, Gaspar Ros-Berrueto¹, Francisco Javier García-Alonso¹ and Manuel Canteras-Jordana³

¹Department of Food Science and Nutrition. Faculty of Veterinary Sciences. Regional Campus of Excellence "Campus Mare Nostrum". University of Murcia. Murcia, Spain.

²Functional Foods Forum. Faculty of Medicine. University of Turku. Turku, Finland. ³Department of Biostatistics. Faculty of Medicine. Regional Campus of Excellence "Campus Mare Nostrum". University of Murcia. Murcia, Spain

Abstract

Background: overweight and obesity have been increasing, and university students are an important target for prevention programs. Previous studies have reported differences in the diagnosis between different anthropometric methods, so some students can be misclassified depending on the method used.

Objective: to evaluate the efficacy of different anthropometric methods to detect those university students in a probable status of overweight, including a comparison with a new proposed method, the normalized weight-adjusted index (NWA).

Methods: different anthropometric methods (waist circumference, waist-hip ratio, waist-height ratio, body mass index, conicity index, bioimpedance and Brozek, Siri and Heath-Carter equations) were calculated for 505 university students. By k-means cluster analysis, students with higher values according to variables involved in overweight were identified. Parameters of accuracy were calculated by operating characteristic curves.

Results: NWA showed significant correlations with the most used methods. Prevalence of students with body fat excess varied from 5.9% to 48.4% for women and from 8.5% to 49.0% for men depending of the method employed, being demonstrated a great variability between the different methodologies. Body mass index for women and waist circumference for men resulted to be the most accurate methods to detect a probable situation of excess of body fat or cardiovascular risk associated. NWA resulted also a good alternative for overweight classification.

Conclusions: differences between anthropometric methods for overweight and cardiovascular disease risk classification were confirmed. Classical cut-off point may misdiagnose overweight or health risk in Spanish university students depending of the method employed.

Key words:

Anthropometry.
University students.
Overweight. Early
detection.

Resumen

Introducción: el sobrepeso y la obesidad han ido en aumento, y los estudiantes universitarios son un objetivo importante para los programas de prevención. Estudios previos demuestran diferencias en el diagnóstico según el método antropométrico utilizado.

Objetivo: evaluar la eficacia de diferentes métodos antropométricos para detectar a los estudiantes universitarios en un probable estado de sobrepeso y comparar con un nuevo método, el índice normalizado ajustado al peso (INAP).

Metodología: se utilizaron diferentes métodos antropométricos (circunferencia de cintura, cociente cintura-cadera, relación cintura-altura, índice de masa corporal, índice de conicidad, bioimpedancia y ecuaciones de Brozek, Siri y Heath-Carter) para 505 estudiantes universitarios. Se identificaron los estudiantes con valores más altos de acuerdo a las variables involucradas en el sobrepeso y se calculó la precisión de los distintos métodos antropométricos.

Resultados: el INAP mostró correlaciones significativas con los métodos más utilizados. La prevalencia de estudiantes con exceso de grasa corporal varió para las mujeres del 29,4% al 78,1% y para los varones del 12,0% al 54,0% dependiendo del método empleado. El índice de masa corporal para las mujeres y la circunferencia de cintura para los hombres fueron los métodos más precisos para detectar un probable exceso de grasa corporal o riesgo cardiovascular asociado. El INAP resultó una buena alternativa para la clasificación de sobrepeso.

Conclusiones: se confirmaron las diferencias entre los métodos antropométricos para el sobrepeso y la estimación de riesgo cardiovascular. Los puntos de corte clásicos pueden diagnosticar erróneamente sobrepeso o riesgo para la salud en estudiantes universitarios españoles dependiendo del método empleado.

Palabras clave:

Antropometría.
Estudiantes
universitarios.
Sobrepeso. Detección
temprana.

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Correspondence:

Guillermo Doménech-Asensi. Department of Food Science and Nutrition. Faculty of Veterinary Sciences. Universidad de Murcia. Campus de Espinardo. Calle Campus Universitario, 7. 30100 Murcia, Spain
e-mail: gdomenech@um.es

INTRODUCTION

Overweight and obesity are defined as abnormal or excessive fat accumulation in adipose tissue and, according to the World Health Organization (WHO) in 2014, it is an escalating epidemic, affecting developed and developing countries (1). Overweight is defined as a body mass index (BMI) between 25 and 30 and obesity, when it is higher than 30 (2). Obesity is a complex, multifactorial chronic disease, which is caused by the interaction of genetic and environmental factors, and is associated with increases in all-cause mortality. Moreover, these individuals with obesity may also suffer from social stigmatization and discrimination (3).

Obesity has an increasing tendency in all countries, and the worldwide prevalence of obesity has nearly doubled since 1980 (1). In 2014, 39% of adults aged 18 years and older (38% of men and 40% of women) were considered to be overweight or obese. This increment in obesity is associated with an increased risk of cardiovascular disease (CVD), type-2 diabetes, some types of cancer and other health problems (4).

There are several anthropometric methods available to estimate health status, methods to estimate the body fat percentage (BF%) including measurements based on skinfold thickness such as Brozek (5), Heath-Carter (6) and Siri (7) equations, or bioimpedance-based measurements that utilize differences in the electrical transmission capability between water and fat. Other methods are those indexes used as predictors of the cardiovascular risk where the BMI is the principal criterion used to define obesity (1,8,9), but it is also correlated with CVD-related risks, particularly cholesterol plasma levels and high blood pressure in adolescents (10). Other indexes are included in this group which estimate abdominal fat and the consequent CVD risk, such as the weight-height ratio (WHtR), waist circumference (WC), waist-hip ratio (WHR) or conicity index (CI) (11,12).

Given the rising incidence of obesity in the young, there has been growing concern about the accuracy of the different body composition measurement methods (10,13). Studies of population-specific cut-off points are needed, considering variables such as gender, ethnic origin, geographical location and socio-economic status. In addition, studies of novel variables that could enhance the role of anthropometry in health monitoring are needed (14).

University students are at a critical juncture in their lives because they are beginning to be independent. In this population, where prevalence of overweight and obesity is usually low, an early detection is very important to prevent health disorders in adult ages (15,16). But one problem for the early detection is the fact evidenced by some studies which refer differences in overweight and obesity classification depending on the anthropometric method used (17,18).

Knowing the probable disparity of results between the different anthropometric equation and indexes, especially in those cases near overweight, it would be necessary to detect also that group of students close to that status that may be misdiagnosed as healthy depending on the method used, so that they could be warned early about their lifestyle and dietary habits.

Furthermore, in the present study, a new anthropometric index to identify this group of students has been proposed, the normalized weight-adjusted index (NWA), structured as a sum of components, making the statistical treatment in epidemiological studies easier. Equations with squared variables in the denominator as BMI or other more complex as BF% are not easy to treat statistically, especially with small samples size, so non-parametric analyses should be needed either transformations of data. The NWA data, due to its linear structure, do not need to be transformed and parametric analyses could be employed whenever possible.

The aim of this study was to compare the employment of different anthropometric methods to detect, in a population of university students with low prevalence of overweight and obesity, those with overweight or with cardiovascular risk associated to body fat mass, including a comparison with the new NWA.

MATERIAL AND METHODS

STUDY DESIGN, VOLUNTEERS AND ANTHROPOMETRIC MEASUREMENTS

Setting and study design

A cross-sectional study of 505 healthy students of the Degree of Nursery was conducted at the University of Murcia. The sample was composed of 388 females and 117 males aged 18-30 years, with a mean age of 21 ± 4 .

Anthropometric measurements and indexes

All measurements were taken on the same visit to the nutrition laboratory of the University of Murcia. The experimental protocol was approved by the local ethics committee at the University of Murcia. The following anthropometric measurements were performed:

1. Body weight was measured to the nearest 0.1 kg, and body height was measured to the nearest 0.1 cm, using standard medical equipment in subjects wearing light indoor clothing without shoes, jackets or sweaters (19).
2. BMI was calculated as the body mass divided by height squared (kg/m^2) (20). Participants were classified according to the WHO (2) standards: underweight was defined as a BMI of < 18.5 , normal weight was classified as a BMI of ≥ 18.5 and < 25 , overweight was defined as a BMI of ≥ 25 and < 30 , and obesity was defined as a BMI of ≥ 30 .
3. The skinfold thickness (biceps, triceps, subscapular, supra-iliac, abdominal, thigh and calf) was measured in triplicate on the dominant side of the body to the nearest 0.2 mm, using a Holtain skinfold caliper.
4. The WC and hip circumference (HC) were measured in the mid-way section between the lower edge of the ribs and iliac crest and in the widest portion of the buttocks, using a non-stretchable tape parallel to the floor to an accuracy of 0.1 cm. All mea-

surements were made in duplicate (21). CVD risk was defined as a WC > 80 cm in females and 94 cm in males (2), or when the WHR > 0.8 in women or 0.9 in men (22).

5. The WHtR was calculated by dividing the WC (cm) by the height (cm), with 0.5 used as a cut-off point in both genders (23).
6. The CI was calculated by the formula described by Valdez et al. (24) $[CI = WC/0.109\sqrt{(\text{weight}/\text{height})}]$, with WC and height measured in m and weight in kg. Cut-off points were established at 1.18 for females and 1.25 for males.
7. The BF% was calculated using the following equations:
 - Siri equation: $[BF\% = 100 \times (4.95/D) - 4.5]$ (7).
 - Brozek equation: $[BF\% = 100 \times (4.57/D) - 4.142]$ (25). In the Siri and Brozek equations, D is the human body density, calculated using Durnin and Womersley's formula (26), $[D(g/l) = C - (M \log X)]$, where C and M are coefficients dependent of age and gender, and X is the sum of the tricipital, bicipital, supra-iliac and subscapular skinfold thicknesses.
 - Heath-Carter's equation for men $[BF\% = 0.2585 + 0.1051 \times \sum X]$ and for women $[BF\% = 3.580 + 0.1548 \times \sum X]$, where $\sum X$ is the sum of the tricipital, bicipital, supra-iliac, subscapular, thigh and calf skinfold thicknesses (6).

Bioelectrical impedance analysis (BIA)

BIA measurements of hand-hand impedance (BIA-arm) were obtained using a manual impedancimeter (OMRON BF 300®, OMRON Matoukasa Co. LTD, Japan), and foot-foot impedance (BIA-leg) was measured with a body composition scale (OMRON BF 400®, OMRON Matoukasa Co. LTD, Japan). All the measurements were performed in accordance with the manufacturer's instructions.

Normalized weight-adjusted index (NWA)

The new NWA was built as a linear regression between weight and height. The NWA was defined as follows: $[(\text{weight}/10) - (10 \times \text{height}) + 10]$ with weight measured in kg and height in m. The constant +10 approximates the mean of the distribution to zero. Thus, the values of the index can be positive or negative.

Statistical method

A descriptive analysis was conducted to determine the mean and standard deviation. Statistically significant differences were calculated using a Student's t-test. Pearson's bivariate correlation analysis of all the anthropometric methods was then conducted. A k-means cluster analysis was performed to separate the sample into groups according to the variables that influence overweight or obesity. Receiver operating characteristic (ROC) curves were performed to calculate sensitivity, specificity and area under the curve (AUC) and determine the cut-off points for each anthropometric method.

RESULTS AND DISCUSSION

SAMPLE DESCRIPTION

Table I shows the anthropometric data for the male and female students. Several parameters present significant differences between genders ($p < 0.05$). Weight, height, WC, BMI, WHR, WHtR and CI were higher in men, and triceps, biceps, thigh and calf skinfold thicknesses and BF% for all equations were higher in women. These differences between genders were similar than those reported in studies developed in the University of Basque Country, Spain (17), and in the University of Pernambuco, Brazil (27).

Table I. Anthropometric characteristics of the sample (mean $\pm$ standard deviation)

	Women		Men		p-value*
	Mean	SD	Mean	SD	
Age	21.0	4.5	21.2	4.8	> 0.05
Weight (kg)	61.3	9.7	77.3	13.5	< 0.05
Height (m)	163.9	0.6	176.5	0.7	< 0.05
Waist Circumference (cm)	72.1	7.7	83.4	10.1	< 0.05
Hip circumference (cm)	98.3	8.5	99.9	8.9	> 0.05
<i>Skinfolds (mm)</i>					
Triceps	19.5	5.9	13.3	6.2	< 0.05
Biceps	11.6	5.9	7.2	4.2	< 0.05
Subscapular	13.6	5.1	13.5	4.8	> 0.05
Supra-iliac	16.5	6.3	16.4	8.2	> 0.05
Abdominal	20.3	6.7	21.2	9.1	> 0.05
Thigh	28.9	8.4	21.1	9.5	< 0.05
Calf	22.5	7.6	15.8	7.6	< 0.05
BMI	22.79	3.46	24.74	3.75	< 0.05
WHR	0.73	0.05	0.83	0.05	< 0.05
WHtR	0.44	0.06	0.47	0.06	< 0.05
CI	1.08	0.06	1.16	0.06	< 0.05
NWA	-0.27	0.95	0.07	1.19	< 0.05
<i>Body fat %</i>					
BIA-arm	27.76	7.53	20.04	7.56	< 0.05
BIA-leg	29.95	6.92	17.27	4.94	< 0.05
Heath-Carter equation	22.34	4.85	13.14	4.20	< 0.05
Siri equation	28.66	4.35	18.58	4.63	< 0.05
Brozek equation	27.71	4.01	18.41	4.28	< 0.05

BMI: body mass index; WHR: waist-hip ratio; WHtR: waist-height ratio; CI: conicity index; NWA: normalized weight-adjusted index; BIA-leg: bioimpedance analysis foot-foot; BIA-arm: bioimpedance analysis hand-hand. *Differences between gender calculated by Student's t-test.

In relation to the NWAI, it also resulted significantly higher in men ($p < 0.05$). Mean value for women was -0.27 with a range from -0.81 to 4.80; for men, the mean value was 0.07, ranging from -0.47 to 4.40.

The mean value for the anthropometric indexes (BMI, WHtR, WC, WHR and CI) and BF% were in both genders in the range of normality. On the other hand, the values of BIA-leg in women (29.95%) and BIA-arm in men (20.04%) are in the high limit recommended by the SEEDO (Spanish Society for the Study of Obesity) (20-30% for women and 12-20% for men) (28).

Results exert great variability depending on the index or equation used. The mean BF% for men varied from 13.14% using the Heath-Carter equation to 20.04% using the BIA-arms. In women, it varied from 22.34% using the Heath-Carter equation to 29.95% using the BIA-legs.

Figure 1 shows the differences between the classifications according to BF% estimation. In women, the proportion of volunteers with higher BF% than recommended (overweight and obesity) varies from 29.4% with the Heath-Carter equation to 78.1% with Siri equation. In the case of men, it ranges from 12.0% with the Heath-Carter equation to 54.0% with the BIA-arm. The cases of volunteers with lower BF% than recommended were very low or inexistent for all methods. Watching BMI, we observe that differences are greater for women, so only 17.9% of females are considered to be overweight or obese. We can see that, in both genders, the Heath-Carter equation provides much lower BF% values than other equations and BIA methods.

According to these results, Arroyo et al. (17) found 6.1% of obesity when measured by Siri equation but only 2.5% by BMI, while the proportion of overweight was 9.7% by Siri equation and 17.2% by BMI, and also differences between BF% equations. Mighelli et al. (18) describe that only 29.7% of individuals catalogued as obese by BF% Lohman equation were also identified as obese by BMI, while this value was 44.2% between WC and BMI. In the present study, it has been found that for women, only 10.7% of the individuals catalogued as obese by Siri equation were also by BMI.

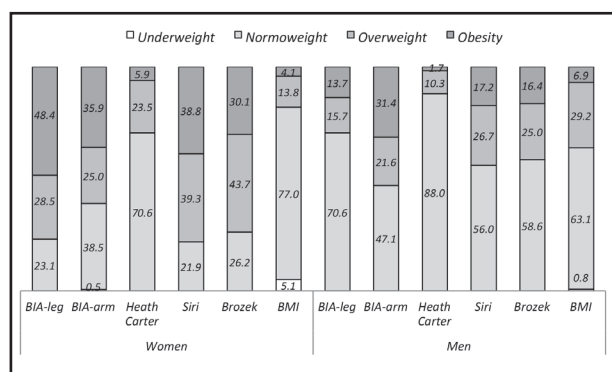


Figure 1.

Distribution body fat percentage classification measured with different anthropometric methods (bioimpedance analyses and body fat percentage equation) than SEEDO criteria and body mass index. BIA-leg: bioimpedance analysis foot-foot; BIA-arm: bioimpedance analysis hand-hand; BMI: body mass index.

By Brozek equation this percentage was 13.9%, by Heath-Carter equation the percentage was 40.9% and by WC, it was 71.4%. In the case of men, percentages were 35.0% for Siri, 36.8% for Brozek and 100% for Heath-Carter and WC. These results indicate that Heath-Carter equation and WC index were better correlated with BMI in this population, and the employment of Siri and Brozek equations should be avoided. In addition, these results should be considered as a warning and the anthropometric indexes and equations should be carefully selected depending of the population group. It seems that the Siri and Brozek equations tend to overestimate the percentage of fat. It could be related to the fact that Siri and Brozek equations are based on measurements of skinfolds in trunk and arms, whereas the Heath-Carter equation uses skinfolds of trunk, arms and legs. As the Heath-Carter equation measures body fat in more regions, it may be a better reflection of total adiposity than the Siri and Brozek equations, but it should be evaluated in further studies.

The method that classified a higher percentage of obesity is BIA-leg in women (48.4%) and BIA-arm in men (31.4%). The prediction of BF% using the BIA-arm or BIA-leg measurement assumes that the impedance determined for hand-to-hand or foot-to-foot is representative of the total body composition, but this is not always the case. Variables, such as the length of the limbs or their complexion, can over/underestimate the total BF% (31). Fat distribution also differs between men and women; while men tend to accumulate fat in the abdominal region and arms, women tend to accumulate fat in the hip and legs, so it seems that BIA tended to overestimate BF% when BIA-arm for men and BIA-leg for women were used in the studied population.

Fig. 2 shows the proportion of volunteers with some cardiovascular risk, associated with the amount and distribution of body fat, estimated with the different anthropometric indexes described. We can see again the great disparity between the different indexes, especially in men. In females, we found from 7.4% by CI up to 17.9% with BMI, whereas for males the range varies from 8.5% measured with CI and WHR to 36.4% by BMI. In the studied popu-

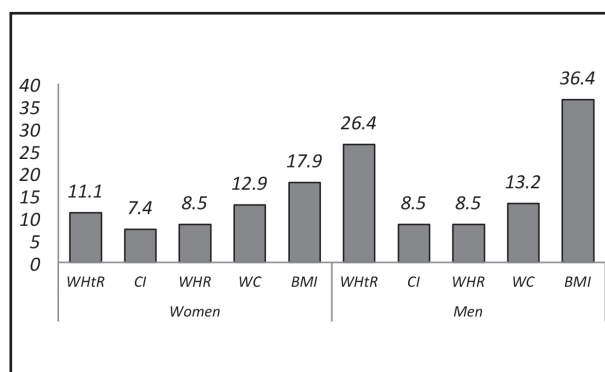


Figure 2.

Proportion of men and women with some risk of cardiovascular disease estimated with each anthropometric method evaluated. WHtR: waist-height ratio; CI: conicity index; WHR: waist-hip ratio; WC: waist circumference; BMI: body mass index.

lation, BMI seems to overestimate cardiovascular risk, which could be related to the fact that it is a young population and BMI does not differentiate between fat and muscular mass, which could introduce a bias in young sportspersons groups.

CORRELATIONS

To assess the results of the NWAI we have made bivariate correlations between all the anthropometric methods used (Table II). NWAI were strongly correlated with all anthropometric methods evaluated ($p < 0.05$), especially BMI ($r = 0.995$ for men and $r = 0.986$ for women), WHtR ($r = 0.931$ for men and $r = 0.871$ for women) and WC ($r = 0.908$ in men and $r = 0.802$ in women). The correlation found between the Brozek and Siri equations ($r = 1.000$) for both genders can be explained by the similar methods used to calculate BF% (5,7,26).

The correlation level between BMI and WC in our study ($r = 0.843$ for women and $r = 0.923$ for men) is similar to those described by Minghelli et al. (18) ($r = 0.884$), taking into account that they assessed correlation for men and women together. Araujo et al. (11) compared BF% by BIA *versus* WC, WHtR, IC and BF% by skinfold thickness. The author described the highest correlation between BIA and WC, being 0.698 for women and 0.792 for men; in our study, this correlation was also higher for men by both BIA methods. As in our study, a low correlation between BIA and IC was found in both genders, being much lower for women (0.217 for women and 0.587 for men). We agree with these authors on the fact that, considering the differences found between different anthropometric methods, it is important to compare the same methods when analyzing different investigations.

With these results, it can be expected that some students might be diagnosed as overweight with some anthropometric methods

while in others they are in healthy weight. Right the opposite, students with a real status of overweight may be misdiagnosed as healthy weight and, therefore, they would not be warned about the real risk of their life style. It must be also noted that other factors such as physical activity or consumption of tobacco or alcohol increase the risk of cardiovascular disease.

K-MEANS CLUSTER ANALYSIS

The k-means cluster analysis was carried out separately for men and women, using all the variables related to overweight or obesity: weight, height, WC, hip perimeter and all skinfold thicknesses. In relation to all these data, the sample was divided into three groups (Table III). In line with the characteristics of the groups, group 1 represented students with low-mid values, group 2 included students with values in the middle range, and group 3 represented students with higher values, those who were already overweight or obese, but also those considered to be in risk of being overweight based on all variables measured. In the case of women, the distribution was the following: group 1, 188 students (48.4%); group 2, 145 students (37.4%); and group 3, 55 students (14.2%). With regard to men, there were 81 (69.3%), 26 (22.2%) and ten (8.5%) students in groups 1, 2 and 3, respectively.

For example, when analyzing the female group 3, we can observe that it includes 55 students with a mean BMI of 28.97. In this group, the person with lower BMI had 23.53. According to the WHO criteria (2), BMI < 25 is not considered as overweight, but in this particular case this student also had a BF% of 26.18, 33.72 and 32.39 measured by Heath-Carter, Siri and Brozek equations, respectively, which is considered as obesity according to the SEEDO (28) criteria. In the opposite side, watching group 2,

Table II. Correlations between all anthropometric methods in men (top of table) and women (bottom of table)

		Men										
		BIA-leg	BIA-arm	Heath-Carter	Siri	Brozek	BMI	WC	WHR	WHtR	CI	NWAI
Women	BIA-leg		0.810*	0.745*	0.804*	0.804*	0.879*	0.842*	0.524*	0.861*	0.652*	0.878*
	BIA-arm	0.650*		0.771*	0.837*	0.837*	0.796*	0.805*	0.496*	0.826*	0.693*	0.804*
	Heath-Carter	0.563*	0.466*		0.926*	0.926*	0.764*	0.770*	0.397*	0.760*	0.602*	0.755*
	Siri	0.600*	0.492*	0.908*		1.000*	0.756*	0.762*	0.448*	0.772*	0.624*	0.756*
	Brozek	0.600*	0.492*	0.908*	1.000*		0.756*	0.762*	0.448*	0.772*	0.624*	0.756*
	BMI	0.795*	0.627*	0.705*	0.723*	0.723*		0.923*	0.557*	0.925*	0.638*	0.995*
	WC	0.639*	0.519*	0.656*	0.690*	0.690*	0.843*		0.680*	0.947*	0.857*	0.908*
	WHR	0.075	0.015	0.209*	0.247*	0.247*	0.285*	0.575*		0.718*	0.764*	0.557*
	WHtR	0.713*	0.581*	0.656*	0.683*	0.683*	0.866*	0.949*	0.569*		0.853*	0.931*
	CI	0.172*	0.138	0.325*	0.367*	0.367*	0.315*	0.727*	0.688*	0.693*		0.635*
	NWAI	0.800*	0.637*	0.692*	0.707*	0.707*	0.986*	0.802*	0.276*	0.871*	0.294*	

BIA-leg: bioimpedance analysis foot-foot; BIA-arm: bioimpedance analysis hand-hand; BMI: body mass index; WC: waist circumference; WHR: waist-hip ratio; WHtR: waist-height ratio; CI: conicity index; NWAI: normalized weight-adjusted index. *Statistical significant differences at $p < 0.05$ by r-Pearson correlation.

Table III. Groups identified after the k-means cluster analysis and its characteristics (number of cases, mean, standard deviation, minimum and maximum) for all anthropometric methods evaluated

Anthropometric method	Group	Women					Men				
		n (388)	Mean	SD	Min	Max	n (117)	Mean	SD	Min	Max
BIA-leg	1	188	26.53	5.65	12.27	50.00	81	15.39	4.02	8.30	24.50
	2	145	31.55	4.78	12.80	39.70	26	20.58	2.32	15.70	24.10
	3	55	38.27	6.78	22.00	51.70	10	25.18	2.90	21.70	28.10
BIA-arm	1	188	24.93	6.58	7.00	45.40	81	17.12	5.91	5.70	28.80
	2	145	28.68	6.26	12.80	41.10	26	24.18	4.25	18.10	30.40
	3	55	36.62	6.15	22.40	46.00	10	33.58	3.74	28.00	38.50
Heath-Carter equation	1	188	18.68	2.62	10.58	25.40	81	10.93	2.04	7.03	15.33
	2	145	24.55	2.75	16.59	31.16	26	17.01	2.62	12.60	22.85
	3	55	29.19	3.88	19.84	37.43	10	21.67	2.67	16.87	25.85
Siri equation	1	188	25.36	2.67	17.00	32.05	81	16.32	3.15	9.32	22.33
	2	145	30.65	2.38	24.21	37.27	26	22.22	2.58	17.32	27.97
	3	55	34.71	2.80	27.25	41.18	10	27.12	2.17	25.36	31.12
Brozek equation	1	188	24.67	2.46	16.95	30.84	81	16.33	2.91	9.86	21.87
	2	145	29.55	2.20	23.61	35.66	26	21.77	2.38	17.25	27.08
	3	55	33.30	2.59	26.41	39.27	10	26.29	2.00	24.67	29.99
BMI	1	188	20.69	1.64	17.01	27.04	81	22.97	2.02	18.47	27.66
	2	145	23.29	1.66	19.16	28.68	26	26.54	2.17	22.09	29.24
	3	55	28.97	3.65	23.53	41.51	10	32.78	2.96	28.40	38.04
WC	1	188	67.41	4.10	58.00	83.00	81	78.70	5.24	65.50	89.00
	2	145	72.56	4.51	62.00	87.50	26	90.62	6.26	79.50	102.00
	3	55	85.38	7.13	74.00	106.60	10	109.02	7.92	98.10	118.00
WHR	1	188	0.73	0.05	0.61	0.97	81	0.82	0.04	0.73	0.99
	2	145	0.73	0.06	0.61	0.97	26	0.85	0.05	0.76	0.93
	3	55	0.77	0.07	0.56	0.99	10	0.91	0.07	0.84	1.04
WHtR	1	188	0.41	0.02	0.35	0.49	81	0.45	0.03	0.38	0.53
	2	145	0.44	0.03	0.39	0.55	26	0.51	0.04	0.42	0.60
	3	55	0.52	0.05	0.45	0.67	10	0.60	0.05	0.53	0.64
CI	1	188	1.06	0.04	0.95	1.16	81	1.14	.05	1.00	1.23
	2	145	1.09	0.07	0.97	1.43	26	1.19	.05	1.10	1.29
	3	55	1.14	0.07	0.97	1.38	10	1.27	.06	1.19	1.36
NWAI	1	188	-0.81	0.51	-2.70	0.95	81	-0.47	0.66	-1.96	1.01
	2	145	-0.15	0.51	-1.32	1.39	26	0.61	0.72	-1.09	1.45
	3	55	1.37	0.98	-0.25	4.80	10	2.63	1.00	1.22	4.40

Group 1: students with low values. Group 2: students with values in the middle range. Group 3: students with higher values. BIA leg: bioimpedance foot-foot; BIA arm: bioimpedance hand-hand; BMI: body mass index; WC: waist circumference; WHR: waist-hip ratio; WHtR: waist-height ratio; CI: conicity index; NWAI: normalized weight-adjusted index.

the case with highest value for BMI was 28.68. This particular case presented BF% of 22.72, 30.69 and 29.59 measured by the Heath-Carter, Siri and Brozek equations, respectively, that is, lower values than the previous case. The same interpretation can be made with all the anthropometric methods and in both genders.

Obviously, when we want to determine whether a subject is in a situation of overweight or not, or if there is cardiovascular risk or not, we usually use only one simple, accurate, or easy to interpret method, being BMI the most widely used method in clinical practice (32). However, as we have previously seen,

making a correct classification depends upon the anthropometric method used.

ROC CURVES

Once the studied population had been divided into three groups, the intention was to determine which anthropometric method was more accurate to define students with probable overweight or excess of fat mass. ROC curves were used to determine the AUC and the cut-off points for all the anthropometric methods evaluated. The AUC is a measure of the degree of accuracy of the method, and in the studied population the accuracy to identify the group of students with overweight or excess of fat mass. The cut-off point is established through sensibility and specificity. Sensitivity refers to the percentage of the population that is correctly identified as having a specific condition, and specificity defines the percentage of healthy people who are correctly identified as not having that condition. Considering that the best cut-off point is that with the highest sensitivity and specificity possible, being inversely correlated, when we study a population with low prevalence of overweight/obesity, as university students, it is more appropriate to establish a cut-off point setting maximum sensibility (1.00) and the highest specificity possible. Thus, we prioritize the diagnosis of all true positives, discarding the highest possible percentage of true negatives (Table IV).

In the case of women, with the value of BMI ≥ 23.53 we would diagnose 100% of students with overweight and discard 80% who are healthy, being the most effective method for diagnosis. On the other hand, we found that with BIA-leg with a cut-off point of 21.9 BF% we would detected 100% of patients with excess body fat but only 14% of students without excess of BF% would

be discarded. The extremely low level of specificity in the case of WHR and CI (0.01 and 0.02, respectively) is remarkable. If we look again at table III, we can see that in group 3 the minimum and maximum WHR values of the whole sample are included. This means that the student with the lowest WHR value may be probable overweight according to other anthropometric methods, so this index would not be useful in this population. The situation for the CI is similar and coincides with the low correlation between the IC and the WHR with the other anthropometric methods that respond in a more homogeneous way. In the case of men, it has been observed that the best methods are the WC, with a cut of 97.5, followed by Siri and Brozek equations, with 25.36% and 24.67% of body fat respectively, which detect 100% of patients at risk discarding 97% of healthy individuals, in the case of WC, and 94% of those in the case of Siri and Brozek equations.

For women, the cut-off points in the present study are lower than those described in the literature. This makes sense because this work focuses on the prevention of overweight, which may be undiagnosed with a single index. However, the opposite occurs in the case of men. The cut-off points reflected after the analysis of the ROC curves are greater than those described in the bibliography for each specific method. For example, we find that for BMI the cut-off point is 28.38, greater than the value 25 that defines overweight. This situation could be explained because, in young people, females and males tend to take different exercises and sports. In particular, men frequently practice sports that increase their muscular mass, with a consequent rise in weight without increasing fat mass.

In the case of the proposed new index, Nwai, we see that for women with a value of -0.25 we detect 100% of students likely to be overweight or with a cardiovascular risk associated, discarding 69% of healthy women. In the case of men the cut-off point 1.20 is more effective as discards 92% of healthy subjects.

Table IV. Cut-off points, sensibility, specificity and the area under the curve for each anthropometric method optimized at maximum sensibility calculated by receiver operating characteristic (ROC) curves

Anthropometric method	Women				Men			
	Value	Sensibility	Specificity	AUC	Value	Sensibility	Specificity	AUC
BIA-leg	21.90	1.00	0.14	0.863	21.45	1.00	0.87	0.951
BIA-arm	22.35	1.00	0.28	0.864	27.85	1.00	0.93	0.987
Heath-Carter equation	19.84	1.00	0.40	0.933	18.52	1.00	0.92	0.983
Siri equation	27.23	1.00	0.46	0.947	25.36	1.00	0.94	0.982
Brozek equation	26.40	1.00	0.46	0.947	24.67	1.00	0.94	0.982
BMI	23.53	1.00	0.80	0.998	28.38	1.00	0.92	0.983
WC	73.75	1.00	0.79	0.978	97.55	1.00	0.97	0.995
WHR	0.61	1.00	0.01	0.711	0.84	1.00	0.69	0.874
CI	0.97	1.00	0.02	0.789	1.19	1.00	0.79	0.949
WHR	0.45	1.00	0.82	0.970	0.53	1.00	0.79	0.979
Nwai	-0.25	1.00	0.69	0.982	1.20	1.00	0.92	0.985

AUC: area under the curve; BIA leg: bioimpedance foot-foot; BIA arm: bioimpedance hand-hand BMI: body mass index; WC: waist circumference; WHR: waist-hip ratio; CI: conicity index; WHtR: waist-height ratio; Nwai: normalized weight-adjusted index.

Comparing both genders, there are differences in the cut-off points between men and women. There are significant differences in body composition between men and women, so, as in the previous study of Price et al. (33), the establishment of different cut-off points for both genders should be considered as necessary.

Depending on the anthropometric method used, there can be great differences in the classification of an individual in a situation of overweight/obesity or cardiovascular risk or, conversely, in a healthy situation. Therefore, the option of integrating certain anthropometric variables related to overweight and cardiovascular risk should be considered in order to determine the cut-off points of each anthropometric method with maximum sensitivity, to define when it should be considered that a student may be in a situation of overweight or cardiovascular risk, and if so, recommend complementary tests to confirm or rule out this situation.

WC and WHtR have been reported as good indicators of CVD risk, followed closely by BMI (34), whereas others studies concluded that BMI was the best indicator for blood pressure but not for lipoprotein plasma levels (35,36). The NWAi measures the same variables as BMI. Furthermore, the correlations between the NWAi and BMI, WC and WHtR were very high. To prevent overweight and obesity or cardiovascular risk among university students, specific cut-off points, or even the proposed NWAi, adapted to the characteristics of that population should be applied to enable more accurate anthropometric evaluations. Although the NWAi is not as accurate as BMI in women, it would be convenient to consider its use for ease in performing statistical treatments because of the linear structure of its equation. WC also meets these criteria, so we thought it would be the first choice. In the case of men, the most precise methods are the Siri and Brozek equations, but they require specific material to measure skinfold thickness and the mathematical structure of their equations would make it difficult to treat them statistically if epidemiological studies are required.

The importance of interventions among those aged 18-29 years to prevent obesity has been highlighted (37). In a similar study, Li et al. (38) reported that the largest increment in WC and WHtR occurred at 18-19 years of age. Both studies, as well as the present study, suggest that intervention efforts to prevent obesity should focus on this age range.

CONCLUSION

In this kind of population there is a low prevalence of overweight or obesity, although it is increasing. Moreover, there are also people close to this status that may be misdiagnosed depending on which anthropometric method is used, so that they cannot be properly warned about it. The cut-off points of classical anthropometric equations or indexes are designed to identify people who are already overweight or at cardiovascular risk. In the present study, we try to eliminate this bias and establish cut-offs that cover the different variables related to health risk derived from overweight, with the aim of persuading these subjects in time so that they could make changes in their lifestyle if necessary.

BMI is the best method to detect women with probability of being overweight in the studied population, with a cut-off value of 23.53, while WC is the best method in case of men, with 97.5 cm. The cut-off points for women and men using the NWAi were -0.25 and 1.22, respectively. The NWAi is economical, easy to apply, it does not require trained staff and it is easy to treat statistically. Thus, the NWAi could be a valid alternative to current indexes for the early detection of overweight/obesity in male and female university students.

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Trabajo Original

Epidemiología y dietética

The relationship between socioeconomic status and beverage consumption in children: The Cuenca Study

Relación entre el estatus socioeconómico y el consumo de bebidas en niños: Estudio de Cuenca

Marta Milla Tobarra^{1,2}, Antonio García Hermoso³, Noelia Lahoz García², Blanca Notario Pacheco², Lidia Lucas de la Cruz², Diana P. Pozuelo Carrascosa², María José García Meseguer⁴ and Vicente Martínez-Vizcaino^{2,5}

¹Hospital Nuestra Señora del Prado. Talavera de la Reina, Toledo, Spain. ²Health and Social Research Center. Universidad de Castilla-La Mancha. Cuenca, Spain. ³Sports, Physical Activity and Health Science Laboratory. Medical Sciences Faculty. Universidad de Santiago. Santiago, Chile. ⁴Faculty of Nursing. Campus de Albacete. Universidad de Castilla-La Mancha. Albacete, Spain. ⁵Faculty of Health Sciences. Universidad Autónoma de Chile. Talca, Chile

Abstract

Introduction: beverage consumption constitutes a source of children's daily energy intake. Some authors have suggested that consumption of caloric beverages is higher in children with a low socioeconomic position because families limit their spending on healthy food in order to save money.

Objective: the aim of this study was to explore the relationship between socioeconomic status and Spanish children's beverage consumption.

Methods: a cross-sectional study was conducted in a sub-sample of 182 children (74 girls) aged 9-11 from the province of Cuenca (Spain). Beverage consumption was assessed using the YANA-C assessment tool, validated for HELENA study. Data for parental socioeconomic status were gathered by using self-reported occupation and education questions answered by parents and classified according to the scale proposed by the Spanish Society of Epidemiology.

Results: beverage intake was higher in children belonging to a middle-status family than in those of upper socioeconomic status ($p = 0.037$). The energy from beverages was similar in most water intake categories, except for water from beverages ($p = 0.046$). Regarding other beverages categories, middle-status children had higher consumption levels. In contrast, lower status children drank more fruit juices and skimmed milk. All of these do not show statistically significant differences.

Conclusions: our study did not find significant associations between beverages consumption and socioeconomic status in children. In fact, intake for most beverage categories was higher in middle-status children than in both other socioeconomic groups. Future research is needed in order to identify this complex relation between socioeconomic inequality and beverage intake behavior.

Key words:

Beverage choice.
Socio-economic status. Youths.
Obesity.

Resumen

Introducción: el consumo de bebidas supone una elevada carga energética en la dieta y algunos autores han sugerido que el consumo de bebidas azucaradas es mayor en niños con un estatus socioeconómico menor, debido a que las familias limitan su gasto en alimentación saludable para ahorrar dinero.

Objetivo: el objetivo de este estudio fue analizar la relación entre el estatus socioeconómico y el consumo de bebidas en niños.

Material y métodos: estudio transversal en el que se analizó una muestra de 182 niños (74 niñas) de 9-11 años de la provincia de Cuenca (España). El consumo de bebidas se obtuvo mediante el software YANA-C, validado para el estudio HELENA. Los datos de estatus socioeconómico de los padres se obtuvieron mediante un cuestionario autoadministrado de preguntas sobre ocupación y educación, clasificado según la Sociedad Española de Epidemiología.

Resultados: el consumo de bebidas fue mayor en niños de estatus socioeconómico medio ($p = 0,037$) con respecto a los niños de estatus socioeconómico alto. Los mismos datos se obtuvieron para la energía proveniente de las bebidas y en la mayoría de las categorías de agua analizadas, aunque solo fue significativo para el agua proveniente de bebidas ($p = 0,046$). En cuanto a otras categorías, los niños de estatus socioeconómico medio tienen mayores consumos. En cambio, los niños de estatus socioeconómico bajo reportan mayores ingestas de zumos de frutas y leches desnatadas, sin significación estadística.

Conclusiones: nuestro estudio no ha encontrado relaciones significativas entre el consumo de bebidas y el estatus socioeconómico en niños. Los mayores consumos de bebidas se dan en niños con un estatus socioeconómico medio con respecto a los otros dos grupos. Son necesarios más estudios para explorar las complejas relaciones entre el estatus socioeconómico y el consumo de fluidos.

Palabras clave:

Estatus socioeconómico.
Elección de bebidas.
Jóvenes. Obesidad.

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Correspondence:

Vicente Martínez Vizcaino. Centro de Estudios Sociosanitarios (CESS). Universidad de Castilla-La Mancha (UCLM). Campus de Cuenca. Ed. Melchor Cano. Av. Santa Teresa de Jornet, s/n. 16071 Cuenca, Spain
e-mail: Vicente.Martinez@uclm.es

INTRODUCTION

In Spain, the prevalence of overweight and obesity has substantially grown in the past three decades (1). A large body of evidence has suggested that the relationship between obesity prevalence and obesity-related metabolic disorders has a socio-economic gradient, in such a way that these disorders affect mostly people with limited resources and racial-ethnic minorities (2). Poor diet is a particular concern when talking about children of a low socioeconomic status (SES), because they eat less fruit and vegetables (3) and more sugar-added food (4). It is evident that the purchase of fruit and vegetables is price sensitive and that their high cost is a barrier to increase intake (5). In order to save money, families limit their spending on food, and tend to consume less healthy but cheaper food, as well as their expenses in relation to recreational physical activities (6).

One dietary factor which has recently been drawing attention is beverage consumption. Beverages are currently providing more calories and a larger percentage of daily energy intake than at any other time in history (7). Some authors have reported that the greatest increase of soft drinks consumption in USA has been observed in children and adolescents from lower SES and minorities (8), noticing also that they consume more soft drinks than their counterparts from high SES (9). Other authors have reported that, in less developed countries, higher levels of maternal education are associated with higher consumption of soft drinks by children, partly because there is no safe water to drink (10). With respect to other beverages, several review studies proved that high-fat dairy consumption within the typical dietary patterns is inversely associated with obesity risk (11,12). Another recent study showed that higher-SES children had higher intakes of water coming from milk (13). In an Australian study, it was found that advantage adolescents who reported greater attachment to family mealtime rules had greater odds of consuming dairy foods frequently (14).

Water consumption is one of most studied questions during the last years. Some authors have proposed that drinking more water could be one method to reduce weight gain since water consumption could replace other caloric beverages and, thereby, reduce the total amount of calories consumed (15). In fact, our study shows that higher consumption of water in children was negatively associated with body mass index (BMI), body fat and other cardiometabolic parameters (16). Moreover, consumption of tap water provides a low cost beverage option and, according to a study carried out in the USA, one in six children does not drink tap water, a figure which is more pronounced among minorities, even in communities where tap water is safe (17). In addition, in some low income countries, like Mexico, the lack of available potable water in households and schools coincides with the increase in soft drinks consumption (18), as it occurs with American children's households, where plain water consumption (bottle and tap) tends to be associated with higher incomes (19). In contrast, no socio-economic gradient for plain water consumption was observed among French children (20).

Due to controversial results and scant evidence, the aim of the present study was to explore if a relationship can be estab-

lished between socioeconomic status and beverage consumption in Spanish children.

MATERIAL AND METHODS

STUDY DESIGN AND PARTICIPANTS

This is a cross-sectional analysis of baseline data from a cluster-randomized trial aimed to assess the effectiveness of a physical activity program on prevention of excess weight in children from 20 public schools in the province of Cuenca (Spain) (21). For this report, data from a sub-sample of 182 children (74 girls) aged between nine and eleven in fifth grade of Primary Education, from 20 public primary schools, were used. The study protocol was approved by the Clinical Research Ethics Committee of the Hospital Virgen de la Luz in Cuenca.

ASSESSMENT OF BEVERAGE INTAKES

Beverage consumption of each participant was estimated using the Young Adolescents Nutrition Assessment on Computer (YANA-C), a self-administered computerized 24h dietary recall validated for European adolescents (22). The Spanish version of the YANA-C questionnaire was administered twice a week, once asking about a weekday and the second time, about a weekend day. The YANA-C program was installed in the computer room of each school, where pupils completed the questionnaire in groups. A trained staff member instructed the children on the software and thereafter, pupils completed it autonomously, although two or three staff members were present to provide assistance in case it was required.

Beverages were grouped in nine categories: a) water as a beverage (plain water, bottled water, and water with flavor without sugars added); b) soft drinks (calorically-sweetened soda and sport drinks); c) diet drinks (non-caloric sweetened beverages, diet sodas, or other diet beverages); d) fruit drinks (< 100% fruit juices and others with added sugars); e) 100% fruit juices (natural fruit juices and commercial 100% fruit juices without added sugars); f) skimmed and semi-skimmed milk; g) whole milk; h) milk drinks (beverages derived from milk with or without sugars); and i) other beverages (soya beverages, vegetable juices, coffee, tea, infusions, *horchata*, cereal drinks, etc.). The last group included various types of beverages consumed sporadically, with the aim of making further analysis. Alcoholic beverages were excluded. Beverage intake was defined as the sum of all these categories.

PARENTAL SOCIOECONOMIC STATUS

Data for parental SES were gathered by using self-reported questions completed by either father or mother about their occupation and education. Paternal and maternal information about their education was classified separately as Primary Education

(functionally illiterate, without any studies or not having completed Primary Education), middle education (Primary Education or high school/Secondary Education) and university education (university degree or PhD). Parental occupation was divided into five categories: a) supervisor/manager or freelance with ten employees or more; b) supervisor/manager or freelance with less than ten employees; c) freelance with no staff; d) non-qualified staff and unskilled worker; and e) household chores, unemployed and others. An index of SES was calculated based on the items that referred to the parents' education and parental occupation classifying SES as: lower-lower/middle, middle and middle/upper-upper, according to the scale proposed by the Spanish Society of Epidemiology (23). Information was gathered in three groups to obtain more accurate results as described below: lower-lower/middle, middle, and middle upper-upper.

CARDIORESPIRATORY FITNESS

Cardiorespiratory fitness (CRF) was assessed by the 20-m shuttle run test (24). Participants were required to run between two lines 20 m apart, while keeping pace with audio signals emitted from a pre-recorded compact disc. The running speed started at 8.5 km/h and increased 0.5 km/h each minute. The children were stopped when they could not follow the signal any more. The last half-stage completed was noted as an indicator of their CRF.

ANTHROPOMETRIC AND BODY COMPOSITION VARIABLES

Children were weighed and measured twice whilst wearing light clothing and without shoes, using a calibrated digital scale to the nearest 0.1 kg for weight and a wall mounted stadiometer to the nearest 0.1 cm for height. The mean of this measurements was used to calculate body mass index (BMI) as weight in kilograms divided by the square of the body height in meters (kg m^2). Waist circumference (WC) was calculated as the average of two measurements taken with flexible tape at the natural waist (the midpoint between the last rib and the iliac crest). Body fat percentage and fat free mass percentage were estimated using a BC-418 bioimpedance analysis system (Tanita Corp., Tokyo, Japan). The mean of two readings taken in the morning after urination and a 15 min rest, with the child without shoes and fasting. All measurements were obtained at the schools by trained nurses.

STATISTICAL ANALYSIS

The distribution of continuous variables was checked for normality before the analysis. Continuous variables were expressed as mean $\pm$ standard deviation for normally distributed continuous data. Categorical variables were expressed as n (%). Normal weight and overweight-obesity were defined according to the BMI cut-offs published for children and adolescents (25). ANOVA models were

estimated to test the differences in beverage intake variables by categories of SES (lower-lower/middle, middle, middle/upper-upper), adjusted for age, sex and CRF. The statistical analyses were conducted with the SPSS version 22 (SPSS Inc., Chicago, IL).

RESULTS

We studied 182 subjects with an average age of 10.04 ± 0.46 years, of whom 40.6% were girls. Table I shows anthropometric and body composition variables, socioeconomic characteristics and beverage intakes of the participants. Body fat percentage was higher in girls ($p < 0.001$), and cardiorespiratory fitness in boys ($p < 0.001$). Obesity prevalence was higher in boys ($p < 0.007$), and no sex differences were found with regard to their SES. Girls presented higher amounts in some categories, such as total beverage intake ($p = 0.041$), water from beverages ($p = 0.042$), water/kg weight ($p = 0.034$) and water as a beverage ($p = 0.020$). Conversely, diet drinks consumption was higher in boys ($p = 0.003$).

In table II, we analyzed beverage intake by SES categories. Energy intake (food and beverages) and energy from beverages were higher in middle status children, although differences were not significant. Also, beverage intake was higher in middle status children ($p = 0.037$) compared to the upper SES. In most of the water intake categories, there was a higher consumption in middle status children, although it was only significant when referring to water from beverages ($p = 0.046$). Regarding other beverages categories, middle status children consumed more soft drinks, diet drinks, fruit drinks, whole milk and milk drinks. In contrast, lower and lower-middle status children's consumption of fruit juices and skimmed milk was higher. All of these results did not show any statistical differences.

DISCUSSION

The current study analyzed beverage consumption by sex and SES in schoolchildren living in Cuenca's province. Overall, no differences by SES were observed, except for beverage intake, which is higher in middle status children than in those with an upper status, and consumption of fruit juices and skimmed milk intakes, which were higher in lower SES categories children. Girls drank more water from beverages and boys, more diet drinks.

FLUID INTAKE AND ENERGY FROM BEVERAGES

Nowadays, some studies have paid particular attention to families' socioeconomic gradients and their relationship with dietary habits (26-28). A recent study in Europe has shown that fluid intake is higher in middle SES children with significant differences with respect to children with other status (29). Similar data were drawn from our analysis.

Table I. Sex and parental socioeconomic status differences in body composition and beverage intake

	Total (n = 182)		Boys (n = 108)		Girls (n = 74)		
	Mean	SD	Mean	SD	Mean	SD	p*
Age	10.04	0.46	10.06	0.47	10.03	0.467	0.687
Anthropometric and body composition							
Height, cm	141.3	6.8	140.3	6.6	142.8	6.9	0.013
Weight, cm	37.6	7.1	37.5	7.7	37.8	6.1	0.773
BMI, kg/m²	18.7	2.7	18.9	3.0	18.4	2.3	0.239
Normoweight, n (%)	131 (71.9)		70 (64.8)		61 (82.4)		0.007
Overweight-obese, n (%)	51 (28.1)		38 (35.2)		13 (17.6)		
Body fat, %	24.2	5.3	23.1	5.8	25.8	3.8	< 0.001
Fat free mass, %	28.2	4.1	28.4	4.2	27.9	3.9	0.370
Waist circumference, cm	67.4	7.4	67.8	8.1	66.8	6.4	0.357
Cardiorespiratory fitness							
Stage, n	3.9	1.8	4.4	1.9	3.1	1.2	< 0.001
Socioeconomic status							
Lower-lower/middle	40	21.9	23	21.3	17	22.9	0.984
Middle	55	30.3	34	31.5	21	28.5	
Middle/upper-upper	87	47.8	51	47.2	36	48.6	
Beverage intakes							
Energy from food and beverages, kcal/day	1,681.8	772.8	1760.2	898.3	1,567.5	525.1	0.070
Energy from beverages, kcal/day	265.5	145.2	259.4	158.6	274.5	123.5	0.471
Beverage intake, ml/ day	996.4	389.4	948.8	396.8	1,066.6	369.8	0.041
Water from food and beverages, ml/day	1,461.1	515.3	1,425.1	491.8	1,513.6	546.7	0.266
Water from beverages, ml/day	936.1	377.7	890.1	380.1	1,005.1	366.1	0.042
Water from food, ml/day	524.2	255.7	534.9	250.1	508.5	264.7	0.500
Water/kg weight, ml/kg	12.5	10.2	11.1	9.4	14.5	11.0	0.034
Water/kcal day, ml/kcal	0.35	0.47	0.32	0.56	0.38	0.30	0.355
Water as a beverage, ml/day	464.1	376.4	409.1	352.7	544.4	397.8	0.020
Soft drinks, ml/day	88.5	158.8	98.2	165.4	74.4	148.7	0.312
Diet drinks, ml/day	33.4	94.1	48.3	114.8	11.9	43.1	0.003
Fruit juices, ml/day	76.4	136.7	73.7	135.5	80.3	139.2	0.752
Fruit drinks, ml/day	35.8	78.8	28.1	71.6	47.2	87.7	0.124
Skimmed milk, ml/day	97.8	135.9	99.4	123.5	95.6	153.3	0.861
Whole milk, ml/day	137.8	143.3	134.1	149.5	143.3	134.7	0.666
Milk drinks, ml/day	56.8	95.5	53.7	92.9	61.4	99.7	0.600
Other beverages, ml/day	5.5	31.8	3.8	20.5	8.1	43.4	0.425

Values are means (standard deviations $\pm$ SD) and number and proportions (%) for categorical data. BMI: body mass index.

Table II. Mean differences between beverage intake and socioeconomic status in children adjusted for age, sex and cardiorespiratory fitness

	Parental socioeconomic status			p
	Lower-lower/middle (L) n = 40	Middle (M) n = 55	Middle/upper-upper (U) n = 87	
Energy from food and beverages, kcal/day	1,593.95 ± 547.21	1,816.40 ± 779.68	1,637.26 ± 849.85	0.291
Energy from beverages, kcal/day	280.71 ± 127.23	297.78 ± 165.51	238.19 ± 135.34	0.052
Beverage intake, ml/ day	956.77 ± 339.43	1,094.76 ± 393.25	952.55 ± 401.25	0.037*
Water from food and beverages, ml/day	1,422.37 ± 389.39	1,571.43 ± 506.16	1,409.10 ± 563.83	0.119
Water from beverages, ml/day	893.38 ± 324.47	1,028.14 ± 376.97	899.25 ± 394.54	0.046
Water from food, ml/day	529.00 ± 196.47	543.29 ± 233.72	509.85 ± 292.25	0.787
Water/kg weight, ml/kg	10.86 ± 8.32	13.45 ± 9.41	12.66 ± 11.43	0.284
Water/kcal day, ml/kcal	0.28 ± 0.24	0.34 ± 0.29	0.38 ± 0.62	0.533
Water as a beverage, ml/day	383.50 ± 296.11	505.58 ± 356.44	475.01 ± 417.77	0.188
Soft drinks, ml/day	96.74 ± 201.81	104.93 ± 167.29	74.34 ± 129.02	0.471
Diet drinks, ml/day	26.91 ± 7.02	44.25 ± 116.72	29.66 ± 85.87	0.522
Fruit juices, ml/day	58.87 ± 106.54	29.87 ± 72.58	29.03 ± 65.74	0.099
Fruit drinks, ml/day	83.84 ± 139.39	85.49 ± 147.46	67.24 ± 129.21	0.687
Skimmed milk, ml/day	110.29 ± 167.43	89.36 ± 119.24	97.49 ± 130.99	0.793
Whole milk, ml/day	145.91 ± 162.47	158.34 ± 151.70	121.24 ± 127.45	0.370
Milk drinks, ml/day	40.49 ± 79.02	73.56 ± 113.89	53.76 ± 88.98	0.258
Other beverages, ml/day	10.22 ± 46.88	3.37 ± 18.84	4.78 ± 30.03	0.583

*M > U. Differences between M vs U (p = 0.048).

Conversely, a study conducted on Mexican population reported that medium and high SES people's energy intake from unhealthy beverages was higher than in low SES (30).

SOFT DRINKS AND SWEETENED BEVERAGES

A recent study in Norway has shown that adolescents from higher SES families consume more fruit and vegetables and less soft drinks and sweets than their counterparts (31). This is in line with our data and those reported by other European studies (9), although in these countries soft drinks are more expensive than in our country and perhaps that is the reason why their consumption is lower than in countries where they are very cheap and easy to purchase. In general, in Europe, as in the ToyBox study (29), lower SES schoolchildren consume more soft drinks than their high SES peers; on the contrary, in Latin America (32), as well as in children from other regions such as Lebanon (13), a higher consumption of soft drinks and sweetened beverages in higher SES schoolchildren has been reported.

PLAIN WATER

According to our data, girls drank higher amounts of water than boys. Moreover, in most water categories, middle SES status

children drank higher quantities than children from other status. These data are different than those reported in preschoolers from other European countries, where a lower intake of plain water has been reported in lower SES (29).

FRUIT JUICES

Among our sample, those with low SES consumed more fruit juices than their high and medium status peers. This SES consumption pattern is different from those reported in other countries (13,32). In other analysis carried out on preschoolers, it is described that the consumption of fruit juices is higher in low income families (33), being these data more similar to ours. For example, in the United States it has been reported that children from racial/ethnic minorities and lower income groups (34) consume more 100% fruit juice, possibly because it replaces whole fruit, which is generally more expensive but nutritionally more complete. Moreover, until a few years ago, it existed a popular belief according to which fruit juice consumption was similar to eating a piece of fruit (35). However, this erroneous notion has been discarded, and thus, the current recommendations are to increase the consumption of natural fruits and to reduce the consumption of juices (36,37).

MILK CONSUMPTION

Both in Australia (14) and the USA (38), it has been reported that adolescents from high SES families consumed more dairy foods than their counterparts. Likewise, a similar pattern has been described in Mexico (32). According to the study in Lebanese children, those with a low SES had lower water intakes from milk (unspecified type). Our data confirm these findings, and not many significant differences were found.

LIMITATIONS

This study has some limitations that should be pointed out. First, our study had a cross sectional design, thus observational findings do not allow us to evaluate causal relationships among variables. Second, our sample size lacks enough statistical power to control some potential confounders. Moreover, the assessment of diet in children, either directly or by an adult proxy, has some methodological weaknesses. It has been suggested that 10-year-old children are not able to give valid responses to food frequency questionnaires covering periods longer than one day; however, in our study, the use of pictures in the YANA-C software helped children to remember not only the food eaten during the last 24 hours, but also the portion size.

CONCLUSION

In general, our study did not find a significant relationship between beverages consumption and SES, except for beverages intake and water from beverages categories, which were higher in children from middle-status compared to upper SES children. It is important to emphasize that data were collected before the Spanish economic crisis reached its peak, thus, supposedly, families had not limited their family food spending yet. It is true that most part of less healthy drinks, such as soft drinks and packaged juices, have often very low prices, affordable for people with limited resources. In addition, these products are also easily available to children due to vending machines in schools, hospitals, shopping centers or shops in the streets. For these reasons, the easy access to less healthy drinks should also be controlled for children, and perhaps the installation of free water sources in schools and streets should be considered, since it is shown that it increases their consumption (39). These and other policies can help improve the hydration habits of children in our country independently of socioeconomic status. Future research is needed to identify this complex relation between socioeconomic inequality and eating behaviors', in particular among children.

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Trabajo Original

Epidemiología y dietética

Dietary patterns, physical activity, body mass index, weight-related behaviours and their interrelationship among Romanian university students-trends from 2003 to 2016

Patrones dietéticos, actividad física, índice de masa corporal, conductas relacionadas con el peso y su interrelación entre estudiantes universitarios rumanos entre 2003 y 2016

Lucia Maria Lotrean¹, Ovidiu Stan^{1,2}, Codruta Lencu¹ and Valeria Laza¹¹Iuliu Hatieganu University of Medicine and Pharmacy. Cluj-Napoca, Romania. ²Technical University. Cluj-Napoca, Romania

Abstract

Introduction: promotion of a healthy diet and involvement in physical activity among young people has an important impact on their actual and future lifestyle, health and well being.

Objectives: this study investigates dietary patterns, physical activity, body mass index (BMI) and weight-related behaviours as well as their interrelationship among Romanian university students.

Methods: the study used anonymous questionnaires and was performed in Cluj-Napoca, Romania in 2003 (n = 320) and 2016 (n = 320).

Results: the factor analyse revealed three main dietary structures which were similar at both waves. The first one describes a varied diet. The second one shows a diet rich in white meat, dietary fibres and varied sources of carbohydrates. The last one refers to a diet containing red meat, fat, potatoes, sugar. The first dietary structure protects against overweight and it correlates positively with daily physical activity, while has a negative correlation with using several methods for losing weight. The second dietary factor is also protective for overweight, but has a positive correlation with using several methods for losing weight. It has a negative association with eating frequently in fast food restaurants and with daily physical activity. The last dietary structure is negatively associated with daily physical activity, while being positively associated with eating frequently in fast-food restaurants and with a higher BMI.

Conclusions: the study presents trends in dietary patterns, physical activity, BMI and weight related behaviours among Romanian university students between 2003 and 2016 and highlights the existence of several main dietary structures, which seems stable over time.

Key words:

Dietary patterns.
Physical activity.
Body mass index (BMI). Weight-related behaviours.
Romanian university students.

Resumen

Introducción: en los jóvenes la promoción de una dieta saludable y la realización de actividad física tienen un importante impacto sobre su estilo de vida, presente y futuro, en su salud y en su bienestar.

Objetivos: este estudio investiga los patrones dietéticos, la actividad física, el índice de masa corporal (IMC) y las conductas relacionadas con el peso, así como su interrelación, en los estudiantes universitarios rumanos.

Métodos: el estudio utilizó cuestionarios anónimos y fue llevado a cabo en Cluj-Napoca (Rumania), en 2003 (n = 320) y en 2016 (n = 320).

Resultados: el análisis de los factores a estudio reveló tres estructuras dietéticas principales que fueron similares en las dos ondas. La primera describe una dieta variada. La segunda muestra una dieta rica en carne blanca, fibra y fuentes variadas de carbohidratos. La última presenta una dieta que contiene carne roja, grasas, patatas y azúcar. La primera estructura dietética protege contra el sobrepeso y se correlaciona positivamente con la actividad física diaria, si bien tiene una correlación negativa con el uso de varios métodos para perder peso. La segunda estructura dietética también protege frente al sobrepeso, aunque tiene una correlación positiva con el uso de varios métodos para perder peso, y negativa con comer con frecuencia en restaurantes de comida rápida y con la actividad física diaria. La última estructura dietética se relaciona negativamente con la actividad física diaria, pero se asocia positivamente con comer con frecuencia en restaurantes de comida rápida y con un mayor IMC.

Conclusiones: el estudio describe las tendencias en los patrones dietéticos, la actividad física, el IMC y las conductas relacionadas con el peso en los estudiantes universitarios rumanos entre 2003 y 2016, y resalta la existencia de varias estructuras dietéticas principales que parecen estables en el tiempo.

Palabras clave:

Patrones dietéticos.
Actividad física. Índice de masa corporal (IMC). Conductas relacionadas con el peso. Estudiantes universitarios rumanos.

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Correspondence:

Lucia Lotrean. Iuliu Hatieganu University of Medicine and Pharmacy. Cezar Petrescu Str. No. 6. Cluj-Napoca, Romania
e-mail: llotrean@umfcluj.ro

INTRODUCTION

Promotion of a healthy diet and involvement in physical activity among young people has an important impact on their actual and future lifestyle, health and well-being (1-5). World Health Organization and several health organizations underline the importance of adopting a varied diet, with daily consumption of food products from different food groups, such as meat or meat alternatives, dairy products, fruits and vegetables and grains (1,2,6-10). Moreover, attention should be paid to the quantity of consumed food products as well as to their quality, since among the same food group there are products which are healthier than others and should be included more frequent in the diet (i.e. low fat dairy products, lean meat such as fish and chicken, dark bread, whole grains, fresh fruits and vegetables) (1,2,9,10). The cooking techniques are also important, being underlined the importance of limiting the adding of sugar, salt and different types of fat in the dishes as well as consumption of processed meat and fried foods (10-16).

Food consumption should be divided in three main meals per day plus 1-2 snacks, the starting of a day with a balanced breakfast being very important (1,4,5).

Moreover, the importance of performing physical activity at least half an hour per day among young adults is also emphasised, as well as the benefits of maintaining an appropriate body mass index (BMI) or achieving an appropriate BMI using methods which do not pose threats on health (17).

Nevertheless, several studies in Europe and worldwide underline that there are young people who are not fulfilling several of the recommendations regarding healthy diet and an active lifestyle, the prevalence of the unhealthy behaviours and their determinants varying between countries, but also between different groups from the same country, while different trends across the lifespan or during several periods of time might be also observed (18-26).

Several studies underline that healthy or unhealthy dietary, physical activity and weight related behaviours often do not occur in isolation and are correlated with each other in different ways. Moreover, there is also a possible synergetic effect of multiple health behaviors on the risk of chronic conditions and other health outcomes (22-24,27). One important area of research which needs further investigation is the relationship and accumulation existing between different dietary patterns, physical activity, body mass index and weight-related behaviours.

Romania has changed the communist regime in 1989 and started socio-economical changes which lead to its admission in European Union in 2007. These changes also had influences on the food products available on the market, cultural and gastronomic exchanges with other countries, marketing of different food products, habits related to obtaining, cooking and serving food. Despite this, there is little information with regard to dietary patterns, physical activity and weight related behaviours as well as their interrelationship among young population from Romania (26,28-31).

For university students, the university period is characterised by transition into adulthood, increasing independence, autonomy,

and responsibility, including living apart from their parents and being the only responsible for choosing, buying and cooking their food, deciding the content, the quantity and the moment of their meals and snacks. These results in a shift in composition and quality of the diet and several studies have found that diet quality may worsen during this transition (21-25,32).

Hence, this study focuses on university students from Cluj-Napoca, a big university town situated in the North-West part of Romania and has two main objectives. The first one is to investigate dietary patterns, physical activity, and body mass index and weight-related behaviours among university students, giving a special attention to possible differences between 2003 and 2016 as well as to gender differences at each time point. Second, the study assesses the relationship existing between the investigated issues at both waves.

MATERIAL AND METHODS

STUDY SAMPLE AND PROCEDURE

The study was performed in Cluj-Napoca, an important university town from North-West part of Romania, in 2003 (T1) when limited information with regard to dietary habits, physical activity and weight related behaviours among Romanian youth was available and was repeated in 2016 (T2) in order to have a recent evaluation of the situation. It involved university students randomly chosen from 8 dorms belonging to the 4 main universities of the town. At each wave a number of 80 students (40 girls, respectively 40 boys) living in the selected dorms were randomly chosen from each university, driving to a total sample of 320 students aged 19-24 at each time point. They were informed about the voluntary participation. The refusal rate was low (3.7% in 2003 and 4.7% in 2016) and the students who refused to participate were replaced with students from the same university, living in the same dorm.

The study is part of a research project which received the ethical approval of the Ethic board of University of Medicine and Pharmacy from Cluj-Napoca, Romania.

INSTRUMENT FOR DATA COLLECTION

All students were asked to fill in an anonymous questionnaire, which investigated several socio-demographic characteristics (i.e. age, gender) and a wide range of health related behaviours, including one section focused on nutrition, physical activity and weight related behaviours. Because of the wide range of investigated health risk behaviours and the fact that no instruments for data collection were validated in Romania in 2003, this questionnaire was developed especially for this study based on data from literature and instruments used in other international studies (1,33,34).

The present study is focusing on the following issues: frequency of consumption of several food products, eating breakfast, eating in fast food restaurants more than two times per week, involvement in physical activity, body mass index, body weight

management in the moment of the performance of the survey as well as use of several methods for losing weight in the last year.

Frequency of consumption of several food products was assessed through a short food frequency questionnaire (FFQ), which evaluated the frequency of consumption of several food products in the last month (less than once/month, 2-3 times/month, once/week, two times/week, 3-4 times/week, 5-6 times/week, once every day, more times/day). In 2003 the reliability and the validity of the FFQ questionnaire was evaluated. A pilot survey was performed among 40 students. They filled in the FFQ and one month later they filled in the FFQ again. Comparing the frequency of consumption (less than weekly, 1-2 times/week, 3-4 times/week, 5-6 times/week, every day) assessed by the two FFQs, it was found that the Pearson correlation coefficients varied between 0.34 to 0.74 for the main food products. Between the administrations of the two FFQ the students were also asked to fill in a food diary (FD) for three consecutive days (one day during weekend and two days during the week). Frequency of intake of food items from the FFQ was based on weekly frequencies, while data from the FD were based on frequency over three days. Hence, to provide comparable data, the data assessed through FD were converted into a weekly intake. Since the FD included 2 week days the frequency of food assessed by FD during week days was multiplied by five and divided by two, while for the weekend day the frequency of consumption was multiplied by two; the results were then summed up. Comparing the frequency of consumption of the main food items assessed with food diary and the first FFQ there was noticed a range of the Pearson correlation coefficients between 0.31 and 0.67.

Students were also asked how frequent they eat breakfast in the last week (never, 1-3 times/week, 4-6 times/week, every day) and if they have eaten in fast food restaurants more than two times per week (yes vs. no).

The involvement in physical activity was assessed by asking students about number of days in the last week when they were involved in vigorous physical activity (A) and moderate physical activity, including walking (B) as well as how long (how many minutes) was the duration of vigorous activity (C) and moderate activity (D). Similar with other studies, we considered that 30 minutes of vigorous physical activity were equivalent to 60 minutes of moderate physical activity (8,34). The medium number of minutes per day (PA) of moderate physical activity was calculated according with the following formula:

$$PA = [2(A \times C) + (B \times D)]/7$$

Height and weight were auto-estimated and declared in the questionnaire by each participant and body mass index (BMI) was calculated using the following formula: BMI = weight / (height x height). Cut-off values for body mass index were considered as follows (8):

- Underweight (BMI < 18.5).
- Normal (BMI 18.5-24.9).
- Overweight (BMI ≥ 25).
- Obese (BMI ≥ 30).

The students were also asked what are they currently doing with regard to their weight (losing weight, gaining weight, maintaining their current weight, nothing) as well as if they have used any methods in the last year for losing weight (dieting, sport, vomiting, pills, special tea, sauna/massage).

DATA ANALYSES

The prevalence of the investigated behaviours was calculated and χ^2 tests were used to assess differences between the two waves with regard to weekly and daily consumption of several food products, BMI, performing of physical activity, methods used for losing weight.

The factor analysis using the method of principal components with unrotated factor solution was used to recognize major dietary structures according to 24 food products. Similar with other studies, we considered that main dietary structures referred to the factors with Eigenvalues of over 1.5 (28). The regression method was used to measure the scores of factors for every pattern and for each person.

Pearson correlation was used to assess the association at each wave between gender and frequency of consumption for different food products, main dietary structures, consumption of breakfast, eating in fast food restaurants more than two times/week, involvement in physical activity, BMI, methods used for losing weight.

Moreover, at each time point Pearson correlation was used also for evaluation of the associations between the main dietary structures, consumption of breakfast, eating in fast food restaurants more than two times/week, involvement in physical activity, BMI, methods used in the last year for losing weight. According to Cohen, strong correlation was considered at $r > 0.50$, while medium and small correlation was considered at $r > 0.30$ and $r > 0.10$, respectively.

Data analysis was performed with SPSS-20 statistics program. Statistical significance is reported at $p < 0.05$.

RESULTS

DIETARY PATTERNS

Table I presents the frequency of consumption of several food products in 2003 and 2016. It shows that daily consumption of dairy products decreased between T1 and T2 from half of the students to one third of the students, while the percentage of those who consume dairy products less than once per week increased from 5% to 10%.

With respect to meat consumption, it is noticed that pork meat, chicken meat, processed meat (ham, salami, sausages) are the most preferred by the study samples, with consumption of processed meat and pork meat being quite similar at T1 and T2, while chicken consumption at least once per week as well as daily increased statistically significant between the two waves. Around half of the students ate beef at least once/week, without signifi-

Table I. Dietary patterns

Food products	2003				2016			
	Less than once/week %	1-2 times/week %	3-6 times/week %	Every day %	Less than once/week %	1-2 times/week %	3-6 times/week %	Every day %
Milk and dairy products	5.0 ^a	18.2	29.6	47.2 ^b	10.7	23.5	32.6	33.2
Pork meat	26.7	43.6	21.0	8.7	23.6	42.6	24.7	9.1
Beef meat	50.0	39.7	9.7	0.6	55.0	31.9	12.2	0.9
Chicken	21.2 ^a	41.2	29.5	8.1 ^b	14.7	42.2	28.8	14.3
Fish	79.7 ^a	15.6	4.4	0.3	63.0	27.0	7.5	2.5
Processed meat (salami, sausages, ham)	25.9	26.6	24.1	23.4	22.2	27.8	23.4	26.6
Eggs	22.5	38.5	29.7	9.3	20.5	44.9	24.6	10
Pulses	83.1	12.2	3.8	0.9	84.7	7.8	5.3	2.2
Soya	94.6	3.6	1.8	0	92.1	4.4	1.6	1.9
Seeds	54.3	32.2	12.6	0.9	52.5	27.2	17.2	3.1
Nuts	75	20.6	3.5	0.9	72.0	21.8	5.3	0.9
Fruits	10.6	29.7	39.7	20	10	29.1	39.1	21.8
Vegetables (cooked or fresh, except potatoes)	14.1	33.1	41.6	11.2	15.3	30.6	40.6	13.5
Potatoes	6.6	33.7	39.7	20.0	6.0	37.6	33.6	22.8
White bread	13.5	8.8	7.5	70.2	12.7	9.3	9.3	68.7
Dark bread	64.6	11.6	9.1	14.7	60.3	10.2	12.9	16.6
Pasta	48.1 ^a	42.2	9.1	0.6	53.4	35.9	10.7	0
Cereals	71.9 ^a	20.3	5.3	2.5 ^b	51.7	26.3	12.4	9.6
Rice	66.5 ^a	26.3	4.7	2.5	57.3	35.9	5.9	0.9
Sweets, cakes	13.1	25.9	41.3	19.7	14.4	28.8	34.2	22.6
Soft drinks	21.5	24.1	31.9	22.5 ^b	19.7	21.8	30.1	29.4
Chips/snacks	42.8	21.0	30.3	5.9	43.8	20.0	29.4	6.9
Pizza	80.3 ^a	15.6	2.5	1.6	64.6	24.0	6.4	5.0
Bacon fat	72.8 ^a	18.8	7.2	1.2	83.3	9.1	4.6	3.0

^aStatistically significant differences at χ^2 tests between the two waves with regard to weekly consumption. ^bStatistically significant differences χ^2 tests between the two waves with regard to daily consumption.

cant differences between the two waves, while the consumption of fish at least once/week increased from 20% in 2003 to 37% in 2016. Around 80% of students ate eggs at least once per week and one out of ten students declared daily eggs consumption both at T1 and T2.

The majority of students eat fruits and vegetables at least once per week, but only 20% of them eat fruit every day, while around 13% eat vegetables every day, without to be noticed statistically significant differences between the two waves.

Less than 20% of students eat pulses at least once/week and less than 10% eat soya at least once per week; no statistical differences were noticed between T1 and T2. Half of the students eat seeds at least once per week, while one third consumed different types of nuts at least once per week. Again, no statistical differences were noticed between the two waves.

With regard to the consumption of grains and potatoes we noticed the preference of students for white bread (more than 85% eat at least once a week and around 70% eat it every day) and potatoes (more than 90% eat at least once a week, while around 20% eat every day), while dark bread was consumed at least once per week by one third of the students, with a slightly increased between the two waves. Half of the students eat pasta at least once a week and the percentage remains quite similar between the two waves. Breakfast cereals at least once/week increased from one third of the students to half of them, while the daily consumption increased from 2.5 to almost 10% from T1 to T2.

The majority of students declared consumption of sweets as well as soft drinks at least once a week. At both waves one out of five students declared eating sweets/cakes every day, with no

statistically significant difference, while the daily consumption of soft drinks increased from 22.5% to 29.4%.

Half of the students eat chips/snacks at least once/week and around 6% do it every day, without to be noticed statistical differences between the two waves. The consumption of traditional fat similar with fatty bacon at least once per week decreased from 27% to 18% from T1 to T2, while consumption of pizza at least once/week increased from 20% to 40% between the two waves.

The results of the factor analyses reveal three main dietary structures at both waves.

As shown in table II, factor one describes a varied diet and included at both waves consumption of dairy products, pork and chicken meat, fruits and vegetables, white bread and sweets/cakes. Factor two describes a diet rich in white meat, dietary fibres and varied sources of carbohydrates and comprised of consumption of dairy products, chicken and fish meat, pulses, soya, nuts

(only at T1), fruits and vegetables, pasta, rice, cereals. Factor three reveals a diet high in red meat, fat, sugar and included consumption of pork meat, processed meat (ham, salami, sausages), potatoes, seeds, chips/snacks, traditional fat, pizza (only at T2), sweets/cakes as well as soft drinks. The explained variance was 39.2% at T1 and 40.2% at T2.

On the other hand, eating in fast food increased statistically significant from 8.4% to 19.4% between the two waves, while eating breakfast every day was 26.5% at T1 and 27.5% at T2.

The results of the Person correlation reveal several issues with regard to gender differences regarding dietary patterns. At T1 girls consumed less frequent pork meat ($r = -0.181$), processed meat ($r = -0.218$), traditional fat similar with fatty bacon ($r = -0.223$), chips/snacks ($r = -0.120$), and more frequent dairy products ($r = 0.133$) and fruits ($r = 0.124$), while at T2 girls consumed less frequent pork meat ($r = -0.165$), pizza ($r = -0.170$),

Table II. Main dietary structures-results of factor analyses^a

Food products ^b	2003			2016		
	Factor 1 Diverse diet	Factor 2 White meat, carbohydrates, fibres	Factor 3 Red meat, fat, sugar	Factor 1 Diverse diet	Factor 2 White meat, carbohydrates, fibres	Factor 3 Red meat, fat, sugar
Milk and dairy products	0.45	0.35		0.33	0.38	
Pork meat	0.45		0.41	0.37		0.40
Beef meat						
Chicken	0.33	0.46		0.30	0.43	
Fish		0.68			0.66	
Processed meat			0.51			0.58
Eggs			0.47			0.55
Pulses	-0.33	0.73		-0.34	0.72	
Soya	-0.39	0.72		-0.33	0.71	
Seeds			0.62			0.66
Nuts		0.30				0.33
Fruits	0.55	0.41		0.61	0.30	
Vegetables	0.37	0.40		0.45	0.30	-0.37
Potatoes			0.65			0.60
White bread	0.30	-0.47		0.40	-0.42	
Dark bread						
Pasta		0.61			0.56	
Cereals		0.58			0.54	
Rice		0.68			0.66	
Sweets, cakes	0.38		0.32	0.40		0.33
Soft drinks			0.52			0.56
Chips/snacks			0.72			0.72
Bacon fat	-0.42		0.59			0.55
Pizza						0.32

^aFactor loadings higher than 0.30 are depicted. ^bFrequency of consumption was coded as follows (0)-less than once/week, (1)-1-2 times/week, (2)-3-6 times/week, (3)-every day.

chips/snacks ($r = -0.150$), and more frequent white bread ($r = 0.126$) and fruits ($r = 0.120$).

Girls had lower scores for factor 3 at both T1 ($r = -0.150$) and T2 ($r = -0.211$).

On the other side, at both waves girls were less likely than boys to go to fast food restaurants more than two times/week ($r = -0.124$ at T1 and $r = -0.318$ at T2) and were more likely than boys to eat breakfast daily at T1 ($r = 0.201$).

PHYSICAL ACTIVITY, BODY MASS INDEX AND WEIGHT RELATED BEHAVIOURS

The average time spent for physical activity per day for the whole sample was 97 minutes ($SD = 61$) at T1 and 89 minutes ($SD = 58$) at T2. Table III shows that one out of five students did not perform at least half an hour of physical activity per day, without to be noticed statistically significant differences between the two waves. The percentage of those who perform more than one hour of physical activity per day decreased significantly between the two waves from 45.7% to 35.1%.

Table III. BMI, physical activity and weight-related behaviours

	2003 %	2016 %
<i>BMI</i>		
Underweight	8.7	9.4
Normal weight	77.8 ^a	70.9
Over weight	11.6	16.5
Obesity	1.9	3.2
<i>Weight related behaviours</i>		
Lose weight	22.2 ^a	34.7
Gain weight	13.9	11.6
Maintain weight	30.8	34.1
Nothing	32.1 ^a	19.7
<i>Ways of losing weight in the last year</i>		
Vomiting	1.2 ^a	4.3
Pills	2.2 ^a	7.8
Dieting	20	23.4
Sport	30	29.1
Tea	4.6 ^a	9.7
Sauna/massage	3.1 ^a	12.2
<i>Daily physical activity</i>		
Less than 30 min	20	23.8
30 min-1 h	34.3 ^a	41.1
More than 1 hour	45.7 ^a	35.1

^aStatistically significant differences at χ^2 test between the two waves.

The mean BMI for the whole sample was 21.7 ($SD = 2.7$) at T1 and 22.4 ($SD = 3.2$) at T2. The normal BMI decreased from 77.8% at T1 to 70.9% at T2, while the overweight or obesity increased statistically significant from 13.5% at T1 to 19.7% at T2.

With respect to weight related behaviours, less than one quarter of the students tried to lose weight in 2003, while one third of students declared this at T2. The percentage of those who wanted to gain weight was 13.9% in 2003 and 11.6% in 2016. The methods used in the last year for losing weight were mainly physical activity and dieting, without to be noticed statistically significant differences between the two waves. On the other side, it is noticed a statistically significant increase in the use of vomiting (1.2% vs. 4.3%), pills (2.2% respectively 7.8%), tea (4.6% vs. 9.7%), sauna/massages (3.1% vs. 12.2%).

The results of Person correlation analyses show that at both waves girls were more likely than boys to have a lower BMI ($r = -0.228$ at T1, $r = -0.201$ at T2) and were likely to use in the last year methods for losing weight such as dieting ($r = 0.244$ at T1, $r = 0.184$ at T2) and massage ($r = 0.242$ at T1 and $r = 0.162$ at T2). Vomiting was more frequent among girls at T2 ($r = 0.160$).

INTERRELATIONSHIPS BETWEEN DIETARY PATTERNS, PHYSICAL ACTIVITY, BMI AND WEIGHT-RELATED BEHAVIOURS

Table IV presents the association between the main dietary structures and several alimentary habits, involvement in physical activity, BMI and methods used for losing weight in the last year.

At both waves, the dietary structure characterised by a diverse diet was positively associated with a higher involvement in physical activity, lower BMI and at T2 it was negatively associated with using in the last year of dieting methods such as pills and tea.

The dietary structure composed of eating white meat, diverse sources of carbohydrates, high fibre content was negatively associated with eating in fast food restaurants more than two times/week (at both waves) and with involvement in physical activity (at T1), but it was positively associated with using of different methods for losing weight such as tea and sauna/massage (at both waves), as well as pills, dieting, sport (at T2).

The last dietary structure described by red meat consumption, high fat and sugar content was positively associated with eating in fast food restaurants more than two times/week and higher BMI at both waves. It was negatively associated with eating breakfast frequently at T1 and less daily physical activity (at T2), as well as with the use of different methods for losing weight like sport (both at T1 and T2), dieting (at T1) and vomiting (at T2).

As shown in table V, consumption of breakfast every day was inversely associated with eating frequently in fast food restaurants at T1 and with daily involvement in physical activity at T2. Moreover eating at fast food restaurants was associated with lower involvement in physical activity at T2 and higher BMI at T2. Higher involvement in daily physical activity was inversely associated with BMI at both waves. At the same time those with higher BMI were more likely to use vomiting for losing weight.

Table IV. Associations between main dietary structures, alimentary habits, BMI and weight-related behaviours

	2003			2016		
	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3
Breakfast ^a	NS	NS	-0.169	NS	NS	NS
Fast food more than 2 times/week ^b	NS	-0.141	0.258	NS	-0.376	0.244
Daily physical activity ^c	0.123	-0.128	NS	0.116	NS	-0.121
BMI ^d	-0.142	-0.138	0.163	-0.202	-0.221	0.212
Vomiting ^e	NS	NS	NS	NS	NS	-0.196
Pills ^e	NS	NS	NS	-0.139	0.359	NS
Dieting ^e	NS	NS	-0.197	NS	0.159	NS
Sport ^e	NS	NS	-0.204	NS	0.169	-0.177
Tea ^e	NS	0.163	NS	-0.196	0.352	NS
Massage/sauna ^e	NS	0.186	NS	NS	0.376	NS

NS: non-significant. ^aNot eating breakfast every day (0) vs. eating breakfast every day (1). ^bNot eating in fast food restaurants more than 2 times/week (0) vs. eating in fast food restaurants more than 2 times/week (1). ^cPerforming daily physical activity less than 30 minutes/day (1), 30 minutes-1 hour/day (2), more than 1 hour (3).

^dUnderweight (1), normal weight (1), overweight (2), obesity (4). ^e0-No, 1-Yes.

Table V. Associations between alimentary habits, BMI and weight-related behaviours

		Breakfast	Fast food	Physical activity	BMI	Vomiting	Pills	Dieting	Sport	Tea	Masage/sauna
Breakfast ^a	T1		-0.162	NS	NS	NS	NS	NS	NS	NS	NS
	T2		NS	-0.161	NS	NS	NS	NS	NS	NS	NS
Fast food ^b	T1			NS	NS	NS	NS	NS	NS	NS	NS
	T2			-0.137	0.223	NS	NS	NS	NS	NS	NS
Physical activity ^c	T1				-0.143	NS	NS	NS	0.172	-0.168	NS
	T2				-0.134	NS	NS	-0.245	NS	-0.198	-0.279
BMI ^d	T1					NS	NS	NS	NS	NS	NS
	T2					0.166	NS	NS	NS	NS	NS
Vomiting ^e	T1						0.192	NS	NS	0.138	0.160
	T2						0.262	NS	-0.162	0.180	NS
Pills ^e	T1							0.122	NS	0.155	NS
	T2							0.279	NS	0.535	0.532
Dieting ^e	T1								0.310	NS	NS
	T2								NS	0.143	0.245
Sport ^e	T1									NS	0.206
	T2									NS	NS
Tea ^e	T1										NS
	T2										0.588

NS: non-significant. ^aNot eating breakfast every day (0) vs. eating breakfast every day (1). ^bNot eating in fast food restaurants more than 2 times/week (0) vs. eating in fast food restaurants more than 2 times/week (1). ^cPerforming daily physical activity less than 30 minutes/day (1), 30 minutes-1 hour/day (2), more than 1 hour (3).

^dUnderweight (1), normal weight (1), overweight (2), obesity (4). ^e0-No, 1-Yes.

There are also several correlations between different methods for losing weight. The strongest correlation was between use of pills, tea and massage/sauna (especially at T2). There were also associations

between pills use and dieting, as well as sport and dieting. Vomiting was inversely associated with sport (at T2) and positive associated with consumption of pills, tea (at both waves) and massage (at T1).

DISCUSSION

This study describes dietary patterns, physical activity and weight related behaviours among Romanian university students from one big city situated in North-West Romania. It has three main strengths. The first one is the study sample, since it represents one segment of Romanian population which was not included in national representative studies performed until now. Second, it assesses trends between 2003 and 2016. Thirdly, it investigates several main dietary structures and their relationship with alimentary habits, physical activity, body-mass index and weight related behaviours.

The results underline that daily fruit and vegetable intake remain low, but stable, while milk and dairy products consumption every day decreased in 2016 compared with 2003. Other studies from Romania also underline the insufficient consumption of fruits and vegetables among several age groups (31,36-38). Eurostat study shows that two thirds of the Romanian population older than 15 years is not eating fruits and vegetables on daily bases (39).

Processed meat, pork meat, chicken meat and eggs were the most preferred types of meat and alternatives, with daily consumption of chicken meat increasing between the two waves. Fish meat consumption was very low, but its consumption at least once/week increased between two waves. Other studies also underline the preferences for these types of meat and alternatives, including consumption of processed meat products in this area of Romania (29,38). The increase in fish consumption might be the consequence of a better availability as well as educational messages with regard to its health benefits.

With regard to the consumption of grains and potatoes, it is noticed the preference of students for white bread and potatoes, their daily consumption being similar at both time points. Other studies also present similar preferences among different Romanian population groups (29,38). Weekly consumption of dark bread had a slightly increased, while the weekly as well as daily consumption of cereals has significantly increased. This tendency is in accordance with the increase and diversification of the availability of these products on the Romanian market combined with a more intense marketing and advertisement.

Consumption of sweets/cakes has been relatively constant over time, while the soft drinks consumption increased. The weekly consumption of the traditional fatty bacon decreased, but the weekly consumption of pizza increased. Furthermore, the percentage of students who eat in fast food restaurants more than two times/week doubled between the two waves. This is in accordance with the opening and promotion of several fast food restaurants in the last years in Romania.

Eating breakfast every day was low, but similar at both waves. Several studies from Romania shows an inappropriate consumption of breakfast among adolescents and young people as well its tendency to decrease with age (4,5,32).

There were several interesting relationships identified between dietary patterns, physical activity, BMI and weight related behaviours.

The eating patterns were interrelated and the factor analyses revealed three main dietary structures which were similar at both waves. The first one describes a varied diet including dairy products, pork and chicken meat, fruits and vegetables, white bread and sweets/cakes. The second one shows a diet rich in white meat (chicken and fish meat), dietary fibres (pulses, soya, nuts, fruits, vegetables) and varied sources of carbohydrates (pasta, rice, cereals) as well as dairy products. The last one refers to a diet which contains red meat (pork meat, processed meat), fat (chips/snacks, traditional fat, pizza), potatoes, sugar (sweets/cakes as well as soft drinks).

The first dietary structure seems to be protective against overweight and obesity and it is positively associated with higher enrolment in physical activity, while has a negative association with using methods for losing weight such as pills and special tea.

The second dietary factor is also protective for overweight and obesity. Moreover, it has a negative association with eating in fast food restaurants more than two times/week, but it is also negatively associated with daily physical activity (at T1). It is also characterised through an association with a higher preoccupation for using several methods for losing weight such as dieting, sport, pills, tea, and massage.

The last dietary structure is not presenting only a cumulative risk by a combination of red meat, high fat and sugar content, but it is negatively associated with involvement in physical activity, while being positively associated with eating in fast-food restaurants more than 2 times/week. It is associated with a higher BMI, which is not surprising since it contains several patterns which predispose to overweight, but the preoccupation for methods for losing weight seems quite low. Girls had lower scores than boys with respect to this dietary structure.

The study underlines that involvement in physical activity at least 30 minutes per day remained similar, but involvement in more than one hour daily decreased. The overweight or obesity increased significantly between the two waves, as well the preoccupation for losing weight. The unhealthy method for losing weight by induced vomiting increased significantly. Pills use for losing weight has also increased; the availability and marketing of these types of products in Romanian have also increased. Similar with other studies, girls had a lower BMI in comparison with boys, but higher tendency for using methods for losing weight (4,26).

Similar with other studies, higher BMI was associated with lower involvement in physical activity and eating in fast food restaurants more than two times per week (39). There are also several correlations between different methods for losing weight. The strongest correlation was between use of pills, tea and massage/sauna. Sport was positively associated with dieting and negative associated with vomiting.

This study is subject of several limitations: it has a cross-sectional design and a limited sample of Romanian university students from Cuj-Napoca, it used a short food frequency questionnaire which did not get information regarding quantities, while the weight and height were not measured and rely on students own perception.

In conclusion, the results of the study presents trends in dietary patterns, physical activity and BMI as well as weight related behaviours among Romanian university students, showing several unhealthy habits which should be addressed through educational and policy measures. Moreover, it highlights the existence of several main dietary structures, which seems stable over time and are associated with BMI and various physical activity and weight related behaviours. Future studies should further focus on development, implementation and evaluation of comprehensive programs which address the complex issue of promotion of healthy nutrition, active lifestyle and appropriate management of body weight among Romanian university students.

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Trabajo Original

Epidemiología y dietética

Repercusiones clínicas y económicas de la desnutrición relacionada con la enfermedad en un servicio quirúrgico

Clinical and economic implications of disease-related malnutrition in a surgical service

Beatriz Torres Torres^{1,2}, María D. Ballesteros-Pomar^{2,3}, Susana García Calvo^{1,2}, M.^a Ángeles Castro Lozano^{1,2}, Beatriz de la Fuente Salvador^{1,2}, Olatz Izaola Jáuregui^{1,2}, Juan José López Gómez^{1,2}, Emilia Gómez Hoyos^{1,2}, Carlos Vaquero Puertas⁴ y Daniel de Luis Román^{1,2}

¹Servicio de Endocrinología y Nutrición. Hospital Clínico Universitario de Valladolid. Valladolid. ²Instituto de Endocrinología y Nutrición. Universidad de Valladolid. Valladolid.

³Unidad de Nutrición Clínica y Dietética de Endocrinología y Nutrición. Complejo Asistencial Universitario de León. León. ⁴Servicio de Angiología y Cirugía Vascular. Hospital Clínico Universitario de Valladolid. Valladolid

Resumen

Introducción: la desnutrición relacionada con la enfermedad (DRE) tiene una alta prevalencia e importantes repercusiones clínicas y económicas. Nuestro objetivo es valorar la factibilidad e importancia de establecer una estrategia de cribado nutricional en nuestro medio.

Pacientes y métodos: estudio prospectivo realizado en una planta quirúrgica. Se realizó el *Malnutrition Universal Screening Tool* (MUST) al ingreso y semanalmente, hasta el alta hospitalaria, a todos los pacientes. Cuando fue necesario, se realizó valoración e intervención nutricional así como codificación al alta de los diagnósticos y procedimientos nutricionales. Datos de estancia hospitalaria (EH), costes hospitalarios y parámetros clínicos fueron analizados posteriormente.

Resultados: en un 15,6% de pacientes, el MUST detectó riesgo de desnutrición (≥ 2 puntos). Los pacientes con desnutrición al ingreso (DI) presentaron una estancia hospitalaria (EH) cuatro días superior y mayor tasa de mortalidad y de reingresos urgentes (2,4 y 2,0 veces, respectivamente), un año después del alta hospitalaria. La edad y el ingreso urgente fueron los factores asociados a mayor tasa de mortalidad anual.

Un 9% de los pacientes con MUST < 2 inicial sufrieron un deterioro del estado nutricional (DEN) durante el ingreso. Estos pacientes, tuvieron mayor EH (siete días) a igualdad de comorbilidad.

Considerando los costes relacionados con la EH, en los pacientes que presentaron DI o DEN se observó un sobrecoste del 57% y el 145%, respectivamente.

Conclusión: los pacientes con DI presentaron mayor EH y tasa de mortalidad y de reingresos urgentes un año después del alta hospitalaria. Los pacientes con DI o DEN ocasionan un sobrecoste económico. El cribado nutricional es indispensable para el manejo y la detección precoz de la DRE.

Palabras clave:

Desnutrición hospitalaria. MUST. Servicio quirúrgico. Soporte nutricional.

Abstract

Introduction: disease-related malnutrition (DRM) is currently a major challenge in our hospitals, both because of its high prevalence and because of the clinical and economic impact. Our study aims to assess the feasibility and importance of establishing a nutritional screening strategy in our Health Care System.

Patients and methods: this is a prospective study carried out in a Surgery Ward. The nutritional risk was assessed by applying to patients MUST at admission and weekly until discharge. Nutritional evaluation and nutritional intervention were performed if required, as well as coding of diagnoses and nutritional procedures at discharge. Clinical data, length of stay (LOS) and hospital costs were analyzed.

Results: MUST detected 15.6% of patients at risk of malnutrition at admission. Patients with malnutrition at admission (MA) had four days longer LOS, higher annual mortality rate and urgent hospital readmissions in 2.4 and 2.0 times, respectively, one year after discharge. Age and urgent hospital admission were the factors associated with a higher annual mortality rate. Nine per cent of patients with an initial MUST < 2 suffered deterioration in their nutritional status during admission (DNS). These patients had longer LOS in seven days with equal comorbidity. Considering only the costs related to LOS in patients who presented MA or DNS, an overcost of 57% and 145%, respectively, was observed.

Conclusion: patients with malnutrition on admission had longer LOS, higher mortality rate and urgent hospital readmissions one year after discharge. Patients who present MA or DNE cause an economic cost overrun. A nutritional screening tool is essential for the management and early detection of DRM.

Key words:

Hospital malnutrition. MUST. Surgical Ward. Nutritional Support.

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Correspondencia:

Beatriz Torres Torres. Servicio de Endocrinología y Nutrición. Hospital Clínico Universitario de Valladolid. Av. Ramón y Cajal, 3. 47003 Valladolid
e-mail: beatriztorrestorres@hotmail.com

INTRODUCCIÓN

La desnutrición relacionada con la enfermedad (DRE) es en la actualidad un reto importante en nuestros hospitales, tanto por su alta prevalencia como por las repercusiones clínicas y económicas que conlleva. El estudio PREDYCES, un estudio transversal, observacional y multicéntrico, en condiciones de práctica clínica habitual, que incluyó 1.707 pacientes en 31 hospitales españoles, evaluó la presencia de DRE, así como la incidencia de complicaciones asociadas a la desnutrición, el exceso de estancia hospitalaria y los costes sanitarios asociados (1). La prevalencia de DRE fue del 23,7% en el momento del ingreso, siendo destacable que en el momento del alta la situación era incluso peor, ya que mantenía la desnutrición un 71,8% de los pacientes desnutridos al inicio y se desnutrió adicionalmente un 9,6% de los pacientes con buen estado inicial. La desnutrición se asoció a un incremento de la estancia hospitalaria, especialmente en aquellos pacientes que ingresaron sin desnutrición y que presentaron desnutrición al alta (15,2 vs. 8,0 días; $p < 0,001$), con un gasto adicional asociado de 5.829 € por paciente (1).

En nuestra Comunidad Autónoma, un estudio multicéntrico transversal en nueve hospitales de Castilla y León que incluyó 213 pacientes detectó una prevalencia de desnutrición valorada por Mini Nutritional Assessment (MNA) (2) en el 23,9% de los pacientes ingresados en servicios de Medicina Interna, presentando, además, un 50,2% de los pacientes riesgo de desnutrición. Se establecía una clara correlación entre el descenso de peso y el aumento de estancia hospitalaria y el incremento de puntuación en el MNA y la menor estancia hospitalaria (3).

En el contexto nacional, nace en 2013 el Proyecto Masnutridos, una iniciativa de la Sociedad Española de Nutrición Parenteral y Enteral (SENPE) y la Fundación Abbott, que ha evolucionado en 2015 a Alianza másnutridos (<http://www.alianzamasnutridos.es/>). Esta alianza incluye a todos los organismos y sociedades implicadas en el cuidado de los pacientes y actualmente está formada por el Consejo General de Colegios Oficiales de Farmacéuticos, el Consejo General de Enfermería, la Alianza General de Pacientes, la Sociedad Española de Medicina de Familia y Comunitaria (SEMFYC), la Sociedad Española de Médicos de Atención Primaria (SEMERGEN), la Sociedad Española de Endocrinología y Nutrición (SEEN), la Sociedad Española de Geriátrica y Gerontología, la Sociedad Española de Gastroenterología, Hepatología y Nutrición Pediátrica (SGHNP) y la Sociedad Española de Directivos de Salud (SEDISA). Su objetivo es aumentar el conocimiento y la importancia de la desnutrición en el ámbito sanitario y sus costes entre las administraciones públicas, de manera que se incluya la lucha contra la desnutrición en todas las áreas y estrategias a nivel nacional y regional en las que se aborde la mejora de la calidad del Sistema Nacional de Salud, así como el tratamiento de patologías específicas con especial relevancia. Además, pretende conseguir iniciativas regionales que incluyan actuaciones contra la desnutrición y contemplen el cribado de la desnutrición relacionada con la enfermedad.

La desnutrición hospitalaria tiene un impacto económico importante, ya que se relaciona no solo con un retraso en la recupera-

ción, sino también con mayores tasas de morbimortalidad, mayor estancia hospitalaria y mayores tasas de reingreso.

En este sentido, nuestro estudio se plantea como una de esas iniciativas regionales, en el marco de la Comunidad de Castilla y León, y tiene como objetivo valorar la factibilidad e importancia de establecer una estrategia de cribado nutricional en nuestro medio, en este estudio en concreto, dentro de una planta quirúrgica.

En nuestra serie de pacientes se realizó un seguimiento diario de la implantación y manejo del MUST para garantizar su correcta realización durante el periodo de estudio.

PACIENTES Y MÉTODOS

Se trata de un estudio prospectivo realizado en una planta de hospitalización de Cirugía Vascular, en el que se incluyeron todos los pacientes que ingresaron durante los meses de febrero, marzo y abril de 2015. El estudio fue aprobado por el Comité Ético de Investigación Clínica del Hospital Clínico Universitario de Valladolid (HCUV).

El cribado nutricional fue realizado por el personal de Enfermería al ingreso del paciente en la planta de hospitalización de Cirugía Vascular del 1 de febrero al 30 de abril de 2015. El personal de Enfermería de la planta recibió previamente formación en las repercusiones de la desnutrición relacionada con la enfermedad y la herramienta de cribado nutricional que se iba a utilizar. Se ha empleado como herramienta de cribado el Malnutrition Universal Screening Tool (MUST, <http://www.bapen.org.uk/screening-for-malnutrition/must/must-toolkit/the-must-itself/must-espanol>). Desde la Consejería de Sanidad de Castilla y León (SACYL), se incluyó dentro del sistema de información sanitario de cuidados de enfermería GACELA CARE un apartado destinado a incluir los datos necesarios para obtener la puntuación del MUST de forma automática (Fig. 1). Por lo tanto, se obtuvo la talla y el peso de todos los pacientes en el momento del ingreso (o se estimaron en caso de no poder realizarse, siguiendo las recomendaciones de la British Association of Parenteral and Enteral Nutrition (BAPEN) (4) y se incluyeron en GACELA los datos necesarios para poder obtener el MUST según el esquema reflejado en la figura 1. Como se recoge en el esquema, aquellos pacientes con una puntuación igual o superior a 2 en el MUST se consideran de riesgo alto y son subsidiarios de tratamiento nutricional, por lo que la Unidad de Nutrición Clínica y Dietética (UNCyD) realizó una valoración nutricional completa y estableció tratamiento nutricional según procedía. Se repitió el cribado de forma semanal en todos aquellos pacientes con una puntuación MUST de 0 o 1 al ingreso. En todos los pacientes, además, se recogieron los motivos de ingreso y se valoró la comorbilidad mediante el índice de comorbilidad de Charlson (5). También se registraron el número de reingresos no programados durante el periodo de estudio, a los seis y a los 12 meses del alta, así como datos de mortalidad durante el ingreso y de mortalidad acumulada anual.

Tras la valoración nutricional, se obtuvo un diagnóstico nutricional según los criterios establecidos de forma conjunta por SENPE y la Sociedad Española de Documentación Médica (SEDOM) (6). Se realizó intervención nutricional en los pacientes que así lo requirieron según la práctica clínica habitual de la sección de nutrición clínica y dietética UNCyD del HCUV. Se realizó la codifi-

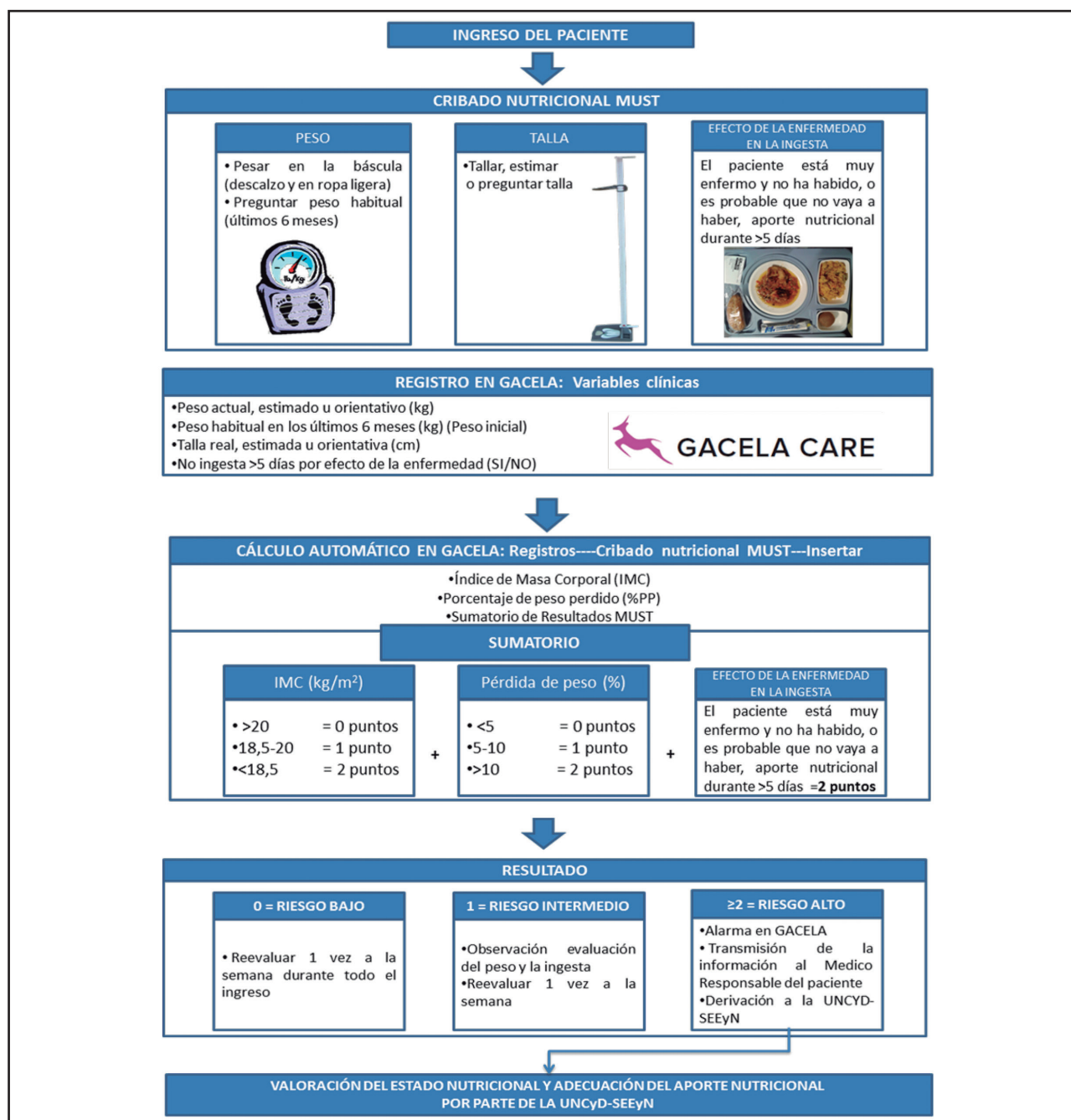


Figura 1.

Realización de MUST e inclusión en el programa GACELA CARE.

cación del tipo de desnutrición y del procedimiento utilizado para revertirla (7), adicional a lo informado por el médico que firmaba el alta del paciente. Se calculó el peso medio antes y después de incluir los datos relacionados con la desnutrición.

De este modo, hemos podido analizar las diferencias en los costes de los pacientes en función de su situación nutricional. Se evaluaron los costes de la hospitalización en Cirugía Vascular durante el año previo a la hospitalización, que arrojaron una media

por día de estancia hospitalaria de 540 euros por paciente y día, excluyendo en estos los gastos de Farmacia.

El estudio estadístico se realizó mediante el paquete IBM SPSS Statistics 19. Los datos se han expresado mediante media y desviación estándar (DE) y se compararon mediante test t de Student, con un valor de significación de $p < 0,05$, tras comprobar que siguieran una distribución normal (peso, índice de masa corporal [IMC], edad). Las variables que no seguían una distribución normal

se expresaron como mediana y rango intercuartil (RIC). Puesto que los datos de estancia y costes hospitalarios de pacientes no seguían una distribución normal, se han utilizado pruebas no paramétricas (U de Mann Whitney) para su comparación.

RESULTADOS

Durante los tres meses de estudio, ingresaron en la planta del Servicio de Cirugía Vascular 237 pacientes. Un 80,6% fueron varones y la edad media fue de 70,0 (DE 13,0) años. La mediana de estancia hospitalaria fue de siete días (RIC 8,7) y el índice de comorbilidad de Charlson, de 6 (RIC 2,5). Un 2,5% de los pacientes fallecieron durante el ingreso hospitalario. Un 43% de los pacientes recibieron únicamente tratamiento conservador, no quirúrgico. El 58% de los ingresos eran programados.

La herramienta MUST detectó en el momento del ingreso riesgo bajo de malnutrición (MUST = 0) en 171 pacientes (72,2%), riesgo intermedio de malnutrición (MUST = 1) en 29 (12,2%) y riesgo alto de malnutrición (MUST $\geq$ 2) en 37 pacientes (15,6%).

Los pacientes con riesgo bajo de malnutrición tenían menor edad, menor estancia media y un mayor IMC en el momento del cribado inicial, sin diferencias en cuanto a sexo o comorbilidad (Tabla I).

Además, un 9% de los pacientes con un MUST inicial $<$ 2 presentaron durante el ingreso hospitalario un empeoramiento de su situación nutricional. Tras un cribado positivo, se confirmó el diagnóstico de desnutrición en el 83% de los pacientes. Por tanto, el 13% del total de los pacientes cumplían criterios de desnutrición en el momento del ingreso.

CARACTERÍSTICAS DE LOS PACIENTES CON DESNUTRICIÓN EN EL MOMENTO DEL INGRESO

No se encontraron diferencias en el sexo ni en el índice de comorbilidad de Charlson en relación con su situación nutricional. Sin embargo, los pacientes con desnutrición eran de mayor edad (77,5 [9,9] años vs. 68,8 [13,0] años, $p < 0,001$), presentaban una mayor estancia hospitalaria (11,0 días vs. 7,0 días) y tenían un IMC menor (21,3 [4,7] kg/m² vs. 26,2 [4,5] kg/m², $p < 0,001$) (Tabla II).

Los pacientes con desnutrición no recibieron tratamiento quirúrgico en más ocasiones que los normonutridos (60% vs. 40%, $p = 0,12$).

La tasa de reingresos urgentes a los 12 meses del alta hospitalaria fue superior en los pacientes desnutridos (53% vs. 35%,

Tabla I. Características de los pacientes según cribado de desnutrición en el momento del ingreso

	MUST = 0 (n = 171)	MUST = 1 (n = 28)	MUST $\geq$ 2 (n = 38)	P
Sexo (% hombres)	83%	72%	71,4%	$< 0,001$
Edad (años)	68,2 (12,3)	75,9 (12,8)	73,3 (14,6)	$< 0,05$
Estancia (días)	5 (7)	8,5 (12,75)	8 (11,25)	$< 0,05$
Fallecidos durante el ingreso (%)	2,4	3,4	2,8	0,4
Peso ingreso (kg)	76 (13,4)	62,3 (13,9)	57,4 (12,8)	$< 0,001$
IMC ingreso (kg/m ²)	27,1 (4,0)	22,8 (4,7)	21,2 (4,7)	$< 0,001$
Ingresos urgentes (%)	31,0	55,2	74,0	$< 0,001$
Comorbilidad Charlson	6 (2,5)	7 (3)	7 (3)	0,06

Tabla II. Características de los pacientes con desnutrición en el momento del ingreso

	No desnutrición	Desnutrición	p
Sexo (% hombres)	81%	75%	0,390
Edad (años)	68,8 (13,0)	77,5 (9,9)	$< 0,001$
Estancia (días)	7,0 (7,0)	11,0 (12,0)	$< 0,001$
Fallecidos (%) durante el ingreso	2,5	3,2	0,585
Tratamiento no quirúrgico	40%	60%	0,12
Reingresos urgentes, anual (%)	37,2%	52,6%	0,025
Índice de Charlson	6 (3)	7 (3)	0,051
Ingresos urgentes	35,6%	76,2%	$< 0,001$
IMC ingreso (kg/m ²)	26,2 (4,5)	21,2 (4,7)	$< 0,001$
IMC alta (kg/m ²)	26,3 (4,4)	21,3 (4,6)	$< 0,001$

$p = 0,025$), con un RR de 2,0 (1,1-4,1, $p = 0,048$), sin que se alcanzase significación estadística al mes y a los seis meses del alta hospitalaria (Fig. 2).

En los pacientes desnutridos la tasa de mortalidad durante el ingreso no fue superior, aunque tras reevaluar este dato un año después se observó que era más elevada en este grupo (23,7% vs. 10,5%, $p < 0,05$) (Fig. 2).

El análisis multivariante ajustado por edad mostró que la desnutrición al ingreso (RR 2,4 [2,25-2,7], $p < 0,001$) y el ingreso urgente (RR 4,9 [4,4-5,5], $p < 0,001$) eran factores predictivos independientes de mortalidad anual.

Los pacientes mayores de 70 años tenían una mayor tasa de desnutrición al ingreso (21,7% vs. 10,3%, $p < 0,05$) y de *exitus* anual (19,2% vs. 6%, $p < 0,005$) que los pacientes de 70 años o menos, sin que se alcanzase significación estadística en cuanto a la tasa de reingreso urgente anual (36,7 vs. 39,2%, $p = 0,67$).

Se realizó intervención nutricional en los pacientes con diagnóstico de desnutrición, en la mayor parte de los casos mediante modificaciones dietéticas (62%), un 27% de los pacientes requirió suplementación nutricional oral, un 7% precisó nutrición parenteral y un 4%, nutrición enteral. No se observó descenso del IMC

al alta hospitalaria en los pacientes desnutridos (21,16 kg/m² vs. 21,2 kg/m², $p = 0,25$).

CARACTERÍSTICAS DE LOS PACIENTES EN FUNCIÓN DEL TIPO DE INGRESO

El 58% de los ingresos eran programados (Tabla III). Los pacientes ingresados de manera urgente tenían más edad (75,2 [12,3] años vs. 68,3 [10,9] años, $p < 0,001$), mayor índice de comorbilidad de Charlson (7 [3] vs. 5 [3], $p < 0,001$), y menor IMC (24,1 [5,3] kg/m² vs. 26,4 [4,4] kg/m², $p < 0,001$), presentando, además, mayor estancia hospitalaria (10 [11,2] días vs. 6 [4,0] días, $p < 0,001$) y mayor prevalencia de desnutrición (19% vs. 4%, $p < 0,001$). No existían diferencias en cuanto al sexo.

La tasa de mortalidad acumulada anual fue superior en los ingresos urgentes (25,8% vs. 1,7%, $p < 0,001$); sin embargo, no hubo diferencias en la tasa de reingresos acumulada anual.

CARACTERÍSTICAS DE LOS PACIENTES QUE EMPEORARON SU SITUACIÓN NUTRICIONAL DURANTE EL INGRESO

Como señalamos anteriormente, un 9% de los pacientes con un MUST < 2 al inicio presentaron durante el ingreso hospitalario un empeoramiento de su situación nutricional (lo que supone un 7,6% del total de pacientes).

De los pacientes con MUST < 2 al ingreso, el 42,2% (84 pacientes) tuvo una estancia hospitalaria superior a siete días. Un 21,4% de estos pacientes sufrió un deterioro de su situación nutricional, objetivado en la reevaluación semanal como MUST ≥ 1 (si inicialmente presentaban un MUST = 0) o con MUST > 1 (si inicialmente presentaban MUST = 1). En este grupo, se observaba una disminución del IMC al alta con respecto al IMC inicial (25,3 [4,81] kg/m² vs. 24,1 (3,78) kg/m², $p < 0,01$) así como una estancia media siete días superior respecto al grupo que no modificó su situación nutricional.

No se alcanzaron diferencias significativas en cuanto a reingresos urgentes anuales, ni a la tasa de mortalidad acumulada anual (Tabla IV).

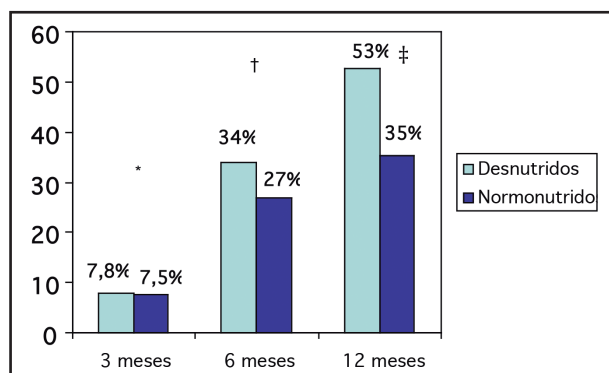


Figura 2.

Tasa de reingresos urgentes en pacientes con desnutrición y normonutridos al ingreso (* $p = 0,7$; † $p = 0,24$; ‡ $p = 0,02$).

Tabla III. Características de los pacientes según el tipo de ingreso

Ingreso	Urgente	Programado	p
Sexo (% hombres)	77,4	83,5	0,32
Edad (años)	75,2 (12,3)	68,35 (10,97)	< 0,001
Índice de Charlson	7 (3)	5 (3)	0,001
IMC ingreso (kg/m ²)	24,1 (5,3)	26,4 (4,4)	0,001
Desnutrición (%)	19,2	4,0	< 0,001
Estancia (días)	10 (11,2)	6 (4)	< 0,001
Tasa <i>exitus</i> anual (%)	25,8	1,7	< 0,001
Reingreso anual (%)	44	50	0,12

Tabla IV. Características de los pacientes que presentaron un empeoramiento de su situación nutricional durante el ingreso (en pacientes con ingresos > 7 días)

	MUST < 2 sin cambios durante todo ingreso	MUST < 2 que aumentó durante hospitalización	p
Sexo (% hombres)	86,4	83,3	0,7
Edad (años)	70,9 (12,1)	73,6 (10,0)	0,38
Estancia (días)	10,0 (9,0)	17,2 (10,7)	0,004
Charlson	6 (3)	7 (2,5)	0,37
Reingreso anual (%)	45	50	0,7
Tasa exitus acumulada anual (%)	12,0	16,7	0,6
IMC ingreso (kg/m ²)	26,2 (4,97)	25,3 (4,81)	0,45
IMC alta (kg/m ²)	26,3 (4,99)	24,1 (3,78)	0,059

ESTUDIO DE GASTOS RELACIONADOS CON LA DESNUTRICIÓN

El incremento en la estancia hospitalaria supone un mayor coste del ingreso en los pacientes que se desnutren. En nuestro estudio, los gastos relacionados con la desnutrición se basaron en el aumento del gasto secundario al incremento de estancia hospitalaria. Considerando los datos de incremento de la estancia, podemos decir que los pacientes que presentan desnutrición al ingreso presentan un sobrecoste de 2.544€ por ingreso (+57%). Este sobrecoste alcanza los 5.049€ por ingreso (+145%) en aquellos pacientes que sufrieron deterioro del estado nutricional durante el ingreso (Fig. 3).

Solo teniendo en cuenta el incremento de gasto asociado a la estancia hospitalaria, y considerando que durante 2014 ingresaron en el Servicio de Cirugía Vascular 2.415 pacientes, la desnutrición implica un exceso de gastos relacionados con la desnutrición de 1.482.624€ anuales en este servicio.

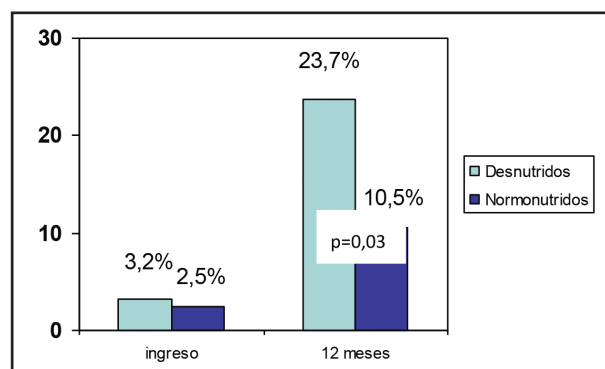
DATOS DE CODIFICACIÓN E ÍNDICES HOSPITALARIOS

La adecuada codificación de los diagnósticos de desnutrición y los procedimientos empleados para revertirla en los pacientes incluidos en el estudio ha implicado un aumento en el peso medio de 2,000 a 2,050 ($p < 0,05$), así como una mejora en los índices de funcionamiento (0,984 vs. 1,051, $p < 0,05$) e índice de estancia media ajustada (IEMA) (0,885 vs. 0,892, $p < 0,05$).

Esta mejora en los índices hospitalarios pone de manifiesto una mayor complejidad de los pacientes ingresados y una mejor utilización de los recursos sanitarios en codificación.

DISCUSIÓN

Los datos del estudio multicéntrico PREDYCES en nuestro país pusieron de manifiesto la alta prevalencia de DRE en nuestros hospitales. La prevalencia de desnutrición observada, valorada

**Figura 3.**

Tasa de exitus acumulada en función de la existencia de desnutrición y normonutrición durante el ingreso y a los 12 meses.

mediante la herramienta Nutritional Risk Screening 2002 (NRS 2002) (8), fue del 23,7% en el momento del ingreso, siendo mayor en los mayores de 70 años, en mujeres y en los ingresos urgentes. En servicios quirúrgicos, la prevalencia de desnutrición fue del 17% (1).

En nuestro estudio, la herramienta empleada fue el MUST, que detectó un cribado positivo en un 15,6% de los pacientes ingresados en un servicio de Cirugía Vascular. La herramienta de cribado nutricional MUST se ha mostrado útil y sencilla para cribar DRE, a pesar de la dificultad de obtener la talla y el peso de los pacientes en una planta de Cirugía Vascular en la que muchos pacientes tenían imposibilitada la bipedestación.

La elección de la herramienta de cribado empleada en el estudio estuvo condicionada por un estudio previo del grupo de Calleja y cols. (9), en el que se realizó un estudio comparativo global de las diferentes herramientas empleadas en el cribado nutricional con la valoración subjetiva global. El MUST fue la herramienta que demostró un mejor rendimiento (mejor área bajo la curva), con una sensibilidad del 82,4% y una especificidad del 93,4%. Estos resultados, unidos a la sencillez de la herramienta, hacen que haya sido la elegida para hacer un cribado universal en nuestro hospital. En Reino Unido, el MUST es la herramienta implantada

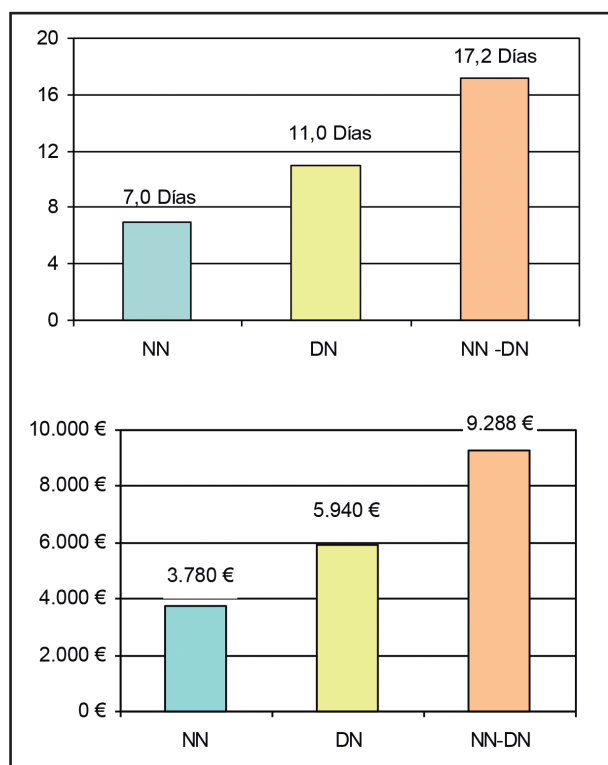


Figura 4.

Estancia hospitalaria y gasto sanitario en pacientes con $MUST < 2$ al ingreso (NN), pacientes desnutridos al ingreso (DN), pacientes con $MUST < 2$ al ingreso y con deterioro de su situación nutricional durante el ingreso (NN-DN).

tanto en Atención Primaria como en Especializada para la detección universal precoz de la desnutrición (10). Para una correcta implantación de una herramienta de cribado nutricional, es fundamental una adecuada formación del personal sanitario. Tewar y cols. (11) observaron cómo, en una planta de Cirugía Vascular donde el MUST estaba implantado como herramienta de cribado nutricional universal, aumentaba el número de pacientes a los cuales se realizaba el MUST (93% vs. 72%) con menor número de errores en su realización y un diagnóstico más frecuente de pacientes con $MUST \geq 2$ (8% vs. 4%) (11), tras recibir el personal sanitario formación al respecto. Además, al menos inicialmente, sería recomendable un estrecho control en su realización para conseguir que el cribado nutricional se lleve a cabo de manera adecuada hasta su total implantación (12).

En nuestra serie, se realizó formación al personal sanitario y un seguimiento de la implantación del MUST por parte del personal de la UNCyD, observándose cómo el 83% de los pacientes con un cribado positivo cumplían criterios de desnutrición al ingreso, lo que supone una prevalencia de desnutrición al ingreso del 13%.

Tal y como se refleja en varios estudios, los pacientes de mayor edad y menor peso son los que presentan mayor riesgo nutricional (1,13). En nuestro grupo de pacientes desnutridos no se encontraron diferencias en cuanto a sexo, aunque sí presentaban más edad, menor IMC y, en más de las tres cuartas partes de

los casos, eran ingresos no programados, por lo que la propia situación de desnutrición pudo condicionar un ingreso urgente.

Como se observó en el estudio PREDyCES (1), la prevalencia de desnutrición fue también superior en los pacientes mayores de 70 años.

Por otra parte, el grupo de pacientes desnutridos al ingreso presentó una mortalidad un año después del alta hospitalaria 2,4 veces superior, y una tasa de reingreso anual 2,0 veces mayor que los pacientes normonutridos. Estos resultados están en línea con los publicados por Lin Lim y cols. (14), que mostraban un riesgo relativo de mortalidad un año después del alta hospitalaria tres veces superior y una tasa de readmisión 1,5 veces superior a los seis meses en los pacientes desnutridos.

En nuestro grupo, la prevalencia de desnutrición (13%) fue menor a la descrita en otras series quirúrgicas, como la del grupo de Thomas y cols. (15), con una prevalencia de desnutrición del 24%, o el grupo de Lin Lim y cols. (14), con prevalencias del 15-30% en función del tipo de servicio quirúrgico.

Esta baja prevalencia, probablemente, está condicionada por que los ingresos eran programados en más del 50% de los pacientes. Sin embargo, si tenemos en cuenta únicamente los ingresos urgentes, la prevalencia de desnutrición al ingreso es del 19%, mucho más acorde con otras series quirúrgicas (1,14-16).

Allard y cols. (17) demostraron cómo la estancia hospitalaria aumentaba si existía una pérdida de peso mayor del 5% o un deterioro del estado nutricional durante el ingreso en los pacientes con ingresos de más de siete días, datos concordantes con nuestra serie, donde un 7% de los pacientes con una estancia hospitalaria de siete días o más presentaron un empeoramiento de su situación nutricional durante el ingreso hospitalario. Fueron estos pacientes los que tuvieron mayor estancia hospitalaria y coste sanitario. Este grupo presentó, además, un descenso del IMC durante el ingreso y una tendencia no significativa a un aumento de la tasa de mortalidad anual y del número de reingresos, probablemente no significativos debido al escaso número de pacientes en el grupo con deterioro del estado nutricional. Asimismo, en este grupo el IMC fue menor y la estancia hospitalaria, más prolongada (siete días), respecto a los que no sufrieron deterioro del estado nutricional, a igualdad de comorbilidades.

Los costes de hospitalización, gastos por estancia hospitalaria, fueron un 65% superiores en los pacientes desnutridos al ingreso, coste que se incrementó en un 127% en los pacientes que sufrieron deterioro del estado nutricional durante el ingreso. En el estudio PREDYCES (1) también se observó que el mayor gasto sanitario procedía del grupo de pacientes con deterioro del estado nutricional durante el ingreso hospitalario (18).

Podemos deducir fácilmente que el empeoramiento del estado nutricional durante el ingreso tiene mucho más impacto en la estancia media de los pacientes y en los costes que la desnutrición previa. Estos datos se reflejan también en el reciente estudio de Gastalver-Martín y cols. (19), que incluyeron en sus estimaciones, además, los gastos de ingreso en planta y cuidados intensivos, pruebas diagnósticas y de laboratorio, fármacos y suplementos nutricionales, y encontraron un gasto superior (entre un 45 y un 102%) en los pacientes malnutridos, especialmente cuando no mejoraban durante la hospitalización.

La mayor limitación de este estudio es el elevado número de ingresos programados, por lo que probablemente no sea una muestra muy representativa de la población quirúrgica hospitalaria, ya que minimiza la prevalencia de desnutrición, menor a la observada en otros estudios. Sin embargo, los resultados obtenidos reflejan un aumento de la estancia hospitalaria y, por tanto, de los recursos sanitarios, asociado a un aumento de la morbilidad y al número de reingresos después de un año de seguimiento en los pacientes desnutridos y en aquellos que sufrieron un deterioro de su situación nutricional durante el ingreso.

CONCLUSIONES

La herramienta MUST detectó en el momento del ingreso un elevado porcentaje de pacientes con riesgo de desnutrición. Además, un 9% de los pacientes que ingresaron con un buen estado nutricional desarrollaron desnutrición durante la estancia hospitalaria y una mayor estancia. Los pacientes con desnutrición al ingreso presentaron mayor estancia hospitalaria y una mayor tasa de *exitus* y de reingresos urgentes en el primer año después del alta hospitalaria. Por último, los pacientes que presentan desnutrición al ingreso o deterioro del estado nutricional durante su estancia hospitalaria ocasionan un sobrecoste económico.

Teniendo en cuenta los resultados anteriores, no hay duda de que un correcto y precoz manejo de la DRE es fundamental para disminuir la morbilidad no solo hospitalaria, sino también tras el alta hospitalaria. Para poder realizar un correcto manejo de estos pacientes, es fundamental el uso de herramientas de cribado nutricional de manera universal en todas las unidades de hospitalización, en el momento del ingreso y durante la hospitalización, de manera periódica. Por tanto, una correcta dotación de recursos materiales y humanos en las unidades de Nutrición Clínica y Dietética es fundamental para una adecuada prevención y manejo de la DRE.

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Trabajo Original

Epidemiología y dietética

Efectos de la dieta lacto-vegetariana y ejercicios de estabilización del core sobre la composición corporal y el dolor en mujeres con fibromialgia: ensayo controlado aleatorizado

Effects of lacto-vegetarian diet and stabilization core exercises on body composition and pain in women with fibromyalgia: randomized controlled trial

Alejandro Martínez-Rodríguez¹, Belén Leyva-Vela², Alba Martínez-García³ y Yolanda Nadal-Nicolás⁴

¹Departamento de Química Analítica, Nutrición y Bromatología. Facultad de Ciencias. Universidad de Alicante. Alicante. ²Hospital Universitario del Vinalopó. Elche, Alicante.

³Departamento de Enfermería Comunitaria. Facultad de Ciencias de la Salud. Universidad de Alicante. Alicante. ⁴Departamento de Patología y Cirugía. Facultad de Medicina. Universidad Miguel Hernández. Elche, Alicante

Resumen

Introducción: la fibromialgia es una enfermedad de origen desconocido caracterizada por dolor muscular crónico. La falta de conocimientos sobre esta enfermedad es una de las principales causas por las que resulta complejo realizar un diagnóstico y tratamiento adecuados.

Objetivo: el objetivo principal de este estudio fue conocer la eficacia de un tratamiento de fisioterapia combinado con una intervención dietético-nutricional lacto-vegetariana, sobre el dolor bajo de espalda y la composición corporal en mujeres con fibromialgia.

Métodos: en el estudio participaron 21 mujeres, que fueron divididas aleatoriamente en 3 grupos: A (ejercicios estabilización core + dieta lacto-vegetariana), B (placebo + dieta lacto-vegetariana) y C (control). La intervención tuvo una duración de 4 semanas y se realizaron evaluaciones del dolor (escala EVA), y de la composición corporal (bioimpedancia), al inicio y final de la intervención.

Resultados: el grupo A mostró cambios significativos en la reducción del dolor y la composición corporal al final de la intervención, aumentando la masa muscular y disminuyendo la masa grasa. Además, este grupo mejoró significativamente los resultados en comparación con los grupos B y C. Las correlaciones realizadas mostraron una relación entre la masa muscular y la disminución del dolor referido al final del estudio en las pacientes del grupo A.

Conclusiones: un programa de intervención de 4 semanas de duración en el que se combina ejercicios de estabilización de core más dieta lacto-vegetariana en pacientes con fibromialgia que presentan dolor bajo de espalda contribuye a la reducción del dolor y la mejora de la composición corporal.

Palabras clave:

Fisioterapia. Dieta.
Índice de masa
corporal. Dolor
crónico.

Abstract

Background: fibromyalgia is a disease of unknown origin characterized by chronic muscular pain. The lack of knowledge about this disease is one of the main causes that makes complex to make a diagnosis and an appropriate treatment.

Objective: the main objective of this study was to know the efficacy of a physiotherapy treatment combined with a lacto-vegetarian dietary-nutritional intervention, on low back pain and body composition in women with fibromyalgia.

Methods: twenty-one women were randomly divided into three groups: A (core stabilization exercises + lacto-vegetarian diet), B (placebo + lacto-vegetarian diet) and C (control). The intervention lasted 4 weeks. Pain assessments (EVA scale) and body composition (bioimpedance) were performed at the beginning and at the end of the intervention.

Results: group A showed significant changes in pain reduction and body composition at the end of the intervention, increasing muscle mass and decreasing fat mass. In addition, this group significantly improved outcomes compared to groups B and C. The correlations showed a relationship between muscle mass and pain reduction referred to at the end of the study in patients in group A.

Conclusions: four-week intervention program combining core stabilization exercises plus lacto-vegetarian diet in patients with fibromyalgia who have low back pain contributes to pain reduction and improved body composition.

Key words:

Physiotherapy. Diet.
Body mass index.
Chronic pain.

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Correspondencia:

Alejandro Martínez-Rodríguez. Departamento Química Analítica, Nutrición y Bromatología. Facultad de Ciencias. Universidad de Alicante. Carretera de San Vicente del Raspeig, s/n. 03690 San Vicente del Raspeig, Alicante
e-mail: amartinezrodriguez@ua.es

INTRODUCCIÓN

Se podría definir la fibromialgia como un cuadro clínico de origen desconocido. Fue definido en 1990 por el Colegio Americano de Reumatología como la presencia de dolor crónico, durante más de tres meses de duración, así como generalizado, es decir, que afecte al menos a tres de los cuatro cuadrantes corporales (1). Además, los pacientes que la presentan refieren once o más puntos dolorosos específicos, de los dieciocho posibles.

Sin embargo, a medida que se evoluciona en el conocimiento de dicha enfermedad, parece ser que el contenido de esta ha dejado de centrarse exclusivamente en la sintomatología asociada al aparato locomotor (2,3). Por este motivo, el mismo Colegio Americano de Reumatología reformula su propuesta, estableciendo nuevos criterios que ya no requieren la palpación de puntos dolorosos y que evalúan al paciente en función del número de regiones dolorosas, una escala de gravedad de la fatiga, del sueño no reparador y de los síntomas cognitivos (1-3).

Al respecto, quedan constatadas las dificultades que se pueden presentar a la hora de realizar un diagnóstico para la fibromialgia, que acompañados de la falta de conocimientos en relación a los mecanismos fisiopatológicos de la enfermedad, complica las propuestas terapéuticas. Sin embargo, los criterios del Colegio Americano de Reumatología son los más aceptados pese a sus limitaciones (2). En definitiva, cabe indicar que el diagnóstico de la fibromialgia se basa principalmente en síntomas. Asimismo, hay que incidir en que la fibromialgia presenta un tratamiento y seguimiento complejo, ya que a pesar de las investigaciones al respecto, no queda del todo definido (2,4,5).

Según datos epidemiológicos del año 2000, en España, existe una prevalencia próxima al 2,5%, siendo la población de mujeres las que presentan un mayor número de afecciones por fibromialgia, y cuya edad con mayor prevalencia se sitúa en el rango de los 40 a los 50 años (1,6). A nivel europeo la prevalencia también oscila alrededor del 2,5%, mientras que a nivel mundial aumenta, obteniéndose informes del 3-6% de la patología. Dentro de las enfermedades crónicas, las estadísticas ponen de manifiesto que la fibromialgia está en segunda posición en cuanto a prevalencia (2,4,7,8).

Actualmente, se pone de manifiesto la importancia de una gestión multidisciplinar en el tratamiento de la fibromialgia, cuyo objetivo no es otro que proporcionar al colectivo con esta enfermedad un cuidado más completo en busca de una mejora de la salud y la calidad de vida (7,8). Entre estas estrategias se encuentran el ejercicio físico y el apoyo dietético-nutricional.

Por un lado, la fibromialgia está asociada con niveles bajos de capacidad funcional y capacidad física (9). Es por ello que la realización de ejercicio va a conllevar efectos beneficiosos en pacientes con dolores musculares crónicos (10). Esto se debe a que la fibromialgia está íntimamente relacionada con otros trastornos reumáticos y musculoesqueléticos, como es el dolor bajo de espalda o LBP por sus siglas en inglés "low back pain" (2). Cabe destacar que hay diversos autores (11-14) que afirman que diferentes estudios biomecánicos y epidemiológicos han relacionado alteraciones en el control neuromuscular de la estabilización del *core* con la aparición

de lesiones en la columna lumbar y en los miembros inferiores. El *core* se podría definir como un núcleo, que está representado como un cilindro de doble pared, situado en la zona lumbar, abdomen, espalda superior y pecho. En la parte interna de este cilindro se encuentran los músculos más profundos del *core*, también llamados musculatura local: diafragma, transverso del abdomen, multifido lumbar o segmentario, psoas posterior, y musculatura del suelo pélvico. La parte externa del cilindro está compuesta por los músculos más superficiales o musculatura exterior global del núcleo: oblicuos del abdomen, multifidos superficial y espinales, psoas anterior, fibras oblicuas del cuadrado lumbar y contribuciones de la musculatura del suelo pélvico.

En este sentido, en las últimas décadas, los profesionales de la salud han incrementado la aplicación y desarrollo de los ejercicios de estabilidad del *core* (15-17). En cuanto a los programas de rehabilitación basados en ejercicios de estabilización de *core*, estos ejercicios se centran básicamente en el mantenimiento del raquis en posición neutra, conservando las curvaturas fisiológicas cuando este es sometido a fuerzas internas o externas que ponen a prueba su estabilidad.

En cuanto a la investigación en relación a los requerimientos energéticos y hábitos alimentarios en esta población, parece ser que las dietas vegetarianas podrían tener algunos efectos beneficiosos, entre otros asociados al bajo consumo de grasas de origen animal y el aumento de la ingesta de antioxidantes (18). Además, debido a que hay una alta prevalencia de obesidad y sobrepeso en las personas con fibromialgia (18,19), los programas dietético-nutricionales vegetarianos podrían ayudar también al control de peso, y de este modo, ser una herramienta complementaria para mejorar los síntomas de la enfermedad (18,20).

Por todo ello, la hipótesis del estudio se basa en que una intervención con ejercicios que se centren en la estabilidad del tronco van a mejorar la lumbalgia en mujeres con fibromialgia. Asimismo, dicha intervención acompañada de una propuesta dietético-nutricional lacto-vegetariana adaptada a los requerimientos energéticos de las mujeres con fibromialgia, también contribuirá a que se produzca un cambio en la composición corporal, en base a un incremento de la masa muscular y mejora de la región muscular implicada dolorida.

El objetivo fue conocer los efectos después de la intervención, de un protocolo de rehabilitación, centrado en la lumbalgia o dolor bajo de espalda, en combinación con una intervención dietético-nutricional (dieta lacto-vegetariana) sobre el dolor y la composición corporal en mujeres diagnosticadas de fibromialgia, así como comparar los efectos obtenidos en cada grupo en función de la intervención. Además, se estudió la relación entre las variables de dolor y composición corporal en pacientes de fibromialgia.

METODOLOGÍA

DISEÑO DEL ESTUDIO

Estudio de diseño cuasi-experimental de 4 semanas de duración con 2 grupos experimentales y un grupo control aleatorizados

(distribución a ciegas) (21) a través de un *software* informático online “randomization.com” según recomendaciones publicadas (22). Previo a la recogida de datos y al inicio del programa de entrenamiento, una semana antes de la intervención, se evaluaron las variables dependientes, como se describe a continuación. Los sujetos fueron evaluados por el mismo investigador, utilizando el mismo protocolo y en el mismo momento del día en las semanas 0 y 5.

PARTICIPANTES

Formaron parte del presente estudio 21 mujeres diagnosticadas de fibromialgia (edad: 34 ± 3 años; peso: $61,9 \pm 5,6$ kg; talla: $1,63 \pm 0,06$ m). Se realizó un muestreo aleatorio simple con el fin de agrupar a la muestra en dos grupos experimentales y un grupo control (C). La selección y distribución de las participantes, según los criterios Consort (23) se representan en la figura 1. Las

mujeres del grupo experimental A ($n = 7$) realizaron un programa de rehabilitación basado en la estabilización del *core* y una dieta isocalórica lacto-vegetariana. El grupo experimental B ($n = 7$), grupo placebo, realizaron un programa de rehabilitación basado en la aplicación de ultrasonidos con el dispositivo apagado y sin la utilización de gel conductor; y que también siguieron una dieta isocalórica lacto-vegetariana. El grupo C ($n = 7$) no realizó ningún programa de rehabilitación y siguieron una dieta isocalórica sin restricciones de grupos de alimentos.

Los *criterios de inclusión* para el estudio fueron: ser mujer mayor de 21 años de edad (finalización etapa desarrollo y crecimiento) hasta los 40 años de límite de edad con independencia funcional. Tener diagnosticada fibromialgia (no solamente presentar la sintomatología, para asegurar su presencia). No presentar problemas cardiovasculares o cardiorrespiratorios (que pudieran condicionar la aplicación del programa de rehabilitación). No consumir fármacos analgésicos (que pudiesen enmascarar los efectos del programa propuesto sobre la reducción del dolor),

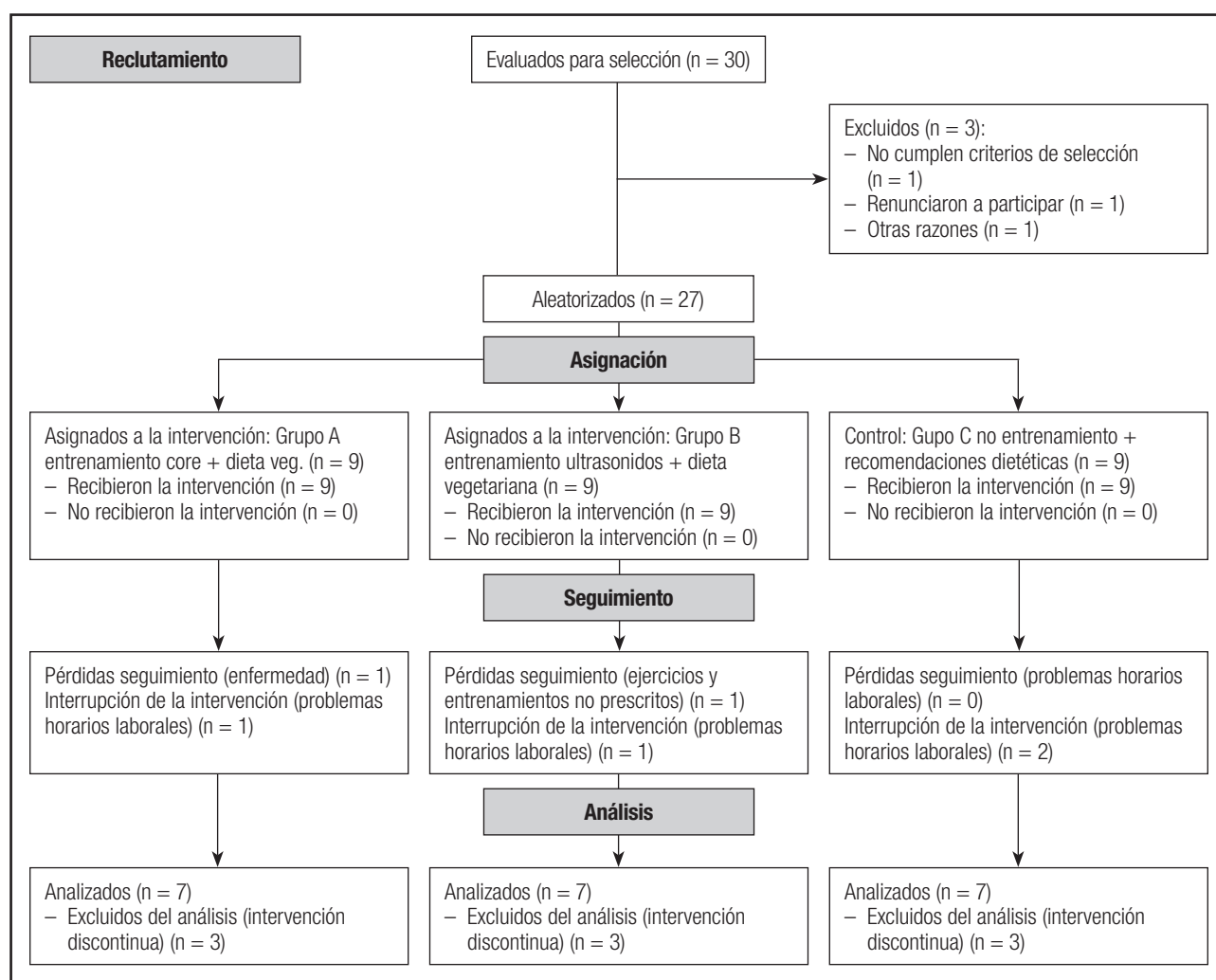


Figura 1.

Diagrama de flujo Consort de selección de la muestra (23).

psicofármacos u otros. Los *criterios de exclusión* fueron dejar de realizar las actividades y programas propuestos (ya que no cumpliría con el propósito de la presente investigación para evaluar el efecto de los mismos) y/o dejar de cumplir con los criterios de inclusión.

Todas las participantes firmaron un consentimiento informado de acuerdo con los principios de la Declaración de Helsinki.

PROGRAMA DIETÉTICO-NUTRICIONAL

La programación dietético-nutricional se consideró como variable independiente. Los grupos A y B de estudio siguieron un programa dietético-nutricional (sin suplementación) adaptado a sus requerimientos energéticos (24) (adaptados tanto al programa de rehabilitación como la a la actividad diaria ligera de cada una de las participantes del estudio) y cantidad diaria recomendada de micronutrientes para la población española, diseñado y planificado por un dietista-nutricionista colegiado (A.M). Antes del inicio de la intervención con el programa de rehabilitación o sin rehabilitación (grupo C), todas las participantes, incluso las del grupo C, iniciaron un programa previo de educación nutricional para que pudiesen seguir el programa dietético durante la intervención sin ningún problema. El consumo proteico estuvo en torno a los 1,2-1,4 g/kg (< 20% del total calórico) de peso corporal; la ingesta de hidratos de carbono que ingirieron los individuos fue de 5-8 g/kg (50-60% del total calórico) de peso corporal y los lípidos alrededor de 1 g/kg (20-30% del total calórico) de peso corporal (20). Los grupos A y B siguieron una planificación dietético-nutricional lacto-vegetariana individualizada y personalizada, mientras que el grupo C no tuvo restricción de ningún alimento de origen animal y tan solo se aportaron pautas de alimentación equilibrada. El balance total de la dieta fue isocalórica en los grupos A y B, ya que no se realizó ninguna restricción energética. En el grupo C el balance fue ligeramente hipocalórico (incremento del 5-10% del total calórico). Todas las participantes recibieron por escrito todas las indicaciones en relación a la ingesta de alimentos, así como el momento para llevarlas a cabo. Las participantes podían tener contacto con el dietista-nutricionista para resolver cualquier duda.

PROGRAMA DE REHABILITACIÓN MEDIANTE EJERCICIOS DE CORE

El programa de rehabilitación también se consideró como variable independiente en el presente estudio. Los ejercicios propuestos consistieron en mantener el raquis en posición neutra conservando las curvaturas fisiológicas cuando este es sometido a fuerzas internas o externas que ponen a prueba su estabilidad (15-17). Las pacientes realizaron un programa de ejercicios de 30 minutos dos veces por semana, siempre en el mismo horario. La intervención duró 4 semanas donde los ejercicios iban progresivamente aumentando su dificultad en base a la ejecución técnica e intensidad del ejercicio (25). La intensidad del ejercicio

se evaluó mediante la escala de percepción del esfuerzo para mujeres con fibromialgia (26).

Las participantes comenzaron las primeras sesiones con ejercicios básicos de estabilización lumbo-pélvica centrados en el movimiento de anteversión y retroversión de pelvis. Finalizaron la intervención con los ejercicios propuestos y entendidos como habituales dentro de los programas de estabilidad de *core*. Ejercicios como puentes donde sin apoyar la pelvis en el suelo se tuvieron que mantener posturas en contra de la fuerza de gravedad, o “perro de muestra” y “bicho muerto”, en el cual las pacientes mantuvieron la columna en posición neutra ante fuerzas provocadas por el movimiento de sus extremidades (15-17).

El protocolo de ejercicios consintió en la realización de 10 ejercicios básicos de *core* (27) con el fin de que al paciente le resultara fácil recordarlos para poder incorporarlos más adelante a su rutina de ejercicios en de su vida cotidiana. Estos ejercicios presentaron variables más difíciles para las pacientes con mejor forma física, que se añadieron en los casos necesarios en las últimas sesiones de la intervención. El número de series y repeticiones dependió de la condición física previa de cada paciente, empezando por 1 serie 5 a 10 repeticiones para cada ejercicio y siguiendo las recomendaciones adaptadas a las guías de ejercicio publicadas por el American College of Sport Medicine (28).

Todos los ejercicios se realizaron de forma controlada y progresiva, sin provocar molestias musculares, dolor, ni ocasionar elevadas fatigas. Los últimos 5 minutos de la sesión fueron destinados para realizar una serie de estiramientos sencillos para finalizar la sesión, correspondiente con vuelta la calma.

INSTRUMENTOS DE EVALUACIÓN

Composición corporal

Para evitar posibles sesgos en la valoración de la composición corporal, como variable dependiente, todo el procedimiento se realizó siguiendo el protocolo de la Sociedad Internacional para el Avance de la Cineantropometría (ISAK, por sus siglas en inglés) (24). La valoración de la composición corporal mediante bioimpedanciometría (peso total, porcentaje de masa grasa y masa muscular en kg) se llevó a cabo con la báscula digital Tanita BC-418 MA (Tanita Corporation, Arlington Heights, IL), con una precisión de 100 g. La altura se midió en m, sin zapatos utilizando el estadiómetro Seca 202 (Seca, Hamburg, Germany) con una precisión de 0,01 m. El estado nutricional se valoró mediante la fórmula “peso (kg) / talla² (m)” para obtener el índice de masa corporal (IMC).

Escala visual analógica

La escala visual analógica (EVA) es un instrumento empleado para evaluar la puntuación de la intensidad del dolor somático (29), interpretado como variable dependiente. Esta escala tiene una puntuación de 0 a 10, donde 0 hace referencia a la ausencia de dolor o “sin dolor” y 10 a “peor dolor posible”.

Escala percepción del esfuerzo

Se empleó, también como variable dependiente de estudio, la puntuación de la escala de percepción del esfuerzo de Borg CR-10 (30) validada para mujeres españolas con fibromialgia (25). La puntuación de la escala presenta 10 puntos en función del esfuerzo percibido por las mujeres, que varía de 0 (nada en absoluto) hasta 10 (muy, muy fuerte).

ANÁLISIS ESTADÍSTICO

El análisis estadístico se llevó a cabo a través del software SPSS® (versión 24.0 IBM para Windows). Se realizaron análisis de estadísticos descriptivos (media $\pm$ desviación estándar [DS]), prueba de distribución de la normalidad Kolmogorov-Smirnov para una muestra, prueba T para muestras relacionadas y ANOVA de un factor entre-sujetos y consiguientes pruebas *post-hoc* (Bonferroni). Para comparar los resultados entre los diferentes grupos, se calculó el delta (Δ) de cada una de las variables de estudio, y que consistió en la siguiente operación: " Δ variable = valor variable post - valor variable pre". Se emplearon pruebas paramétricas debido a que los datos analizados presentaron una distribución normal. Se empleó el test de correlación de Pearson para establecer relaciones entre las variables de estudio. Se fijó un nivel de significación de $p < 0,05$. El tamaño del efecto (TE) se calculó siguiendo las directrices de Cohen (31). El TE se consideró despreciable ($< 0,2$), pequeño ($0,2-0,5$), moderado ($0,5-0,8$) y grande ($> 0,8$).

RESULTADOS

En la tabla I se presentaron los estadísticos descriptivos, comparaciones intragrupo e intergrupos (basal) de las participantes en el estudio. La comparación basal (ANOVA) entre grupos no mostró diferencias significativas entre estos.

La comparación intragrupo entre las pacientes mostró que aquellas pacientes dentro del grupo A incrementaron significativamente al final de la intervención la masa libre de grasa (kg y %), y disminuyeron también de forma significativa la masa grasa (kg y %) y la puntuación total en la escala EVA. Asimismo, también se observó que el TE fue grande en todas las variables indicadas a excepción de la masa libre de grasa en kg, que fue pequeño. Sin embargo, en el peso y el IMC no se observaron diferencias significativas y el TE fue despreciable.

En cuanto a las pacientes del grupo B, no se observaron diferencias significativas antes y después de la intervención en las variables de composición corporal, tampoco en la escala EVA. El TE fue despreciable en todas ellas.

Aquellas participantes que no siguieron la intervención con el ejercicio ni dieta específica, grupo C, incrementaron la masa grasa significativamente (% y kg), así como redujeron significativamente la masa muscular en kg. La escala EVA también presentó un incremento de su puntuación al final de las 4 semanas sin intervención. El TE en las variables porcentuales de composición

Tabla I. Descriptivos, comparaciones intragrupo e intergrupos (basal)

	Grupo A (n = 7)			Grupo B (n = 7)			Grupo control (n = 7)			ANOVA basal
	Basal	Post	TE	Basal	Post	TE	Basal	Post	TE	
	Media $\pm$ DS	Media $\pm$ DS		Media $\pm$ DS	Media $\pm$ DS		Media $\pm$ DS	Media $\pm$ DS		
Edad (años)	34 $\pm$ 2			34 $\pm$ 3			33 $\pm$ 3			ns
Talla (m)	1,62 $\pm$ 0,1			1,63 $\pm$ 0,3			1,64 $\pm$ 0,2			ns
Peso (kg)	63,1 $\pm$ 5,8	63 $\pm$ 5,8	0,0	61,7 $\pm$ 7,1	61,8 $\pm$ 7,1	0,0	61,1 $\pm$ 4,2	61,8 $\pm$ 3,9	0,2	ns
IMC (kg/m ²)	23,5 $\pm$ 0,8	23,5 $\pm$ 0,8	0,0	23 $\pm$ 1,2	23 $\pm$ 1,2	0,0	23,5 $\pm$ 0,7	23,7 $\pm$ 0,8	0,3	ns
Masa libre de grasa (%)	67,7 $\pm$ 1,6	69,8 $\pm$ 1,2 [†]	1,7	67,4 $\pm$ 3,0	67,4 $\pm$ 3,0	0,0	67,7 $\pm$ 1,3	65,9 $\pm$ 1,5 [†]	1,2	ns
Masa grasa (%)	28,9 $\pm$ 1,6	26,8 $\pm$ 1,2 [†]	1,5	29,2 $\pm$ 3,0	29,2 $\pm$ 3,0	0,0	28,9 $\pm$ 1,3	30,7 $\pm$ 1,5 [†]	1,2	ns
Masa libre de grasa (kg)	42,8 $\pm$ 4,8	44 $\pm$ 4,8 [†]	0,3	41,6 $\pm$ 4,6	41,6 $\pm$ 4,6	0,0	41,3 $\pm$ 2,5	40,8 $\pm$ 2,1	0,2	ns
Masa grasa (kg)	18,1 $\pm$ 1,1	16,9 $\pm$ 1 [†]	1,1	18,1 $\pm$ 3	18,1 $\pm$ 3,1	0,0	17,7 $\pm$ 1,7	19 $\pm$ 1,9 [†]	0,7	ns
Escala Dolor EVA	6,7 $\pm$ 1,1	3,0 $\pm$ 1,4 [†]	2,9	6,1 $\pm$ 0,7	6,3 $\pm$ 1,1	0,2	6,5 $\pm$ 1,0	7,6 $\pm$ 0,5 [†]	1,4	ns

IMC: índice de masa corporal; Post: después de la intervención o evaluación final; DS: desviación estándar; TE: tamaño del efecto (d Cohen); *pvalor < 0,05; †pvalor < 0,01; ns: diferencias no significativas.

corporal presentó un efecto grande, al igual que en la puntuación de la escala EVA. En el caso de la masa grasa en kg, el TE fue mediano, así como en el resto de las variables el TE fue pequeño.

En lo relativo a la comparación entre los grupos con intervención A y B así como con el grupo control (Tabla II), hubieron diferencias significativas en cuanto a la masa grasa y la masa libre de grasa (en kg y %), además de en la escala EVA, entre ambos grupos y el grupo control. El grupo A mostró valores Δ superiores frente al grupo B y al grupo C en relación a la masa libre de grasa (kg y %), con un TE grande en ambos casos. De igual forma, el grupo A presentó valores inferiores en las variables de masa grasa (kg y %), así como en la escala EVA, y que también mostraron un tamaño del efecto grande.

Entre el grupo B y el grupo C también se dieron diferencias significativas en las variables de masa grasa, masa libre de grasa y escala EVA. El grupo B mostró diferencias significativas frente al grupo C, cuyos valores Δ de masa grasa y masa libre de grasa, fueron los dos primeros mayores y menores respectivamente frente al grupo B, que no mostró variaciones. En los valores de la escala EVA se observaron diferencias significativas entre ambos grupos, cuya puntuación mayor fue para el grupo C. En todos estos casos el TE fue grande para cada una de las variables estudiadas.

Se estudiaron las correlaciones entre todas las participantes del estudio y cada una de las variables de composición corporal en relación con la escala EVA y no se obtuvieron diferencias significativas. Asimismo, se realizó por separado el estudio correlacional entre las mismas variables en cada uno de los grupos de estudio, también en función de los momentos de la valoración: pre, post o Δ , y tampoco se encontraron relaciones entre estas, a excepción de las variables masa libre de grasa y escala EVA en la valoración post en el grupo A, con un relación negativa entre ambas ($R = -0,856$; $p = 0,014$).

DISCUSIÓN

En mujeres con fibromialgia que presentan dolor bajo de espalda, se encontró que un programa de estabilización del *core*

acompañado de una dieta lacto-vegetariana isocalórica, redujo el dolor de las participantes de forma significativa, en base a los resultados de la escala EVA al final de la intervención. También mejoró los parámetros de composición corporal de las participantes del grupo A, incrementando su proporción de masa muscular y disminuyendo la masa grasa. Estos efectos no se consiguieron en pacientes que siguieron una dieta lacto-vegetariana isocalórica, pero que no recibieron un entrenamiento específico de estabilización del *core*, sino que fueron tratados con placebo. Los resultados obtenidos apuntan hacia la misma dirección que otros estudios con intervenciones sobre la estabilidad del *core* (11,12,15-17), en las que la evidencia disponible sugiere que los especialistas en el tratamiento de estas lesiones o afecciones crónicas deben basarse en el fortalecimiento y acondicionamiento de la pared abdominal y la región lumbar. Todo ello en base a la implementación de ejercicios multifuncionales con autocargas, para entrenar adecuadamente los músculos estabilizadores del tronco (16).

Por ello, en base a las revisiones sistemáticas anteriores (13,14), y en función de los hallazgos del presente trabajo, se ha demostrado que los programas de ejercicios básicos de estabilidad pueden ser efectivos para poblaciones específicas con dolor bajo de espalda, particularmente aquellas con afección crónica, como puede ser el caso de pacientes con fibromialgia, ya que reducen de forma significativa el dolor referido y que se han mostrado en los resultados de la escala EVA, con una disminución de más de 3 puntos en la escala de dolor.

En cuanto a los cambios en la composición corporal, debido a que las pacientes han llevado una dieta isocalórica lacto-vegetariana, es normal que no hayan presentado variaciones en el peso o IMC (ya que esta depende del peso) antes y después de la intervención en los grupos A y B. Sin embargo, el grupo control, con tan solo unas recomendaciones de hábitos alimentarios, sí que ha incrementado el peso final, en base a la masa grasa. La importancia de la aplicación conjunta entre dieta y ejercicio reside en las modificaciones que esta combinación va a reportar sobre los compartimentos corporales, y que ha sido estudiado

Tabla II. Comparación intergrupos (ANOVA)

	Grupo A (n = 7)					Grupo B (n = 7)			Grupo Control (n = 7)	
	Media $\pm$ DS	TE (B)	Sig (B)	TE (C)	Sig (C)	Media $\pm$ DS	TE (C)	Sig (C)	Media $\pm$ DS	
Δ Peso (kg)	0,0 $\pm$ 0,1	0,0	ns	3,3	*	0,0 $\pm$ 0,1	1,1	ns	0,7 $\pm$ 0,9	
Δ IMC (kg/m ²)	0,0 $\pm$ 0,1	1,0	ns	1	*	0,1 $\pm$ 0,1	0,7	ns	0,3 $\pm$ 0,4	
Δ Masa libre de grasa (%)	2,0 $\pm$ 0,7	3,8	†	4,6	†	0,0 $\pm$ 0,2	2,6	†	-1,7 $\pm$ 0,9	
Δ Masa grasa (%)	-2,0 $\pm$ 0,7	3,9	†	4,6	†	0,0 $\pm$ 0,2	2,6	†	1,7 $\pm$ 0,9	
Δ Masa libre de grasa (kg)	1,2 $\pm$ 0,4	4,1	*	3,5	†	0,0 $\pm$ 0,1	1,4	*	-0,6 $\pm$ 0,6	
Δ Masa grasa (kg)	-1,3 $\pm$ 0,5	3,6	†	4,3	†	0,0 $\pm$ 0,1	2,6	†	1,3 $\pm$ 0,7	
Δ Escala EVA	-3,7 $\pm$ 1,4	3,4	†	4,4	†	0,1 $\pm$ 0,7	1,4	*	1,1 $\pm$ 0,7	

Δ : valor post intervención-valor basal; IMC: índice de masa corporal; DS: desviación estándar; TE: tamaño del efecto (d Cohen); TE (B): TE comparado con el grupo B; Sig (B): significación de p comparado con el grupo B; TE (C): TE comparado con el grupo control; Sig (C): significación de p comparado con el grupo control; *pvalor < 0,05; †pvalor < 0,01; ns: diferencias no significativas.

en numerosas ocasiones (32-37). Los resultados de la presente investigación apoyan también una mejora significativa cuando las participantes mantienen una dieta isocalórica lacto-vegetariana y ejercicio (grupo A) en la masa grasa, viéndose disminuida alrededor de 1 kg, con una compensación por su parte de la masa muscular, también de alrededor de 1 kg. En el caso de las pacientes del grupo B, no presentaron variaciones en la composición corporal; es decir, la dieta lacto-vegetariana de forma aislada no va a contribuir a la mejora de estos parámetros, no obstante, parece servir como medida de control para no aumentar de peso y mantener constante la proporción de masa grasa y masa muscular, que probablemente continúe estable debido a las actividades diarias cotidianas, ya que no se ingieren más calorías de las necesarias. Sin embargo, cuando la dieta no se controla, se ha observado en este estudio, que las pacientes incrementan el peso, lo que se asocia a un incremento significativo de masa grasa, al igual que en otros estudios (38-40). Asimismo, también sería interesante poder comparar diferentes aplicaciones o programas dietético-nutricionales, ya que en otro estudio (41) también se ha empleado otra actuación diferente, como la dieta FOODMAP (*low fermentable oligo-di-mono-saccharides and polyols diet*) y se han conseguido resultados beneficiosos sobre el peso, pero no de forma significativa sobre la modificación en la masa grasa y masa muscular, o en la escala de dolor, como en la presente investigación.

Las correlaciones mostraron una relación entre la masa muscular y la reducción de la puntuación en la escala de dolor EVA. Esto parece indicar que debido a que mediante la dieta se consiguen mejores adaptaciones al entrenamiento en base a la mejora de la masa muscular en contrapartida de la masa grasa, las pacientes referirán progresivamente un menor dolor de la zona baja de la espalda, apoyado por un incremento en la estabilización del *core*.

Entre las limitaciones del estudio se presentan, entre otras, la posibilidad de realizar valoraciones electromiográficas de la activación de la musculatura afectada para contrastar los efectos asociados al programa de entrenamiento. Asimismo, también sería conveniente realizar valoraciones más exhaustivas de los cambios en la composición corporal mediante densitometría. En cuanto a los parámetros circulantes, para futuras investigaciones, puede ser interesante valorar los cambios en analíticas sanguíneas relacionados con el aporte específico de macro y micro-nutrientes asociados a dietas vegetarianas en combinación con un programa de entrenamiento. De este modo también se podrán obtener indicadores objetivos de la fatiga o daño muscular de los sujetos participantes, sobre todo en aquellas poblaciones que presentan un dolor crónico.

CONCLUSIONES

Un programa de intervención de 4 semanas de duración en el que se combinan ejercicios de estabilización del *core* más dieta vegetariana isocalórica en pacientes con fibromialgia que presentan dolor bajo de espalda, reduce el dolor y mejora la composición corporal, disminuyendo la masa grasa e incrementando

la masa libre de grasa. Este estudio también sugiere que un incremento en la masa muscular alcanzada mediante entrenamientos de estabilización del *core* contribuye a la reducción del dolor bajo de espalda.

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Trabajo Original

Epidemiología y dietética

Factores asociados al desarrollo de diabetes mellitus tipo 2 en Chile

Risk factors associated with type 2 diabetes in Chile

Ana María Leiva¹, María Adela Martínez², Fanny Petermann³, Alex Garrido-Méndez⁴, Felipe Poblete-Valderrama⁵, Ximena Díaz-Martínez⁶ y Carlos Celis-Morales^{3,7}; en representación del Grupo de Investigación ELHOC

¹Instituto de Anatomía, Histología y Patología. Facultad de Medicina. Universidad Austral de Chile. Valdivia, Chile. ²Instituto de Farmacia. Facultad de Ciencias. Universidad Austral de Chile. Valdivia, Chile. ³BHF Glasgow Cardiovascular Research Centre. Institute of Cardiovascular and Medical Science. University of Glasgow. Glasgow, United Kingdom. ⁴Escuela de Educación Física. Universidad San Sebastián. Concepción, Chile. ⁵Escuela de Kinesiología. Facultad de Salud. Universidad Santo Tomás, Sede Valdivia. Valdivia, Chile. ⁶Grupo de Investigación Calidad de Vida. Departamento de Educación. Universidad del Bío-Bío. Chillán, Chile. ⁷Centro de Investigación en Fisiología del Ejército-CIFE. Universidad Mayor. Santiago, Chile

Resumen

Antecedentes: la prevalencia de diabetes mellitus tipo 2 (DMT2) se ha duplicado en los últimos años a nivel mundial, en gran medida como consecuencia de la modificación del estilo de vida de las personas. Existen muchos factores asociados al desarrollo de DMT2; sin embargo, es necesario identificar cuáles de estos factores tienen mayor o menor implicancia en población chilena. En consecuencia, el objetivo de este estudio fue identificar qué factores sociodemográficos, de estilo de vida y salud tienen mayor implicancia con el riesgo de padecer DMT2 en Chile.

Metodología: estudio de prevalencia basado en los resultados de la Encuesta Nacional de Salud 2009-2010, a partir de una muestra de 4.700 personas (4.162 normales; 538 diabéticos). Se evaluaron factores sociodemográficos, antropométricos, de estilo de vida, salud y bienestar y variables metabólicas. La asociación entre los factores analizados y DMT2 se determinó mediante regresión logística.

Resultados: entre los principales factores de riesgo no modificables asociados a DMT2 se encuentra la edad ≥ 45 años, sexo femenino y antecedentes familiares de DMT2. Los factores de riesgo modificables más significativos fueron: hipertensión arterial, sobrepeso, obesidad, obesidad central, inactividad física y alto nivel de sedentarismo.

Conclusión: la identificación y control de los principales factores de riesgo modificables de DMT2, es clave para disminuir la prevalencia de esta patología y mejorar la calidad de vida de la población.

Palabras clave:

Diabetes mellitus tipo 2. Factores de riesgo. Factores protectores. Enfermedades cardiovasculares. Estilo de vida.

Abstract

Background: worldwide, prevalence of type 2 diabetes has doubled in the last years, mainly due to unhealthy lifestyle behaviours. They are many risk factors associated with diabetes, however, which factors are associated with diabetes in the Chilean population remains unknown. Therefore, the aim was to determine what risk factors are associated with the development of diabetes in Chile.

Methods: four thousand and seven hundred participants from the cross-sectional 2009-2010 National Health Survey were included in this study (4,162 normal; 538 diabetics). Risk factors assessed were socio-demographic, anthropometric, lifestyle, well-being and comorbidities. The association between diabetes and risk factors was examined using logistic regression.

Results: the main non-modifiable risk factors associated with diabetes were age ≥ 45 year, female and family history of diabetes; whereas the main modifiable risk factors were hypertension, overweight, obesity, central obesity, physical inactivity and higher levels of sitting time.

Conclusion: the identification of modifiable risk factors for DMT2 is key to control and decrease the prevalence of this pathology and to improve the quality of life of the population.

Key words:

Type 2 diabetes. Risk factors. Protective factors. Cardiovascular diseases. Lifestyle.

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Autoría: AML, MAM y FP contribuyeron igualmente en este manuscrito y son primeras autoras compartidas.

Declaración de autoría: CCM concibió la pregunta de investigación. CCM y FP realizaron los análisis estadísticos. AML, MAM y FP escribieron el manuscrito. Todos los autores revisaron críticamente el manuscrito y están de acuerdo con su versión final. CCM, en nombre del resto de las personas firmantes, garantiza la precisión, transparencia y honestidad de los datos y la información contenida en el estudio; que ninguna información relevante ha sido omitida; y que todas las discrepancias entre autores han sido adecuadamente resueltas y descritas.

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Correspondencia:

Carlos Celis-Morales. Glasgow Cardiovascular Research Centre. Institute of Cardiovascular and Medical Science. University of Glasgow. G12 8TA. Glasgow, United Kingdom
e-mail: Carlos.Celis@glasgow.ac.uk

INTRODUCCIÓN

La diabetes mellitus tipo 2 (DMT2) es considerada una de las cuatro enfermedades crónicas no transmisibles (ECNT) de mayor prioridad en la actualidad. A nivel mundial, su prevalencia se ha duplicado desde el año 1980, pasando del 4,7% al 8,5% en la población adulta en 2014, siendo este aumento más rápido en los países de bajos y medianos ingresos (1,2). La Federación Internacional de Diabetes (IDF) ha estimado que existen 415 millones de diabéticos en el mundo, cifra que se espera podría aumentar hasta alcanzar los 642 millones en el año 2040 (3).

La drástica transición sociodemográfica y epidemiológica que ha experimentado Chile en los últimos 30 años se ha visto reflejada en el aumento de la prevalencia de las ECNT como la DMT2. Las últimas encuestas nacionales de salud, realizadas en personas mayores de 15 años, han evidenciado un aumento de esta patología de un 6,3% en el año 2003 a un 9,4% el año 2010; es decir, un incremento del 49% en siete años (4,5). Datos más recientes proporcionados por la IDF en 2015 estiman que 1.372.700 personas padecen esta enfermedad en Chile, lo que corresponde a un 11% de la población adulta de entre 20 y 79 años (3).

Existen muchos factores relacionados con el desarrollo de DMT2, algunos no modificables como edad, sexo, historia familiar de DMT2, región de origen, a los que se suman los modificables, relacionados con el estilo de vida como peso corporal, inactividad física, tabaquismo y consumo de alcohol. El conocimiento de dichos factores es la clave para su prevención y tratamiento (6-8). En consecuencia, se hace necesario identificar cuáles de estos factores tienen mayor implicancia en el desarrollo de DMT2 en la población chilena. Por lo anterior, el objetivo de investigación fue determinar de qué forma los factores sociodemográficos, de estilo de vida y salud se asocian con el riesgo de padecer DMT2, en población adulta chilena (4).

MATERIALES Y MÉTODOS

DISEÑO DEL ESTUDIO

Para este estudio se utilizó la base de datos generada por la Encuesta Nacional de Salud 2009-2010 (ENS 2009-2010), que corresponde a un estudio de prevalencia realizado en hogares en una muestra nacional, probabilística, estratificada y multietápica, desarrollada entre octubre de 2009 y septiembre de 2010. De un total de 5.412 personas mayores de 15 años con representatividad nacional, regional y área urbana/rural, la muestra seleccionada correspondió a 4.700 personas (4.162 normales, 538 diabéticos), quienes tenían información disponible en relación a su nivel de actividad física y contaban con medición de glucosa en ayuno de al menos ocho horas. El protocolo de estudio fue aprobado por el Comité de Ética de la Escuela de Medicina de la Pontificia Universidad Católica de Chile. Todos los participantes firmaron un consentimiento informado (4).

MEDICIONES ANTROPOMÉTRICAS Y METABÓLICAS

El estado nutricional fue determinado a través del índice de masa corporal (IMC) y clasificado según los criterios de la Organización Mundial de la Salud (OMS) (normal: 18,5-24,9 kg/m²; sobrepeso: 25,0-29,9 kg/m²; obeso: $\geq 30,0$ kg/m²). La obesidad central fue definida a través de la medición del perímetro de cintura (PC), utilizando como puntos de corte los sugeridos por la ENS 2009-2010; ≥ 83 cm y ≥ 88 cm en mujeres y hombres, respectivamente. Los parámetros metabólicos, tales como glicemia basal, hemoglobina glicosilada (HBA 1C), colesterol total, colesterol HDL y triglicéridos fueron medidos en ayuno con métodos estandarizados y previamente descritos en la ENS 2009-2010 (4). Para la detección de DMT2, se consideró una glicemia en ayuno > 126 mg/dl o el autorreporte de diagnóstico médico de DMT2. Se excluyeron las pacientes con diagnóstico de DM gestacional.

Se consideró síndrome metabólico (SM) a la presencia de tres o más de cinco criterios definidos en *ATP III Update 2004* (9). La presión arterial fue definida a través de tres mediciones $\geq 140/90$ mmHg o autorreporte de tratamiento farmacológico de hipertensión arterial (HTA).

ESTIMACIÓN DEL ÍNDICE DE DIETA SALUDABLE (IDS) Y VARIABLES SOCIODEMOGRÁFICAS

La estimación del índice de dieta saludable (IDS) fue realizada en base a la metodología reportada por Dussailant y cols. en el año 2015 (10). El IDS se calculó como la suma de los puntajes asignados a cuatro grupos de alimentos: verduras, frutas, cereales integrales y pescado, quedando con un rango posible de puntaje de entre 0 y 4 puntos (un puntaje alto refleja una alimentación saludable, mientras que un puntaje bajo refleja una alimentación no saludable).

Las variables sociodemográficas, los datos asociados con estilos de vida y la información relacionada con la autopercepción de salud y el tiempo promedio destinado a dormir en un día normal (para efectos de este estudio se clasificó como: bajo, < 7 horas al día; normal, 7-9 horas al día; y alto, > 9 horas por día) se obtuvieron mediante la aplicación de cuestionarios validados y descritos en la ENS 2009-2010 (4), cuyas categorizaciones están descritas en las tabla y figuras de resultados.

CLASIFICACIÓN DE ACTIVIDAD FÍSICA

El tiempo destinado a actividad física (AF) relacionada con el transporte y las actividades de intensidad moderada o vigorosa realizadas durante el tiempo libre y/o en el trabajo se determinó a través de la guía de análisis de GPAQ (Global Physical Activity Questionnaire v2) (11). La AF total fue expresada en MET/hora/semana. Se consideró como punto de corte para inactividad física un gasto energético < 600 METs/minutos/semana, según la reco-

mendación de la OMS y las especificaciones en la guía de análisis de GPAQ (11,12). El tiempo sedente se determinó mediante el autorreporte del tiempo destinado a actividades que involucren estar sentado o reclinado durante el tiempo libre o de trabajo y fue medido en hora/día. Según los niveles de sedentarismo, se clasificó a los participantes con niveles altos (≥ 4 horas al día) y bajos (< 4 horas al día), determinados mediante el uso de la media (o percentil 50).

ANÁLISIS ESTADÍSTICO

Los datos de caracterización de la población estudiada se presentan como promedio y desviación standard (DE) para variables continuas y como porcentaje para variables categóricas.

Para establecer diferencias significativas entre variables de tipo continua, se utilizó la prueba de t-test para muestras independientes y Chi-cuadrado para variables categóricas.

Para determinar los principales factores asociados al desarrollo de DMT2 se realizaron análisis de regresión logística. Estos análisis fueron mutuamente ajustados por edad, sexo, zona geográfica, educación, ingresos económicos, tabaquismo, consumo de sal, actividad física, sedentarismo, IDS, historia familiar de DMT2, HTA e IMC (esta última variable fue eliminada si el factor de exposición utilizado fue obesidad central). Los datos para estos análisis fueron presentados como *odds ratio* (OR) y su respectivo intervalo de confianza del 95% (95% IC). Para todos los análisis se utilizó el módulo de análisis de muestras complejas del programa Stata/SE v14 y todos los resultados fueron estimados utilizando muestras expandidas según la ENS 2009-2010 (4). El nivel de significancia fue definido como $p < 0,05$.

RESULTADOS

En la tabla I se presentan las características de la población estudiada según diagnóstico de DMT2 (diabético/no diabético). Al analizar las características sociodemográficas se puede apreciar que los participantes diagnosticados con DMT2 tienen mayor edad (mayores de 45 años), menor nivel educacional y pertenecen al grupo de menor ingreso económico, en comparación con la población no diabética. En relación a las características antropométricas, los diabéticos presentan un mayor peso corporal, mayor IMC, mayor PC y una mayor prevalencia de obesidad general y central, al compararlos con los sujetos sin DMT2. Respecto a los estilos de vida, al comparar los diabéticos con los no diabéticos, estos reportaron menor AF total, con mayor prevalencia de inactividad física y mayor tiempo de actividades sedentarias. En cuanto al consumo de alimentos, los diabéticos declararon un mayor consumo de sal, frutas y verduras, además de presentar un mayor IDS. También presentan una mayor prevalencia para exfumadores o no fumadores y tienen de mala a regular percepción de salud/bienestar. Se destaca que los diabéticos presentaron mayores complicaciones metabólicas y antecedentes familiares de DMT2, en comparación con los no diabéticos.

Las figuras 1 y 2 presentan los factores asociados a DMT2 en mujeres y hombres, respectivamente. Al analizar estos resultados, se puede apreciar que en ambos sexos la probabilidad de ser diabéticos es mayor en los participantes pertenecientes al grupo etario ≥ 45 años, con sobrepeso u obesidad, quienes presentan obesidad central, así como también aquellos que declararon dormir más de nueve horas, ser inactivos físicamente y con alto nivel de sedentarismo. Además, se puede observar que, en ambos sexos, las personas con HTA y antecedentes familiares de DMT2 presentan mayor riesgo de desarrollar DMT2. Por el contrario, para ambos sexos se aprecia que aquellas personas con nivel educacional medio o superior, que son fumadores y tienen buena percepción de bienestar/salud presentan menor riesgo de DMT2. Las únicas diferencias observadas entre sexos fueron que las mujeres pertenecientes al nivel de ingresos alto presentan una menor probabilidad de padecer DMT2 (OR: 0,42 [95% IC: 0,25-0,71], $p = 0,001$) (Fig. 1) y los hombres con un nivel medio de IDS presentan mayor riesgo de DMT2 (OR: 1,52 [95% IC: 1,10-2,10], $p = 0,011$) (Fig. 2). Para ambos sexos no se encontraron asociaciones significativas entre zona geográfica de residencia y consumo de alcohol con el riesgo de ser diabético.

DISCUSIÓN

En este trabajo se identificó que las personas que tienen mayor riesgo de desarrollar DMT2 son aquellas que tienen una edad superior a 45 años, presentan antecedentes familiares para esta enfermedad, son del sexo femenino, presentan exceso de peso, son físicamente inactivas y padecen HTA.

Dentro de los factores de riesgo no modificables, la edad es uno de los principales factores de riesgo para el desarrollo de esta patología, ya que la incidencia de esta enfermedad aumenta en la vida adulta (3). Estos datos se ven confirmados en el presente trabajo, donde cerca del 90% de la población diagnosticada con DMT2 se ubica en los rangos de mayor edad. Aunque el riesgo de DMT2 en mujeres se presenta a edades más tempranas en comparación a los hombres (25 y 45 años, respectivamente), el mayor riesgo se identificó para ambos sexos sobre los 65 años. Considerando que Chile se encuentra en una etapa avanzada de transición hacia el envejecimiento demográfico, esto debe ser un llamado de atención, ya que se espera que en el año 2020 la población mayor de 60 años aumente a 17,3% (13).

En relación al sexo, este estudio identificó que en población chilena la prevalencia de DMT2 es mayor en mujeres, lo que coincide con las estimaciones proporcionadas por la IDF en 20 países de las regiones del Sur y Centroamérica (3). Esto tendría relación con factores sociodemográficos, que sitúan a la población femenina de estas regiones como objeto de las mayores desigualdades sociales y económicas, lo que las predispone a presentar prevalencias de obesidad que superan a los hombres en más de diez puntos porcentuales en más de 20 países de esta zona y, consecuentemente, aumenta el riesgo de desarrollar enfermedades metabólicas, entre ellas la DMT2 (14).

Tabla I. Características de la población según diagnóstico de diabetes mellitus tipo 2

	No diabético	Diabético	Valor p
Sociodemográficas			
n	4.162	538	
Mujeres, (%)	59,7 (58,2; 61,2)	60,4 (56,1; 64,4)	0,771
Edad (años)	44,5 (43,9; 45,0)	61,2 (59,9; 62,3)	< 0,0001
Grupo etario, (%)			< 0,0001
< 25 años	98,9 (97,8; 99,5)	1,1 (0,5; 2,1)	
25-44 años	96,7 (95,7; 97,5)	3,3 (2,4; 4,2)	
45-64 años	83,7 (81,8; 85,4)	16,3 (14,5; 18,2)	
≥ 65 años	74,7 (71,7; 77,4)	25,3 (22,6; 28,2)	
Zona geográfica, (%)			0,772
Rural	88,2 (85,5; 90,4)	11,8 (9,5; 14,4)	
Urbano	88,6 (87,6; 89,5)	11,4 (10,4; 12,4)	
Nivel educacional, (%)			
Básica	79,2 (76,9; 81,4)	20,7 (18,6; 23,1)	< 0,0001
Media	91,6 (90,4; 92,6)	8,4 (7,4; 9,6)	
Técnico universitaria	93,2 (91,2; 94,7)	6,8 (5,3; 8,7)	
Nivel de ingreso, (%)			0,005
Bajo	87,2 (85,8; 88,4)	12,8 (11,5; 14,2)	
Medio	90,1 (88,5; 91,5)	9,9 (8,5; 11,5)	
Alto	90,7 (87,8; 92,9)	9,3 (7,0; 12,2)	
Antropométricas			
Peso (kg)	71,2 (70,7; 71,6)	76,5 (75,0; 77,9)	< 0,0001
IMC (kg/m ²)	27,5 (27,3; 27,6)	30,6 (29,9; 31,2)	< 0,0001
Estado nutricional, (%)			< 0,0001
18,5-24,9 kg/m ²	94,1 (92,7; 95,2)	5,9 (4,7; 7,2)	
25,0-29,9 kg/m ²	90,4 (88,9; 91,7)	9,6 (8,3; 11,0)	
≥ 30,0 kg/m ²	82,4 (80,2; 84,4)	17,6 (15,6; 19,7)	
Perímetro de cintura (cm)	95,5 (95,1; 95,9)	103,5 (102,1; 104,8)	< 0,0001
Obesidad central (%)			< 0,0001
Normal	95,1 (93,4; 96,1)	4,9 (3,8; 6,0)	
Obeso central	86,5 (85,2; 87,7)	13,5 (12,3; 14,7)	
Estilo de vida			
Actividad física total (MET/hora/semana)	121,9 (117,3; 126,4)	96,1 (85,1; 107,1)	0,0001
Actividad física de transporte (min/día)	50,7 (48,0; 53,3)	37,8 (31,4; 44,2)	0,001
Actividad física moderada (min/día)	106,2 (101,6; 110,8)	86,2 (74,0; 98,4)	0,035
Actividad física vigorosa (min/día)	52,1 (48,3; 55,9)	40,9 (32,0; 49,8)	0,045
Prevalencia inactividad física, (%)			< 0,0001
Activo	90,2 (89,1; 91,1)	9,8 (8,8; 10,9)	
Inactivo	82,4 (80,0; 84,5)	17,6 (15,4; 20,0)	
Tiempo sedente (hora/día)	3,4 (3,2; 3,4)	3,9 (3,7; 4,2)	< 0,0001
Consumo de frutas y vegetales (g/día)	214,2 (209,6; 218,7)	229,0 (216,1; 241,9)	0,029
Índice de dieta saludable (IDS)	1,5 (1,47; 1,53)	1,6 (1,51; 1,67)	0,028
Consumo de sal (g/día)	9,6 (9,5; 9,7)	10,5 (10,1; 11,0)	< 0,0001

(Continúa en la página siguiente)

Tabla I (Cont.). Características de la población según diagnóstico de diabetes mellitus tipo 2

	No diabético	Diabético	Valor p
Estilo de vida			
Consumo de alcohol (g/día)	54,7 (49,7; 59,5)	45,4 (32,8; 58,0)	0,252
Tabaquismo, (%)			< 0,0001
Nunca	86,6 (85,1; 88,1)	13,4 (11,8; 14,9)	
Exfumador	85,3 (83,1; 87,3)	14,7 (12,7; 16,8)	
Fumador	93,1 (91,7; 94,2)	6,9 (5,7; 8,2)	
Autorreporte salud/bienestar, (%)			< 0,0001
Mala	79,3 (72,1; 85,1)	20,7 (14,9; 27,9)	
Regular	85,3 (83,4; 87,1)	14,7 (12,9; 16,5)	
Buena	90,6 (89,5; 91,6)	9,4 (8,4; 10,5)	
Metabólicas			
Glucosa (mmol/l)	5,0 (4,9; 5,1)	8,7 (8,3; 9,0)	< 0,0001
HbA1C (%)	5,8 (5,7; 5,9)	8,2 (8,0; 8,5)	< 0,0001
Síndrome metabólico, (%)			< 0,0001
No	96,3 (95,2; 97,1)	3,7 (2,8; 4,7)	
Sí	76,5 (73,5; 79,1)	23,5 (2,8; 26,4)	
Colesterol total (mmol/l)	5,0 (4,9; 5,1)	5,3 (5,1; 5,4)	0,0001
Colesterol HDL (mmol/l)	1,2 (1,1; 1,3)	1,2 (1,1; 1,3)	0,0006
Triglicéridos (mmol/l)	1,6 (1,5; 1,7)	2,2 (2,0; 2,4)	< 0,0001
Antecedentes familiares de DMT2, (%)			< 0,0001
No	92,3 (91,3; 93,1)	7,7 (5,8; 8,7)	
Sí	81,0 (78,8; 82,9)	19,0 (17,1; 21,2)	
HTA, (%)			< 0,0001
No	94,3 (93,5; 95,1)	5,7 (4,9; 6,5)	
Sí	76,8 (74,6; 78,9)	23,2 (21,1; 25,4)	
PAS (mmHg)	125,6 (124,9; 126,2)	141,9 (139,7; 144,1)	< 0,0001
PAD (mmHg)	75,6 (75,2; 75,9)	79,5 (78,4; 80,5)	< 0,0001

Datos presentados como media para variables continuas y como porcentaje para variables categóricas con sus respectivos intervalos de confianza del 95% (95% IC). El valor p representa diferencias significativas entre personas diabéticas y no diabéticas; este valor fue estimado con t-test para variables continuas y con Chi-cuadrado para variables categóricas.

Otro factor de riesgo no modificable son los antecedentes familiares para DMT2. Numerosos estudios confirman una correlación significativa entre los factores hereditarios y el riesgo de desarrollar la enfermedad en algún momento de la vida (15-18), lo que es coherente con los resultados de este estudio. Esta asociación significativa acentúa la importancia de conocer la historia familiar, ya que es una herramienta útil que permite predecir el riesgo de DMT2 y aplicar tempranamente medidas preventivas, interviniendo sobre aquellos factores de riesgo que son susceptibles de ser modificados.

El exceso de peso es considerado uno de los factores de riesgo modificables más importantes para DMT2 (19-21). Un 84% de los diabéticos chilenos presenta sobrepeso u obesidad y el 86,3%, obesidad central. Así, el riesgo de tener DMT2 se incrementa con el aumento del peso corporal y los marcadores de obesidad eleva-

dos, tales como IMC y PC (20,22,23). A nivel mundial, el acelerado proceso de urbanización y mecanización, asociado al desarrollo económico, ha traído como consecuencia una reducción en la necesidad del movimiento humano y, con ello, una disminución de los niveles de AF, predominando actualmente las actividades sedentarias que, sumadas a los malos hábitos alimentarios, han incidido notablemente en el aumento de la prevalencia de obesidad y DMT2 en la población (24-26).

Es conocido que tanto la inactividad física como el sedentarismo (tiempo prolongado de estar sentado) (27) contribuyen al aumento del riesgo de DMT2 (28). Lamentablemente, existe poca consciencia en relación a este factor de riesgo, lo cual ha sido evidenciado por Biddle y cols., a partir de un estudio realizado en un grupo de personas en riesgo de desarrollar DMT2, que concluyó que las personas no son capaces de dimensionar el riesgo inme-

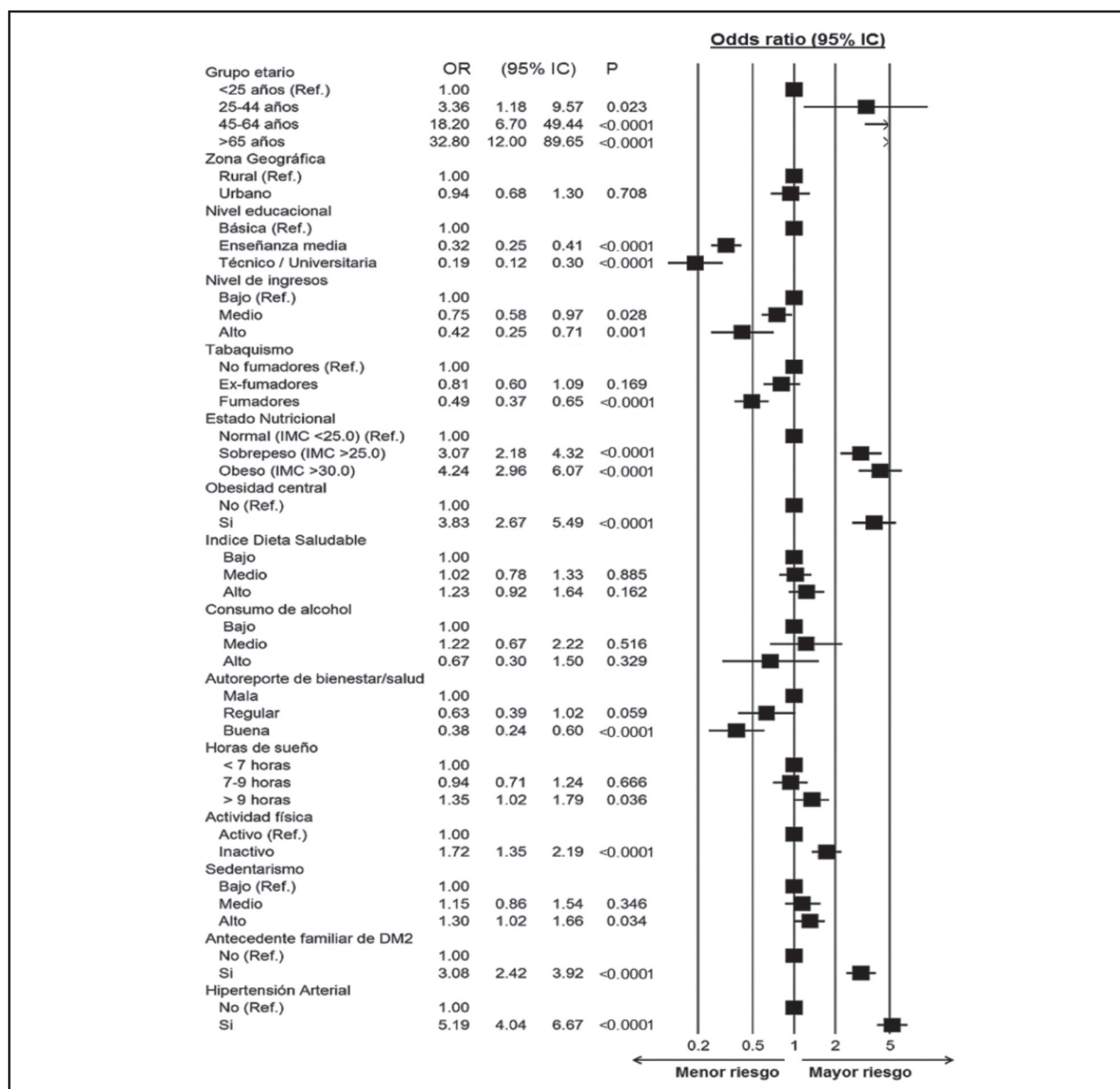


Figura 1.

Factores asociados a diabetes mellitus tipo 2 en mujeres. Datos presentados como *odds ratio* y su respectivo 95% IC. Los análisis fueron ajustados mutuamente por los factores de riesgo incluidos en la figura (edad, sexo, zona geográfica, educación, ingresos económicos, tabaquismo, IMC, consumo de sal, actividad física, sedentarismo, índice de dieta saludable, historia familiar de diabetes mellitus, hipertensión arterial e IMC). La obesidad central no fue ajustada por IMC debido a la alta correlación entre estas variables.

diato de permanecer muchas horas sentado (29). Nuestro estudio encontró que, para ambos sexos, existe un aumento significativo del riesgo de DM2, tanto en personas físicamente inactivas como en aquellas con niveles altos de sedentarismo (≥ 4 horas al día). Cambios en el estilo de vida tendientes a aumentar la actividad física diaria, como caminar o andar en bicicleta y usar las escaleras en lugar del ascensor, representan claras oportunidades para contrarrestar el riesgo de adquirir enfermedades metabólicas (30), como fue evidenciado por nuestro equipo de investigación en un

trabajo previo en el cual se encontró una tendencia significativa ($p < 0,002$) a disminuir la prevalencia de DM2 al incrementar los niveles de AF moderada/intensa en mujeres y hombres (31).

La HTA es considerada una de las complicaciones asociadas a DM2, observándose que entre el 40 y el 60% de las personas que sufren DM2 también presentan HTA, condición que empeora y acelera el daño ocasionado por la DM2, aumentando así el riesgo de infarto al miocardio, insuficiencia renal o accidente cerebrovascular (32-34). Al analizar la realidad chilena en este

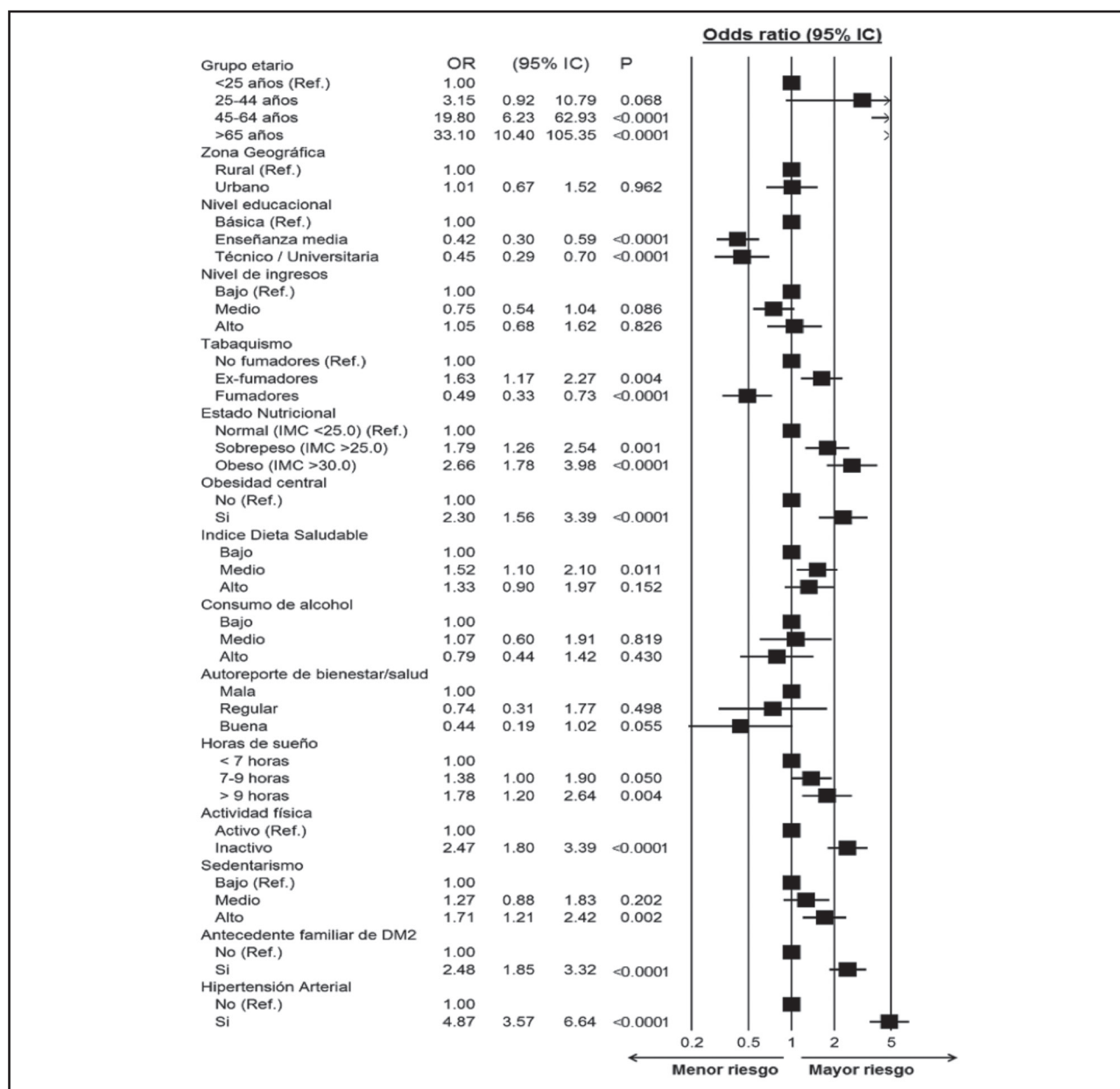


Figura 2.

Factores de riesgo asociados a diabetes mellitus tipo 2 en hombres. Datos presentados como *odds ratio* y su respectivo 95% IC. Los análisis fueron ajustados mutuamente por los factores de riesgo incluidos en la figura (edad, sexo, zona geográfica, educación, ingreso económico, tabaquismo, consumo de sal, actividad física, sedentarismo, índice de dieta saludable, historia familiar de diabetes mellitus, hipertensión arterial e IMC). La obesidad central no fue ajustada por IMC debido a la alta correlación entre estas variables.

trabajo, el 65,4% de los diabéticos padecen HTA, lo que confirma la relación existente entre estas dos patologías, situándola como uno de los principales factores de riesgo de DMT2. Por otra parte, de todos los factores de riesgo analizados en este estudio, la HTA es el segundo factor de riesgo que tiene mayor asociación con DMT2, después de la edad.

Resulta interesante que los análisis asocien a los fumadores con un menor riesgo de desarrollar DMT2; no obstante, la dirección de estos resultados podría explicarse por causalidad reversa,

la cual es una limitación de los estudios de corte transversal. Por ende, futuros estudios con un diseño longitudinal o intervenciones con grupo de control randomizadas son necesarias para comprobar estos hallazgos. Otra limitación que es importante tener en cuenta es el diagnóstico utilizado para diabetes, ya que, si bien este obedece a las recomendaciones de la OMS y la IDF, no podemos descartar que algunos de los casos identificados de diabetes sean debidos a no cumplir con la recomendación de ayuna de ocho horas.

Finalmente, es importante recalcar que este estudio evidenció los principales factores asociados a DMT2 en población chilena, ratificando que, a pesar de que la edad (≥ 45 años) es el factor de mayor riesgo para el desarrollo de esta patología, existe un grupo de factores modificables cuya presencia resulta ser de alto riesgo para desarrollar la enfermedad; estos son HTA, obesidad, obesidad central e inactividad física. Estos hallazgos son de suma importancia a nivel de políticas públicas, ya que del control de estos factores depende disminuir la prevalencia de esta patología y mejorar la calidad de vida de la población. De esta manera, pequeños cambios en el estilo de vida de las personas, tales como mejorar la alimentación y aumentar la AF diaria, podrían hacer grandes diferencias en términos de salud.

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Trabajo Original

Epidemiología y dietética

Diversidad de la dieta en mujeres que habitan en inseguridad alimentaria en México, beneficiarias de un programa de ayuda alimentaria

Dietary diversity in women who live in food insecurity settings in Mexico, beneficiaries of a food support program

María del Carmen Morales Ruán¹, Danae Gabriela Valenzuela Bravo¹, Alejandra Jiménez Aguilar¹, Lucía Cuevas Nasu¹, Ignacio Méndez Gómez Humarán² y Teresa Shamah Levy¹

¹Centro de Investigación en Evaluación y Encuestas. Instituto Nacional de Salud Pública. Cuernavaca, Morelos. México. ²Centro de Investigación en Matemáticas A.C. Unidad Aguascalientes. Aguascalientes, México

Resumen

Introducción: la diversidad alimentaria es una aproximación de la calidad de la dieta. En México, el Programa de Apoyo Alimentario (PAL) otorga apoyos en efectivo (PAL EFECTIVO) o a través de transferencias monetarias en una tarjeta destinada exclusivamente para la compra de alimentos (PAL SIN-HAMBRE) a familias en situación de pobreza alimentaria, buscando mejorar la diversidad de su alimentación.

Objetivo: comparar la diversidad de la dieta en mujeres beneficiarias de ambos esquemas y su asociación con el nivel de inseguridad alimentaria (IA) en el hogar.

Métodos: se realizó un estudio transversal, en una muestra aleatoria nacional de 243 beneficiarias del PAL EFECTIVO y 277 del PAL SIN-HAMBRE en 14 estados. Se construyó un modelo de regresión logística multinomial para medir la asociación entre el índice de percepción de IA y su relación con el PAL y el índice de diversidad de la dieta.

Resultados: se observó que el esquema PAL SIN-HAMBRE se asocia a menor probabilidad de IA leve y severa con respecto al PAL EFECTIVO. Al observar la interacción entre el tipo de esquema y el índice de diversidad de la dieta, el esquema PAL EFECTIVO mostró menor probabilidad de IA severa cuando el índice de diversidad de la dieta es mayor con respecto al PAL SIN-HAMBRE.

Conclusiones: la IA en el hogar y la baja diversidad de la dieta están asociadas en mujeres en edad fértil y dicha relación es mayor en aquellas pertenecientes al PAL SIN-HAMBRE.

Palabras clave:

Dieta. Inseguridad alimentaria. Programas de ayuda alimentaria.

Abstract

Introduction: food diversity is an approximation of diet quality. In Mexico, the Food Support Program (PAL, by its acronym in Spanish) grants support to families facing food poverty, in form of cash (PAL EFECTIVO) or through monetary transfers on a card intended exclusively for the purchase of food (PAL SIN-HAMBRE), seeking to improve their food diversity.

Objective: to compare the dietary diversity in women beneficiaries of both schemes and their association with the level of food insecurity (FI) at household level.

Methods: a cross-sectional study was carried out in a national random sample of 243 women beneficiaries from PAL EFECTIVO and 277 from PAL SIN-HAMBRE in 14 states. A multinomial logistic regression model was constructed to measure the association between the FI perception index and its relationship with the PAL and the dietary diversity index.

Results: the PAL SIN-HAMBRE scheme is associated with a lower probability of mild and severe FI with respect to the PAL EFECTIVO. The interaction between the type of scheme and the dietary diversity index showed that the PAL EFECTIVO had a lower probability of severe FI when the dietary diversity index was greater with respect to the PAL SIN-HAMBRE.

Conclusions: the FI in the household and the low dietary diversity seem to be strongly associated in women of childbearing age and this relationship is higher in those beneficiaries of the PAL SIN-HAMBRE scheme.

Key words:

Diet. Food insecurity. Food aid programs.

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Correspondencia:

Teresa Shamah Levy. Instituto Nacional de Salud Pública. Av. Universidad, 655. Santa María Ahuacatlán. 62100 Cuernavaca, Morelos
e-mail: tshamah@insp.mx

INTRODUCCIÓN

La diversidad alimentaria se refiere a la medición del consumo de alimentos para conocer el acceso que tienen los hogares a una variedad de alimentos (1) y se mide a través de índices validados. Esta medición es una aproximación de la calidad de la dieta y puede identificar si la población consume de manera adecuada alimentos ricos en micronutrientes como vitamina A, vitamina C, ácido fólico, hierro y zinc, entre otros, necesarios para el desarrollo, crecimiento y funcionamiento adecuado de mujeres y niños (2,3). El puntaje propuesto por el Proyecto de diversidad alimentaria en la mujer (WDDS, por sus siglas en inglés) muestra mayor adecuación de micronutrientes en la dieta de mujeres en edad fértil (1), por lo que una mayor diversidad medida a través de este puntaje puede ser indicador de un mejor estado de nutrición.

En México, el Programa de Apoyo Alimentario (PAL) atiende a familias en situación de pobreza alimentaria con el objetivo de mejorar la cantidad, calidad y diversidad de la alimentación, buscando así elevar su estado de nutrición (4). El PAL otorga apoyos monetarios a sus beneficiarios de manera bimestral, ya sea de manera directa, en efectivo (PAL EFECTIVO) o a través de transferencias monetarias en una tarjeta (PAL SIN-HAMBRE). Esta última es de uso exclusivo para la adquisición de 14 alimentos básicos (harina de trigo, harina de maíz, leche en polvo, frijol, maíz, chocolate, avena, café, arroz, aceite, atún, chiles, sardina y huevo) en tiendas comunitarias de Diconsa, unidades móviles y Centros de Atención a Beneficiarios (CABES).

Diconsa es una empresa estatal que pertenece al Sector Desarrollo Social. Tiene el propósito de contribuir a la superación de la pobreza alimentaria mediante el abastecimiento de productos básicos y complementarios a localidades rurales de alta y muy alta marginación, con base en la organización y la participación comunitaria.

Cabe mencionar que el PAL privilegia la entrega de apoyos a las mujeres jefas de hogar. Uno de los objetivos principales del programa es mejorar la diversidad de la alimentación en la población beneficiaria. Por ello, el presente estudio tuvo el objetivo de medir la diversidad de la dieta en mujeres beneficiarias del esquema PAL SIN-HAMBRE en comparación con las beneficiarias del esquema PAL EFECTIVO y su asociación con el nivel de inseguridad alimentaria en el hogar.

MATERIAL Y MÉTODOS

Se realizó un estudio transversal durante el año 2014 en una muestra aleatoria nacional de 520 beneficiarias de ambos esquemas de atención del PAL (243 del PAL EFECTIVO y 277 de PAL SIN-HAMBRE). El levantamiento de la información fue realizado por personal previamente capacitado y estandarizado en 14 estados de la República Mexicana, en donde el programa opera (Baja California, Baja California Sur, Chiapas, Chihuahua, Guanajuato, Guerrero, Jalisco, México, Michoacán, Oaxaca, Querétaro, Quintana Roo, Tamaulipas y Veracruz).

TAMAÑO DE MUESTRA

Para calcular el tamaño de muestra se utilizó como variable de interés el número de alimentos encontrados en los hogares. Como información inicial para la estimación de varianzas, se utilizó la generada en una evaluación del programa en 2005 en hogares beneficiarios que recibían despensas o efectivo (5). Para el número de alimentos se estimó una desviación estándar máxima aproximada de 8,2 alimentos identificados en ambos grupos y se consideró una diferencia mínima a detectar de 2,1 alimentos en promedio. Se fijaron un nivel de confianza del 95% y una potencia de prueba del 80%, y se eligió *a priori* un efecto de diseño aproximado de 2,0, con lo cual se calculó un tamaño de muestra de 480 beneficiarias.

El muestreo fue realizado en dos etapas. En la primera se seleccionaron 44 localidades beneficiarias del programa con el procedimiento de probabilidad proporcional al tamaño, utilizando el número de beneficiarios de ambos grupos como medida de tamaño. En la segunda etapa se seleccionó a las beneficiarias de cada grupo con un procedimiento aleatorio. Se calcularon 240 beneficiarias del esquema PAL SIN-HAMBRE y 240 del esquema PAL EFECTIVO. Sin embargo, el tamaño de muestra obtenido fue de 277 y 243 beneficiarias respectivamente previendo posibles pérdidas en el seguimiento.

VARIABLES DE ESTUDIO

Diversidad de la dieta

La medición de diversidad de la dieta se realizó a través de un cuestionario de frecuencia de consumo de alimentos semicuantitativo (FCA) de 140 alimentos y bebidas, el cual se aplicó a la mujer beneficiaria del hogar, previamente utilizado en población mexicana, con la finalidad de captar la dieta habitual. La metodología de este cuestionario ha sido detallada por Rodríguez y cols. (6). Para este estudio se utilizó la información con respecto a los alimentos consumidos y el número de días que se consumieron.

Posteriormente se midió la diversidad de la dieta a través de un índice validado que contempla nueve grupos de alimentos (féculas; verduras de hoja verde oscuro; frutas y verduras ricas en vitamina A; otras frutas y verduras; carne de vísceras; carne y pescado; huevo; legumbres, nueces y semillas; y leches y productos lácteos) de acuerdo al puntaje obtenido en el proyecto WDDS (1). Cuando la mujer consumió un grupo de alimentos ≥ 3 días a la semana se le otorgó un puntaje de 1, y si lo consumió < 3 días se le asignó un puntaje de 0. A partir de esto se construyó el índice sumando los puntajes, donde el valor mínimo fue de 0 y el máximo, de 9.

El análisis del índice se realizó a través de la comparación del puntaje promedio obtenido entre las mujeres beneficiarias de acuerdo a los dos esquemas de apoyo. Además, el índice se estratificó en tres categorías: de 0 a 3 grupos, de 4 a 6 y de 7 a 9, para identificar dentro de cada categoría los grupos de alimentos consumidos.

Inseguridad alimentaria (IA)

La IA se midió usando la versión armonizada para México de la Escala Latinoamericana y Caribeña de Seguridad Alimentaria (ELCSA) (7). Esta escala mide el índice de percepción de IA a través de las experiencias de falta de alimentos en el hogar, y ha sido previamente validada (8,9). Las preguntas hacen alusión a la preocupación de que disminuya la calidad de los alimentos, que estos se terminen o que algún miembro del hogar haya experimentado hambre o haya dejado de comer por falta de alimentos. La ELCSA consta de 15 preguntas con opciones de respuesta "sí" o "no" dirigidas a la persona encargada de comprar y/o preparar los alimentos en el hogar. El periodo de referencia para las preguntas son los tres meses previos a la aplicación de la escala (10). La escala clasifica a los hogares en cuatro categorías (seguridad, inseguridad leve, inseguridad moderada e inseguridad severa) dependiendo del número de respuestas positivas y si cuentan o no con integrantes menores de 18 años.

En los hogares con algún integrante menor de 18 años, la IA se clasificó como leve cuando se obtuvo un puntaje de 1 a 5; moderada, con un puntaje de 6 a 10; y severa, con un puntaje de 11 a 15. En los hogares donde no había algún integrante menor de 18 años, la clasificación fue leve con un puntaje de 1 a 3; moderada, con un puntaje de 4 a 6; y severa, con un puntaje de 7 a 8.

Índice de condiciones de bienestar

Para comparar los dos grupos de estudio se construyó un índice de condiciones de bienestar con base en un análisis de componentes principales y se utilizó la matriz de correlaciones policóricas construida a partir de nueve variables de características de la vivienda, bienes y servicios disponibles (11,12). Dicho índice ya ha sido utilizado en México para proyectos nacionales de nutrición (13). Se seleccionó como índice el primer componente que acumuló el 42,4% de la variabilidad total con un valor propio (λ) de 3,82. El índice se clasificó en cinco categorías utilizando los quintiles de su distribución como puntos de corte.

Otras variables sociodemográficas

La edad se consideró en años cumplidos como lo reportó en entrevista la mujer seleccionada. El tipo de localidad se clasificó en rural en aquellas localidades con < 2.500 habitantes y urbana en aquellas con $\geq$ 2.500 habitantes. La escolaridad de las beneficiarias se clasificó de acuerdo al último grado escolar cursado en cuatro categorías: ninguna, primaria, secundaria, preparatoria o equivalentes y más.

Para los análisis descriptivos las diferencias entre esquemas fueron identificadas a través del intervalo de confianza al 95%.

Análisis estadístico

Se construyó un modelo de regresión logística multinomial para medir la asociación entre el índice de percepción de inseguridad

alimentaria como dependiente y su relación con el programa PAL y el índice de diversidad de la dieta, probando una interacción entre el tipo de participante y el índice de diversidad de la dieta. Además, se incluyeron la edad, el índice de bienestar y el tipo de localidad como variables de ajuste.

Para la interpretación del modelo se consideraron como significativos los términos denominados efectos principales con significancia del 5% ($p \leq 0,05$) y el de la interacción con significancia del 10% ($p \leq 0,10$).

Los análisis se realizaron utilizando el paquete estadístico Stata 14. Se utilizaron las rutinas de distribución libre "gsample" para la selección probabilística de las localidades y la rutina "polychoricpc" para el análisis de componentes principales.

CONSIDERACIONES ÉTICAS

Este estudio fue aprobado por los Comités de Investigación, Ética y Bioseguridad del Instituto Nacional de Salud Pública y se obtuvo consentimiento informado de cada una de las participantes.

RESULTADOS

Se obtuvo información de 277 mujeres beneficiarias del esquema PAL SIN-HAMBRE y 243 del esquema PAL EFECTIVO. Cabe mencionar que no se obtuvieron datos de la percepción de inseguridad alimentaria en una mujer de cada grupo.

En la tabla I se muestran las características socioeconómicas de los grupos de estudio. Aunque se observó un mayor nivel de seguridad alimentaria en mujeres beneficiarias del PAL SIN-HAMBRE en comparación con las beneficiarias del PAL EFECTIVO, también se observó un mayor porcentaje de inseguridad alimentaria severa; no obstante, las diferencias no fueron significativas. Tampoco se observaron diferencias significativas entre los grupos de estudio para quintiles de nivel socioeconómico, tipo de localidad, escolaridad e índice de diversidad de la dieta. Por otro lado, se observó una diferencia importante en el promedio de edad en años de las mujeres beneficiarias, que fue de 43 (intervalo de confianza [IC] 95%, 40,7-45,2) en el grupo de PAL EFECTIVO, en comparación con 35,1 (IC 95% 33,1-37,0) en el grupo de PAL SIN-HAMBRE.

Al estratificar por las categorías de diversidad alimentaria, de acuerdo con el número de grupos consumidos, en el grupo PAL SIN-HAMBRE se observó que cuatro mujeres consumieron de cero a tres grupos de alimentos; 156 mujeres, de cuatro a seis grupos; y 117 mujeres, de siete a nueve grupos; mientras que en el grupo PAL EFECTIVO tan solo dos mujeres consumieron de cero a tres grupos de alimentos; 129 mujeres de cuatro a seis grupos; y 112 mujeres, de siete a nueve grupos (Tabla II).

En la categoría de diversidad intermedia (de cuatro a seis grupos consumidos) de ambos grupos de estudio, más del 70% de las mujeres consumieron féculas, otras frutas y verduras ricas en vitaminas, carne y pescado, huevos, legumbres, nueces y semillas

Tabla I. Características socioeconómicas de las mujeres beneficiarias del Programa de Apoyo Alimentario en sus dos esquemas. México

	Tipo de beneficiarios					
	PAL SIN-HAMBRE			PAL EFECTIVO		
	n	%	IC 95%	n	%	IC 95%
<i>Niveles de seguridad alimentaria</i>						
Seguridad alimentaria	38	13,7	(9,2-20,2)	22	9,1	(5,9-13,7)
Inseguridad leve	84	30,3	(24,7-36,8)	84	34,6	(28,2-41,9)
Inseguridad moderada	92	33,2	(28,0-39,1)	86	35,4	(29,5-42,1)
Inseguridad severa	62	22,4	(18,0-27,7)	50	20,6	(15,4-27,1)
Total	276	100,0		242	100,0	
<i>Índice de nivel socioeconómico (quintiles)</i>						
Q1	66	23,8	(15,9-34,1)	39	16,0	(11,0-22,8)
Q2	58	20,9	(16,5-26,2)	45	18,5	(13,1-25,5)
Q3	53	19,1	(14,7-24,6)	51	21,0	(15,3-28,1)
Q4	43	15,5	(11,1-21,3)	58	23,9	(18,4-30,4)
Q5	57	20,6	(12,8-31,4)	50	20,6	(13,8-29,5)
Total	277	100,0		243	100,0	
<i>Tipo de localidad</i>						
Urbano	208	75,1	(54,5-88,4)	233	95,9	(86,6-98,8)
Rural	69	24,9	(11,6-45,5)	10	4,1	(1,2-13,4)
Total	277	100,0		243	100,0	
<i>Escolaridad</i>						
Ninguna	21	7,6	(4,3-13,0)	27	11,3	(8,3-15,3)
Primaria	96	34,7	(29,1-40,7)	100	42,0	(36,8-47,5)
Secundaria	124	44,8	(39,0-50,7)	94	39,5	(32,0-47,6)
Preparatoria, equivalentes o más	36	13,0	(9,9-16,9)	17	7,1	(4,7-10,8)
Total	277	100,0		238	100,0	
	n	Media	IC 95%	n	Media	IC 95%
<i>Diversidad de la dieta</i>						
Suma de índice de diversidad de la dieta	277	6,1	(6,0-6,3)	243	6,3	(6,1-6,6)
<i>Edad</i>						
Edad (promedio)	277	35,1	(33,1-37,0)	243	43,0	(40,7-45,2)

y leche y productos lácteos, mientras que menos del 25% consumieron verduras de hoja verde oscuro, otras frutas y verduras y carnes de vísceras.

En la categoría de diversidad alta (de siete a nueve grupos consumidos) del PAL SIN-HAMBRE, más del 95% de las mujeres consumieron féculas, otras frutas y verduras ricas en vitaminas, carne y pescado, huevos, legumbres, nueces y semillas y leche y productos lácteos; el 76,9% consumió otras frutas y verduras; el 32,5% consumió verduras de hoja verde oscuro; y el 23,1%, carne de vísceras. En la misma categoría de diversidad en el grupo de PAL EFECTIVO, más del 90% de las mujeres consumieron féculas, otras frutas y verduras ricas en vitaminas, carne y pescado, huevos, legumbres, nueces y semillas y leche y productos lácteos; el 83,9% consumió otras frutas y verduras; el 51,8% consumió verduras de hoja verde oscuro; y el 29,5%, carne de vísceras.

Al observar la asociación entre el índice de diversidad de la dieta y la inseguridad alimentaria, se aprecia una tendencia hacia la disminución en la media del puntaje de diversidad de la dieta conforme se incrementa la categoría de inseguridad en el esquema PAL SIN-HAMBRE; sin embargo, las diferencias no son significativas. Por otro lado, en el esquema PAL EFECTIVO la media de diversidad es muy similar en las categorías de inseguridad leve y moderada, y el puntaje promedio de diversidad de la dieta es significativamente menor en la categoría de inseguridad severa (5,9; IC 95% 5,6-6,2) en comparación con el puntaje promedio de la categoría de seguridad alimentaria (7,0; IC 95% 6,6-7,3) (Tabla III).

En el modelo de regresión logística multinomial (Tabla IV) se observa que el PAL SIN-HAMBRE se asocia con una probabilidad de inseguridad alimentaria leve y severa con respecto al PAL EFECTIVO. Además, existe una interacción significativa entre el

Tabla II. Presencia de grupos de alimentos de acuerdo a la categoría de diversidad de la dieta, según el número de grupos de alimentos consumidos por las mujeres en edad reproductiva beneficiarias del Programa de Apoyo Alimentario en sus dos esquemas

PAL SIN-HAMBRE									
Grupos de alimento	0 a 3			4 a 6			7 a 9		
	n	%	IC 95%	n	%	IC 95%	n	%	IC 95%
1.Féculas	4	100,0	-	156	100,0	-	117	100,0	-
2.Verduras de hoja verde oscuro	0	0,0	-	11	7,1	(3,4-13,9)	38	32,5	(23,4-43,1)
3.Otras frutas y verduras ricas en vitaminas	0	0,0	-	127	81,4	(73,8-87,2)	114	97,4	(92,4-99,2)
4.Otras frutas y verduras	1	25,0	(3,1-77,8)	28	17,9	(12,4-25,2)	90	76,9	(68,9-83,3)
5.Carne de vísceras	0	0,0	-	6	3,8	(1,7-8,2)	27	23,1	(16,6-31,1)
6.Carne y pescado	1	25,0	(3,1-77,8)	125	80,1	(71,4-86,7)	113	96,6	(91,1-98,7)
7.Huevos	1	25,0	(3,1-77,8)	110	70,5	(62,9-77,2)	116	99,1	(94,2-99,9)
8.Legumbres, nueces y semillas	4	100,0	-	153	98,1	(94,4-99,4)	117	100,0	-
9.Lече y productos lácteos	0	0,0	-	134	85,9	(78,7-90,9)	117	100,0	-
PAL EFECTIVO									
Grupos de alimento	0 a 3			4 a 6			7 a 9		
	n	%	IC 95%	n	%	IC 95%	n	%	IC 95%
1.Féculas	2	100,0	-	129	100,0	-	112	100,0	-
2.Verduras de hoja verde oscuro	0	0,0	-	9	7,0	(3,0-15,4)	58	51,8	(43,4-60,1)
3.Otras frutas y verduras ricas en vitaminas	2	100,0	-	100	77,5	(69,2-84,1)	111	99,1	(93,3-99,9)
4.Otras frutas y verduras	0	0,0	-	32	24,8	(17,5-33,9)	94	83,9	(77,0-89,1)
5.Carne de vísceras	0	0,0	-	6	4,7	(1,8-11,4)	33	29,5	(22,4-37,7)
6.Carne y pescado	1	50,0	(5,3-94,7)	102	79,1	(65,6-88,2)	108	96,4	(90,7-98,7)
7.Huevos	1	50,0	(5,3-94,7)	101	78,3	(69,7-85,0)	105	93,8	(88,0-96,8)
8.Legumbres, nueces y semillas	0	0,0	-	120	93,0	(88,7-95,8)	111	99,1	(94,0-99,9)
9.Lече y productos lácteos	0	0,0	-	104	80,6	(71,5-87,4)	110	98,2	(92,8-99,6)

Tabla III. Índice de diversidad de la dieta promedio, de acuerdo a las categorías de inseguridad alimentaria en las mujeres en edad reproductiva beneficiarias del Programa de Apoyo Alimentario en sus dos esquemas. México

Categorías de inseguridad alimentaria	PAL SIN-HAMBRE			PAL EFECTIVO		
	n	Media	IC 95%	n	Media	IC 95%
Seguridad	38	6,2	(5,8-6,5)	22	7,0	(6,6-7,3)
Leve	84	6,2	(5,9-6,5)	84	6,3	(6,0-6,6)
Moderada	92	6,1	(5,9-6,4)	86	6,4	(6,1-6,8)
Severa	62	5,9	(5,7-6,2)	50	5,9	(5,6-6,2)
Total	276			242		

PAL SIN-HAMBRE y el índice de diversidad de la dieta para las probabilidades de inseguridad alimentaria leve e inseguridad alimentaria severa, donde a mayor diversidad de la dieta se observa menor prevalencia de inseguridad alimentaria. Esto se ejemplifica

claramente en la figura de las prevalencias de inseguridad alimentaria severa estimadas con el modelo (Fig. 1), donde también se observa que las beneficiarias del esquema PAL EFECTIVO muestran menor inseguridad alimentaria severa conforme incrementa

Tabla IV. Modelo de regresión logística multinomial con categorías de seguridad/ inseguridad alimentaria. México

Seguridad alimentaria	Coeficiente	p > z	Intervalo de confianza 95%	
Inseguridad leve				
PAL SIN-HAMBRE	-3,90	0,034*	-7,50	-0,30
Índice de diversidad	-0,48	0,025*	-0,89	-0,06
Interacción PAL SIN-HAMBRE-Índice de diversidad	0,49	0,076†	-0,05	1,02
Edad	0,01	0,394	-0,01	0,03
Quintil 2	-0,18	0,748	-1,29	0,93
Quintil 3	0,01	0,983	-1,09	1,11
Quintil 4	-0,93	0,089	-2,00	0,14
Quintil 5	-0,15	0,797	-1,27	0,97
Localidad rural	0,62	0,234	-0,40	1,64
_constante	4,41	0,006	1,24	7,57
Inseguridad moderada				
PAL SIN-HAMBRE	-3,10	0,088	-6,67	0,46
Índice de diversidad	-0,42	0,048*	-0,83	0,00
Interacción PAL SIN-HAMBRE-Índice de diversidad	0,37	0,170	-0,16	0,90
Edad	0,01	0,505	-0,02	0,03
Quintil 2	-0,41	0,459	-1,49	0,67
Quintil 3	-0,49	0,381	-1,58	0,60
Quintil 4	-1,04	0,051	-2,08	0,00
Quintil 5	-0,53	0,348	-1,63	0,57
Localidad rural	0,48	0,359	-0,54	1,49
_constante	4,40	0,006	1,26	7,55
Inseguridad severa				
PAL SIN-HAMBRE	-4,11	0,034*	-7,90	-0,31
Índice de diversidad	-0,76	0,001*	-1,21	-0,31
Interacción PAL SIN-HAMBRE-Índice de diversidad	0,54	0,065†	-0,03	1,12
Edad	0,01	0,409	-0,01	0,03
Quintil 2	-0,82	0,154	-1,95	0,31
Quintil 3	-1,10	0,061	-2,25	0,05
Quintil 4	-2,08	0,000*	-3,23	-0,93
Quintil 5	-0,79	0,172	-1,93	0,34
Localidad rural	0,50	0,367	-0,58	1,57
_constante	6,34	0,000	3,02	9,65

Categoría de referencia (seguridad alimentaria). *Diferencia estadísticamente significativa $p \leq 0,05$. †Diferencia estadísticamente significativa $p \leq 0,01$. Categorías de referencia para variables regresoras: PAL EFECTIVO; Quintil 1; Localidad urbana.

el índice de diversidad de la dieta con respecto a las beneficiarias del PAL SIN-HAMBRE.

Ni la edad ni el tipo de localidad muestran asociación con las probabilidades de inseguridad alimentaria, mientras que el quintil 4 del índice de bienestar socioeconómico está asociado a las prevalencias de inseguridad alimentaria más bajas de cualquier nivel, siendo significativo únicamente para inseguridad alimentaria severa.

DISCUSIÓN

Nuestro estudio documenta que, aun cuando el esquema PAL SIN-HAMBRE se asocia a menor probabilidad de IA leve y severa con respecto al PAL EFECTIVO, al observar la interacción entre el tipo de esquema y el índice de diversidad de la dieta, el esquema PAL EFECTIVO mostró menor probabilidad de IA severa cuando

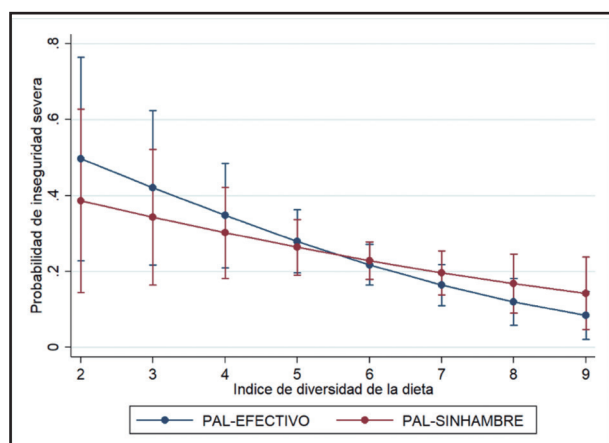


Figura 1.

Gráfica de la interacción del tipo de participante y el índice de diversidad de la dieta sobre la prevalencia de inseguridad alimentaria severa.

el índice de diversidad de la dieta es mayor con respecto al PAL SIN-HAMBRE (Tabla IV). Este último es, de acuerdo a los criterios de selección del programa analizado en el estudio, el que tiene mayores índices de pobreza y carencias. Dichos hallazgos son importantes, puesto que en nuestro conocimiento es uno de los primeros estudios que documentan en México la asociación de la diversidad de la dieta con la inseguridad alimentaria en mujeres beneficiarias de un programa de ayuda alimentaria cuyo fin se relaciona con mejorar la carencia a la alimentación.

Al respecto, más del 55% de la muestra de este análisis, independientemente del esquema PAL al que pertenecía, habitaba en hogares con inseguridad alimentaria moderada y severa, aun cuando un porcentaje mínimo de mujeres del esquema PAL EFECTIVO residía en localidades rurales, con una edad promedio mayor a las mujeres asignadas al esquema PAL SIN-HAMBRE.

Aunado a ello, la deficiencia en el consumo de alimentos de las mujeres, quienes en la mayoría de los casos son las responsables de la alimentación familiar, no solo compromete su propio consumo alimentario y nutricional debido a una baja diversidad de la dieta (14), sino también el de sus familias. Por esta razón, los índices de calidad o diversidad de la dieta son comúnmente utilizados como un indicador sensible de la inseguridad alimentaria, pues se vinculan con las condiciones socioeconómicas y el acceso a los alimentos y la dieta de las mujeres (15).

Se ha documentado que la disminución en la diversidad de la dieta con un incremento en la inseguridad alimentaria se asocia a una reducción de la disponibilidad de alimentos de origen animal, lo cual cobra sentido puesto que son alimentos de mayor precio, a los cuales las mujeres de menor nivel socioeconómico no pueden acceder frecuentemente. Además, también es evidente la falta de alimentos de origen vegetal de alto valor biológico, como leguminosas, semillas, frutas y verduras ricas en betacarotenos.

Los resultados que obtuvimos muestran diferencias significativas entre los dos esquemas de asignación tan solo en el grupo de verduras de hoja verde oscuro (fuentes de vitaminas de complejo

B y hierro) a favor de las mujeres PAL EFECTIVO, quizás por una mayor disponibilidad y acceso a alimentos frescos. En este sentido, nuestro estudio también refiere un promedio de grupos de alimentos mayor en mujeres asignadas al programa PAL EFECTIVO, que habitan en hogares con seguridad alimentaria (Tablas II y III).

Dichos hallazgos son consistentes con otros estudios en mujeres en edad fértil (16) que han mostrado un gradiente en el riesgo de disminuir la ingesta frecuente de diversos grupos de alimentos que aportan nutrientes, lo que conlleva a una menor diversidad de la dieta y, por ende, a inseguridad alimentaria, y el nivel socioeconómico, junto con la edad de las mujeres y el nivel educativo explican en menor medida este fenómeno. No obstante, el nivel socioeconómico y la educación materna han sido reconocidos como determinantes importantes de la calidad de la dieta (17).

Estos resultados se apoyan también en otros estudios que han referido que, aun cuando existe un consumo frecuente de alimentos con fuentes de proteína animal como pollo, pescado y carne, en mujeres en edad fértil residentes de áreas pobres de Malasia y Burkina Faso hay presencia de inseguridad alimentaria (utilizando una escala de medición similar a la de este estudio) asociada a baja diversidad de la dieta (18-20).

Una de las limitaciones de nuestro estudio es que no medimos directamente la ingesta de energía, pero no obstante de ello se reconoce que tanto los índices de diversidad de la dieta (18,19) como la ingesta de energía (21,22) se correlacionan negativamente con la inseguridad alimentaria y la energía se correlaciona positivamente con la variedad de la dieta y la adecuación de nutrientes. Lo cual probablemente sobreestima la fuerza de la asociación entre inseguridad alimentaria y diversidad de la dieta al no controlar por ingesta de energía, lo cual sería recomendable estimar en estudios futuros.

Es probable que otra de las limitaciones de nuestro análisis se relacione con la naturaleza de la medición de la seguridad/inseguridad alimentaria. Sin embargo, dada la complejidad de su medición, se ha documentado que las escalas de percepción como la ELCSA (23,24), utilizada en este estudio, y otras similares como las del Departamento de Agricultura de Estados Unidos (en su módulo de seguridad alimentaria) (25,26) tienen características psicométricas que ya han sido suficientemente validadas para evaluar el acceso a los alimentos por falta de recursos económicos, por lo que su validez se limita a esta dimensión de la seguridad alimentaria (27,28).

Concluimos que, en México, la inseguridad alimentaria en el hogar y la baja diversidad de la dieta parecen estar fuertemente asociadas en mujeres en edad fértil y dicha relación es mayor en aquellas pertenecientes al esquema PAL SIN-HAMBRE, quizás por tener menos disponibilidad de alimentos, que puede afectarlas no solamente a ellas sino también a sus hogares.

Este es un problema que debe ser abordado de manera estructural y en el cual la pobreza juega un papel que se asocia a las carencias, por lo que los programas de ayuda alimentaria cuyo fin sea el aliviar la pobreza y apoyar la alimentación y la reducción de la inseguridad alimentaria deben considerar la disponibilidad de alimentos nutritivos que apoyen la alimentación familiar como uno de muchos factores a incluir en los programas.

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Trabajo Original

Otros

Effects of red wine, grape juice and resveratrol consumption on bone parameters of Wistar rats submitted to high-fat diet and physical training

Efectos del consumo de vino rojo, jugo de uva y resveratrol sobre los parámetros óseos de las ratas Wistar presentadas con dieta rica en grasas y entrenamiento físico

Letícia Monteiro da Fonseca Cardoso, Nina da Matta Alvarez Pimenta, Raiza da Silva Ferreira Fiochi, Bruna Ferreira Mota, Juliana Arruda de Souza Monnerat, Cristiane Correia Teixeira, Renata Beatriz da Rocha Ramalho, Isabelle Waleska Santos de Medeiros Silva, Manuela Dolinsky, Gilson Teles Boaventura, Vilma Blondet, Sergio Girão Barroso, Carlos Alberto Soares da Costa and Gabrielle de Souza Rocha

Laboratory of Experimental Nutrition. Department of Nutrition and Dietetics. Universidade Federal Fluminense. Rio de Janeiro, Brazil

Abstract

Introduction: intake of diets with high saturated fat may produce deleterious effects on bone mineralization. Lifestyle changes help reduce the bone loss observed in osteoporosis. Resveratrol, present in grape juice and red wine, has osteogenic and osteoinductive effects, being potentially beneficial for bone health.

Objective: to evaluate the effects of red grape juice, red wine and resveratrol consumption on bone parameters in Wistar rats submitted to a high-fat diet and physical training.

Method: female Wistar rats, with 90 days of age, were divided into five groups and followed up for 60 days: a) control group; b) high-fat group; c) grape juice group; d) red wine group; and e) resveratrol group. The different groups of animals performed a physical training protocol. Animal's weight and consumption were monitored weekly. After 60 days, femoral dimensions, bone mineral density (BMD) and bone mineral content (BMC) were evaluated.

Results: there was no difference in body mass; however, all groups consuming the high-fat diet had higher consumption ($p < 0.05$). RWG presented a greater distance between the epiphyses, femoral mass and BMC ($p < 0.05$). RWG and RG presented greater mean diaphysis point width and BMD ($p < 0.05$).

Conclusion: the results suggest that the bioactive compounds present in red wine and resveratrol solution together with regular exercise were able to promote beneficial effects on bone health, even when associated with a high saturated fat diet.

Key words:

High-fat diet.
Resveratrol. Grape juice. Red wine.
Physical activity. Bone health.

Resumen

Introducción: el consumo de dietas ricas en grasas saturadas puede producir efectos nocivos sobre la mineralización ósea. Los cambios en el estilo de vida ayudan en la reducción de la pérdida ósea que se produce en la osteoporosis. El resveratrol, presente en el zumo de uva y el vino tinto, tiene efectos osteogénicos y osteoinductores, y es potencialmente beneficioso para la salud ósea.

Objetivo: evaluar los efectos del consumo de zumo de uva roja, vino tinto y resveratrol sobre los parámetros óseos en ratas sometidas a una dieta alta en grasa y entrenamiento físico.

Métodos: ratas Wistar, hembras, con 90 días, fueron divididas en cinco grupos y monitorizadas durante 60 días: a) grupo de control; b) grupo hiperalimentado; c) grupo zumo de uva roja; d) grupo de vino tinto; y e) grupo de resveratrol. Los distintos grupos de animales fueron sometidos a un protocolo de entrenamiento físico. El peso y el consumo de los animales se monitorizaron semanalmente. Después de 60 días, se evaluaron el tamaño del fémur, la densidad mineral ósea (DMO) y el contenido mineral óseo (CMO).

Resultados: no hubo diferencias en el consumo, sin embargo, todos los grupos que consumieron la dieta rica en grasas tenían un mayor consumo ($p < 0,05$). GV tenía una mayor distancia entre las epífisis, mayor tamaño del fémur y un mayor CMO ($p < 0,05$). SGS y GR tenía mayor anchura media de diáfisis y una mayor DMO ($p < 0,05$).

Conclusión: Los resultados sugieren que los compuestos bioactivos presentes en el vino tinto y la solución de resveratrol, combinados con el ejercicio físico regular, fueron capaces de promover efectos beneficiosos sobre la salud ósea, incluso cuando se asocian con una dieta alta en grasas saturadas.

Palabras clave:

Dieta alta en grasas.
Resveratrol. Zumo de uva. Vino tinto.
Actividad física. Salud ósea.

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Correspondence:

Letícia Monteiro da Fonseca Cardoso. Laboratory of Experimental Nutrition. Department of Nutrition and Dietetics. Universidade Federal Fluminense. Rio de Janeiro, Brazil
e-mail: ticia.c@gmail.com

INTRODUCTION

Osteoporosis is a skeletal disease occurring due to the normal aging process and characterized by progressive loss of bone mass and disorders in its microstructure, which cause brittleness and make the bone susceptible to fractures (1). This loss of bone mass occurs from an imbalance in bone remodeling, where bone resorption overcomes bone formation (2). Bone health is influenced by several factors. Some of these factors cannot be modified, such as age, sex, ethnicity and genetics, while other can be modified, such as hormonal factors, smoking, physical activity and dietary patterns (3).

The Brazilian population has undergone a nutritional transition process characterized by a high saturated fat diet followed by a reduction in physical activity levels (4). Intake of dietary fats produces deleterious effects on bone mineralization, as a diet with high saturated fats can interfere with the absorption of intestinal calcium, due to insoluble calcium soaps formed by free fatty acids, contributing to a lower absorption of this mineral (4,5).

Osteoporosis is a major public health problem; it is necessary to create therapeutic strategies that act positively on bone health, such as regular physical exercise and ingestion of some foods and nutrients, contributing to the formation, and reducing or preventing their loss (6). Physical activity causes changes in bone structure and geometry due to the mechanical load that is applied during activity. Thus, it stimulates osteogenic responses and helps to prevent or slow down bone mass loss, as it occurs in osteoporosis (7).

Studies have shown that resveratrol is potentially beneficial for bone health. It is a polyphenol naturally synthesized by vines to protect plants against fungal infection (6). It is present in red wine and in a wide variety of foods of plant origin such as grapes, walnuts and blackberries (8). *In vitro* studies show that resveratrol can promote osteoblasts activity and formation and antagonize the effects of osteoclasts, which are the cells responsible for bone resorption. This is due to resveratrol's ability to inhibit the transcription activity of NF- κ B, which acts directly on osteoclast genesis. In addition, it has osteogenic and osteoinductive effects through increased levels of osteocalcin and alkaline phosphatase (6).

Thus, the objective of this study was to evaluate the effects of red grape juice, red wine and resveratrol consumption on bone parameters in adult female Wistar rats submitted to a high-fat diet and physical training.

METHOD

The present study was performed with 50 adult female, Norvegicus Wistar Albinus rats (90 days of age), initially weighing around 230 g, from the Laboratory of Experimental Nutrition. Animals were individually housed in cages in a controlled environment. All experimental procedures were approved by the Ethics Committee and complied with the regulations for the use of laboratory animals.

During the experiment, animals were kept in individual polypropylene cages in an environment with constant temperature

(22 °C $\pm$ 2 °C) and adequate lighting (light and dark cycle every 12 hours).

Animals were divided in five groups, with food and water offered in free demand and followed for 60 days. The rations used in the experiment were prepared according to the American Institute of Nutrition (AIN) 93M recommendations (9) for *Rattus norvegicus* and manipulated at the Laboratory of Experimental Nutrition (Table I). Rats were distributed in five different groups: a) control group (CG), receiving a balanced diet based on casein (AIN 93M); b) high-fat group (HFG), receiving a high-fat casein-based diet (20%), when the usual fat content is 4-8%; c) resveratrol group (RG), receiving a high-fat casein-based diet (20%), and 15 ml of a resveratrol solution 4% (diluted in distilled water) per day; d) grape juice group (GJG), receiving high-fat casein-based diet (20%) and 15 ml of whole grape juice per day; and e) red wine group (RWG), receiving high-fat casein-based diet (20%) and 10 ml of red wine per day. Both whole grape juice (Aurora Tinto Integral®) and red wine (Góes Tempos®) were purchased at the local market; the resveratrol solution was prepared every day and dispensed to the animals (Table II).

Animals groups were submitted to adaptation on a treadmill for small animals with six bays and activated by a 12V motor; the adaptation period started two weeks before the beginning of the experiment. During the adaptation period, the animals were placed on the treadmill three days a week on alternate days and each training day was increased one minute, starting with three

Table I. Composition of the control and high-fat diets used in the experiment

Ingredients (g/100 g)	Control	High-fat
Protein	11.62	11.946
Carbohydrate	61.59	48.742
Lipids	4.182	20.599
Casein ¹	14	14
Starch ²	62.07	46.07
Sugar ³	10	10
Mist. of minerals ¹	3.5	3.5
Mist. of vitamins ¹	1	1
Soya oil ⁴	4	-
Lard ⁴	-	20
Cellulose ⁵	5	5
B-choline ⁶	0.25	0.25
L-cystine ⁶	0.18	0.18
B HT	0.008	0.008
Total	100.01	100.01
Kcal	331.85	428.14

Balanced diet according to the recommendations of the AIN 93 M (9). ¹M. Cassab Comércio e Indústria Ltda. ²Maisena - Unilever Bestfoods Brasil Ltda. ³União. ⁴Liza Cargill Agricultura Ltda. ⁵Macrocel - Blanver Ltda. ⁶Comércio e Indústria Famos Ltda.

Table II. Nutritional composition of the grape juice and red wine used in the experiment

Nutritional information Serving of 200 ml		
	Whole grape juice	Red wine
Energy (kcal)	120	123.2
Carbohydrates (g)	30	-
Protein (g)	0	-
Total fat (g)	0	-
Dietary fiber (g)	0	-
Sodium (mg)	0	-
Alcohol (% vol)	-	11

Nutritional composition of the grape juice and red wine that were offered to animals during the 60 days of experiment.

minutes and increasing one minute a day until eight minutes. Speeds varied as follows: 0.3 m/min, 0.4 m/min, 0.6 m/min, 0.8 m/min and 0.9 m/min. At the beginning of the experiment, when the animals completed 90 days of life, the five groups of animals executed the running protocol at a speed of 10 m/min for the slip of the canvas, which consequently induced movement of the animal under study. The training session had a ten minute duration and was carried out for 60 days, five days a week until the end of the experiment (10).

Food intake and body weights were monitored weekly. The amount of ration, grape juice, red wine and resveratrol solution were quantified to obtain daily intake. For body mass gain analysis, animals were weighed twice a week in a digital scale (Filizola®), with 3 kg capacity and 0.05 g accuracy.

After 60 days of treatment, animals were anesthetized with Thiopentax® (thiopental sodium, 0.1 mg/100 g) and euthanized by exsanguination. Right femurs were collected, cleaned of soft tissues and stored at -80 °C for further analysis. Bone dimensions: distance between epiphyses and diaphysis midpoint thickness were evaluated using a tachymeter, with a reading capacity of 0.01 mm, and then femurs were weighed (g). Femur bone mineral densities (BMD, g/cm²) and bone mineral content (BMC, g) were determined by Dual-Energy X-Ray Absorptiometry (DXA) using Lunar DXA equipment 200368 GE instrument and software encore 2008 version 12.20 (GE Healthcare, Madison, Wisconsin). The evaluation was blind, since the DXA technician did not know the experimental protocol (11).

Results were expressed through descriptive statistics as mean and standard deviation. The data were evaluated for their normality using the Kolgomorov-Smirnov test. The ANOVA one way test was used for the comparison between groups, and the Newman-Keuls' was used as post-test. A $p < 0.05$ was considered as significant. Graph Pad Prism software version 5.00, 2007 (San Diego, CA) was used for these analyses.

RESULTS

At the end of the experiment, there were no significant differences in the final weights of each group (Fig. 1).

Differences in energy consumption between groups were observed. The RWG and RG groups consumed more energy when compared to the other groups, but there were significant differences among them (Fig. 2).

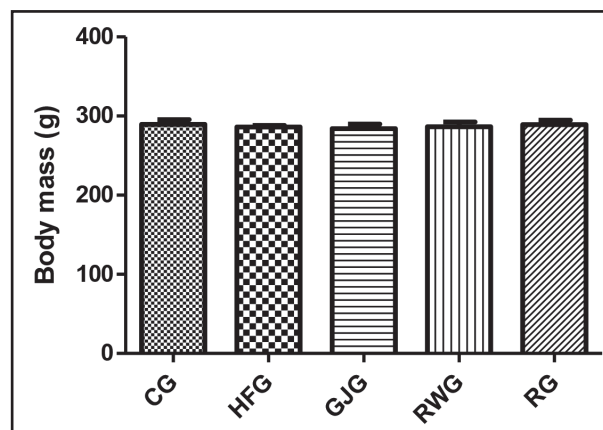


Figure 1.

Body mass of animals after 60 days of experiment. CG: Control group, fed with control diet; HFG: High-fat group, fed with high-fat ration; GJG: Grape juice group, fed with high-fat ration and receiving whole grape juice; RWG: Red wine group, fed with high-fat ration and receiving red wine; RG: Resveratrol group, fed with high-fat ration and receiving 4% solution of resveratrol. Results are expressed as mean $\pm$ standard deviation. *Univariate analysis of variance, followed by the Newman-Keuls test post.

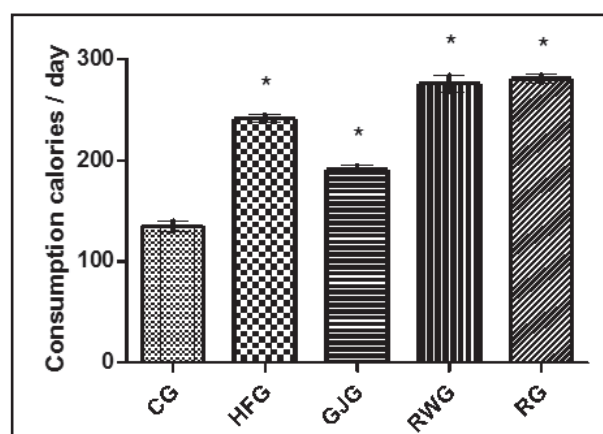


Figure 2.

Daily energy intake (kcal) (ration + experimental drinks) of the groups during the 60 days of experiment. CG: Control group, fed with control diet; HFG: High-fat group, fed with high-fat ration; GJG: Grape juice group, fed with high-fat ration and receiving whole grape juice; RWG: Red wine group, fed with high-fat ration and receiving red wine; RG: Resveratrol group, fed with high-fat ration and receiving 4% (RG) solution of resveratrol. *Considered significant values ($p < 0.05$, univariate analysis of variance, followed by the Newman-Keuls test post).

At the end of the 60 day experiment, the distance between the epiphyses was significantly higher in the RWG when compared to CG, HFG and GJG ($p < 0.05$). The mean point of the diaphysis width was significantly higher in RWG and RG when compared to CG, HFG and GJG ($p < 0.0001$). However, no significant difference was found between RWG and RG.

DXA analysis showed significantly higher bone mineral density in RWG and RG when compared to CG, HFG and GJG ($p < 0.0001$). Nevertheless, no significant difference was found between RWG and RG. Regarding bone mineral content, it was significantly higher in RWG when compared to CG, HFG and GJG ($p < 0.05$). There were no significant differences between RWG and RG (Table III).

DISCUSSION

The groups receiving only high-fat ration and high-fat ration associated with polyphenol-rich beverages presented higher energy consumption when compared to the control group. However, the higher energy consumption did not influence the final weight of the animals receiving a high-fat diet. Physical exercise associated with polyphenol-rich beverages may have contributed to maintenance and control of body mass (12).

Distance between epiphyses, femoral mass and BMC were greater only in the group receiving red wine, while BMD and mid-point of the diaphysis width were higher in both wine and resveratrol solution groups. Among the positive effects of resveratrol on bone mass, it stimulates early osteoprogenitor cells in bone marrow due to the osteoblastic line effect on bone formation, besides inhibiting signaling pathways for osteoclast differentiation (13). As cortical bone microarchitecture is considered to be one of the main determinants of bone resistance, it might be suggested an ability of these beverages to increase bone resistance (14).

Studies have shown that resveratrol has both osteogenic and osteoinductive effects. Resveratrol acts by activating Sirtuin 1 (Sirt 1), a NAD⁺-dependent histone deacetylase, which leads to NK-1B deacetylation induced by RANKL, inhibiting its transcriptional activation (15). This process inhibits osteoclasts differentiation by prevent-

ing bone loss. *In vitro* studies have shown that resveratrol increases the activity of alkaline phosphatase (a biomarker for osteoblastic differentiation), indicating its ability to stimulate osteoblasts differentiation, cells responsible for bone formation (16).

Resveratrol has been characterized as a phytoestrogen based on its ability to bind to and activate estrogen receptor (17). Alcohol, in moderate amounts, induces estrogen production in a post-menopausal woman, explaining alcohol protection against bone loss. Estrogen plays an important role in bone maintenance. In adult women, estrogen slows down bone remodeling, maintaining the proper balance between bone formation and resorption. The effects of estrogen deficiency are related to an improvement in the activity of cells responsible for bone resorption, osteoclasts, leading to an increase in fracture risk (18).

In addition, acute ingestion of small amounts of alcohol induces secretion of calcitonin, a molecule which protects bone tissue (18). Red wine, in addition to resveratrol effects, also has benefits associated with its alcohol content. Therefore, this may justify a better red wine result against the bone parameters compared to resveratrol.

The minor results of grape juice when compared to red wine and the resveratrol solution can be explained by its bioavailability. Absorption and bioavailability of resveratrol vary among individuals, but they are independent of diet or amount of lipids in the diet. However, grape juice has a lower amount of free resveratrol, suggesting a lower bioavailability of resveratrol compared to the pure compound.

Cao et al. (2010) and Chen et al. (2010) showed lower bone mass associated with increased bone resorption and decreased bone formation. However, in this study, it was observed that even animals receiving only high-fat diet did not present inferior bone parameters, compared to the animals in the control group. This can be explained by the beneficial effects mechanical load exerts on bone tissue during physical activity.

CONCLUSION

It is concluded that this study provided evidence of the beneficial effects of red wine and resveratrol solution, along with regular

Table III. Bone parameters of the femur of female Wistar rats submitted to physical training after 60 days of experiment

	CG	HFG	GJG	RWG	RG	p value
Femur (g)	0.833 ± 0.11	0.81 ± 0.06	0.774 ± 0.06	0.939 ± 0.10*	0.867 ± 0.07	0.003
Distance between the epiphyses (mm)	34.26 ± 1.07	34.04 ± 0.79	33.65 ± 0.29	35.34 ± 0.59*	34.35 ± 1.39	$p < 0.0001$
Width of the midpoint of the diaphysis (mm)	3.202 ± 0.30	3.209 ± 0.19	3.252 ± 0.15	3.743 ± 0.26*	3.557 ± 0.19*	0.0096
BMD (g/cm ²)	0.152 ± 0.01	0.152 ± 0.007	0.149 ± 0.008	0.175 ± 0.01*	0.166 ± 0.007*	$p < 0.0001$
BMC (g)	0.353 ± 0.05	0.358 ± 0.05	0.34 ± 0.05	0.433 ± 0.05*	0.388 ± 0.06	0.0026

CG: Control group, fed with control diet; HFG: High-fat group, fed with high-fat ration; GJG: Grape juice group, fed with high-fat ration and receiving whole grape juice; RWG: Red wine group, fed with high-fat ration and receiving red wine; RG: Resveratrol group, fed with high-fat ration and receiving 4% solution of resveratrol; BMD: Bone mineral density; BMC: Bone mineral content. Results expressed as mean ± standard deviation. *Considered significant values ($p < 0.05$, univariate analysis of variance, followed by the Newman-Keuls test post).

physical exercise, on bone health even when associated with a high saturated fat diet.

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Trabajo Original

Otros

Comparative study of the nutritional status of vitamin A in pregnant women and in women who became pregnant or did not after Roux-en-Y gastric bypass

Estudio comparativo del estado nutricional de la vitamina A en mujeres embarazadas y en mujeres que quedaron embarazadas o no tras el bypass gástrico en Y de Roux

Sabrina Cruz¹, Suzana Nunes Machado¹, Suelem Pereira da Cruz², Sílvia Pereira³, Carlos Saboya⁴ and Andréa Ramalho⁵

¹School of Medicine. Federal University of Rio de Janeiro. Center for Research on Micronutrients (NPqM). Institute of Nutrition Josué de Castro. Universidade Federal do Rio de Janeiro/UFRJ (Federal University of Rio de Janeiro). Rio de Janeiro, Brazil. ²Center for Research on Micronutrients (NPqM). UFRJ (Federal University of Rio de Janeiro). Rio de Janeiro, Brazil. ³School of Medicine. Federal University of Rio de Janeiro. Clínica Cirúrgica Carlos Saboya. Center for Research on Micronutrients (NPqM). UFRJ (Federal University of Rio de Janeiro). Rio de Janeiro, Brazil. ⁴Universidade Federal de São Paulo/UNIFESP. Member of the Brazilian Society of Bariatric and Metabolic Surgery. Clínica Cirúrgica Carlos Saboya. Center for Research on Micronutrients (NPqM)/INJC/UFRJ (Federal University of Rio de Janeiro). Rio de Janeiro, Brazil. ⁵ENSP/FIOCRUZ. Department of Social and Applied Nutrition. Institute of Nutrition at UFRJ (Federal University of Rio de Janeiro). Center for Research on Micronutrients (NPqM)/INJC/UFRJ (Federal University of Rio de Janeiro). Rio de Janeiro, Brazil

Abstract

Introduction: the changes in digestive physiology after Roux-en-Y gastric bypass (RYGB), as well as pregnancy, maximizes the risk of vitamin A deficiency (VAD) and both can result in harm to the mother and child health.

Objective: to compare the nutritional status of vitamin A among women who became pregnant or did not after RYGB and in pregnant women who did not undergo surgery, and to assess the impact of VAD on the mother and child health.

Methods: this is a cross-sectional study of the analytical type. The women were divided into: group 1 (G1) with 80 pregnant women; group 2 (G2) with 40 pregnant women who had previously undergone RYGB, both in their third trimester of pregnancy; and group 3 (G3) with 77 non-pregnant women who had previously undergone RYGB. Serum concentrations of retinol and β -carotene, night blindness (NB), gestational and neonatal interferences were investigated. The significance level adopted was $p < 0.05$.

Results: RYGB, *per se*, had a greater impact on the inadequacy of retinol, β -carotene, and on the increased percentage of NB when compared to non-surgical pregnant women. When surgery was associated with pregnancy, more than 75% of inadequacy of retinol and β -carotene was noted, as well as a higher percentage of individuals with NB. G2 also showed increased prevalence ratio for developing gestational and neonatal interferences, when compared to G1.

Conclusion: RYGB provides greater negative impact on the nutritional status of vitamin A compared to pregnancy, and surgery associated with pregnancy can create even greater risks.

Key words:

Pregnancy. Roux-en-Y gastric bypass. Vitamin A. Gestational interferences. Obstetric and neonatal outcomes.

Resumen

Introducción: los cambios en la fisiología digestiva después del bypass gástrico en Y de Roux (BGYR), así como la gestación, maximizan el riesgo de deficiencia de vitamina A (DVA), ambos pueden resultar dañinos para la salud materna e infantil.

Objetivo: comparar el estado nutricional de la vitamina A entre las mujeres que quedaron embarazadas o no después del BGYR y en embarazadas que no se sometieron a cirugía, y evaluar el impacto del DVA en la salud de la madre y el niño.

Métodos: se trata de un estudio transversal del tipo analítico. La cohorte se dividió en: grupo 1 (G1) 80 mujeres embarazadas; grupo 2 (G2) 40 mujeres embarazadas que habían sido sometidas anteriormente a BGYR, ambos en su tercer trimestre de gestación; y grupo 3 (G3), 77 mujeres no embarazadas que habían previamente sometido a BGYR. Se investigaron las concentraciones séricas de retinol y β -caroteno, ceguera nocturna (CN), interacciones gestacionales y neonatales.

Resultados: BGYR, por sí mismo, tuvo un mayor impacto en la inadecuación de retinol, β -caroteno y en el aumento del porcentaje de CN en comparación con las mujeres embarazadas no quirúrgicas. Cuando la cirugía se asoció con el embarazo, se observó más del 75% de la inadecuación de retinol y β -caroteno, así como un mayor porcentaje de individuos con CN. El G2 también mostró una mayor proporción de prevalencia para desarrollar interacciones, en comparación con el G1.

Conclusión: BGYR proporciona un mayor impacto negativo sobre el estado nutricional de la vitamina A en comparación con el embarazo; la cirugía asociada con el embarazo puede proporcionar aún mayores riesgos.

Palabras clave:

Embarazo. Derivación gástrica en Y de Roux. Vitamina A. Intercurrencias gestacionales. Resultados obstétricos y neonatales.

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Correspondence:

Sabrina Pereira da Cruz. Cidade Universitária - Ilha do Fundão. Av. Carlos Chagas, 373. Edifício do Centro de Ciências da Saúde, 2.º andar, Sala 49. CEP: 21.941-902. Rio de Janeiro, Brazil
e-mail: sabrina.cruz.ufrj@gmail.com

INTRODUCTION

Bariatric surgery is performed to control body weight in individuals with class III and II obesity with associated diseases (1). It can generate benefits in the quality of life and it can significantly promote fertility in women with normalization of hormonal concentrations and menstrual cycle, thus facilitating pregnancy (2-4).

Among the existing surgical procedures, the most performed worldwide is the Roux-en-Y gastric bypass (RYGB) that accounts for 45% of surgeries (5). In Brazil, the choice for RYGB is even more expressive, accounting for 70% of surgeries (5). Despite the weight loss and improvement of the factors associated with obesity, metabolic disorders deriving from the surgical procedure can cause deficiencies (6,7) of macro and micronutrients (8), including vitamin A deficiency (VAD) (9).

VAD is considered a serious public health problem that affects 19 million of pregnant women in the world and can contribute to increased maternal and infant mortality rates (9). Furthermore, there are specific recommendations about the need of assessing the nutritional status of vitamin A during the prenatal care period (10).

Thus, the objective of the present study is to assess the inadequacy of the nutritional status of vitamin A caused by pregnancy, by RYGB, or by the occurrence of both pregnancy and RYGB concomitantly, as well as the impact of this vitamin deficiency on the mother and child health under the conditions addressed by the study.

METHODS

This is a retrospective analytical cross-sectional study conducted with adult women of reproductive age. Pairing by age and pre-surgery body mass index (BMI) was used for the women who had previously undergone RYGB, and pairing by age and prepregnancy BMI was used for pregnant women. The study was conducted in healthcare institutions located in the city of Rio de Janeiro from January 2011 to December 2012. The women who met the study inclusion criteria were divided into three groups (G1, G2 and G3), as described in figure 1.

All participants read and signed an informed consent, in accordance with Resolution n.º 196 of 10/10/1996 of the National Council of Health. The study was approved by the Research Ethics Committee of Hospital Universitário Clementino Fraga Filho of the Federal University of Rio de Janeiro.

For the anthropometric assessment of G1 and G2, data were collected on height, prepregnancy weight informed or measured until pregnancy week 13, prepartum weight or weight recorded in the last prenatal visit, besides presurgery weight in G2. With respect to measures obtained in G3, data were collected on height and weight (presurgery and maximum of 2 years after surgery). In all groups, these variables were used to calculate BMI for their subsequent classification, according to the cut-off points established by the World Health Organization (WHO) (1998) (11).

	<i>G1</i> <i>Pregnant women</i>	<i>G2</i> <i>Pregnant women who had</i> <i>previously</i>	<i>G3</i> <i>Non-pregnant women who had</i> <i>undergone RYGB</i>
Inclusion criteria	Adult women. Single fetus pregnancy. Third trimester. Prenatal routine (started between week 8 until week 12)	Adult women. Single fetus pregnancy. Third trimester. Prenatal routine (started between week 8 until week 12) and follow-up by the surgeon and the nutritionist of the surgical team. Routine supplementation with 5,000 IU of retinol acetate. RYGB prior to pregnancy	Adult women. Maximum period of 2 years after surgery. Follow-up by the surgeon and the nutritionist of the surgical team Routine supplementation with 5,000 IU of retinol acetate
Exclusion criteria	Prior restrictive and disabsorptive surgeries. Disabsorptive syndromes, prior disabsorptive and restrictive surgeries, restrictive diets, diabetes mellitus, neoplasia, liver and/or kidney diseases. Use of supplement containing vitamin A during pregnancy. No routine prenatal care	Restrictive and disabsorptive surgeries prior to RYGB. Disabsorptive syndromes, disabsorptive and restrictive surgeries prior to RYGB, restrictive diets, diabetes mellitus, neoplasia, liver and/or kidney diseases. Intake of less than 80% of the amount of prescribed supplements. No follow-up by the surgeon and the nutritionist of the surgical team and no routine prenatal care	Restrictive and disabsorptive surgeries prior to RYGB. Disabsorptive syndromes, disabsorptive and restrictive surgeries prior to RYGB, diabetes mellitus, neoplasia, liver and/or kidney diseases. Intake of less than 80% of the amount of prescribed supplements. No follow-up by the surgeon and the nutritionist of the surgical team

Figure 1.
Description of groups, inclusion and exclusion criteria.

In pregnant women, the other data collected were used to calculate the total gestational weight gain (TGWG) through subtraction of prepregnancy weight from parturition weight. The adequacy of gestational weight gain was classified in accordance with the Institute of Medicine recommendation (2009) that considers a 5-9 kg weight increase appropriate and a weight increase below or above these values inappropriate (12).

For the anthropometric assessment of newborns, information on weight, height, and gestational age at birth (GAB) was selected. For classification of birth weight, the criteria of the Ministry of Health (2005) were used: low birth weight (less than 2,500 g), insufficient weight (between 2,500 and 2,999 g), appropriate weight (between 3,000 g and 3,999 g), and overweight or macrosomia (4,000 g or more) (13).

As for GAB, were considered born preterm the newborns with GAB < 37 weeks, at term those born between 37 and 42 weeks, and post-term those born with GAB ≥ 42 weeks, according to the date of the last menstrual period (DLMP) (13). Based on the information on weight and GAB, the correlation of weight/GAB was assessed according to the growth curve proposed by Pedreira et al. (2011), and the newborns were classified into small for gestational age (SGA < P10), appropriate for gestational age (AGA, P10-P90), and large for gestational age (LGA > P90) (14).

The referred information was used for assessment of neonatal intercurrents, and the newborn was classified into low weight, appropriate weight, and macrosomic according to birth weight, and into preterm, at term, or post-term according to GAB.

Information about the maternal intercurrents developed during pregnancy was collected through consultations of medical records, maternity cards, and interpretation of laboratory tests.

The following pregnancy intercurrents were: presence of hypertensive syndromes of pregnancy (HSP), anemia and urinary tract infection (UTI), as recommended by the Ministry of Health (2000) (15), as well as dumping syndrome in the case of pregnant women who underwent surgery before pregnancy. The cut-off point for the presence of anemia in the third trimester was 11.0 g/dL, in accordance with recommendations of the Centers for Disease Control and Prevention (1998) (16).

For assessment of serum concentrations of retinol and β -carotene, the method of High Performance Liquid Chromatography with ultraviolet detector (HPLC-UV) was used. The following cut-offs points were used to indicate inadequacy: retinol serum values < 1.05 $\mu\text{mol/L}$ (30 $\mu\text{g/dL}$ <) and β -carotene ≤ 40 $\mu\text{g/dL}$ (17).

In the functional assessment of VAD, the presence of night blindness (NB) was investigated in the three groups through an interview standardized by the WHO (1996) (18) and the Pan-American Health Organization (1999) (19), and adapted and validated for pregnant women by Saunders et al. (20,21). Both the biochemical and the functional assessments were performed in G1 and G2 during or immediately after delivery and in G3 in the postoperative period, for a maximum of two years after surgery.

The instrument used in data collection was pre-tested and comprised a completed form filled by a single interviewer, with data from the interview and consultation of the prenatal care records.

In relation to the statistical analysis, for verification of normal-

ity the Kolmogorov-Smirnov and Shapiro-Wilk tests were used. Quantitative data were described in measures of central tendency and dispersion, and in the comparison of the means of the groups either the Mann-Whitney test or the Kruskal-Wallis test was used. To test the homogeneity of proportions between categorical variables the Chi-square test was used, and prevalence ratio was calculated. In the analysis, a significance level of 5% was adopted. The overall statistical assessment was carried out in the SPSS statistical package for Windows, version 21.0.

RESULTS

CHARACTERIZATION OF PATIENTS

The study was conducted with adult women aged 20-49 years. Pregnant women were paired by age (G1: 30.80 ± 4.45 vs. G2: 29.3 ± 5.35 ; $p = 0.129$) and prepregnancy BMI (G1: 26.84 ± 3.14 vs. G2: 25.72 ± 3.23 ; $p = 0.072$), while the women who had previously undergone bariatric surgery were paired by age (G2: 32.56 ± 4.69 vs. G3: 30.8 ± 4.45 ; $p = 0.075$) and presurgery BMI (G2: 42.91 ± 3.17 vs. G3: 43.10 ± 5.08 ; $p = 0.809$). When the postsurgical BMI of G2 (the last one recorded before pregnancy) and of G3 (end of the second year after surgery) were considered, no significant differences were found between the groups (G2: 26.84 ± 3.14 vs. G3: 26.43 ± 3.20 ; $p = 0.638$).

INADEQUACY OF VITAMIN A

The percentages of inadequacy of retinol and β -carotene showed significant differences among the three groups (Table I). Women who became pregnant after RYGB showed percentage of inadequacy of retinol three times higher when compared to women who only became pregnant or women who just underwent bariatric surgery ($p < 0.001^*$, for both). It was also noted that although the percentage of inadequacy of retinol in G1 and G3 remained similar, β -carotene was significantly higher in women in the latter group ($p = 0.001$).

When considering the mean concentrations of retinol and β -carotene, it was observed that both were significantly higher for the women who became pregnant when compared to the women who became pregnant or did not become pregnant after RYGB ($p < 0.001^*$, for all) (Table I). In addition, pregnant women who had previously undergone RYGB showed means of retinol and β -carotene significantly below those found in the women who had only undergone this surgery ($p = 0.0052$ and $p = 0.014$, respectively).

Thus, it was noted that RYGB, per se, had a greater impact on the inadequacy of retinol and β -carotene when compared to non-surgical pregnant women. When surgery was associated with pregnancy, more than 75% of inadequacy of vitamin A (retinol and β -carotene) was noted, as well as a higher percentage of individuals with NB. Similar results were found for NB, as demonstrated below (Table I).

Table I. Percentage of inadequacy, means and standard deviation of retinol, β -carotene and presence of night blindness in the assessed groups

	G1 (n = 80)	G2 (n = 40)	G3 (n = 77)	p-value
<i>Retinol ($\mu\text{mol/L}$)</i>				
Percentage (%)	22.5%	75%	22.2%	< 0.001*
Mean and standard deviation	1.75 $\pm$ 0.89	0.99 $\pm$ 0.39	1.09 $\pm$ 0.29	< 0.001*
<i>β-carotene ($\mu\text{g/dl}$)</i>				
Percentage (%)	23.8%	87.5%	55.6%	< 0.001*
Mean and standard deviation	87.36 $\pm$ 62.19	28.87 $\pm$ 15.07	35.40 $\pm$ 16.68	< 0.001*
<i>Night blindness</i>				
Percentage (%)	20.0%	75%	40%	< 0.001*

Chi-square test was used for categorical variables and Kruskal Wallis test was used for continuous variables (* $p < 0.05$); G1: comprising 80 pregnant women; G2: comprising 40 pregnant women who had previously undergone RYGB; G3: comprising 77 non-pregnant women who had previously undergone RYGB.

FUNCTIONAL ASSESSMENT OF VITAMIN A

The percentage of women with NB was significantly higher in G2 when compared to G1 or G3 ($p < 0.001$ and $p = 0.001$, respectively), and yet, women who had only undergone RYGB presented higher NB percentages than pregnant women who had not undergone this surgery ($p = 0.016$) (Table I). In addition, we found association and concordance between inadequacy of retinol and presence of NB in G1 and G3 (association: $p = 0.006$; $p = 0.008$ and concordance: $p = 0.003$; $p = 0.006$), and between inadequacy of retinol and inadequacy of β -carotene and presence of NB in G2 and G3 (association: $p = 0.01$; $p < 0.001$ and concordance: $p = 0.002$; $p < 0.001$).

OBSTETRIC VARIABLES AND GESTATIONAL AND NEONATAL INTERCURRENCES

Analysis of the obstetrical variables showed that mean time interval between the DLMP and the RYGB in women who became pregnant after surgery was 21.07 ± 14.15 months. Moreover, gestational intercurrents were significantly higher when pregnancy occurred after surgery, namely UTI (G1: 1.3% vs. G2: 35%, with $p < 0.001$) and anemia (G1: 30% vs. G2: 75%, with $p < 0.001$); however, HSP showed no significant differences between the groups (G1: 10% vs. G2: 2.5%, with $p = 0.269$). In relation to neonatal intercurrents, preterm (G1: 5% vs. G2: 2.5%, with $p = 0.664$), SGA (G1: 7.5% vs. G2: 17.5%, with $p = 0.122$), LGA (G1: 7.5% vs. G2: 0%, with $p = 0.177$), macrosomia (G1: 2.5% vs. G2: 0%, with $p = 0.552$) and low birth weight (G1: 6.3% vs. G2: 2.5%, with $p = 0.662$) showed no differences between the groups. In addition, it should be noted that dumping syndrome was present in almost half of the women in G2 (42.5%).

When comparing the serum concentrations of retinol and β -carotene among women who showed gestational intercurrents, we observed that the concentrations of retinol (G1: 2.08 ± 0.95 vs. G2: 1.07 ± 0.22 , with $p < 0.001$) and β -carotene (G1: $80.72 \pm$

65.15 vs. G2: 28.81 ± 13.77 , with $p < 0.001$) were significantly lower in pregnant women who underwent bariatric surgery, with β -carotene showing mean below the cut-off point. In relation to the presence of neonatal intercurrents, a similar result was found since the mean concentrations of retinol (G1: 2.08 ± 0.94 vs. G2: 0.75 ± 0.46 , with $p < 0.001$) and β -carotene (G1: 82.18 ± 35 vs. G2: 9.75 ± 15.01 , with $p = 0.017$) were significantly lower in G2.

When dividing women who showed such intercurrents according to the groups studied, we found that G2 had serum concentrations of retinol and β -carotene significantly lower in relation to the presence of anemia and SGA infants (Table II). It is important to note that G2 was also seven times more likely to develop anemia and 42 times more likely to develop UTI. Thus, it was observed that G2 showed increased prevalence ratio for developing gestational/neonatal intercurrents (UTI, SGA, and anemia), when compared to G1.

DISCUSSION

The gestational period is a physiological time which, in isolation, results in increasing demands of numerous vitamins and minerals, especially vitamin A that can have its requirements increased by 40% for maintenance of placenta and fetal development (22,23). In addition, bariatric surgery, *per se*, can also facilitate the occurrence of these inadequacies and, in this scenario, vitamin A stands out as it has been considered one of the most reduced micro-nutrients (24,25). This can be observed in the current study, since the percentage of inadequacy of retinol in both G1 and G3 was more than 20%, and β -carotene was the most depleted in women who underwent the surgical procedure.

This greater reduction of serum concentrations of β -carotene can be justified by the likely bioconversion to retinol, since it is its most powerful precursor, demonstrating the existence of a synergistic relationship between them (26). The highest percentage of inadequacy observed in G3 can be justified by metabolic disorders derived from the surgical procedure, especially regarding

Table II. Means of serum concentrations of retinol and β -carotene of pregnant women who showed gestational and neonatal intercurrents

Variables	Retinol (μmol/L)			β-carotene (μg/dL)		
	G1	G2	p-value	G1	G2	p-value
	(n = 80)	(n = 40)		(n = 80)	(n = 40)	
Gestational intercurrents						
HSP	1.89 ± 1.09	1.00	0.245	65.57 ± 60.15	8.0	0.121
UTI	2.17	0.94 ± 0.31	0.09	81.27	30.57 ± 13.88	0.104
Anemia	2.05 ± 0.86	1.02 ± 0.28	< 0.001*	81.55 ± 66.84	27.96 ± 14.13	< 0.001*
Neonatal intercurrents						
Preterm	2.32 ± 1.01	-	-	90.67 ± 29.71	-	-
Post-term	2.30 ± 1.06	0.0	0.157	96.24 ± 73.33	30.00	0.157
SGA	2.50 ± 0.83	0.85 ± 0.37	0.002*	104.76 ± 62.06	29.7 ± 16.21	0.032*
LGA	1.39 ± 0.69	-	-	77.50 ± 60.83	-	-
LWB	2.88 ± 0.75	1.00	0.137	89.48 ± 78.95	9.00	0.137
Macrosomic (n = 2)	1.70 ± 0.27	-	-	106.85 ± 86.02	-	-

HSP: hypertensive syndromes in pregnancy; UTI: urinary tract infection; SGA: small for gestational age.

the exclusion of the duodenum in conjunction with the proximal portion of jejunum, main sites of absorption of micronutrients such as vitamin A (24,27,28).

Thus, the occurrence of pregnancy after bariatric surgery can worsen VAD, especially in the third trimester of pregnancy, period of the greatest transfer of this vitamin to the fetus. This can occur not only due to the changes caused by surgery regarding digestion, absorption and transport, but also due to the hemodilution that occurs in pregnancy in a physiological way (29).

In this context, the current study showed that the serum concentrations of retinol and β -carotene were significantly lower in pregnant women who had previously undergone RYGB compared to pregnant women, or women who only underwent this surgical procedure. In addition, means of retinol and β -carotene in G2 were below the mean of adequacy (retinol: 0.99 $\pm$ 0.39; β -carotene: 28.87 $\pm$ 15.07), while in G1 they were above the mean of adequacy, and in G3 only β -carotene showed means below recommendation. Such findings show that post-bariatric pregnancy can contribute to greater demands of vitamin A, and that the surgery, in isolation, can exert more influence on the inadequacy of the nutritional status of vitamin A when compared to pregnancy without a prior surgery.

Post-bariatric pregnant women also showed a percentage of gestational intercurrents significantly higher for UTI (G1: 1.3% vs. G2: 35%, $p < 0.001$) and anemia (G1: 30% vs. G2: 75%, $p < 0.001$), and those who developed anemia in pregnancy had the mean concentrations of this vitamin below the cut-off point, and these concentrations were significantly lower when they were compared to the ones found in G1 (retinol: G1: 2.05 $\pm$ 0.86 vs. G2: 1.02 $\pm$ 0.28, $p < 0.001$ *; β -carotene: G1: 81.55 $\pm$ 66.84 vs. G2: 27.96 $\pm$ 14.13, $p < 0.001$ *).

The increase in cases of anemia in G2 can be justified by hemodilution in pregnancy, in addition to the presence of hypochlorhydria in the postoperative period and to the high percentage of pregnant women with VAD (G1: 30% and G2: 75%) (30).

It has been recognized that anemia is a common complication after RYGB, iron deficiency being its main etiology (31). Belogolovkin et al. (2012) (32) reported that the odds of developing anemia are 4.3 times higher in pregnant women who had previously undergone bariatric surgery when compared to pregnant women who had not undergone this surgery, a finding in line to the one in the current study with prevalence ratio 7 times higher.

There is evidence that VAD can also be related to UTI since its presence can facilitate the negative impact on the immune system, favoring its development (33). This can occur with growing intensity during pregnancy, due to the anatomical and physiological changes occurring in the urinary tract such as: increased urine output and the expansion of the collector system caused by uterus compression, hypertrophy of the ureter musculature, and peristaltic activity reduction resulting from the action of progesterone. The referred changes promote urinary stasis and, consequently, the presence of UTI (34). In this regard, G2 was 42 times more likely to develop urinary infection when compared to G1, which may indicate that such clinical symptoms can be intensified after bariatric surgery.

In relation to neonatal intercurrents, G2 was 2.6 times more likely to give birth to SGA infants when compared to G1, and, moreover, serum concentrations of retinol and β -carotene were significantly lower, which may suggest a possible influence of this nutrient on SGA infants, an intercurrent that can happen more intensely in this segment (35).

It is important to highlight that dumping syndrome, found in almost half of the pregnant women in G2 (42.5%), may have contributed to the greatest inadequacies of vitamin A and to the gestational/neonatal interurrences shown. This syndrome can have intensified the decrease of food intake and contributed to a tendency to avoid the consumption of various foods, including those considered good sources of vitamin A after RYGB (7).

Regarding the functional assessment, we noted that pregnancy made possible the occurrence of NB in 20% of the participants, which can be justified by major demands of vitamin A (retinol/ β -carotene) imposed by such physiological status. Similar results were found in studies conducted in Brazil showing percentages of pregnant women affected by NB with values ranging from 9.9% to 18.7% (36,37). It is worth mentioning that gestational NB has high prevalence in several regions of the world and is not only limited to regions of extreme poverty. High prevalences of VAD in pregnant women were observed in developed countries, as demonstrated in a recent systematic review carried out by (38).

It should be noted that in cases of zinc deficiency, the hepatic synthesis of retinol-binding protein (RBP) can be damaged, resulting in secondary deficiency of vitamin A even in the presence of adequate liver stores of this vitamin. Therefore, in situations of high nutritional demand, such as the gestational period, zinc deficiency can occur and decrease RBP production, which can lead to VAD (39).

Thus, it can be observed that the percentage of pregnant women with no previous surgery with NB in national studies feature values close to those found in the present study even when they are not located in regions of extreme poverty. In addition, information on the role played by zinc in the formation of RBP and its transport to target tissues was also added.

Regarding RYGB, it was possible to evidence that it contributes to the lack of vitamin A, as the percentage of women affected doubled, possibly due to the absorptive changes promoted by the surgery. When pregnancy occurred after RYGB, the percentage of individuals affected was even more expressive (75%), and it is worth highlighting that the occurrence of both pregnancy and RYGB can further compromise this segment. In addition, association and concordance were found between the presence of NB and the inadequacy of retinol or β -carotene in all groups, thus pointing out the existing relationship. Such aspect was confirmed by a recent systematic review highlighting that VAD in women who became pregnant after bariatric surgery was a contributing factor to the presence of gestational NB (40).

This study was the first to evaluate the biochemical and functional status of vitamin A nutritional status in three distinct segments and its purpose was to measure and compare the magnitude of inadequacy and possible adverse consequences of VAD to the mother and child binomial, although showing a small sample size and no assessment of serum zinc and RBD. Since NB was exacerbated in pregnant women after bariatric surgery, we suggest further investigation about the synergy between vitamin A, zinc and RBP, under the conditions studied here.

CONCLUSION

Our study showed that RYGB, in isolation, provides greater negative impact on the nutritional status of vitamin A compared to pregnancy. When pregnancy occurs after surgery, it can result in even greater risks for the serum inadequacy of retinol and β -carotene in addition to the occurrence of NB, which intensifies gestational and neonatal interurrences. Thus, this study reinforces the importance of monitoring the serum concentrations of this vitamin in the segments studied, aiming to adjust the nutritional status of vitamin A and, consequently, bringing benefits to the mother and child health.

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Trabajo Original

Otros

Prevention of oral mucositis secondary to antineoplastic treatments in head and neck cancer by supplementation with oral glutamine

Prevención de la mucositis oral secundaria a los tratamientos antineoplásicos en el cáncer de cabeza y cuello mediante suplemento con glutamina oral

Jerónimo Pachón Ibáñez¹, José Luis Pereira Cunill², Giovana Fernanda Osorio Gómez³, Jose Antonio Irlés Rocamora⁴, Pilar Serrano Aguayo², Begoña Quintana Ángel¹, José Fuentes Pradera⁵, Manuel Chaves Conde⁵, María José Ortiz Gordillo¹ and Pedro Pablo García Luna²

Departments of ¹Radiation Oncology and ³Dermatology and Venereology. Hospital Universitario Virgen del Rocío. Sevilla, Spain. ²Clinical Nutrition Unit. Hospital Universitario Virgen del Rocío. Sevilla, Spain. ⁴Endocrinology and Nutrition Clinical Management Unit. Hospital Universitario Nuestra Señora de Valme. Sevilla, Spain. ⁵Department of Medical Oncology. Hospital Universitario Nuestra Señora de Valme. Sevilla, Spain

Abstract

Objectives: to evaluate the efficacy of glutamine in the prevention of the incidence of oral mucositis secondary to cancer therapies in patients with head and neck cancer (HNC). Secondary objectives were to know the incidence of odynophagia, interruptions of treatment and the requirements of analgesia and nasogastric tube.

Material and methods: prospective cohort study of patients with squamous cell carcinoma of HNC treated with radiotherapy ± concomitant chemotherapy. We compared 131 patients receiving glutamine orally at a dose of 10 g/8 hours with 131 patients who did not receive it.

Results: patients not taking glutamine had a hazard ratio 1.78 times higher of mucositis (95% CI [1.01-3.16], $p = 0.047$). Regarding odynophagia, patients not taking glutamine had a hazard ratio 2.87 times higher (95% CI [1.62-5.18], $p = 0.0003$). The 19.8% of patients who did not take glutamine discontinued treatment *versus* 6.9% of patients who took ($p = 0.002$). Regarding support requirements, 87.8% of patients without glutamine required analgesia *versus* 77.9% of patients with glutamine ($p = 0.03$) and nasogastric tube was indicated in 9.9% and 3.1% respectively ($p = 0.02$).

Conclusion: oral glutamine in patients receiving cancer treatments for HNC prevents the incidence of oral mucositis and odynophagia, and decreases treatment interruptions and the use of analgesia and nasogastric tube.

Key words:

Glutamine. Head and neck cancer. Mucositis.

Resumen

Objetivos: evaluar la eficacia de la glutamina en la prevención de la incidencia de mucositis secundaria a las terapias oncológicas en pacientes con carcinoma de cabeza y cuello. Los objetivos secundarios fueron conocer la incidencia de odinofagia e interrupciones de los tratamientos y los requerimientos de analgesia y sonda nasogástrica.

Material y métodos: estudio prospectivo de cohortes de pacientes con carcinoma epidermoide de cabeza y cuello tratados con radioterapia ± quimioterapia concomitante. Se compararon 131 pacientes que recibieron glutamina oral a una dosis de 10 g/8 horas con 131 pacientes que no la recibieron.

Resultados: los pacientes que no tomaron glutamina tuvieron una *hazard ratio* 1,78 veces mayor de mucositis (IC 95% [1,01-3,16], $p = 0,047$). Respecto a la odinofagia, los pacientes que no tomaron glutamina tuvieron una *hazard ratio* 2,87 veces mayor (IC 95% [1,62-5,18], $p = 0,0003$). El 19,8% de los pacientes que no tomaron glutamina interrumpieron el tratamiento *versus* 6,9% de los pacientes que la tomaron ($p = 0,002$). En cuanto a los tratamientos de soporte, el 87,8% de los pacientes sin glutamina requirieron analgesia *versus* 77,9% de los pacientes con glutamina ($p = 0,03$) y la sonda nasogástrica fue indicada en un 9,9% y 3,1% respectivamente ($p = 0,02$).

Conclusión: la glutamina oral en pacientes que reciben tratamiento por carcinoma de cabeza y cuello, previene la incidencia de mucositis oral y odinofagia y disminuye las interrupciones de tratamientos y el uso de analgesia y sonda nasogástrica.

Palabras clave:

Glutamina. Cáncer de cabeza y cuello. Mucositis.

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Correspondence:

Jerónimo Pachón Ibáñez. Department of Radiation Oncology. Hospital Universitario Virgen del Rocío. Av. Manuel Siurot, s/n. 41013 Sevilla, Spain
e-mail: jpachoni@telefonica.net

INTRODUCTION

Head and neck cancer (HNC) constitute the fifth neoplasm in incidence in the world population, being the third most prevalent tumor. In Spain, it causes 19.19 deaths per 100,000 inhabitants per year in men and 1.12 deaths per 100,000 inhabitants per year in women (1). The treatment of HNC using radiotherapy (RT) exclusively or in combination with surgery and/or chemotherapy is increasingly effective, but it is associated with clinically important effects such as mucositis and odynophagia, which can deteriorate nutritional status by hindering swallowing, leading to weight loss and dehydration, hospital admissions and increasing costs. Mucositis secondary to RT or chemoradiotherapy in HNC occurs in 85-100% of treated patients (2). It is the most important acute toxicity, being the main cause of discontinuation of treatment, and may limit the dose of RT. This factor implies a decrease in the probability of tumor control (3), and worsening the prognosis. Of all types of tumors, HNC are those with more evidence that an unplanned disruption has a negative effect on the outcome (4-7). Therefore, the prevention of mucositis can have a significant impact on improving treatment outcome in patients with HNC (8). Measures against mucositis are extremely important (9), mainly in patients with pain and inflammation.

The Cochrane Library has reviewed the preventive and therapeutic studies of oral mucositis in cancer patients (10,11), concluding that the strength of these measures is variable and that well-designed trials are needed. In the same line, a review focused exclusively on HNC (12) reported that, to date, no intervention is useful by itself and that it would be necessary to combine different ones acting in the distinct phases of mucositis.

Glutamine is the most abundant amino acid in the body, being present in muscles and blood. It is obtained by endogenous synthesis in muscle, and from the diet, in foods with high protein content. Glutamine provides nitrogen to metabolic activities, has a buffer effect that neutralizes acid excess in muscles and participates in the immune-response, and is the main energetic substrate of the epithelial cells of the oral and intestinal mucosa (13). As a non-essential amino acid, the organism can synthesize it from other amino acids, although in situations of metabolic stress it is considered to be "semi-essential". In such situations, such as trauma, infection, neoplasia and cancer treatments, the organism may not be able to synthesize sufficient endogenous glutamine (14,15) to optimally maintain mucosal structure and function. Glutamine is well absorbed in the small intestine. Clinical data suggests that a safe dose of glutamine is 20-40 g/day. The response to glutamine appears to be dose dependent (16). Regarding the efficacy of glutamine studies in the prevention of oral mucositis in HNC, Cerchiatti et al. (17) showed in 29 patients that intravenous glutamine reduced the severity of mucositis. In the recent study by Pattanayak et al. (18), performed in 162 patients, glutamine delayed mucositis occurrence and decreased severity significantly.

In the present work, given the little scientific evidence in the prevention of mucositis in HNC along with the importance of this clinical issue, we intend to study the preventive effect of oral supplementation with glutamine in patients with HNC.

MATERIAL AND METHODS

We conducted a prospective, comparative, non-randomized, cohort study to know the efficacy of a preventive intervention with glutamine. The study was approved by the Subcommittees on Health Ethics and Health Research at the University Hospital Virgen del Rocío of Seville.

The inclusion criteria were: HNC squamous cell carcinoma patients, without mucositis and no other prophylactic measures, and older than 18 years. All included patients received radiation therapy with curative intent, 70 Gy by 2 Gy/day, five fractions per week. The different therapeutic regimens were: radiotherapy, radiotherapy plus cisplatin 100 mg/m² on days 1, 22 and 43 of irradiation, radiotherapy plus cetuximab 400 mg/m² in the week prior to radiotherapy, followed by 250 mg/m² weekly during irradiation, induction chemotherapy with cisplatin 100 mg/m², docetaxel 75 mg/m² and 5-fluorouracil 1,000 mg/m² for three cycles every 21 days, followed by chemoradiotherapy.

All patients were referred prior to initiation of any therapeutic scheme to the Nutrition Service for initial assessment and follow-up. Depending on the nutritional status, nutritional support was indicated as needed. Glutamine was given orally at a dose of 10 g every eight hours.

During the follow-up, patients were examined by different specialists in Radiation Oncology to avoid the possible bias of the coordinator of the study. All clinicians used the RTOG/EORTC scales to rate the degree of mucositis and/or odynophagia (19). All patients were examined once a week and, when requested, assessed for symptoms of mucositis and/or odynophagia and supportive treatment was prescribed if necessary.

SAMPLE SIZE

Sample size was calculated based on the presence of mucositis as the main dependent variable. The incidence of mucositis in patients who do not receive glutamine, secondary to radiotherapy or chemoradiotherapy in HNC, is nearly 90% (2). As indicated in the introduction section, in patients with this condition receiving glutamine, the incidence of mucositis is not well established; however, indirect data from one study (17) showed that the incidence of severe mucositis decreased by 33%. Based on this data, and for the calculation of the sample size, it is assumed that in patients with glutamine the incidence of mucositis can decrease by half, which is 16%. With the above parameters, starting from an unpaired study, and assuming an alpha error of 5% and a statistical power of 90%, it was estimated that it was necessary to compare 131 consecutive patients who had not received glutamine with 131 consecutive patients who received glutamine once it was decided to include glutamine in the supportive nutrition in the hospital (Epi Info version 3.5.1).

STATISTICAL ANALYSIS

The results are presented as frequencies (%) for qualitative variables and means with standard deviation or median with

ranges for quantitative variables. For the univariate analysis, the statistical comparison of the qualitative variables was performed using the Chi-squared test. For the analysis of continuous variables, the Student's t-test or analysis of variance (ANOVA) when comparing more than two variables were used. To assess the factors independently associated with the appearance of mucositis, a logistic regression model type step by step backwards was used, where factors with a $p > 0.05$ were excluded. A $p < 0.05$ was considered as significant. The analysis was performed using the SPSS statistical package (version 14.0, Chicago, IL, USA).

RESULTS

DEMOGRAPHICS AND HABITS

Of the 131 patients who received glutamine, 87% ($n = 114$) were males and 13% ($n = 17$) were females. Regarding the 131 patients who did not receive glutamine, 84% ($n = 110$) were males and 16% ($n = 21$) were females. The age was 60.72 ± 11.51 years and 58.52 ± 11.72 years in those receiving or not receiving glutamine, respectively. In terms of anthropometric data, the heights, weights and body mass index were 166.4 ± 7.5 cm, 72.1 ± 17.1 kg and 25.8 ± 5.4 kg/m² vs 167.4 ± 8.3 cm, 72.5 ± 15 kg and 26.5 ± 4.4 kg/m² in those receiving or not receiving glutamine, respectively. Tobacco smokers and alcoholic drinkers represented 90.8% ($n = 119$) and 58% ($n = 76$) vs 84% ($n = 110$) and 57.3% ($n = 75$) of those who received glutamine vs those who did not receive it.

HEAD-AND-NECK TUMOR CHARACTERISTICS AND TREATMENTS

The locations of neoplasms as a function of whether they received glutamine are detailed in table I. Table II shows the distribution by stages of neoplasia in patients who received and did not receive glutamine. There were no differences in these variables between those patients receiving or not receiving glutamine supplementation.

Table I. Locations of head-and-neck tumors in the groups with and without glutamine

Locations	Glutamine % (n)	No glutamine % (n)
Oral cavity	26.7 (35)	16.8 (22)
Oropharynx	22.9 (30)	26.7 (35)
Supraglottis	25.2 (33)	18.3 (24)
Glottis	10.7 (14)	17.6 (23)
Other locations*	14.5 (19)	20.7 (27)

* Nasopharynx, hypopharynx, paranasal sinuses.

Table II. Tumor stages in the groups with and without glutamine

Stages	Glutamine % (n)	No glutamine % (n)
Stage I	6.1 (8)	12.3 (16)
Stage II	15.3 (20)	8.4 (11)
Stage III	23.7 (31)	21.4 (28)
Stage IVA	50.4 (66)	53.4 (70)
Stage IVB	4.6 (6)	4.6 (6)

Table III indicates the different therapeutic schemes for HNC. In both groups, 100% of patients received radiotherapy, until reaching a dose of 70 Gy, achieving all of them the prescribed radiotherapy dosage. In both groups, glutamine and non-glutamine, the frequency of surgical interventions was equal, 27.5% ($n = 36$); radiotherapy was given with a complementary intention to surgery in these cases. In the other 72.5% ($n = 95$) radiotherapy was indicated with radical intention. As for chemotherapy, it was prescribed in 58.8% ($n = 77$) of patients with glutamine vs 59.5% ($n = 78$) of patients without glutamine. There were no differences in the types of treatment between both groups.

ANALYSIS OF FACTORS ASSOCIATED TO THE INCIDENCE AND SEVERITY OF MUCOSITIS AND ODYNOPHAGIA

Overall, mucositis was present in 50.4% ($n = 66$) of patients of the glutamine group and in 59.5% ($n = 78$) of those who did not receive it ($p = 0.14$). Among patients receiving glutamine, the mean doses were 0.42 g/kg and 0.43 g/kg in those who developed mucositis vs those who did not ($p = 0.55$). Regarding the tumor localization, mucositis incidence was higher in those without glutamine supplementation in the oropharynx disease vs those with glutamine (Table IV). Odynophagia incidence and severity were more common in oropharynx and supraglottis dis-

Table III. Treatments used in the groups with and without glutamine

Treatments	Glutamine % (n)	No glutamine % (n)
Radiotherapy	25.2 (33)	21.4 (28)
Chemoradiotherapy	37.4 (49)	44.3 (58)
Induction chemotherapy followed by chemoradiotherapy	4.6 (6)	5.3 (7)
Surgery followed by radiotherapy	10.7 (14)	18.3 (24)
Surgery followed by chemoradiotherapy	16.8 (22)	9.2 (12)
Radiotherapy plus cetuximab	5.3 (7)	1.5 (2)

Table IV. Mucositis incidence in different tumor localizations regarding the presence or not of glutamine supplementation (univariate analysis)

Locations	Mucositis		p
	Glutamine (%)	No glutamine (%)	
Oral cavity	80	81.8	0.87
Oropharynx	53.3	77.1	0.04
Supraglottis	27.3	43.5	0.21
Glottis	7.1	30.4	0.1

eases in patients without glutamine supplementation vs those with glutamine (Tables V and VI).

In the multivariate analysis to identify the variables associated to the presence of mucositis, age, sex, body mass index, smoking and alcohol drinking habits, tumor localizations, stages, chemotherapy, and glutamine supplementation were included. Two variables were associated to the incidence of mucositis: tumor localization and glutamine supplementation. Regarding tumor localization, the supraglottis (risk ratio [RR] and 95% CI: 0.12 [0.05-0.27]), glottis (RR and 95% CI: 0.05 [0.02-0.15]) or hypopharyngeal (RR and 95% CI: 0.08 [0.02-0.27]) diseases were associated with lower mucositis than the disease in the oral cavity (< 0.001). Patients without glutamine had a mucositis RR of 1.78

Table V. Odynophagia incidence in different tumor localizations regarding the presence or not of glutamine supplementation (univariate analysis)

Locations	Odynophagia		p
	Glutamine (%)	No glutamine (%)	
Oral cavity	42.9	54.5	0.39
Oropharynx	53.3	80	0.02
Supraglottis	63.6	100	0.001
Glottis	71.4	91.3	0.11

Table VI. Odynophagia grades III-IV in different tumor localizations regarding the presence or not of glutamine supplementation (univariate analysis)

Locations	Odynophagia grades III-IV		p
	Glutamine (%)	No glutamine (%)	
Oral cavity	8.6	27.3	0.17
Oropharynx	10	40	0.01
Supraglottis	15.2	60.9	0.0002
Glottis	14.3	43.5	0.1

(95% CI: 1.01-3.16; $p = 0.047$) compared with those receiving glutamine. In terms of severity, grade I-II mucositis had 35.1% ($n = 46$) of patients with glutamine vs 40.5% ($n = 53$) of those without glutamine, and grade III-IV, 15.3% ($n = 20$) vs 19.1% ($n = 25$), respectively ($p = 0.32$). In the multivariate analysis to identify factors associated to the severity of mucositis, no independent variables among those patients with mucositis were found.

Odynophagia was present in 55.7% ($n = 73$) of patients with glutamine and in 77.9% ($n = 102$) of those without it ($p = 0.0001$). Regarding those with glutamine, the mean dose was not different ($p = 0.34$) among patients who did not have odynophagia (0.44 g/kg) vs those who did (0.42 g/kg). In the multivariate analysis, factors independently associated to odynophagia were glutamine supplementation, chemotherapy and tumor localization. Regarding localization, supraglottis (RR and 95% CI: 5.18 [2.21-12.84]; $p = 0.0002$), glottis (RR and 95% CI: 7.53 [2.64-24.28]; $p = 0.003$) and hypopharynx (RR and 95% CI: 4.14 [1.2-17.2]; $p = 0.03$) diseases were associated with greater odynophagia than the disease of the oral cavity. Patients who did not receive glutamine had a RR of having odynophagia of 2.87 (95% CI: 1.62-5.18; $p = 0.0003$). Patients who did not require chemotherapy had lower odynophagia incidence (RR 0.4, 95% CI: 0.22-0.73; $p = 0.003$). As for severity, odynophagia grade I-II had the 43.5% ($n = 57$) of patients with glutamine vs 35.1% ($n = 46$) of those without it, and odynophagia grade III-IV had 12.2% ($n = 16$) of the glutamine group vs 42.7% ($n = 56$) in patients without glutamine ($p < 0.0001$). In the multivariate analysis of factors associated to the severity of odynophagia, only patients with odynophagia were included; the RR for grade III-IV odynophagia was 4.33 (95% CI: 2.24-8.74; $p < 0.0001$) in those who did not receive glutamine vs those with glutamine.

In respect of other clinical features, 6.9% ($n = 9$) of patients receiving glutamine discontinued oncological treatment as a result of mucositis and/or odynophagia vs 19.8% ($n = 26$) of patients who did not receive it ($p = 0.002$). In addition, 77.9% ($n = 102$) of patients with glutamine required analgesia vs 87.8% ($n = 115$) without it ($p = 0.03$). Finally, regarding the need for a nasogastric tube, it was indicated in 3.1% ($n = 4$) of patients with glutamine and in 9.9% ($n = 13$) of patients without glutamine ($p = 0.02$).

DISCUSSION

The present study shows that the supplementation of oral nutrition with glutamine, at a dose of 10 g every eight hours, until reaching a total daily dose of 30 g, reduced the incidence of oral mucositis in patients with chemoradiotherapy because of HNC. None of the other variables included in the multivariate analysis, such as age (less or more of 65 years old), smoking or alcoholic drinking habits, body mass index as an expression of nutrition, TNM classification, chemotherapy and sex were associated with the presence of mucositis during the treatment. Moreover, the present study analyzed odynophagia, since it has an important impact on the quality of life of patients with HNC (20,21) and besides, this clinical feature has not been well analyzed previously (17,18). In the multivariate analysis, the glutamine supplementa-

tion was associated with less odynophagia incidence, such as the absence of chemotherapy; in addition, patients with oral cancer had less odynophagia than those with other tumor localizations. Regarding odynophagia severity, the presence of grades III-IV was significantly decreased in patients receiving glutamine. Patients with oropharynx and supraglottis diseases were those with greater improvement after taking glutamine, in terms of mucositis and odynophagia incidences and odynophagia severity. However, this data should be confirmed by a multivariate analysis, which requires a larger sample size in each tumor location.

With respect to the dose of glutamine that the patients should receive, the present results suggest 10 g every eight hours as adequate, reaching a total daily dose of 30 g. Since there were no differences among the patients taking glutamine, in incidence of mucositis and odynophagia in relation to the mean dose in g/kg of weight, it seems that the response is not dose dependent. Nevertheless, this statement must be taken with caution since it is not based on a multivariate analysis.

Other findings of the present study seem relevant, such as the incidence of treatment interruptions because of mucositis and/or odynophagia and the impact on the requirements of analgesia and nasogastric tube. The incidence of treatment discontinuation was significantly lower among patients taking glutamine. Patients with glutamine required significantly fewer prescriptions of analgesia. Also of great interest, being an expression of mucositis and/or severe odynophagia, was the analysis of the use of nasogastric tube, which was significantly lower in patients with glutamine. Based on the reduced need for analgesia and nasogastric tube in patients with glutamine, we believe that a possible added advantage would be a reduction of other economic costs in the treatment of these patients. This statement would require another type of analysis and must be taken with caution.

A strong point in the present study is that the patients included are representative of the normal population of HNC, in terms of age, risk factors and location (22). In addition, other factors merit being highlighted, because they were present with the same frequencies in both groups of patients. The antineoplastic treatments received by patients with glutamine and without glutamine supplementation showed no differences. Thus, in both groups, the frequency of surgery was the same. In both groups, all patients received 70 Gy, ending all cases with the planned radiation therapy. Regarding the indication of chemotherapy, 58.8% and 59.5% of patients with and without glutamine, respectively, received it.

The present study has some limitations, especially that it is a non-randomized study in which patients were included before and after the glutamine use as an amino acid supplementation in the nutritional support of patients with HNC in our institution. However, the sample size of 262 patients, 131 without and 131 with glutamine, was calculated to have enough statistical power, as previously explained.

CONCLUSIONS

Oral glutamine supplementation prevents the incidence of oral mucositis and the incidence and severity of odynophagia second-

ary to antineoplastic treatment in patients with HNC. In addition, it produces less interruption of treatments, together with a lower requirement of analgesia and nasogastric tube. Therefore, these results suggest that glutamine is deserving of future studies, to confirm the exposed points, by conducting randomized double-blind clinical trials. If these results are confirmed, the use of glutamine should be included in treatment protocols in patients with HNC.

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Trabajo Original

Otros

Alteration of inflammatory adipokines after four months of smoking abstinence in multidisciplinary intervention program

Cambio en las adipocinas inflamatorias tras cuatro meses de abstinencia de fumar en un programa de intervención multimodal

Mayla Cardoso Fernandes Toffolo¹, Arthur da Silva Gomes², Henriqueta Vieira van Keulen², Maira Barros Louro³, Flávia Márcia Castro e Silva⁴, Sheila Cristina Potente Dutra Luquetti⁵, Ana Paula Ferreira⁶ and Aline Silva de Aguiar⁷

¹Postgraduate Program in Brazilian Health. Medical School. Federal University of Juiz de Fora. Juiz de Fora, MG. Brazil. ²Postgraduate Program in Health and Nutrition. Nutrition School. Federal University of Ouro Preto. Ouro Preto, MG. Brazil. ³Postgraduate Program in Health and Nutrition. Federal University of Minas Gerais. Belo Horizonte, MG. Brazil. ⁴Postgraduate Program in Biological Sciences. Federal University of Juiz de Fora. Juiz de Fora, MG. Brazil. ⁵Department of Nutrition. Institute Biological Sciences. Federal University of Juiz de Fora. Juiz de Fora, MG. Brazil. ⁶Department of Nutrition. Institute Biological Sciences. Federal University of Juiz de Fora. Juiz de Fora, MG. Brazil. ⁷Institute Biological Sciences. Federal University of Juiz de Fora. Postgraduate Program in Biological Sciences. Federal University of Juiz de Fora. Juiz de Fora, MG. Brazil.

Abstract

Background: many endocrine-metabolic changes are involved in smoking.

Objectives: to evaluate serum concentrations of inflammatory adipokines in smokers at baseline and after four months of treatment for smoking cessation.

Methods: the serum concentrations of inflammatory cytokines were evaluated in smokers and abstinent. Nutritional assessment was based on measurements of body weight, height, and waist circumference (WC), to calculate body mass index (BMI), body adiposity index (BAI) and waist-to-height ratio (WHtR). Biochemical parameters were analyzed: total cholesterol, LDL-c, HDL-c, triglycerides, glucose, cortisol and insulin. The serum levels of leptin, adiponectin and ghrelin were determined by enzyme-linked immunosorbent assay (ELISA). The leptin/adiponectin ratio (L/A) was calculated.

Results: a total of 29 subjects were included in this study (22 women and seven men). The mean age of participants was 50.7 ± 10.47 years. The medium values of WHtR and BAI were above of the proposed cutoff point, indicating abdominal obesity. The biochemical parameters did not present statistically significant differences when comparing the initial and final values. At the end of treatment, the abstinent had higher levels of adiponectin when compared to those who remained smoker ($p = 0.024$). There was an increase in leptin levels and L/A, and a reduction in adiponectin levels after the treatment in abstinent and smokers ($p < 0.05$).

Conclusion: this study has demonstrated that smoking cessation improves adiponectin levels when compared with smokers. Leptin and L/A levels increased throughout the treatment in both groups. The increased values of leptin and L/A in abstinent participants may indicate risk of metabolic events associated with smoking history that should be investigated.

Key words:

Ghrelin. Adiponectin. Leptin. Smokers. Abstinent. Smoking cessation.

Resumen

Introducción: en el tabaquismo están involucrados un gran número de cambios endocrino-metabólicos.

Objetivos: evaluar las concentraciones séricas de adipocinas inflamatorias en fumadores al inicio y después de cuatro meses de tratamiento para dejar de fumar.

Métodos: se evaluaron las concentraciones séricas de citocinas inflamatorias en fumadores y no fumadores. La evaluación nutricional se basó en las mediciones del peso corporal y la altura, para calcular el índice de masa corporal (IMC), la circunferencia de la cintura (CC), el índice de adiposidad corporal (IAC) y la relación cintura/estatura (RCE). Se analizaron los parámetros bioquímicos: colesterol total, LDL-c, HDL-c, triglicéridos, glucosa, cortisol e insulina. Los niveles séricos de leptina, adiponectina y grelina se determinaron mediante ensayo de inmunoadsorción enzimática (ELISA). Se calculó la relación leptina/adiponectina (L/A).

Resultados: se incluyeron un total de 29 personas (22 mujeres y siete hombres). La edad media de los participantes fue de $50,7 \pm 10,47$ años. Los valores medios de CC e IAC se mostraron por encima del punto de corte propuesto, indicando obesidad abdominal. Los parámetros bioquímicos no presentaron diferencias estadísticamente significativas al comparar los valores iniciales y finales. Al final del tratamiento, los abstinentes tenían niveles más altos de adiponectina cuando se comparaban con los de aquellos que seguían fumando ($p = 0,024$). Hubo un aumento en los niveles de leptina y L/A y reducción de los niveles de adiponectina después del tratamiento en abstinentes y fumadores ($p < 0,05$).

Conclusiones: este estudio ha demostrado que el abandono del hábito de fumar mejora los niveles de adiponectina en comparación con los fumadores. Los niveles de leptina y L/A aumentaron a lo largo del tratamiento en ambos grupos. Los valores aumentados de leptina y L/A en abstinentes pueden indicar riesgo de eventos metabólicos asociados al historial de tabaquismo que deben ser investigados.

Palabras clave:

Grelina. Adiponectina. Leptina. Fumadores. Abstinente. Dejar de fumar.

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Correspondence:

Aline Silva de Aguiar. Institute Biological Sciences. Department of Nutrition. Federal University of Juiz de Fora (UFJF). Cidade Universitária, São Pedro. 36036-900 Juiz de Fora, MG. Brazil
e-mail: aline.aguiar@ufjf.edu.br

INTRODUCTION

Smoking, determined by nicotine dependence, is now considered by the World Health Organization (WHO) as the leading cause of preventable death in the world (1). Furthermore, it is a triggering factor for many diseases, among which some stand out, such as cardiovascular condition, cancer and obstructive pulmonary chronic disease (2).

Adipose tissues produce adiponectin and leptin to regulate eating behavior and also generate pro and anti-inflammatory behaviors of adipokines to modulate inflammatory responses (3). While adiponectin protects, the leptin accelerates the development of atherosclerosis. Therefore, it is suggested that these adipokines establish a close correlation between smoking and the appearance of cardiovascular and metabolic diseases (4).

The interaction of leptin with its receptor in the hypothalamus alters the release signals that affect appetite (5). Its action on the central nervous system inhibits food intake, increases energy expenditure and regulates the metabolism of glucose, fats and neuroendocrine function (6). In addition, leptin is involved in the recruitment process, activation and survival of inflammatory cells (7), and it has been considered as a potential mediator of weight gain after smoking cessation (8). However, studies on the association of smoking and leptin are still controversial, with reduced and increased reports, or no effect on it (9-11).

Adiponectin is associated with insulin sensitivity, a marker of metabolic syndrome (12). It acts in inhibiting proliferation of vascular smooth muscle cells, suppresses the conversion of macrophages into foam cells (13), and also acts in the reduction of mediators related to pro-inflammatory effects such as C-reactive protein, interleukin-6 and tumor necrosis factor (14). Studies conducted with smokers have pointed to a reduction in adiponectin levels in smokers (15-16).

Ghrelin is a peptide produced in the stomach with properties of energy balance and induction of appetite. It is known that fasting stimulates its activity mediated by hypothalamic neuropeptide Y and agouti-related protein system (17). According to previous studies, plasma ghrelin levels do not correlate with smoking years, but with the current smoking, indicating acute effects of smoking in the ghrelin concentrations (17,18).

Nicotine acutely increases energy expenditure and may reduce appetite, which probably explains lower body weight among smokers (19).

The weight gain evidenced in smoking cessation can be attributed to the reduction of the thermogenic effect caused by tobacco and to an increased food intake. These senses may be affected by continued cigarette use, favoring inadequate food choices, such as high caloric density and low nutritional quality foods, exacerbating weight gain (20). Attention should be given to excessive weight gain and the return of smoking, in order not to increase the risk of morbidity and mortality by endocrine-metabolic, cardiovascular, pulmonary, circulatory, gastrointestinal diseases and cancers (19,21).

Considering the many endocrine-metabolic changes involved in smoking which are not fully understood, the small number of studies that assessed leptin, ghrelin and adiponectin simulta-

neously in smoking cessation (22) and the impact of smoking mortality in the public health, it is important to know the anthropometric, biochemical and endocrine profiles of smokers in withdrawal process.

It is believed that smoking cessation may lead to reduced serum levels of inflammatory parameters such as leptin, LDL cholesterol and triglycerides, and improve the level of anti-inflammatory parameters such as adiponectin and HDL cholesterol. Therefore, the aim of this study was to evaluate serum concentrations of pro- and anti-inflammatory substances in smokers at baseline and after four months of treatment for smoking cessation.

METHODS

DELINEATION AND STUDY POPULATION

The present study was an intervention study conducted with a non-probabilistic sample, consisting of evaluated smokers attended at the Interdisciplinary Center for Research and Intervention on Tobacco, University Hospital, Federal University of Juiz de Fora (CIPIT/HU-UFJF), for the treatment in intensive approach in the period from September 2011 to February 2014.

The work by CIPIT included prevention activities, treatment and tobacco control, with a multidisciplinary approach based on the guidelines of the National Tobacco Control Program (NTCP) of the National Cancer Institute. Smokers received intensive smoking cessation counseling in structured weekly sessions for one month, followed by two biweekly and then monthly sessions for 12 months. For the maintenance of abstinence, the study participants used the Nicotine Replacement Therapy (NRT) as therapeutic scheme proposed by the doctor clinic.

INCLUSION AND EXCLUSION CRITERIA

Participants were men and women over 18 years of age who were diagnosed by physician-administered CIPIT HU/UFJF with smoking by the International Classification of Diseases, 10th edition, used tobacco as a principal drug and accepted to participate in the research by signature of the Free and Clarified Consent Term. The following patients were excluded from the study: patients under 18 years; pregnant women; patients with kidney disease, acquired immunodeficiency syndrome, liver disease, chronic obstructive pulmonary disease; and those who refused to participate. The proposal was approved by the Ethics in Research Committee of the Federal University of Juiz de Fora (CAAE: 0067.0.180.420-11/no. 081/2011). The study protocol conforms to the ethical guidelines of the National Health Council no. 466/2012.

SMOKING HISTORY

We accessed the smoking history of abstinent and smokers, including the amount of cigarettes smoked per day and the duration

of smoking. The smoking index was available (number of cigarettes smoked per day $\times$ number of years that the smoker remains smoking) (23). The scores of the Fagerstrom test of nicotine dependence (FTND) to identify the behavior of smokers were also evaluated. The sum of the values indicates one score of the degree of dependence: low (0-4 points), moderate (5 points) or high (5-10 points) (24).

VARIABLES ANTHROPOMETRIC ANALYZED

Anthropometric assessment was performed at baseline, after one month, and at the end of the treatment (four months). Nutritional assessment was based on measurements of body weight and height to calculate body mass index (BMI). To measure body weight, Welmy® was used, with a capacity of 150 kg and precision of 0.1 kg, with the participants standing barefoot and wearing light clothing. The classification was performed as proposed by the World Health Organization (25). To measure the height, the portable anthropometric Alturaexata® was used.

Waist circumferences (WC) were measured in the mid-point between the lower end of the rib cage and the top of the iliac crest in a standing position (25).

The body adiposity index (BAI) was determined by measurements of hip circumference (HC) and height to access the body fat: $BAI = (HC [cm]/height [m]) \sqrt{height [m]} - 18$. The cut-off points used were 32 for women and 27 for men (26).

Waist-to-height ratio (WHtR) was determined by the ratio of $(WC [cm]/height [cm])$ and the cut-off point adopted for discrimination of central obesity and cardiovascular risk was ≥ 0.5 for both sexes (27).

The HOMA index, described by Matthews et al. (28), was evaluated by the equation $HOMA-IR = \text{fasting insulin (mU/l)} \times \text{fasting blood glucose (mmol/l)} / 22.5$.

BIOCHEMICAL ANALYSIS

Blood samples were collected after eight-hour fasting and centrifuged within 30 to 45 minutes of collection and stored at -80°C until analysis. Laboratory tests were requested at the beginning and after four months of treatment by the CIPIT-HU/UFJF doctor and performed in the Clinical Analysis Laboratory at HU/UFJF. The cut-off points for the biochemical variables analyzed were: total cholesterol (140-200 mg/dl), LDL-c (100-129 mg/dl), HDL-c (40-60 mg/dl), triglycerides (65-150 mg/dl), glucose (70-99 mg/dl), cortisol (5-23 mcg/dl) and insulin (1.9-23 mg/dl).

ANALYSIS OF ADIPOKINES AND GHRELIN

The serum levels of leptin, adiponectin and ghrelin was determined by ELISA. The kits for measurement of adiponectin, leptin and ghrelin were produced by Millipore®, USA. The sensitivity of detection of leptin were 0.78-100 ng/ml, 1.5-100 µg/ml for adiponectin and 50-5,000 pg/ml for ghrelin.

STATISTICAL ANALYSIS

For sample characterization, descriptive tables with measures of central tendency and dispersion of variables were used.

The Kolmogorov-Smirnov test was used for the assessment of the normality of data. Wilcoxon paired tests were used for the initial variables and after four months of treatment. Spearman's correlations were used to assess the association between anthropometric and biochemical variables, and serum levels of adipokines and ghrelin. The U-Man Whitney test was used to compare the variables between smokers and abstainers. Linear regression was used to adjust the concentration of leptin by BMI and WC. The values of ghrelin and adiponectin did not need to be adjusted because they did not present statistical significance in the linear regression, only leptin. The significance of the model was evaluated by the F test of analysis of variance and the quality of it by the adjusted determination coefficient (adjusted R²). The residues were evaluated according to the suppositions of normality, zero mean, constant variance and independence, and all the assumptions were followed. The L/A ratio was calculated (29).

The data were processed and analyzed using SPSS 23.0 software and, for the purpose of interpretation, the limit type I error was up to 5% ($p < 0.05$).

RESULTS

After four months of treatment, among the 86 participants in the study, 29 completed the treatment for smoking cessation, including 22 women and seven men. Of those, 22 were abstinent and seven had some cigarette consumption. The mean age of participants was 50.7 ± 10.47 years. These 29 previous smokers have had a long duration of smoking (34.57 ± 12.21 years) and had smoked almost one pack/day (19.3 ± 7.98 cigarettes/day). The smoke index was 666.84 ± 396.37 (cigarettes/day)/year. The nicotine addiction was high for most of the group (40%), as confirmed by high mean of FTND score (5.20 ± 2.12). The variables did not have statistically significant differences when the values for the abstinent and smokers were compared (smoking duration, $p = 0.85$; cigarettes/day, $p = 0.08$; smoke index, $p = 0.23$; FTND score, $p = 0.58$).

When comparing smokers and abstinent, in those who completed treatment, they had similar values for all anthropometric (Table I) and biochemical (Table II) parameters evaluated at the beginning and end of the treatment. For BMI, both abstinent and smokers had overweight classification as average values. The BAI indicated excess of body adiposity for 100% of the patients, at the beginning and at the end of the treatment. WHtR was high in both groups at the beginning and end of treatment. However, the abstainers showed a reduction in mean values and median of WHtR (Table I).

The variation of anthropometric variables, such as weight, BMI, WC, BAI and WHtR, at the beginning and end of treatment were similar between smokers and abstinent ($p > 0.05$). However, the

Table I. Comparison of the mean values of anthropometric parameters at the beginning and after four months of treatment for smoking cessation, according to smoking status

Variables	Smoking			Abstinent		
	n	Mean $\pm$ SD	Median (minimum-maximum)	n	Mean $\pm$ SD	Median (minimum-maximum)
BAI initial	7	66.76 $\pm$ 15.63 ^{Aa}	65.27 (49.61-94.45)	21	62.78 $\pm$ 8.56 ^{Aa}	61.57 (48.30-78.39)
BAI final	7	65.15 $\pm$ 11.89 ^{Aa}	67.29 (48.87-80.47)	21	63.11 $\pm$ 8.69 ^{Aa}	64.28 (49.52-77.77)
Weight initial (kg)	7	71.07 $\pm$ 15.00 ^{Aa}	72.60 (49.50-9.60)	21	70.84 $\pm$ 15.10 ^{Aa}	66.45 (41.60-95.90)
Weight final (kg)	7	72.30 $\pm$ 18.27 ^{Aa}	74.60 (41.60-4.40)	21	72.70 $\pm$ 15.19 ^{Ab}	70.60 (43.00-96.75)
BMI initial (kg/m ²)	7	29.13 $\pm$ 5.57 ^{Aa}	29.97 (22.66-7.29)	21	27.82 $\pm$ 5.67 ^{Ab}	26.64 (18.49-38.14)
BMI final (kg/m ²)	7	29.61 $\pm$ 6.97 ^{Aa}	30.50 (18.73-9.29)	21	28.31 $\pm$ 5.37 ^{Ab}	28.29 (19.11-37.95)
WC initial (cm)	7	88.04 $\pm$ 13.15 ^{Aa}	88.50 (63.50-102.00)	21	87.48 $\pm$ 13.22 ^{Aa}	88.05 (65.5-109.00)
WC final (cm)	7	89.38 $\pm$ 12.62 ^{Aa}	90.60 (65.00-103.00)	21	88.81 $\pm$ 13.05 ^{Ab}	89 (68.00-111.00)
WHR initial	7	0.56 $\pm$ 0.09 ^{Aa}	0.56 (0.42-0.66)	21	0.56 $\pm$ 0.08 ^{Aa}	0.55 (0.41-0.75)
WHR final	7	0.57 $\pm$ 0.07 ^{Aa}	0.58 (0.44-0.66)	21	0.55 $\pm$ 0.08 ^{Ab}	0.55 (0.42-0.74)

Note: ^{A,B}different capital letters on the same line and ^{a,b}different lowercase letters in the same column for each type of variable indicate a statistically significant difference, adopting $p < 0.05$.

BAI: Body adiposity Index; BMI: body Mass Index; WC: waist circumference; WHtR: ratio waist/height

Table II. Comparison of the mean values, median, minimum and maximum of biochemical parameters at the beginning and after four months of treatment for smoking cessation, according to smoking status

Variables	Smoking			Abstinent		
	n	Mean $\pm$ SD	Median (minimum-maximum)	n	Mean $\pm$ SD	Median (minimum-maximum)
Cortisol initial (mcg/dl)	6	14.72 $\pm$ 9.87 ^{Aa}	11.90 (7.30-3.60)	21	10.72 $\pm$ 4.83 ^{Aa}	8.6 (2.0-21.80)
Cortisol final (mcg/dl)	6	10.45 $\pm$ 5.22 ^{Aa}	7.40 (6.00-8.70)	20	10.19 $\pm$ 4.85 ^{Aa}	9.90 (5.20-6.00)
Glycemia initial (md/dl)	5	93.00 $\pm$ 46.54 ^{Aa}	104 (14-135)	20	98.41 $\pm$ 18.54 ^{Aa}	94 (83.00-72.00)
Glycemia final (md/dl)	5	135.42 $\pm$ 91.12 ^{Aa}	105 (81-340)	20	101.50 $\pm$ 30.85 ^{Aa}	93.50 (76.00-23.00)
Insulin initial (mclU/ml)	6	12.73 $\pm$ 9.93 ^{Aa}	9.15 (3.8-30)	20	9.09 $\pm$ 4.91 ^{Aa}	7.5 (5.1-21.70)
Insulin final (mclU/ml)	6	11.28 $\pm$ 9.39 ^{Aa}	7.75 (3-23)	21	10.86 $\pm$ 6.65 ^{Aa}	9.40 (3.8-29.10)
Cholesterol (mg/dl)	6	219 $\pm$ 37.16 ^{Aa}	205 (181-270)	22	210.68 $\pm$ 40.16 ^{Aa}	208 (148-289)
Cholesterol final (mg/dl)	7	201 $\pm$ 96.57 ^{Aa}	252 (156-269)	20	208.85 $\pm$ 34.82 ^{Aa}	201 (156-269)
LDL initial (mg/dl)	5	152 $\pm$ 40.19 ^{Aa}	150 (109-207)	14	135.42 $\pm$ 34.73 ^a	208 (148-289)
LDL final (mg/dl)	4	129 $\pm$ 52.32 ^{Aa}	110.5 (89-207)	13	129.61 $\pm$ 32.42 ^{Aa}	201 (156-269)
HDL initial (mg/dl)	5	40.6 $\pm$ 9.65 ^{Aa}	38 (31-56)	15	43.73 $\pm$ 9.14 ^{Aa}	42 (27-63)
HDL final (mg/dl)	4	41.5 $\pm$ 10.91 ^{Aa}	42.5 (28-53)	13	45.46 $\pm$ 7.27 ^{Aa}	45 (33-62)
Triglycerides	6	152.16 $\pm$ 55.79 ^{Aa}	136 (88-236)	22	162.77 $\pm$ 95.26 ^{Aa}	141.5 (38-413)
Triglycerides final (mg/dl)	7	166.57 $\pm$ 55.79 ^{Aa}	146 (114-231)	20	158.55 $\pm$ 80.56 ^{Aa}	131.5 (55-324)
HOMA index initial	7	3.84 $\pm$ 3.92 ^{Aa}	2.20 (0.34-10.00)	22	2.29 $\pm$ 1.48 ^{Aa}	1.57 (1.07-5.89)
HOMA index final	7	3.43 $\pm$ 2.59 ^{Aa}	3.09 (0.60-6.86)	22	2.86 $\pm$ 2.12 ^{Aa}	2.14 (0.82-8.77)

Note: ^{A,B}different capital letters on the same line and ^{a,b}different lowercase letters in the same column for each type of variable indicate a statistically significant difference, adopting $p < 0.05$.

abstinent showed weight gain and abdominal fat accumulation in the period of four months, with increased weight $p < 0.001$, BMI $p = 0.006$, and WC $p = 0.017$ (Table I).

Comparing the initial and final values of biochemical parameters and insulin resistance, no statistically significant differences ($p > 0.05$) were found (Table II).

Table III. Comparison of the mean values, median, minimum and maximum of cytokines at the beginning and after four months of treatment for smoking cessation, according to smoking status

Variables	Smoking			Abstinent		
	n	Mean $\pm$ SD	Median (minimum-maximum)	n	Mean $\pm$ SD	Median (minimum-maximum)
Leptin BMI initial*	7	14.07 $\pm$ 6.68 ^{Aa}	15.07 (5.61-3.84)	22	12.50 $\pm$ 6.75 ^{Aa}	11.09 (1.33-4.85)
Leptin BMI final*	7	14.93 $\pm$ 7.87 ^{Aa}	15.93 (2.65-5.86)	21	13.46 $\pm$ 6.07 ^{bA}	13.43 (3.08-1.29)
Leptin WC initial†	7	12.93 $\pm$ 5.24 ^{Aa}	13.11 (3.06-8.50)	22	12.82 $\pm$ 5.27 ^{Aa}	12.93 (3.93-1.29)
Leptin WC final†	7	16.27 $\pm$ 6.46 ^{bA}	14.65 (7.82-5.24)	21	16.35 $\pm$ 5.21 ^{bA}	16.28 (7.09-4.09)
Adiponectin initial (μ g/ml)	6	10.59 $\pm$ 2.83 ^{Aa}	10.12 (7.34-4.14)	21	16.02 $\pm$ 10.33 ^{Aa}	13.70 (4.26-6.20)
Adiponectin final (μ g/ml)	7	6.68 $\pm$ 3.45 ^{bA}	5.66 (3.19-3.71)	19	11.57 $\pm$ 4.32 ^{bB}	11.57 (4.09-8.98)
Leptin/adiponectin initial	6	1.37 $\pm$ 1.07 ^{Aa}	1.64 (0.00-2.41)	21	1.06 $\pm$ 1.09 ^{Aa}	0.69 (0.06-4.60)
Leptin/adiponectin final	7	2.32 $\pm$ 1.69 ^{Ab}	2.93 (0.15-4.56)	19	1.40 $\pm$ 1.41 ^{Ab}	1.31 (0.04-6.00)
Ghrelin initial (ng/ml)	7	27.07 $\pm$ 26.42 ^{Aa}	21.23 (0.87-71.23)	17	12.51 $\pm$ 19.02 ^{Aa}	4.37 (0.88-64.17)
Ghrelin final (ng/ml)	6	15.89 $\pm$ 12.03 ^{Aa}	14.98 (2.33-34.5)	17	11.71 $\pm$ 17.96 ^{Aa}	5.25 (0.74-71.23)

*Leptin adjusted by BMI. †Leptin adjusted by WC. Note: ^{Aa} different capital letters on the same line and ^{ab} different lowercase letters in the same column for each type of variable indicate a statistically significant difference, adopting $p < 0.05$.

At the beginning of the treatment, all smokers had similar levels of adiponectin. At the end, the abstinent had higher levels of adiponectin compared with those who remained smokers ($p = 0.024$) (Table III). Regarding adipokines, there was an increase in the average of leptin/WC (abstinent $p < 0.001$; smokers $p = 0.028$) and a reduction in adiponectin levels after treatment, in both, abstinent ($p = 0.048$) and smokers ($p = 0.043$). The value of leptin/BMI initial was increased only among abstinent $p = 0.003$. The L/A index increased during the treatment for smokers ($p = 0.028$) and abstinent ($p = 0.044$) (Table III).

Table IV shows the correlation between the initial and final levels of leptin adjusted for BMI and WC, leptin/adiponectin ratio, ghrelin and adiponectin with the initial and final anthropometric variables, according to the status of abstinent or smokers. Among those who continued smoking, there was a positive association between the initial leptin/BMI with WC, WHtR and BAI; initial leptin/WC with BMI, WHtR and BAI. There was a positive association between the final leptin/BMI with weight, WC and BAI; final leptin/WC with BMI, weight WHtR and BAI; and final L/A with BMI, weight and BAI.

Among the abstinent, there was a positive association between initial leptin/BMI with weight, WC, WHtR, BAI and HOMA-IR; initial leptin/WC with BMI, WHtR, weight, BAI and HOMA-IR; and initial L/A with BMI, WHtR and HOMA-IR. The variables with a significant correlation after four months among abstinent were leptin/BMI with weight, WC, WHtR, BAI and HOMA-IR; leptin/WC with BMI, weight, WHtR, BAI and HOMA-IR; and final L/A with BAI (Table IV). The ghrelin did not correlate with any of the analyzed variables (data not shown in table IV).

DISCUSSION

The results of this study showed that smokers who completed the treatment at the Interdisciplinary Center presented a high

degree of dependence, cigarette consumption and long duration of smoking. These factors may make treatment difficult and precipitate relapse; however, the benefits of smoking cessation should be used as support: the risk of cardiovascular diseases is reduced by half when compared with those who continued smoking. Between five and 15 years post-smoking, the risk of stroke and coronary heart disease is similar to that of those who never smoked (30).

Smoking cessation has been shown as an improvement factor in adiponectin profile with different time periods in various studies (4, 9, 12 and 24 weeks) (4,22,32,33).

We could not find a significant difference in our study, most likely because of the small sample size. Nevertheless the abstinent group showed higher serum levels after four months of treatment. Some authors have identified a reduction in adiponectin levels in smokers (18). Nicotine, the main active component of cigarettes, may decrease adiponectin in part by altering the ATP-dependent potassium channels in adipocytes (31).

The increase in body weight among the abstinent may have attenuated the response of adiponectin at the end of the treatment, as it has been demonstrated that body weight reduction increases adiponectin levels in plasma. It has been suggested that adiponectin may be under rigorous regulation of feedback of body fat (34). In assessing abstinent participants who gained and maintained body weight at the end of the treatment (35), reduced adiponectin serum levels were found in the group gaining weight. Among abstinent whose body weight remained stable, the same was not observed. In this study, there was no significant correlation between adiponectin and final weight, BMI, BAI and WC in abstinent.

The sensitizing effect of insulin occurs through binding to the adipor1 and adipor2 receptors, leading to activation of AMP-activated protein kinase (AMPK), protein phosphorylation receptor- α activator (PPAR- α) and, supposedly, other signaling pathways still

Table IV. Association coefficient between baseline leptin levels adjusted for BMI and WC, leptin/adiponectin ratio (L/A) and adiponectin with the initial and final anthropometric variables, according to smoking status

Variables	Leptin/BMI initial		Leptin/WC initial		L/A initial		Adiponectin initial	
	Smoking	Abstinent	Smoking	Abstinent	Smoking	Abstinent	Smoking	Abstinent
Initial								
BMI	-	-	0.893*	0.895 [‡]	Ns	0.473*	ns	ns
Weight	0.893 [‡]	0.837 [‡]	1.00 [‡]	0.891 [‡]	Ns	ns	ns	ns
WC	0.893 [‡]	0.894 [‡]	-	-	Ns	ns	ns	ns
WHR	0.929 [‡]	0.944 [‡]	0.964 [‡]	0.942 [‡]	Ns	0.546 [‡]	ns	ns
BAI	0.964 [‡]	0.895 [‡]	0.929 [‡]	0.734 [‡]	Ns	ns	ns	ns
HOMA-IR	Ns	0.594 [‡]	ns	0.657 [‡]	Ns	0.583 [‡]	ns	ns
	Leptin/BMI final		Leptin/WC final		L/A final		Adiponectin final	
	Smoking	Abstinent	Smoking	Abstinent	Smoking	Abstinent	Smoking	Abstinent
Final								
BMI	—	—	0.893 [‡]	0.928 [‡]	0.871 [‡]	ns	Ns	Ns
Weight	0.893 [‡]	0.849 [‡]	1.00 [‡]	0.857 [‡]	0.798*	ns	0.786*	Ns
WC	0.714*	0.880 [‡]	—	—	Ns	ns	0.929 [‡]	Ns
WHR	ns	0.911 [‡]	0.786*	0.922 [‡]	Ns	ns	0.893 [‡]	0.913 [‡]
BAI	0.929 [‡]	0.842 [‡]	0.929 [‡]	0.714 [‡]	0.908 [‡]	0.626 [‡]	ns	ns
HOMA-IR	ns	0.663 [‡]	ns	0.717 [‡]	Ns	ns	ns	ns

Ns: not statistically significant; * $p < 0.05$; [‡] $p \leq 0.01$; [‡] $p \leq 0.001$.

unknown. In insulin resistance associated with obesity, the adiponectin receptors and adiponectin are repressed (31). Unexpectedly, in this study, no significant association between adiponectin and HOMA-IR was found for smokers and abstinent at the beginning and the end of the treatment.

Various measures of insulin sensitivity are strongly dependent on the L/A ratio, emphasizing the role of adipocyte dysfunction in the pathogenesis of insulin resistance (36). In this study, the L/A ratio did not have a positive correlation with HOMA-IR in abstinent at the beginning of the treatment. In a different study population, Kappelle et al. (2012) (37) suggest that the leptin/adiponectin ratio is a preferential marker of atherosclerosis susceptibility, and a preferential marker of associated cardiovascular events with adipokines in men. At the end of the treatment, L/A ratio demonstrated a positive correlation with BAI values, reinforcing the role of adipocytes in the control of serum leptin levels.

The increase in L/A levels over the treatment for smokers and abstinent found in this study may suggest a risk of cardiovascular events; however, this relationship should be investigated in the smoking population in order to predict and monitor the risk of associated cardiovascular events to tobacco.

The impact of smoking cessation on serum leptin levels still generates controversial results (9-11). In this study, leptin/WC increased over the treatment for smokers and abstinent. The mechanisms involved in the changes in leptin levels after smoking cessation remain unknown.

Nicotine provides an increase in plasma cortisol concentration and can also promote the increase or decrease in leptin concentration. The results of our preliminary study showed an inverse relationship between leptin concentration and cortisol levels, indicating that higher concentrations of leptin are associated with lower levels of cortisol (16). However, the increase in leptin after treatment has not been accompanied by an increase in cortisol levels, regardless of the smoking status.

Other factors which have not been assessed in this study can directly influence the production of leptin, because the increase in plasma leptin levels occurred even after adjustment for body composition parameters as BMI and WC, as opposed to the findings by Nicklas et al. (38). The increase in body weight and leptin in this study supports the hypothesis that chronic inflammation induced by cigarette metabolites could damage the leptin receptors, thus not interfering in the appetite and reduced weight (39).

Plasma ghrelin levels decreased after smoking cessation, but this change was not significant, as reported by Won et al. (20). The effect of smoking on ghrelin levels appears to be acute (18). The plasma ghrelin levels during treatment did not correlate with any of the body composition parameters.

The weight gain after smoking cessation has been reported in the literature. Studies report that the average weight gain after smoking cessation may be 2.8 kg in women and 3.8 kg in men, able to come to gain 10 kg, in short or long-term (17). Another study showed that, on average, abstinent gained 2.2 kg in two months and continued to gain up to 4.5 kg in 12 months (40).

In this study, the mean weight gain during the four months of treatment was 1.23 kg for smokers and 1.86 kg for abstinent, accompanied by an increase in WC of 1.34 cm for smokers and 1.33 for abstinent. Despite weight gain and WC increase among abstinent patients, there was no significant increase in body fat indicated by BAI. The presence of the Nutrition staff in association with smoking cessation may have influenced the results, supporting volunteers in times of abstinence and anxiety by lack of cigarette, guiding the qualitative food choice. The weight gain in abstinent can be attributed to the influence of smoking in energy metabolism, with reduction of the metabolic rate and the improvement of taste. The perpetuation of some inadequate food choices established during smoking can aggravate weight gain due to energy imbalance, with high caloric density choices and low nutritional value (41). Despite being an intervention study with comparison of anthropometric, biochemical and adiponectin, leptin and ghrelin levels of smokers at the beginning and after four months of treatment for abstinence, it has some limitations. Firstly, the limited sample size due to the abandonment of volunteers throughout the treatment. A total of 159 subjects began treatment, whereas 86 were included in this study, and only 29 subjects remained until the end of the four-month duration treatment. Another limitation is the possible influence of physical activity, medications and genetic predisposition in the results of biochemical tests. In addition, the influence of physical activity on anthropometric results was not evaluated. We have shown that smoking cessation improves adiponectin levels when compared with smokers. The increase of leptin in the period of abstinence, independent of weight gain, still remains as a mechanism which has not been elucidated. The higher leptin/adiponectin rates at the end of the treatment may indicate a risk of cardiovascular events in patients receiving treatment.

The reduction of ghrelin, although not significant, strengthens the role of leptin on its control, since its levels increased throughout the treatment in both groups. Such evidence suggests an association among appetite controlling hormones (ghrelin and leptin) and adiponectin, and energy metabolism, weight change and body composition, which all play a role in body metabolism and fat distribution.

AUTHOR CONTRIBUTIONS

All authors contributed significantly to the work's conception, literature collection and interpretation; and participated in the writing or critical revision of the article in a manner sufficient to establish ownership of the intellectual content.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the National Health Council no. 466/2012 and its later amendments or comparable ethical standards.

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Nutrición Hospitalaria



Revisión

Costes asociados a la desnutrición relacionada con la enfermedad y su tratamiento: revisión de la literatura

Costs associated to disease-related malnutrition and treatment: a literature review

Samara Palma Milla¹, Diego Meneses¹, Marllyn Valero¹, Margarita Calso¹, Natalia García Vázquez², Matías Ruiz Garrido³, Alberto Martín-Vega⁴ y Carmen Gómez-Candela¹

¹Unidad de Nutrición Clínica y Dietética. Hospital Universitario La Paz. IDIPaz. Universidad Autónoma de Madrid. Madrid. ²Servicio de Farmacia, ³Subdirección de Gestión y Servicios Generales y ⁴Control de Gestión. Hospital Universitario La Paz. Madrid

Resumen

Introducción: la desnutrición relacionada con la enfermedad tiene una elevada prevalencia, con consecuencias clínicas potencialmente graves para el paciente y de alto impacto económico para el sistema sanitario.

Objetivos: realizar una revisión de la literatura sobre los costes económicos de la desnutrición asociada a la enfermedad, analizar sus complicaciones y evaluar la utilidad de la nutrición enteral u oral bajo la perspectiva del análisis de costes.

Métodos: se llevó a cabo una revisión de la literatura hasta junio de 2016 sobre los costes económicos de la desnutrición y el análisis de costes del tratamiento nutricional, priorizando las revisiones sistemáticas, los metaanálisis y los ensayos clínicos aleatorizados.

Resultados: se identificaron 31 publicaciones, 15 sobre los costes de la desnutrición relacionada con la enfermedad y 16 de análisis de costes del tratamiento. La desnutrición relacionada con la enfermedad incrementa los costes sanitarios por una mayor estancia hospitalaria, mayor incidencia de complicaciones infecciosas y no infecciosas, mayor necesidad de tratamientos, incremento de los reingresos, estancias más prolongadas en unidades de cuidados intensivos y/o la necesidad de derivación al alta a centros de continuación de cuidados. Las publicaciones evaluadas sobre el tratamiento mediante suplementos nutricionales orales sugieren que los suplementos nutricionales orales son coste-efectivos y coste-útiles tanto en pacientes ambulatorios como en pacientes hospitalizados.

Conclusiones: la desnutrición relacionada con la enfermedad produce un incremento de los costes sanitarios que podría minimizarse, entre otras formas, mediante un diagnóstico y tratamiento precoz de la misma, para lo cual los suplementos nutricionales orales constituyen una herramienta coste-eficaz y coste-útil.

Palabras clave:

Malnutrición.
Análisis de costes.
Soporte nutricional.
Suplementos
nutricionales
orales. Desnutrición
relacionada con la
enfermedad.

Abstract

Introduction: disease-related malnutrition has a high prevalence, with clinical consequences potentially severe for the patient, and of high economic impact for the healthcare system.

Objective: to perform a review of the literature regarding the economic burden of disease-related malnutrition, to assess complications, and to determine the usefulness of enteral or oral nutritional supplementation from a cost analysis perspective.

Methods: a review of the literature up to June 2016 was carried out regarding economic costs of disease-related malnutrition and cost analysis of nutritional treatment, with special focus on retrieval of systematic reviews, meta-analysis, and randomized clinical trials.

Results: a total of 31 publications were selected, 15 on costs of disease-related malnutrition and 16 on costs of treatment. Disease-related malnutrition increases health care costs in relation to a longer hospital stay, higher incidence of infectious and non-infectious complications, greater need of treatment, increase in readmissions, more prolonged stay in the intensive care unit and/or the need of referral to continuing care centers at discharge. Publications regarding treatment with oral nutritional supplements suggest that these oral supplements are cost-effective and cost-beneficial both in ambulatory and hospitalized patients.

Conclusions: disease-related malnutrition causes an increase in health care costs that could be minimized, among other approaches, by an early diagnosis and treatment for which oral nutritional supplements are cost-effective and cost-beneficial.

Key words:

Malnutrition. Health
care costs. Nutritional
status. Dietary
supplements. Disease
related malnutrition.

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Correspondencia:

Samara Palma Milla. Unidad de Nutrición Clínica y Dietética. Hospital Universitario La Paz. Paseo de La Castellana, 261. 28046 Madrid
e-mail: samara.palma@salud.madrid.org

INTRODUCCIÓN

La desnutrición relacionada con la enfermedad (DRE) continúa afectando a un elevado número de pacientes hospitalizados a pesar de su reconocido impacto clínico y económico (1,2). Definir la desnutrición entraña cierta complejidad, de hecho, no existe actualmente una definición universalmente aceptada (3). Las últimas guías de la Asociación Europea de Nutrición Parenteral y Enteral (ESPEN) (4) proponen que la desnutrición sea entendida como el estado que resulta de una disminución de la ingesta de energía y/o nutrientes que se traduce en cambios en la composición corporal (pérdida de la masa libre de grasa) y pérdida de la masa celular corporal que terminan por ocasionar una disminución de la capacidad funcional mental y física así como una peor respuesta frente a la enfermedad (1,3).

En el contexto del paciente enfermo, la desnutrición se conoce como desnutrición relacionada con la enfermedad, señalando a la enfermedad y sus tratamientos como principales factores etiopatogénicos. Existe una influencia mutua entre la enfermedad y la desnutrición, de tal forma que la enfermedad por sí misma condiciona un incremento del riesgo de desarrollar desnutrición y la presencia de desnutrición condiciona una peor evolución clínica de la misma, situación especialmente manifiesta en el paciente hospitalizado.

La enfermedad, ya sea crónica o aguda, constituye la principal causa de desnutrición en los países desarrollados. Entre los principales mecanismos fisiopatológicos cabe destacar la disminución de la ingesta, que *per se* conlleva un incremento del riesgo de desarrollar desnutrición, así como la puesta en marcha de una respuesta inflamatoria con capacidad potencial para instaurar un ambiente metabólico de estrés catabólico con importante repercusión sobre el gasto energético (1). Todo ello empeora la recuperación de la enfermedad y de la cirugía, condiciona mayor morbilidad (aumento de las complicaciones infecciosas y no infecciosas y úlceras por presión), una estancia hospitalaria más larga, mayor tasa de reingresos/institucionalización, mayor mortalidad y mayores costes económicos asociados (2,5-8).

La prevalencia de la DRE varía principalmente en función de los criterios aplicados para el diagnóstico, la enfermedad de base y el entorno analizado (paciente hospitalizado o ambulatorio). De forma global, la desnutrición relacionada con la enfermedad afecta al 25-50% de los pacientes hospitalizados (1,6,8-13). En España, las cifras de prevalencia son similares a las descritas en otros países (6,10,14-16).

La esperanza de vida ha aumentado de forma considerable en los últimos años como resultado, entre otros factores, de una mejoría en la atención sanitaria. De forma prácticamente paralela, los gastos sanitarios han experimentado un incremento que, en la mayoría de los países europeos, supera el propio ritmo de crecimiento económico del país. La desnutrición consume muchos de esos recursos del sistema sanitario. El coste adicional asociado a la malnutrición ha sido estimado en 10,7 millones de dólares anuales en Australia o 7,3 billones de libras en el caso de Reino Unido (17). En Europa, exceptuando Chipre, la mayor parte del gasto sanitario se financia a través de los presupuestos

públicos generales, que, lejos de estabilizarse, se prevé se multiplique en los próximos años como consecuencia, entre otras, del envejecimiento de la población y de la mayor demanda de recursos sanitarios.

Dada la situación económica actual, aquellos países que disfrutan de una Sanidad financiada a partir de los presupuestos generales del Estado se han visto obligados a hacer determinados ajustes en las prestaciones, poniendo de manifiesto el carácter finito de los recursos sanitarios. El análisis económico y su aplicación a la gestión sanitaria se erigen como elemento clave e imprescindible para garantizar la continuidad asistencial, la calidad y las prestaciones sanitarias en un futuro inminente. La economía de la salud, como disciplina, nace con el objetivo de proveernos de las herramientas necesarias para gestionar los recursos sanitarios, por definición escasos y, actualmente, comprometidos con motivo de la crisis económica, de tal forma que los beneficios obtenidos en términos de salud y calidad de vida sean lo más elevados posibles. No se trata, por tanto, de ahorrar recursos, sino de invertirlos mejor, y para ello necesitamos estudios de análisis de costes aplicados a la economía sanitaria.

Básicamente, existen cinco modelos de análisis económicos aplicables en sanidad: estudios de coste-utilidad, coste-eficacia, coste-consecuencia, coste-beneficio y de minimización de costes (17). En el campo de la nutrición clínica, los estudios de análisis de costes son escasos y se han publicado, en su mayoría, en la última década. El modelo de análisis económico más frecuentemente aplicado en el caso de la desnutrición es el de "coste asociado a enfermedad". En este modelo de análisis se cuantifican los costes que se derivan de la desnutrición, que son: los costes directos (hospitalización, fármacos, pruebas complementarias, soporte nutricional), los costes indirectos (derivados de la baja laboral, de la jubilación por enfermedad, del fallecimiento) y los costes psicológicos (asociados al dolor, cambios anímicos, etc., difíciles de traducir a términos económicos) (18).

Los estudios de coste-eficacia comparan los costes asociados a una determinada intervención con una medida de eficacia clínica, por ejemplo, el descenso de la presión arterial sistólica en mmHg para un determinado hipotensor. Ello permite calcular el incremento de la ratio de coste-eficacia, donde los costes adicionales de la intervención se dividen entre los beneficios adicionales tras dicha intervención. Los estudios de coste-utilidad son un subtipo de estudio de coste-eficacia. Comparan los costes asociados a una determinada intervención con una medida de utilidad que generalmente combina los años ganados de vida y la calidad de vida en esos años. La medida de utilidad más comúnmente empleada es "años de vida ajustados por calidad" (*quality-adjusted life-year*, QALY). Algunas instituciones sanitarias han fijado una cuantía por debajo de la cual se estima que la ganancia de un QALY se considera coste-efectiva. En Inglaterra, ese límite se ha cifrado en 20.000 libras (17). Los estudios de minimización de costes se aplican cuando las intervenciones a comparar son idénticas en cuanto a resultados y eficacia y, por tanto, la única diferencia entre ellas es el coste asociado. Los estudios de coste-beneficio comparan en términos puramente económicos los costes de la intervención y los beneficios obtenidos. Los estudios

de coste-consecuencia comparan los costes asociados a una intervención y sus consecuencias, pero sin establecer una ratio entre ellos ni la importancia de la consecuencia.

El objetivo del presente estudio ha sido revisar la literatura existente sobre los costes económicos asociados a la desnutrición relacionada con la enfermedad.

MATERIAL Y MÉTODOS

La revisión de la literatura se llevó a cabo mediante búsqueda bibliográfica en las bases de datos EMBASE, PubMed (MEDLINE), PubMed Health, DARE Database y Cochrane Library de revisiones sistemáticas. En la estrategia de búsqueda en PubMed se utilizaron descriptores MeSH (*medical subject headings*) para facilitar la recuperación de documentos de interés. Se aplicaron los siguientes filtros: sujetos de estudio (humanos, adultos [> 19 años]), tipo de estudio (se dio prioridad a las revisiones sistemáticas, ensayos clínicos aleatorizados y metaanálisis) e idioma de publicación del estudio (inglés o español). No hubo límites respecto a la fecha de publicación, finalizándose la búsqueda en junio de 2016. Los términos descriptores utilizados fueron: “*malnutrition*”, “*costs and cost analysis*”, “*economics*”, “*nutritional support*”, “*dietary supplements*”, “*oral nutritional supplement*” y “*budget impact*”.

Se incluyeron todos los artículos que trataban sobre los costes económicos asociados a la DRE y/o el tratamiento nutricional aplicado. Se excluyeron los artículos referidos a déficits nutricionales concretos, aquellos que tras una lectura exhaustiva no aportaban datos económicos referidos a la desnutrición y/o su tratamiento, los estudios centrados en un grupo determinado de pacientes (por ejemplo, enfermos de VIH, enfermedad renal crónica avanzada en tratamiento con diálisis en cualquiera de sus modalidades, enfermos con ciertas neoplasias, etc.), y también aquellos estudios de diagnóstico de la desnutrición hospitalaria mediante herramientas concretas y/o validadas. En lo que respecta al tipo de soporte nutricional, el objetivo era evaluar, desde una pers-

pectiva económica, los suplementos nutricionales orales y/o las fórmulas de nutrición enteral. No se tuvieron en cuenta aquellos trabajos en los que la intervención nutricional consistió en aportar un determinado nutriente (por ejemplo, vitamina D, ácido fólico, etc.) o una fórmula nutricional enfermedad-específica. Tampoco se incluyeron aquellos trabajos en los que el soporte nutricional indicado fue la nutrición parenteral. Los criterios de inclusión y exclusión de los estudios se detallan en la tabla I.

En aquellos ensayos clínicos aleatorizados se utilizó el sistema de evaluación JADAD para establecer la calidad del estudio, considerándose de calidad pobre aquellos con menos de tres puntos en dicha escala.

RESULTADOS

En total, a través de las distintas búsquedas se identificaron un total de 452 artículos. Las estrategias y los resultados obtenidos fueron los siguientes:

- *Búsqueda 1*: palabras clave “*malnutrition*” AND “*costs, costs analysis*”, con un total de 238 artículos y 33 seleccionados (cociente 33/238). En PubMed se recuperaron 15 estudios, excluyéndose cinco por centrarse en déficits nutricionales concretos y/o suplementos vitamínicos. En PubMed Health y base de datos DARE se identificaron dos estudios de los cuales ninguno fue seleccionado de acuerdo con los criterios de exclusión. En EMBASE/MEDLINE se recuperaron 221 artículos, y se seleccionaron 28.
- *Búsqueda 2*: palabras clave “*dietary supplement*” AND “*costs, costs analysis*”, con un total de 57 artículos y cinco seleccionados (cociente 5/57). En PubMed se recuperaron 31 artículos y se seleccionaron cinco. En PubMed Health se identificaron 23 artículos y en EMBASE/MEDLINE, tres, pero ninguno de ellos fue seleccionado.
- *Búsqueda 3*: palabras clave “*oral nutritional supplements*” AND “*costs, costs analysis*”, con un total de 13 artículos y

Tabla I. Criterios de inclusión y exclusión aplicados durante la evaluación de estudios

Criterios de selección	Criterios de inclusión	Criterios de exclusión
Población	Adultos > 18 años Cualquier estado nutricional Cualquier entorno hospitalario: hospitalizados, institucionalizados, ambulatorios	Estudios en animales Estudios en niños Estudios en embarazadas y/o lactantes Déficits nutricionales concretos Patologías concretas: VIH, ERC, hepatópatas, neoplasias concretas
Intervención	Suplementos nutricionales orales Nutrición enteral	Nutrición parenteral Consejo dietético aislado Fórmulas nutricionales enfermedad-específica Tratamientos de déficits nutricionales específicos
Variables	Costes de la DRE Análisis de costes del tratamiento de la DRE	Validación de herramientas de <i>screening</i> y/o diagnóstico nutricional
Tipo de estudios	Revisiones sistemáticas, metaanálisis, ensayos clínicos aleatorizados, estudios de cohortes	

cinco seleccionados (cociente 5/13). En PubMed se identificaron once artículos y se seleccionaron cinco. En PubMed Health y en EMBASE/MEDLINE se recuperó un artículo de cada una de las bases de datos, pero no se seleccionaron por no cumplir los criterios de inclusión.

- *Búsqueda 4:* palabras clave “*enteral nutrition*” AND “*costs, costs analysis*”, con un total de 35 artículos y uno seleccionado (cociente 35/1). Estos 35 estudios procedían de PubMed (n = 28) y PubMed Health (n = 7) y el único estudio seleccionado se identificó en PubMed. La búsqueda en EMBASE/MEDLINE no dio ningún resultado.
- *Búsqueda 5:* palabras clave “*nutritional support*” AND “*costs, costs analysis*”, con un total de 65 artículos y cuatro seleccionados (cociente 65/4). En PubMed se recuperaron 46 artículos, seleccionándose cuatro. En PubMed Health se recuperaron cinco, de los cuales no se incluyó ninguno. En EMBASE/MEDLINE se identificaron 19 trabajos, aunque ninguno fue seleccionado (la mayoría de ellos centrados en patologías concretas, tales como fractura de cadera, inmunodeficiencia, etc.).
- *Búsqueda 6:* palabras clave “*budget impact*” (no término MeSH) y “*malnutrition*”, con un total de 44 artículos recuperados y uno seleccionado (cociente 44/1). En PubMed no se recuperó ningún artículo y en PubMed Health se identificaron 40, pero no se seleccionó ninguno. En EMBASE/MEDLINE se recuperaron cuatro artículos, de los cuales resultó seleccionado uno.

Una vez recopilados todos los trabajos y eliminados aquellos que habían sido escogidos en más de una estrategia de búsqueda, se seleccionaron un total de 31 artículos incluidos en el estudio. Tras la lectura exhaustiva, algunos tuvieron que ser descartados por no incluir datos completos del análisis económico realizado o por presentar alguno de los criterios de exclusión. Asimismo, en el proceso de lectura se seleccionaron aquellos artículos de costes asociados a la desnutrición y/o sus tratamientos que aparecían como referencia en los artículos incluidos y que cumplían los criterios de inclusión (Fig. 1).

Los artículos evaluados presentan gran heterogeneidad en sus objetivos, metodología y resultados. Para una mejor comprensión de los datos, se clasificaron los artículos en dos grandes categorías: aquellos centrados en los costes de la propia DRE y aquellos centrados en el análisis de costes del tratamiento de la DRE. En las tablas II y III se resumen las principales características de los estudios seleccionados (2,5,16,17,19-46).

COSTES DERIVADOS DE LA DESNUTRICIÓN RELACIONADA CON LA ENFERMEDAD (DRE)

En total se incluyeron 15 estudios, la mayoría publicados en los últimos cinco años, el 20% en los primeros cinco años del siglo XXI y solo uno de los estudios era anterior a dicha fecha (23). En lo que respecta al tipo de estudio, las publicaciones finalmente incluidas fueron las siguientes: comunicaciones a congreso (19), revisiones sistemáticas (20,46), estudios observacionales transversales prospectivos (21-23) y retrospectivos (24), estudios observacionales de

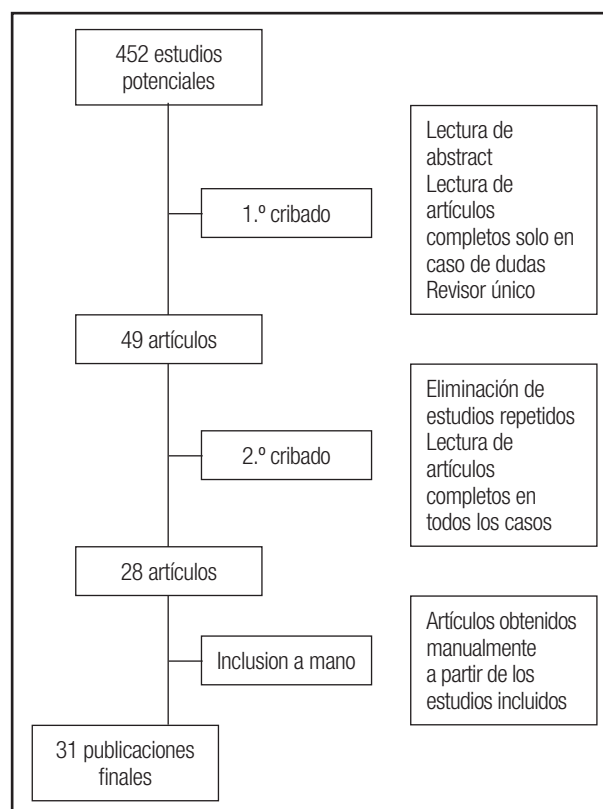


Figura 1.

Diagrama de inclusión de las publicaciones.

cohortes prospectivos (16,25,26,30) y retrospectivos (5), ensayos clínicos aleatorizados prospectivos (28) y análisis de coste-enfermedad (2). El único ensayo clínico aleatorizado que se evaluó en esta selección no reunió criterios JADAD para ser considerado un ensayo clínico de calidad (puntuación JADAD = 2).

En muchas de las publicaciones cuya población de estudio estaba compuesta por pacientes hospitalizados, estos lo estaban a cargo de departamentos médicos y, en algunos casos, se incluyeron también pacientes quirúrgicos (5,16,21,24-26,29,30). Los tamaños de la población de estudio variaron ampliamente entre 143 (la muestra menor) (28) y 1.248.680 (la muestra mayor) (24). La valoración nutricional de los pacientes se llevó a cabo siguiendo herramientas validadas como Nutritional Risk Screening (NRS) 2002 (16,21,22,29), valoración global subjetiva (VGS) (5,22,26), VGS generada por el paciente (VGS-gp) (25), Mini Nutritional Assessment (MNA) (28) u otras estrategias (23,30).

La prevalencia de desnutrición al ingreso hospitalario en los estudios evaluados varía en función de los criterios diagnósticos aplicados, que, en ocasiones, establecían la existencia de riesgo nutricional y, en otras el diagnóstico de desnutrición en cualquiera de sus grados, siendo la cifra mínima del 24,4% (16) y la máxima del 53,6% (22).

De forma global, todos los estudios evaluados constataban el incremento de costes asociados a la desnutrición relacionada con la enfermedad.

Tabla II. Estudios incluidos. Costes de la desnutrición relacionada con la enfermedad

Autor	Tipo	Objetivos	Material y métodos	Resultados	Comentarios
Benković 2012 (19) Croacia	Costes DRE	Establecer los costes de la desnutrición	<i>Análisis de costes directos por enfermedad</i> (hospitalización, fármacos, manejo ambulatorio)	La desnutrición supone un coste adicional de 100 millones de euros en Croacia, < 10% se consume en el soporte nutricional	No se detalla la n ni cómo se estimaron los costes <i>Comunicación a congreso</i>
Rodríguez-Mañas 2014 (20) España	Costes DRE	Revisar la literatura existente	<i>Revisión sistemática</i> Se incluyeron aquellos artículos que abordaban el coste económico en los pacientes malnutridos institucionalizados en España <i>Estudio observacional transversal prospectivo</i> Población: pacientes > 18 años ingresados en dos centros hospitalarios de Portugal Algoritmo de reclutamiento Servicios médicos y quirúrgicos variables: NRS-2002 al ingreso Datos del ingreso Antropometría básica Funcionalidad índice de Katz Los costes económicos se calcularon en función de la estancia hospitalaria y la complejidad diagnóstica al alta La edad, el sexo, la severidad e idiosincrasia de la enfermedad se trataron como variables confusoras	Los costes económicos asociados a la desnutrición casi cuadruplican los de los pacientes normonutridos (5.000,66 euros frente a 1.433,83)	<i>Comunicación a congreso</i>
Amaral 2007 (21) Portugal	Costes DRE	Determinar los costes de la desnutrición en el paciente hospitalizado		n = 469 El 42% de los pacientes analizados estaban en situación de riesgo nutricional Más prevalente en mujeres La codificación de riesgo nutricional al alta fue más frecuente en departamentos médicos que quirúrgicos En los pacientes en riesgo nutricional se estimó un incremento de costes del 20% (4.890,6 € frente a 2.203€) La desnutrición incrementa los costes sanitarios en un 20%	Los pacientes en riesgo nutricional solían ser más mayores, más delgados, más limitados funcionalmente y precisaron ser trasladados más frecuentemente a otros centros Solo se evaluó a los pacientes al ingreso, no al alta
Konturek 2015 (22) Alemania	Costes DRE	Conocer la prevalencia de la desnutrición Conocer la calidad del soporte nutricional a través de la cuantificación de la ingesta Definir los factores de riesgo de desnutrición Determinar la calidad del registro de la malnutrición al alta y el reembolso derivado	<i>Estudio observacional transversal y prospectivo</i> Centro único Departamentos de Medicina Reclutamiento consecutivo prospectivo Variables: NRS-2002 y VGS al ingreso hospitalario La ingesta se recogía diariamente, incluyendo el aporte a través de nutrición artificial Antropometría básica, laboratorio básico con PCR Mini Mental Status, evaluación dental	n = 815 El 53,6% presentaba desnutrición según VGS (35,5% B, 18,3% C), 44,6% según NRS-2002 63,8% de los paciente presentaban enfermedad neoplásica Mayor comorbilidad entre los desnutridos Ingesta media diaria 759 ± 546,8 kcal 39,6% recibieron nutrición parenteral complementaria (556,1 ± 514,7 kcal extras/d), 18,8% recibieron nutrición enteral complementaria (448,3 ± 600 kcal), 6,13% (50 pacientes) recibieron nutrición parenteral y enteral con un aporte calórico de 1.312-1.764 kcal/d Estancia media en el paciente desnutrido: 7,7 días frente a los 4,0 días del paciente normonutrido El 84,5% de los médicos no codificó adecuadamente la desnutrición al alta. Ello generó una pérdida de ingresos de 94.908 euros	La valoración nutricional solo se hizo al ingreso No se midió la ingesta proteica, solo la calórica Destacan la importancia sobre la adecuada codificación de la desnutrición No se recogen datos de mortalidad

(Continúa en la página siguiente)

Tabla II (Cont.). Estudios incluidos. Costes de la desnutrición relacionada con la enfermedad

Autor	Tipo	Objetivos	Material y métodos	Resultados	Comentarios
Chima 1997 (23) EE. UU.	Costes DRE	Determinar la relación entre el estado nutricional, la estancia hospitalaria, destino al alta, reingresos y costes asociados en pacientes ingresados en Medicina interna	<i>Estudio observacional transversal prospectivo</i> Población: pacientes ingresados en servicios médicos Centro único Cribado nutricional al ingreso: existe riesgo si pérdida involuntaria del 10% del peso en el último mes, peso < 75% del peso ideal para la altura y albúmina < 3 g/l El cálculo de costes incluyó: días de estancia, pruebas de laboratorio, medicación, tratamientos y procedimientos, reingresos	n = 173 32% clasificados como pacientes en riesgo La estancia hospitalaria fue mayor para los pacientes en riesgo nutricional (6 frente a 4 d, sign.) La tasa de reingresos fue mayor pero no significativa Mayores costes asociados a la estancia hospitalaria en pacientes en riesgo (6.196 frente a 4.563 \$) El 41% de los pacientes en riesgo fueron dados de alta a domicilio frente al 66% de los pacientes normonutridos El 37% de los pacientes en riesgo precisaron cuidados sanitarios en casa frente al 12% en el caso de los normonutridos	
Corkins 2014 (24) EE. UU.	Costes DRE	Definir la prevalencia del diagnóstico de desnutrición en las altas hospitalarias de los hospitales americanos Comparar las características de los pacientes dados de alta con diagnóstico de desnutrición con respecto a los normonutridos	<i>Estudio observacional transversal retrospectivo</i> Obtención de datos: <i>Healthcare cost and Utilization Project</i> Esta base de datos contiene datos de 1.051 hospitales de 45 estados, lo que supone el 20% de los hospitales en USA Año 2010 Población: pacientes hospitalizados (departamentos médicos y quirúrgicos) en los que se había codificado la desnutrición al alta según CIE 9 Se compararon los diagnósticos y las características demográficas de los pacientes desnutridos con respecto a los malnutridos Se identificó la presencia de comorbilidades y el soporte nutricional en aquellos que lo precisaron	n = 1.248.680 3,2% codificaciones de desnutrición La desnutrición más frecuente fue la desnutrición proteico-calórica no específica (CIE 9: 263,9) Características demográficas (todas significativas): los pacientes diagnosticados de desnutrición fueron mayores, mujeres, blancos no hispanos y con ingresos por debajo del p50, procedentes de otros centros hospitalarios e ingresos de urgencias Los pacientes desnutridos presentaron mayores estancias hospitalarias (12,6 frente a 4,4 d, significativo) El alta a otra dependencia sanitaria fue más frecuente en este grupo (sign.) Los pacientes desnutridos se asociaron a mayores costes sanitarios: 26.944 \$ frente a 9.485 \$ (significativo) Solo el 28,8% de los pacientes desnutridos fueron dados de alta "de forma rutinaria" frente al 72,6% de los normonutridos	Asumen la escasa codificación de la desnutrición (infradiagnosticada) Reafirman la asociación entre la desnutrición y la propensión a la infección (los cinco diagnósticos más frecuentes entre los desnutridos son de etiología infecciosa) Solo el 13,4% de los pacientes con desnutrición recibió soporte nutricional (infratratada)

(Continúa en la página siguiente)

Tabla II (Cont.). Estudios incluidos. Costes de la desnutrición relacionada con la enfermedad

Autor	Tipo	Objetivos	Material y métodos	Resultados	Comentarios
Guerra 2015 (25) Portugal	Costes DRE	Evaluar la habilidad de la fuerza de presión de la mano para predecir los costes asociados a la desnutrición	<i>Estudio observacional de cohortes prospectivo</i> Centro único, dos años de reclutamiento Población: pacientes con ingresos > 24 h, adultos, en cualquier planta de hospitalización (médica o quirúrgica) Variables: estado nutricional (VGS-gp), fuerza de presión de la mano, datos de la hospitalización Los costes se calcularon para cada paciente en función de los códigos GRD al alta	Los pacientes se clasifican en cuatro grupos en función de la fuerza de presión de la mano (cuartiles) Los pacientes con diagnósticos de desnutrición se encontraban en los cuartiles más bajos En lo que respecta a los costes, los pacientes fueron clasificados en función de la desviación de los costes sanitarios Los pacientes en los cuartiles altos de desviación de costes presentaron peor estado nutricional según la VGS-gp Los costes de la hospitalización fueron mayores para los pacientes en los cuartiles bajos, con una mediana intercuartilica de 2.428 \$ Según el modelo de análisis multivariante, tras controlar por posibles variables confusoras, aquellos pacientes en los cuartiles más bajos para la presión de la mano tenían mayor probabilidad de generar más costes asociados a la hospitalización, entre 375 y 458 \$ más n = 637	La desnutrición supuso un incremento del 19,3% de los costes sanitarios en Portugal en el año 2007 En este estudio no se aportan las cifras de prevalencia de la desnutrición y los costes se calculan para un marcador subrogado de la desnutrición (disminución de la fuerza de presión de la mano)
Lim 2012 (26) Singapur	Costes DRE	Evaluar la prevalencia de desnutrición y su impacto en la estancia hospitalaria, reingresos y mortalidad a 3 años en un hospital de Singapur	<i>Estudio de cohortes prospectivo</i> Población: se incluyeron pacientes médicos y quirúrgicos ingresados Centro único Reclutamiento según secuencia Variables: estado nutricional (VSG), estancia y mortalidad hospitalarias, costes de la hospitalización, readmisión en los días 15, 90 y 6 meses Para establecer el efecto de la desnutrición en la estancia hospitalaria y costes comparados con los normonutridos se obtuvieron los GRD	n = 818 4% VSG C, 25% VSG B y 71% VSG A Los pacientes de las plantas de Oncología, Endocrinología y Neumología fueron los que más frecuentemente presentaron desnutrición En los pacientes desnutridos se observó: – Mayor estancia hospitalaria (6,9 frente a 4,6 d) – Mayor tasa de reingresos a los 15 d (incremento del 60%), 90 d y 6 m – Mayor tasa de mortalidad en 3 años – Mayores costes asociados (4.606 frente a 3.707 \$)	No se conoce si hubo o no intervención nutricional
Cangelosi 2014 (46) EE. UU.	Costes DRE	Revisar la literatura con el objetivo de identificar los costes de las principales patologías relacionadas con la desnutrición así como la evaluación de los costes asociados al tratamiento	<i>Revisión sistemática de la literatura</i> Criterios selección: publicaciones en inglés, en los últimos 15 años (1997-2012), ensayos clínicos Humanos > 65 años Exclusión: editoriales, revisiones La estimación de costes se llevó a cabo a través de la cuantificación de enfermedades asociadas a la desnutrición (ITU, UPP, caídas/fracturas, infecciones respiratorias agudas) Los estudios se clasificaron por dominios en función de las variables resultado: funcionales, antropométricas, utilización de servicios sanitarios, enfermedades relacionadas con la desnutrición	Identificación de 85 estudios y 75 protocolos 24 publicaciones para el análisis de costes La desnutrición incrementa los costes sanitarios y la estancia hospitalaria a través del desarrollo de complicaciones asociadas a la desnutrición como las ITU, UPP, caídas/fracturas e infecciones respiratorias La desnutrición ocasiona un incremento medio de costes derivados de: la prescripción de fármacos (2.364 \$), las visitas al médico de Atención Primaria (1.303 \$), las visitas al especialista (2.519 \$)	

(Continúa en la página siguiente)

Tabla II (Cont.). Estudios incluidos. Costes de la desnutrición relacionada con la enfermedad

Autor	Tipo	Objetivos	Material y métodos	Resultados	Comentarios
Holyday 2012 (28) Sídney	Coste DRE	Determinar el impacto de la desnutrición en la estancia hospitalaria y los costes asociados	<i>Ensayo clínico aleatorizado prospectivo</i> Población: pacientes ingresados en departamentos de Geriátria en dos centros en Australia MNA para valoración nutricional Intervención: <i>Malnutrition Care Plan</i> (valoración por nutricionista en las primeras 24 h tras MNA y toma de decisiones terapéuticas oportunas: modificación de texturas prescripción de suplementos, educación nutricional, etc.) En el grupo control se valoraba al paciente cuando el especialista lo solicitaba (práctica habitual) Variables: antropometría, mortalidad, estancia hospitalaria, costes de la hospitalización (GRDs)	n = 143 pacientes 71 en grupo intervención Globalmente, el 22% estaban <i>malnutridos</i>, 61% en riesgo y 17% bien nutridos Del grupo intervención, recibieron soporte nutricional todos los desnutridos, así como el 85% de los pacientes en riesgo Solo el 35% de los desnutridos y el 20% de los pacientes en riesgo recibieron soporte en el grupo control Los pacientes del grupo intervención "consumieron" más tiempo del equipo de nutricionistas (significativo) Las diferencias en las variables resultado solo fueron significativas para los pacientes desnutridos y en los ítems: estancia hospitalaria (10,6 frente a 19,5), así como en las consultas a Urgencias en el primer mes (0,0 frente a 0,21) El coste de la hospitalización en los pacientes desnutridos fue de 720 AUD\$	JADAD 2p Los costes como tal no se exploran, únicamente indican los precios de la cama hospitalaria, el salario medio de los dietistas y el coste medio de los suplementos nutricionales orales Infratratamiento en el grupo control
Freijer 2013 (2) Países Bajos	Costes DRE	Calcular el coste adicional de la DRE en los Países Bajos	Análisis de coste-enfermedad basado en un modelo económico Población: adultos hospitalizados, residencias y ambulatorios en los Países Bajos, año 2011 Variables: - Costes directos de la DRE (costes relacionados con la prevención, diagnóstico, tratamiento, rehabilitación y cuidados) - Sexo, edad, entorno sanitario y enfermedad de base, prevalencia de la desnutrición, peso de la desnutrición como diagnóstico	Los costes adicionales derivados del manejo de pacientes con DRE fueron de 1,9 billones de euros en 2011, lo que equivale al 2,1% del gasto nacional sanitario El coste sanitario fue mayor para las mujeres que para los hombres con DRE (1,1 billones € frente a 777 millones), especialmente, en aquellas institucionalizadas y con enfermedad mental El coste sanitario de la DRE fue 4 veces mayor para los sujetos > 60 años (1,5 billones frente a 403 millones de euros) El 66% de los costes (1,2 billones €) se atribuye al entorno hospitalario, el 24% para los pacientes hospitalizados (453 billones €) y el 10% restante para los pacientes ambulatorios (185 millones €) El uso de suplementos redujo los costes	Solo se tuvieron en cuenta los costes directos de la DRE, no los indirectos

(Continúa en la página siguiente)

Tabla II (Cont.). Estudios incluidos. Costes de la desnutrición relacionada con la enfermedad

Autor	Tipo	Objetivos	Material y métodos	Resultados	Comentarios
León-Sanz 2015 (16) España	Costes de la DRE	Analizar los costes económicos de la desnutrición hospitalaria y los costes asociados con el incremento de la estancia hospitalaria	<i>Estudio de cohortes prospectivo y multicéntrico</i> Población: pacientes adultos en las primeras 48 h de ingreso hospitalario que no ingresaran directamente a UCI, Ginecología, Obstetricia, Dermatología, Oftalmología, Corta Estancia, Cuidados Paliativos, Quemados, Psiquiatría, etc. Hospitales de áreas geográficas distintas y distintos nº de camas NRS-2002 para establecer el riesgo nutricional al ingreso y al alta Variables: complicaciones, costes de la hospitalización, tratamientos, soporte nutricional y tipo	n = 468 pacientes, 114 casos y 354 controles Prevalencia de desnutrición 24,4% al ingreso, 22,6% al alta Casos: mayores, mayor comorbilidad y mayor nº de visitas a Urgencias previamente <i>Solo el 24,6% de los casos recibieron soporte nutricional</i> Los casos recibieron más tratamientos, especialmente antibióticos y fluidos iv Los casos presentaron más complicaciones, aunque estas no fueron estadísticamente significativas La estancia hospitalaria fue significativamente mayor entre los casos (11,5 frente a 8,5 días) La mayor diferencia se observó entre los pacientes que se desnutrieron durante el ingreso Los costes medios de la hospitalización fueron significativamente mayores entre los casos (8.590 frente a 7.085 euros); la diferencia fue mayor para los pacientes que se desnutrieron durante el estudio (13.013 frente a 6.665) Los costes asociados a los tratamientos fueron mayores entre los casos pero no significativos (383,35 frente a 286,98) En total, el coste asociado a la desnutrición hospitalaria en los hospitales participantes en el estudio fue de 1.143.048,270 euros	Infratratamiento de la desnutrición
Correia 2003 (5) Brasil	Costes de la DRE	Correlacionar a través de un modelo de regresión logística el estado nutricional de los pacientes hospitalizados con la incidencia de complicaciones, mortalidad y estancia hospitalaria; los costes hospitalarios también fueron estimados	<i>Estudio de cohortes retrospectivo</i> Los datos provienen de un estudio sobre malnutrición hospitalaria en Brasil Los pacientes habían sido evaluados mediante la VGS en las primeras 72 h del ingreso Variables: - Las complicaciones se clasificaron en infecciosas y no infecciosas - Los costes de los tratamientos se calcularon para aquellos con mayores costes (complicaciones infecciosas)	n = 709 <i>El 26,3% y el 7,9% presentaban la categoría B y C respectivamente de la VGS</i> Las complicaciones fueron significativamente mayores entre los paciente desnutridos y, especialmente, entre los severamente desnutridos La estancia hospitalaria fue más corta en los pacientes normonutridos (10,1 frente a 16,7 días) El análisis de coste mostró que los pacientes desnutridos suponían un mayor coste (228 frente a 138 \$ al día), lo que representa un incremento de los costes del 60,5% Los costes de los fármacos y las pruebas complementarias en aquellos pacientes que presentaron complicaciones infecciosas a nivel respiratorio fueron un 308,9% mayores entre los pacientes desnutridos	

ITU: infección del tracto urinario; UPP: úlcera por presión.

Tabla III. Estudios incluidos. Costes de la desnutrición relacionada con la enfermedad

Autor	Grupo	Objetivos	Material y métodos	Resultados	Comentarios
Schlip 2014 (31) Países Bajos	Estudio de costes sobre el tratamiento nutricional	Evaluar el coste-eficacia de un tratamiento dietético	<i>Ensayo clínico aleatorizado paralelo</i> <i>Análisis de coste eficacia y coste utilidad</i> Población: pacientes > 65 años, reclutamiento en centros de primaria Independientes para ABVD Desnutridos Variables: estado nutricional (SNAQ), calidad de vida tras 6 meses de seguimiento Intervención: valoración por un dietista, cálculo de requerimientos, consejo dietético y soporte nutricional si no cobertura de requerimientos El grupo control recibió los cuidados habituales Análisis de costes: <i>Análisis de coste eficacia y coste utilidad</i> Costes directos: visitas al hospital y Atención Primaria, tratamiento y suplementos Se incluyeron costes sociales (cuidados familiares, taxis, etc.) No incluye costes indirectos (pérdida de productividad) porque se trataba de población en edad de jubilación	n = 146 pacientes, 72 en el grupo intervención 72 intervenciones, 74 controles A los 6 meses, no existían diferencias significativas en peso, ni QALY ni costes totales La intervención no fue más efectiva que la no intervención y tampoco fue coste-útil, ni coste efectiva	DRE: 15-35% No es ciego JADAD 2 Afirman ser los primeros en hacer un estudio de este tipo Relacionan la calidad de vida con la ganancia ponderal
Simmons 2010 (32) EE. UU.	Estudio de costes sobre el tratamiento nutricional	Determinar el coste eficacia de los suplementos nutricionales orales en comparación con la oferta de <i>snacks</i> y la práctica habitual en pacientes institucionalizados Comparar el coste eficacia de dos intervenciones nutricionales: 2 SNO/d, 2 <i>snacks</i> /d frente a los cuidados habituales durante 6 semanas	<i>Estudio piloto de intervención aleatorizado</i> Población: pacientes de residencias con indicación de prescribir suplementos nutricionales Se aleatorizaron en 3 ramas: - Suplementos nutricionales orales 2/d <i>Snacks</i> entre horas 2/d - Práctica habitual Recogida de ingesta a partir de la toma de fotos 6 semanas de seguimiento <i>Análisis coste eficacia</i>, ingesta calórica total e ingesta calórica entre horas Se tuvieron en cuenta los costes de los alimentos/ suplementos ofertados, los minutos de atención por el personal sanitario	n = 63 Basalmente grupos comparables Las dos intervenciones incrementaron la ingesta calórica entre comidas (185 kcal en el grupo de suplementos y 191 en el grupo de los <i>snacks</i>) La ingesta total disminuyó en ambos grupos de intervención, pero solo fue significativa para los suplementos Ninguna de las intervenciones produjo cambios en el peso Análisis coste-eficacia: personal sanitario Los grupos intervención consumieron más tiempo del personal sanitario La intervención de los suplementos resultó algo más costosa para una eficacia similar a la de los <i>snacks</i> Concluyen, a tenor de los resultados, que probablemente los <i>snacks</i> sean mejor opción	No ciego JADAD 1, no describe cómo se aleatorizó a los sujetos Afirman ser el primer estudio de este tipo

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Tabla III (Cont.). Estudios incluidos. Costes de la desnutrición relacionada con la enfermedad

Autor	Grupo	Objetivos	Material y métodos	Resultados	Comentarios
Abizanda 2014 (33) España	Estudio de costes sobre el tratamiento nutricional	Revisar la literatura existente sobre los costes de la desnutrición en pacientes mayores no institucionalizados	Revisión sistemática de la literatura Período: hasta diciembre 2013	Se seleccionaron 9 publicaciones: 4 centradas en los costes asociados a la desnutrición, todos ellos poniendo de relieve la magnitud de los costes adicionales asociados a la desnutrición; 5 centradas en el impacto de los tratamientos nutricionales indicando que, a pesar de la mayor inversión inicial, podrían ser coste efectivas	Comunicación a un congreso No explican criterios de inclusión/exclusión Financiado por Nestlé
Milte 2013 (17) Australia	Estudio de costes sobre el tratamiento nutricional	Revisar los estudios de evaluación económica sobre los suplementos energéticos-proteicos en los pacientes desnutridos o en riesgo Revisar la calidad de la evidencia sobre economía en este campo	<i>Revisión sistemática</i> Estrategia de búsqueda: Seleccionaron artículos que incluyeran evaluación económica sobre el tratamiento de la desnutrición con suplementos nutricionales calórico-proteicos en adultos, hospitalizados, institucionalizados, ambulatorios, 1946-2012 Estudios incluidos: estudios comparativos controlados y no controlados, estudios basados en modelos económicos Se excluyeron los estudios en pacientes críticos, pacientes con cáncer y pacientes con requerimientos altamente específicos También se excluyeron aquellos centrados en nutrientes específicos	16 estudios de una selección inicial de 2.750 – 6 estudios en pacientes malnutridos: 3 de coste-utilidad y 2 de coste-beneficio y 1 de coste-consecuencia. Intervención: SNO ± consejo dietético. Heterogeneidad en los estudios. De forma global, los SNO en los pacientes desnutridos permiten ahorrar costes y mejoran la calidad de vida de los pacientes – 10 estudios en pacientes cuyo estado nutricional no se especificó. Muy heterogéneos; 1 coste utilidad, 4 coste-eficacia. De forma global, la mayoría indican beneficios tanto para el paciente como para el sistema sanitario a un bajo coste relativo Calidad global de estudios baja Concluyen que los SNO son beneficiosos desde una perspectiva económica tanto para el paciente como para el sistema sanitario	La revisión sobre los distintos modelos de análisis económico es muy interesante Proponen el análisis coste-utilidad como el mejor método de evaluación económica en sanidad
Beck 2014 (34) Alemania	Estudio de costes sobre el tratamiento nutricional	Evaluar desde un análisis de coste eficacia una intervención nutricional multidisciplinar en ancianos institucionalizados y con cuidados a domicilio	Ensayo clínico aleatorizado en grupos 11 semanas de intervención Valoración nutricional por el <i>Eating Validation Scheme</i> , puntuación > 2 y aleatorización posterior Intervención: atención por parte de un equipo multidisciplinar (nutricionistas, fisioterapeutas, terapeutas ocupacionales, etc.). El grupo control estaba bajo la supervisión de un coordinador en nutrición Las variables resultado tras la intervención fueron: calidad de vida, capacidad funcional, estado nutricional, caídas, ingresos, necesidad de institucionalización Evolución económica de la intervención multidisciplinar Randomización en 6 <i>clusters</i> : 3 en residencias y 3 en pacientes en cuidados domiciliarios	Aún no tienen resultados publicados como tal ClinicalTrials.gov 2013 NCT01873456	No se aplicó escala JADAD por ser esta publicación un documento preliminar

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Tabla III (Cont.). Estudios incluidos. Costes de la desnutrición relacionada con la enfermedad

Autor	Grupo	Objetivos	Material y métodos	Resultados	Comentarios
Edington 2003 (35) Reino Unido	Estudio de costes sobre el tratamiento nutricional	Determinar si el soporte nutricional tras el alta hospitalaria mejora el estado nutricional, funcional o reduce los costes sanitarios	<i>Ensayo clínico aleatorizado y multicéntrico</i> <i>24 semanas de seguimiento</i> Población: sujetos > 65 años con IMC < 20, IMC entre 20 y 25 y pérdida del 10% del peso en 6 meses o pérdida de > 5% del peso en los 3 meses previos al estudio Intervención: suplementación durante 8 semanas tras el alta 600-1.000 kcal, el paciente elegía el suplemento de entre un grupo de varios Se midieron los costes de las prescripciones, de las visitas a Atención Primaria, enfermera de distrito, ingresos en los 6 meses siguientes al alta <i>Análisis de coste-eficacia</i> Se calculó el uso de las instituciones sanitarias hecho por el paciente, coste de las visitas al médico y costes de otros cuidados sanitarios	n = 100, 51 en el grupo intervención y 49 en el control La ingesta calórica y proteica mejoraron en el grupo de la intervención El peso, IMC y pliegue mejoraron en el grupo intervención La dinamometría mejoró en el grupo intervención en la semana 8 pero no se mantuvo hasta la semana 24 También mejoró el dominio de movilidad en el cuestionario de calidad de vida En ambos grupos disminuyeron los ingresos hospitalarios El coste de la hospitalización solo disminuyó en el grupo control, concluyendo que los suplementos podrían no ser coste-efectivos en esta población en base a los parámetros estudiados	JADAD: 2p
Simmons 2015 (36) EE. UU.	Estudio de costes sobre el tratamiento nutricional	Determinar el coste eficacia de dos intervenciones nutricionales en la comida, bebida, suplementación y peso	<i>Ensayo clínico aleatorizado</i> Población: pacientes de larga estancia en residencias y en los que estuviera indicada la suplementación nutricional Intervención: suplementos nutricionales orales/ <i>snacks</i> 2 al día, 5 días de la semana durante <i>24 semanas</i> Los pacientes elegían los sabores de los suplementos, no especifican si eran HP, HC o HP/HC En el caso de los <i>snacks</i> , el paciente elegía entre una variedad de yogures, pudding, etc. Variables: ingesta, bebida, suplementación, tiempo consumido por el personal sanitario <i>Análisis de coste eficacia</i> : ingesta calórica total e ingesta calórica entre horas Se tuvieron en cuenta los costes de los alimentos/ suplementos ofertados y los minutos de atención por el personal sanitario	n = 154, 52 intervenciones con suplementos nutricionales, 53 con <i>snacks</i> y 49 de práctica habitual En ambos grupos de intervención se realizó satisfactoriamente en el 84% del tratamiento prescrito Ambas intervenciones produjeron un incremento de la ingesta calórica total y entre horas con respecto al basal y con respecto al grupo control Fue significativamente mayor en el grupo de los <i>snacks</i> No hubo cambios en el peso con respecto al basal o entre grupos Análisis de coste eficacia: La intervención supuso un incremento de la frecuencia con la que el personal sanitario realizaba ofrecimientos De media, la intervención mediante suplementos supuso un coste de 0,1 céntimos por kcal ganada y la de los <i>snacks</i> fue de 0,8 céntimos por kcal ganada Los <i>snacks</i> fueron más eficaces para aumentar la ingesta calórica pero también más caros porque requirieron mayor tiempo del personal de hospitalización	El 78% de los pacientes tenía demencia, el 59% de depresión y el 55% disfagia El 81% precisaba ayuda para poder comer JADAD 3p El estudio no fue diseñado para evaluar el coste-eficacia de la intervención en el total de costes de los pacientes de larga estancia

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Tabla III (Cont.). Estudios incluidos. Costes de la desnutrición relacionada con la enfermedad

Autor	Grupo	Objetivos	Material y métodos	Resultados	Comentarios
Neelemaat 2012 (37) Países Bajos	Estudio de costes sobre el tratamiento nutricional	Evaluar el coste-eficacia de la suplementación nutricional en pacientes mayores hospitalizados	<i>Ersayo clínico aleatorizado</i> Intervención: dieta oral enriquecida, suplementos nutricionales orales, calcio y vitamina D, consejo dietético y atención telefónica durante 3 meses tras el alta Grupo control: cuidados habituales Inclusión: pacientes > 60 años, desnutridos (criterios ESPEN) e ingresados en el hospital <i>Análisis de coste utilidad y coste eficacia</i> Los costes se contabilizaron como: - Costes directos (ingresos, visitas al hospital) - Costes indirectos (absentismo laboral) - Costes no relacionados directamente con sanidad (cuidados, medicina alternativa, etc.) También se tuvieron en cuenta los costes de los suplementos, del calcio y la vitamina D y de las llamadas telefónicas Objetivo principal: evaluar la calidad de vida de los pacientes/EuroQol EQ-5D Objetivo secundario: evaluar la capacidad funcional (LASA physical activity questionnaire)	n = 210 pacientes, 105 en cada rama La estancia hospitalaria fue de 13 días en el grupo de la intervención y de 14 días en el grupo control, sin diferencias estadísticamente significativas Tampoco hubo diferencias significativas en los QALY ni mejoría en las actividades, aunque sí para capacidad funcional En ese estudio fue necesario invertir 6.500 € para obtener un 95% de mejora en la capacidad funcional (en los Países Bajos una inversión < 20.000 € se considera coste efectiva) Tampoco hubo diferencias en la utilización de los recursos sanitarios No pudo demostrarse el coste-efectividad ni coste-utilidad de la intervención frente a la práctica habitual	JADAD 3p Tiempo de seguimiento 3 meses
Norman 2011 (38) Alemania	Estudio de costes sobre el tratamiento nutricional	Evaluar el coste eficacia de la suplementación nutricional en pacientes mayores ingresados	<i>Ersayo clínico aleatorizado piloto</i> Población: pacientes desnutridos según VSG (B y C) ingresados en el Departamento de Gastroenterología de un único centro No incluyeron pacientes oncológicos ni insuficiencia renal con creatinina > 1,3 mg/dl Intervención: suplementos nutricionales orales (HP/HC) y consejo dietético a pacientes desnutridos (VGS B o C) con patología intestinal benigna durante 3 meses tras el alta hospitalaria Grupo control: práctica clínica habitual Ambos grupos recibieron consejo dietético al alta Se midió calidad de vida mediante SF36 Se consideró el coste de los suplementos con el menor y mayor precio del mercado <i>Análisis de coste-eficacia y coste-utilidad</i>	n = 114 pacientes, 57 mujeres La estancia hospitalaria, la comorbilidad y los medicamentos al alta fueron similares en ambos grupos El grupo control reingresó más frecuentemente que el grupo intervención Ambos grupos mejoraron en calidad de vida, pero la mejoría fue significativamente mayor en el grupo de la intervención La diferencia en QALY fue mayor en el grupo intervención; la ganancia puede interpretarse como que los pacientes ganaron 16 días adicionales de calidad de vida plena por año La intervención nutricional resultó coste efectiva según los estándares internacionales	

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Tabla III (Cont.). Estudios incluidos. Costes de la desnutrición relacionada con la enfermedad

Autor	Grupo	Objetivos	Material y métodos	Resultados	Comentarios
Freijer 2010 (39) Países Bajos	Estudio de costes sobre el tratamiento nutricional	Evaluar el coste eficacia de los suplementos nutricionales orales en pacientes candidatos a cirugía abdominal	Se construye un <i>modelo de decisión analítica que compara los costes económicos de dos poblaciones de pacientes candidatos a cirugía que difieren únicamente en la prescripción de suplementos</i> <i>Estudio de casos y controles virtual</i> En el modelo se asume: – Prevalencia de desnutrición del 25-40%; – Que el 50% de los pacientes desnutridos tomará los suplementos nutricionales orales; – Precios de los suplementos dentro y fuera del hospital; – Costes de la hospitalización; – Duración del tratamiento con SNO (7-16 días); – Descenso de la estancia hospitalaria en un 25%. <i>Holanda</i> <i>Análisis de coste eficacia</i>	El análisis económico mostró que el uso de suplementos nutricionales <i>orales no incrementa los costes</i> , sino que los reduce (<i>252 £ por paciente</i>) a partir de una reducción de la estancia y de los costes de la hospitalización (0,72 días) El uso de suplementos nutricionales orales conllevaría un ahorro de <i>40,4 millones de libras</i> basados en 160.283 procedimientos quirúrgicos anuales	
Freijer 2014 (40) Países Bajos	Estudio de costes sobre el tratamiento nutricional	Análisis de costes aplicados a la nutrición enteral en el tratamiento de la DRE en adultos en países desarrollados	<i>Revisión sistemática</i> de la literatura para estimar la eficiencia (costes en relación con efectos) de la nutrición enteral en pacientes con DRE en países desarrollados Aplicaron el método PRISMA Sujetos: pacientes adultos desnutridos o en riesgo en cualquier entorno sanitario Intervención: todos aquellos estudios que abordaran evaluaciones económicas, incluyendo costes y consecuencias	Seleccionaron 522 estudios, de los cuales finalmente se incluyeron solo 14 En la mayoría de los estudios (10/14) los suplementos se incluyeron como nutrición enteral: solo 4 evaluaron el valor económico de la nutrición enteral Del total de estudios seleccionados, solo se exploran los resultados de <i>aquellos considerados de alta calidad</i> (8) tras aplicar el cuestionario validado para estudios económicos en salud (QHES) 5/8 artículos provienen de los Países Bajos, 6/8 tuvieron en cuenta los costes sanitarios y no sanitarios Todos menos uno utilizan suplementos nutricionales orales en el contexto de una estrategia multimodal de tratamiento Solo uno de ellos usa nutrición enteral La mayoría incluyeron pacientes > 55 años En sus conclusiones indican que la nutrición enteral oral o por sonda es coste-efectiva en diferentes escenarios Solo se incluyó un estudio de coste utilidad aplicado a la nutrición enteral y el resultado fue coste útil	

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Tabla III (Cont.). Estudios incluidos. Costes de la desnutrición relacionada con la enfermedad

Autor	Grupo	Objetivos	Material y métodos	Resultados	Comentarios
Elia 2008 (41) Reino Unido	Estudio de costes sobre el tratamiento nutricional	Análisis de coste utilidad en pacientes con nutrición enteral	<i>Análisis de coste-utilidad</i> Intervención: nutrición enteral en pacientes ambulatorios (n = 2.888) e institucionalizados (n = 7.007) con disfagia tras accidente cerebrovascular (ACVA) (los datos se obtuvieron a partir de una auditoría sobre la nutrición enteral en Reino Unido) 3 años de seguimiento con contacto cada 3 meses Se utilizó el EuroQol para la calidad de vida En el análisis de costes se incluyeron los costes de la nutrición, del programa de educación, analíticas de sangre y seguimiento	Mayor mortalidad en los pacientes institucionalizados El soporte nutricional con NE en estos pacientes fue coste útil independientemente del escenario (ambulatorios, institucionalizados u hospitalizados) En Reino Unido se considera coste-útil toda intervención que conlleve ganancia de QALY y tenga un coste inferior a 30.000 libras	
Philipson 2013 (42) EE. UU.	Estudio de costes sobre el tratamiento nutricional	Evaluar la eficacia de un SNO en un paciente hospitalizado sobre la estancia hospitalaria, costes por episodio, reingresos	<i>Estudio observacional retrospectivo</i> , 11 años de seguimiento <i>Análisis de coste-eficacia</i> Las variables de estudio se obtuvieron a partir de una base de datos de 44 millones de pacientes hospitalizados Se analizaron por separado aquellos que recibieron SNO y los que no	Del total de pacientes, se seleccionaron aquellos que tomaron suplementos durante la hospitalización y se comparó con una muestra de similares características y tamaño Los pacientes tratados con suplementos <i>redujeron la estancia hospitalaria en 2,3 días y la probabilidad de reingreso en un 2,3%</i> Los costes por episodio en los pacientes tratados disminuyeron 4.734 \$ (21.950 vs. 17.216 \$)	No menciona el estado nutricional de los pacientes
Elia 2016 (43) Reino Unido	Estudio de costes sobre el tratamiento nutricional	Análisis de coste eficacia de los suplementos nutricionales (no específicos) en pacientes hospitalizados	<i>Revisión sistemática de la literatura</i> El estudio se llevó a cabo de acuerdo con las guías de la Cochrane, PRISMA y las del servicio nacional de salud para las revisiones Se incluyeron todos aquellos estudios en cuyos objetivos estaba evaluar la eficacia de los suplementos y los costes asociados	22.819 estudios fueron inicialmente identificados; finalmente, se incluyeron 9 publicaciones con 14 estudios La mayoría de ellos eran estudios <i>retrospectivos</i> El análisis de coste eficacia fue positivo en 12/14 estudios, con un ahorro del 12,2% en aquellos que aportaban datos cuantitativos, fundamentalmente a expensas de una menor tasa de complicaciones (-35%), menor estancia hospitalaria (-2 días), menor incidencia de úlceras por presión y mayor ganancia de años de vida ajustados a calidad de vida (QALY)	Se incluyeron pacientes con cualquier estado nutricional (normonutridos, en riesgo y/o malnutridos)

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Tabla III (Cont.). Estudios incluidos. Costes de la desnutrición relacionada con la enfermedad

Autor	Grupo	Objetivos	Material y métodos	Resultados	Comentarios
Elia 2016 (44) Reino Unido	Estudio de costes sobre el tratamiento nutricional	Análisis de coste eficacia de los suplementos nutricionales (no específicos) en pacientes ambulatorios e institucionalizados	<i>Revisión sistemática de la literatura</i> Se incluyeron aquellos estudios en los que se comparaban suplementos nutricionales orales frente a no suplementos/práctica habitual/consejo dietético en cualquier entorno distinto del hospitalario	22.819 estudios fueron inicialmente identificados; finalmente se incluyeron 19 publicaciones a partir de las cuales se identificaron 31 estudios de costes y 4 de coste-eficacia La mayoría <i>retrospectivos</i> En los estudios en los que la intervención fue < 3 m, la mediana de ahorro de costes fue del 9,2% En aquellos > 3 m, la mediana de ahorro fue del 5% El metaanálisis indica que los suplementos nutricionales reducen un 16,5% la hospitalización de forma significativa y la mortalidad (sign.) Aquellos estudios que analizaron desde una perspectiva de coste-utilidad mostraron una ganancia de QALY en el grupo de la intervención	Se incluyeron pacientes con cualquier estado nutricional (normonutridos, en riesgo y/o malnutridos)
Arnaud- Battandier 2004 (45) Francia	Estudio de costes sobre el tratamiento nutricional	Establecer los costes de la malnutrición y la comorbilidad asociada en pacientes mayores residentes en la comunidad así como la prescripción	<i>Estudio de cohortes prospectivo 12 meses de seguimiento</i> Se seleccionan dos áreas sanitarias en función del volumen de prescripción de suplementos nutricionales orales Variables: estado nutricional, comorbilidades y consumo sanitario	n = 378 pacientes > 70 años Grupo 1: baja prescripción de SNO (202 pacientes) Grupo 2: alta prescripción de SNO (200 pacientes) Los pacientes correspondientes al grupo 2 presentaban mayor prevalencia de desnutrición y con más frecuencia estaban institucionalizados El uso de las instituciones sanitarias y la estancia hospitalaria fue mayor en los pacientes del grupo 1 Los costes atribuibles a los suplementos en el grupo 2 fueron 528 euros superiores a los de los pacientes del grupo 1 Los costes atribuibles a la hospitalización fueron mayores en el grupo 1, con un ahorro de 723 euros	

En algunos estudios se desglosaban los costes sanitarios totales en distintas categorías: estancia hospitalaria, tratamientos aplicados, soporte nutricional, etc.

En cifras globales, la desnutrición relacionada con la enfermedad suponía un coste adicional de 100 millones de euros en Croacia (19), 1,9 billones de euros en los Países Bajos (2) o 1.143 millones de euros en España (16). Los costes de la hospitalización fueron significativamente mayores en los pacientes desnutridos cuando se compararon con los pacientes sin desnutrición (2,5,16,21,23,24,26,29,30). La estancia hospitalaria se alargó en los pacientes desnutridos en una media de entre dos y diez días (5,16,22,23,24,26,28,30). El diagnóstico de desnutrición se asoció a un incremento de los costes sanitarios en las partidas correspondientes a los tratamientos (5,16,27,30), especialmente antibióticos.

Desde una perspectiva clínica, los estudios evaluados corroboraban la repercusión clínica de la desnutrición con una mayor tasa de complicaciones (5,27), altas hospitalarias con derivación a otros centros (23,24), usos de cuidados en domicilio/ambulatorios (23,28,27), reingresos (26) y mortalidad (5,26).

En aquellas publicaciones en las que se recogieron aspectos relacionados con la codificación de la malnutrición en los informes de alta hospitalaria, se constataba que la DRE estaba frecuentemente infradiagnosticada (22,24), generando una pérdida de ingresos adicional. Asimismo, en aquellos estudios en los que se analizó el porcentaje de pacientes desnutridos que recibían soporte nutricional específico formando parte de la práctica clínica habitual se observó un infratratamiento de la misma (16,24,28).

ESTUDIOS DE ANÁLISIS DE COSTES SOBRE EL TRATAMIENTO NUTRICIONAL DE LA DESNUTRICIÓN

En total, se incluyeron 16 artículos, la mayoría publicados en los últimos cinco años (68%), siendo el más antiguo de 2004 (45). En lo que respecta al tipo de estudio, las publicaciones finalmente seleccionadas incluían ensayos clínicos aleatorizados (31,34-37), estudios piloto de intervención (32,38), comunicaciones a congresos (33), revisiones sistemáticas (17,40,43,44), estudios con modelos y pacientes virtuales (39), así como estudios observacionales retrospectivos (42) y prospectivos (45).

La puntuación JADAD permitió identificar dos ensayos clínicos aleatorios de calidad media (JADAD = 3) (36,37). El tipo de análisis económico más frecuentemente aplicado al soporte nutricional en el tratamiento de la desnutrición fue el de coste-eficacia, siendo menos abundantes los estudios de coste utilidad (17,31,37,38,40,41).

Muchos de los estudios se llevaron a cabo en población mayor (> 65 años), institucionalizada (17,32-34,36), durante el ingreso hospitalario (17,37,38,42). Las revisiones sistemáticas (43,44) exploraron los entornos hospitalarios, ambulatorios y/o los cuidados domiciliarios. En los ensayos clínicos aleatorizados, la intervención se realizó, en la mayoría de los casos, con suplementos nutricionales orales y solo en algunos casos con nutrición enteral (40,41).

La duración de la intervención se sitúa entre seis semanas y seis meses, aunque uno de los estudios, utilizando un modelo de decisión analítica, calculó los costes del soporte nutricional a partir de una intervención con suplementos nutricionales durante 7-16 días (39).

En lo que respecta al tamaño muestral de los estudios evaluados, las cifras son muy variables, y destaca el estudio de Philipson y cols. (42), con 44 millones de pacientes seguidos durante once años.

Dos de las revisiones sistemáticas evaluadas se habían publicado en el año en curso; las dos publicaciones pertenecen al grupo de Elia M y cols. (43,44). La primera de ellas se circunscribía al tratamiento nutricional con suplementos nutricionales en pacientes en el ámbito hospitalario y la segunda, en el paciente ambulatorio o con cuidados en domicilio. En ambas revisiones, el número de publicaciones a evaluar finalmente (ensayos clínicos aleatorizados) difícilmente alcanza la veintena, siendo en su mayoría estudios retrospectivos, con las correspondientes limitaciones. En dos revisiones, en lo referente al estado nutricional, se incluyeron estudios en pacientes con cualquier estado nutricional (sin desnutrición, con desnutrición o en riesgo).

En lo que respecta al análisis económico, no todos los estudios presentaban resultados homogéneos, no siendo posible, en algunos casos, demostrar la coste-eficacia de los suplementos nutricionales orales en el tratamiento de la DRE (31,32,35-37). Sin embargo, la mayoría de las publicaciones analizadas, y muy especialmente los dos metaanálisis del grupo de Elia y cols. (43,44), concluían que los suplementos nutricionales orales resultan coste efectivos en el ámbito hospitalario y ambulatorio y/o en cuidados domiciliarios. Estos resultados se explicaban por los efectos beneficiosos sobre la calidad de vida, reducción de las infecciones, de las complicaciones posoperatorias, caídas y fracturas, y limitación de la capacidad funcional. Algunos de los estudios estimaron los costes que podrían ahorrarse de indicar los suplementos nutricionales orales en determinados colectivos en riesgo nutricional. Así, Freijer y cols. (39) calcularon un ahorro de hasta 44 millones de libras anuales.

En lo que respecta a los estudios de coste utilidad, algunas publicaciones no pudieron demostrar el coste-utilidad de los suplementos (31,37), si bien la mayoría de las publicaciones en las que se incluyó este tipo de análisis corroboraban una ganancia de años de vida ajustados por calidad de vida a un coste aceptable según los estándares internacionales (17,38,41,43,44).

DISCUSIÓN

La DRE constituye la patología nutricional más costosa desde una perspectiva clínica y económica, muy por encima de la obesidad. Esta enfermedad es la primera causa de malnutrición en los países desarrollados.

De promedio, uno de cada tres pacientes que ingresan en un hospital presenta desnutrición al ingreso o la desarrollará a lo largo de la hospitalización, y dos de cada tres empeorarán su estado nutricional durante el ingreso (47). Estos datos indican

la magnitud del problema, el cual puede ser incluso mayor en colectivos concretos, como en el paciente oncológico, con patología gastrointestinal o en el paciente anciano (1,9). La DRE afecta negativamente a la morbilidad, la capacidad funcional, la calidad de vida, la mortalidad, la estancia hospitalaria y los costes económicos y sociales (1,48). Snider y cols. (49) observaron que la DRE restaba 670.000 QALY cada año. A pesar de ello, continúa siendo una enfermedad infradiagnosticada e infratratada (16), así como infracodificada (24,50), hechos que perpetúan y magnifican las consecuencias clínicas y económicas de la misma.

Los hallazgos referentes a los costes económicos descritos en los estudios evaluados están en consonancia con los datos macroeconómicos publicados por distintos países a nivel europeo e internacional (16,23). En los países de la Unión Europea, la DRE afecta a 20 millones de pacientes, lo que supone un incremento de los costes de hasta 120 millones de euros anuales (2,40). En países como Reino Unido e Irlanda, los costes de la DRE exceden del 10% del gasto público en salud y cuidados sociales (40,43). La sociedad Británica de Nutrición Parenteral y Enteral estimó un coste asociado a la DRE para el año 2003 de 7,3 billones de libras (8). En otros países de la Unión Europea supone un coste adicional de, por ejemplo, 100 millones de euros en Croacia (19), 1,9 billones en los Países Bajos (2) o 1,14 billones en España (16). En Estados Unidos, aproximadamente el 33-54% de los pacientes hospitalizados padecen desnutrición relacionada con la enfermedad, cifra que aumenta al 65-85% en el grupo de pacientes institucionalizados. Los costes de la DRE en Estados Unidos ascienden a 15,5 billones de dólares (51).

Este incremento de los costes viene determinado fundamentalmente por la mayor estancia hospitalaria (5,16,22-24,26), mayor incidencia de complicaciones infecciosas y no infecciosas (5,48), mayor necesidad de tratamientos (16,30,46), aumento de los reingresos (23,26), estancias más prolongadas en unidades de cuidados intensivos (30) y/o la necesidad de derivar al paciente a centros de cuidados continuados al alta hospitalaria (23,24).

La Sociedad Americana de Nutrición Parenteral y Enteral (ASPEN) promovió ya en 1983 un comunicado especial en el que se señalaban varias circunstancias vigentes a día de hoy. En este documento, además de reconocer el incremento de la morbilidad y mortalidad que confería la desnutrición al paciente hospitalizado, se subrayaba el papel del equipo sanitario en la etiopatogenia de dicha desnutrición. Así, el no realizar cribado nutricional a los pacientes hospitalizados, la imposición de restricciones alimentarias y/o ayunos innecesarios durante la hospitalización, la escasa formación en tratamientos dietéticos y/o soporte nutricional específico y el no contar con un equipo de profesionales específicamente cualificados para el diagnóstico, la prevención y el tratamiento nutricional colocan al paciente, ya en riesgo por su patología de base, en riesgo nutricional por el simple hecho de estar hospitalizado. En un documento de reciente publicación de esta misma sociedad, se ofrece una relación de acciones destinadas a mejorar la calidad de la evaluación nutricional y los cuidados en los pacientes hospitalizados (47). En dicho documento se recogen acciones tan básicas como la necesidad

de implementar un método de cribado, valoración nutricional y dietética, contar con un código de dietas que permita abarcar el mayor número posible de pacientes y patologías, etc.

Una importante estrategia de tratamiento para la DRE son los suplementos nutricionales orales. Esta revisión de la literatura ha puesto de manifiesto que los resultados de los estudios disponibles sobre el uso de estos suplementos en pacientes en distintos entornos (hospitalizados y ambulatorios) sugieren que los suplementos nutricionales orales son eficaces, coste-efectivos y coste-útiles, en tanto que su indicación se asocia a mejoría de la calidad de vida y reducción de la tasa de infecciones, complicaciones, caídas y fracturas (17,43,44,51).

Esta revisión tiene limitaciones. La primera de ellas probablemente está determinada por la propia estrategia de búsqueda, limitada a estudios en inglés y español, con exclusión de estudios centrados en el paciente oncológico o con una patología concreta. Aunque lo ideal sería incluir todos los trabajos relevantes, independientemente del idioma o de la revista de publicación, es cierto que no siempre es posible por cuestiones prácticas. Por otra parte, cabe señalar la escasa formación en economía de la salud de la que disponemos la gran mayoría de los sanitarios, lo que puede dificultar la toma de perspectiva frente a algunos aspectos quizás más técnicos. Asimismo, cabe señalar que de los artículos incluidos a la hora de evaluar desde una perspectiva económica el soporte nutricional, se descartaron todos aquellos estudios que empleaban en sus intervenciones fórmulas enfermedad-específica, así como aquellos que utilizaban nutrición parenteral, circunstancias que, probablemente, también constituyan una limitación del estudio.

CONCLUSIONES

La DRE afecta de media a uno de cada tres pacientes que ingresan en un hospital. Su presencia en ellos determina un importante incremento de la morbimortalidad y se asocia a un incremento de los costes sanitarios como consecuencia de la mayor estancia hospitalaria, mayor número de complicaciones y necesidad de tratamientos. Es imprescindible que la desnutrición relacionada con la enfermedad sea diagnosticada, codificada en los informes de alta y adecuadamente tratada. Los suplementos nutricionales orales constituyen una herramienta terapéutica que, según la literatura recientemente revisada, y desde una perspectiva de economía aplicada a la salud, resulta coste-eficaz y coste-útil.

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Revisión

Clinical-nutritional, inflammatory and oxidative stress predictors in hemodialysis mortality: a review

Predictores clínico-nutricionales, inflamatorios y de estrés oxidativo en la mortalidad por hemodiálisis: una revisión

Andreza P. S. Epifânio¹, Karla P. Balbino¹, Sônia M.R. Ribeiro¹, Sylvia C.C. Franceschini¹ and Helen Hermana M. Hermsdorff¹

¹Department of Nutrition and Health. Universidade Federal de Viçosa. Viçosa, Brazil

Abstract

The evaluation of clinical-nutrition status is essential to increase life quality and improve clinical outcomes of patients in hemodialysis (HD). In the absence of a gold standard, the goal of this integrative review was to present and discuss the latest scientific literature on the ability of clinical-nutritional indicators and inflammatory and oxidative stress markers to predict morbidity and mortality in HD. In this context, the lean and fat mass indexes have become good predictors of mortality in HD individuals, regardless of BMI. Subjective scoring systems have been more sensitive to malnutrition, and altogether anthropometric indicators may result in an early detection of mortality risk in this population. On the other hand, inflammation in HD, as assessed by C-reactive protein, is not only related to cardiometabolic alterations, but it is also one of the key-points in the development of malnutrition, exacerbated by the state of oxidative stress, which has been identified in this group by the increase of the serum levels of gamma-glutamyl transferase and malondialdehyde.

Key words:

Chronic kidney disease. Malnutrition. Hemodialysis. Oxidative stress. Inflammation. Mortality.

Resumen

La evaluación del estado clínico-nutricional es esencial para aumentar la calidad de vida y mejorar los resultados clínicos de los pacientes en hemodiálisis (HD). En ausencia de un patrón oro, el objetivo de esta revisión integrativa fue presentar y discutir la literatura científica más reciente sobre la capacidad de indicadores clínico-nutricionales, y marcadores de estrés oxidativo e inflamatorio, en la predicción de morbilidad y mortalidad en HD. En este contexto, los índices de masa grasa y masa magra se han convertido en buenos predictores de mortalidad en individuos con HD, independientemente del IMC. Los sistemas de puntuación subjetiva han sido más sensibles a la desnutrición y, en conjunto, los indicadores antropométricos pueden resultar en una detección temprana del riesgo de mortalidad en esta población. Por otro lado, la inflamación en HD, evaluada por la proteína C reactiva, no solo se relaciona con alteraciones cardiometabólicas, sino que también es uno de los puntos clave en el desarrollo de la desnutrición, exacerbada por el estado de estrés oxidativo, que ha sido identificado en este grupo por el aumento de los niveles séricos de gamma-glutamyl transferasa y malondialdehído.

Palabras clave:

Enfermedad renal crónica. Desnutrición. Hemodiálisis. Estrés oxidativo. Inflamación. Mortalidad.

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Correspondence:

Helen Hermana M Hermsdorff. Department of Nutrition and Health. Universidade Federal de Viçosa. Av. PH Rolfs, s/n. Viçosa, Minas Gerais, 36570-900, Brazil
e-mail: helenhermana@ufv.br

INTRODUCTION

End-stage renal disease (ESRD), as well as hemodialysis (HD), treatment are marked by clinical-nutritional conditions that increase morbidity and mortality and reduce life quality of patients with this chronic disease (1-3). In this sense, hypoalbuminemia, which is also affected by inflammation status and age, is not able to accurately reflect the nutritional state (4). In turn, body mass index (BMI) has been associated with better prognosis of individuals in HD, which is known as “reverse epidemiology” (5-7). This relationship is influenced by characteristics such as age, inflammation and related-comorbidities (8). In addition, subjective global assessment may help predict mortality, when properly applied (9).

On the other hand, the progressive deterioration of renal function leads to physiological dysfunctions such as changes in cellular energy metabolism, protein catabolism, insulin resistance and synthesis of mediators of inflammation and oxidative stress (10-12). Still, the complex inter-relationship among nutritional indicators and inflammatory and oxidative markers remains the object of investigation on the premise to get better prediction of mortality in patients with ESRD in HD (13).

Overall, the objective of this integrative review was to present and discuss the latest scientific literature on the ability of clinical-nutrition indicators, and inflammatory and oxidative stress markers to predict morbidity and mortality in HD individuals.

STUDY CHARACTERISTICS AND SELECTION CRITERIA

A review search was carried out from the databases LILACS, Medline, PubMed, SciELO and BIREME, using the keywords “hemodialysis and mortality”, “chronic renal failure”, “ESRD”, “biochemical markers”, “inflammatory markers”, “oxidative stress markers”, “anthropometric evaluation”, “nutritional status”, “subjective evaluation”, combined with “mortality”. Publications carried out from 2010 to 2016 with HD individuals were included.

From the selected articles, a reverse search was carried out for studies whose titles would be eligible. Subsequently, the abstracts were read to ensure compliance with the inclusion criteria and then each article was entirely read to confirm its eligibility. Cohort studies with adults and elderly individuals in HD treatment were included. Articles that were not published in full or those presented as tutorials, editorials, news, letters or comments, reviews and experimental testing were excluded. In addition, studies of acute renal disease, chronic kidney disease under conservative treatment or treatment with peritoneal dialysis, transplantation and nephrotic syndrome were excluded.

During the initial selection process, 155 articles were found, from which 108 were excluded, as shown by figure 1. Selected papers are related to anthropometric indicators (four studies), subjective global assessment (five studies), oxidative stress markers (two studies), and inflammatory markers (four studies) as predictors of mortality in HD individuals.

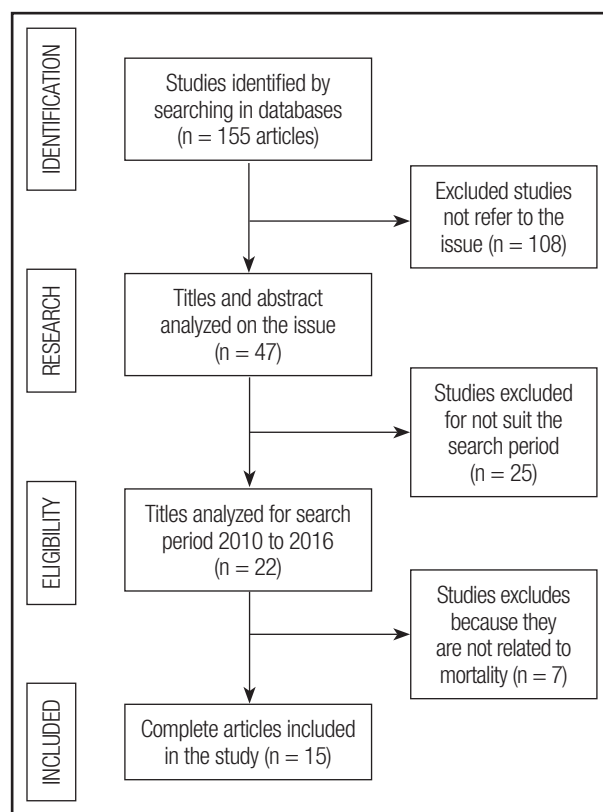


Figure 1.

Flowchart showing selected studies for this review (2010-2016).

CLINICAL-NUTRITIONAL PREDICTORS AND MARKERS OF INFLAMMATION AND OXIDATIVE STATE OF THE STUDY

The 15 selected studies used as anthropometric indicators, BMI, waist circumference (WC), skinfold thickness, arm circumference (AC), Mid-arm circumference (MAC), mid-arm muscle circumference (MAMC) lean tissue index (LTI) and fat tissue index (FTI) and total body fat (TBF), assessed by bioelectrical impedance analysis (BIA). Subjective methods to nutritional assessment were: Subjective Global Assessment (SGA), Modified Subjective Global Assessment (mGSA), Objective Score of Nutrition on Dialysis (OSND), International Society of Renal Nutrition and Metabolism (ISRNM), Malnutrition-Inflammation Score (MIS) and Geriatric Nutritional Risk Index (GNRI).

Hemoglobin, albumin, calcium, phosphorus, parathyroid hormone (PTH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total cholesterol (TC), triglycerides (TG), uric acid, urea, creatinine, Kt/V urea (Kt/V), ferritin and transferrin were used as metabolic markers.

The oxidative stress markers used in the studies were plasma concentrations of gamma-glutamyltransferase (GGT), nitric oxide (NO) and malondialdehyde (MDA); while the inflammatory markers were plasma concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), tumor-necrosis factor alpha (TNF- α) and their receptors (TNFR1 and TNFR 2).

The articles were separated in accordance with categories of predictors of mortality in HD as follows: anthropometric indicators, subjective scores, oxidative stress and inflammation markers (Tables I to IV).

ANTHROPOMETRIC INDICATORS ON MORTALITY IN HD INDIVIDUALS

Studies show that protein-energy malnutrition is present in a range of 23% to 76% of individuals in HD (14). Unlike the general population, a higher BMI in these individuals was associated with better survival, fact presented as reverse epidemiology in the literature (15). However, BMI measures did not present differences between lean and fat mass, making it difficult to quantitatively understand which components of body composition are related to survival in HD individuals with ESRD (16). In order to evaluate body compartments, the studies use the Body Composition Monitor (BCM) based on spectroscopic bioimpedance (BIS). Bioimpedance methodologies, the BCM expresses body composition as a three-compartment model, providing overhydration, lean tissue index (LTI), and fat tissue index (FTI), whereby LTI and FTI are the respective tissue masses normalized to height squared. Also, LTI and FTI percentiles (< 10th percentile [low]; 10th-90th percentile [normal]; and > 90th percentile [high]) relative to an age- and sex-matched healthy pop-

ulation are supplied. The three-compartment model of the BCM has been validated against standard reference methods for assessment of fluid status and body composition in dialysis patients. Castelhan et al. (17) have indicated LTI and FTI reference values (10th and 90th percentiles), adjusted for age and sex, in which lean tissue below the 10th percentile was associated with higher mortality in HD (OR: 1.57). Similarly, considering age, sex and diabetes *mellitus*, higher percentage of lean body mass was associated with better survival (18,19) in HD individuals for the same population.

Moreover, Rosenberger et al. (20) evaluated the relationship between scarcity of lean tissue (expressed as LTI below the 10th percentile) and survival in HD. The possible causes to worse survival (21,22) included malnutrition and inflammation signal (21) as lean mass stocks uremic toxins, in which case, the smaller amount of lean tissue could indicate a higher concentration of uremic toxins in the blood (21,23).

The relation of muscle mass and increased mortality caused by infections in HD individuals is well known, since subjects with ESRD develop an acquired immune deficiency that may be exacerbated in those with low muscle mass and hypoalbuminemia (24). In this sense, Marcellid et al. (16) had found that body composition by multifrequency bioimpedance and LTI and FTI between the 10th and 90th percentiles were associated with improved survival, while the low LTI and FTI, and especially the combination of both, were associated with increased mortality, regardless of BMI.

Table I. Comparative studies of anthropometric predictors in the mortality of hemodialysis patients (cohort studies, 2010-2016)

Author/Year	Sample	Method /Studied variables	Main results
Castellano et al., 2016 (17)	6,325 patients 57 HD units in Spain January 2012 to December 2014 Average age: 67 years 37% women	Body fat distribution variables: LTI; FTI	The presence of the LTI < 10 th percentile was independently associated with increased risk of death even after adjusting for other factors such as moisture and HD time
Marcelli et al., 2015 (16)	37,345 patients 380 HD units in 17 European countries April 2006 to December 2012 Average age: 62 years 57% men	Body fat distribution variables: LTI; FTI Anthropometric variable: BMI	There was lower mortality in individuals in the percentiles > 10 for LTI and < 90 considering FTI of a healthy population
Su et al., 2013 (24)	1,846 patients 15 HD units in the US March 1995 to October 2000 Average age: 58 years 43% men	Anthropometric variables: MAC AC, BMI, TSF, BSF, SSF	Reduction in the values of AC and skinfold thickness was significantly associated with mortality from all causes and cardiac outcomes, especially those with BMI ≤ 25 kg/m ²
Stosovic et al., 2010 (27)	242 patients 1 HD unit in Serbia 1994-2004 Average age: 52 years old 53% men	Anthropometric variables: TSF, BSF, MAMC, MAC BMI Metabolic variables: albumin, creatinine, K / tV, urea Inflammatory variable: CRP	MAC was better predictor of mortality than other anthropometric, metabolic and inflammatory measures evaluated

AC: arm circumference; BMI: body mass index; BSF: bicipital skinfold; CRP: C-reactive protein; FTI: fat tissue indices; HD: hemodialysis; LTI: lean tissue indices; MAC: mid-arm circumference; MAMC: mid-arm muscle circumference; TSF: triceps skinfold; SSF: subscapular skinfold.

Table II. Comparative studies of subjective predictors in the mortality of hemodialysis patients (cohort studies, 2010-2016)

Author/Year	Sample	Method/Studied variables	Main results
Vogt; Caramori, 2016 (31)	163 patients HD Centre in Botucatu (Brazil) July to December 2012 Average age: 58 years 54.6% men	Subjective variables: SGA, ISRNM, MIS Anthropometric variables: MAC, BMI Metabolic variables: serum albumin, the total iron binding capacity and transferrin	SGA and MIS were predictors of all-cause mortality when associated with other parameters
Kwon et al., 2016 (33)	914 patients 36 HD centers in Korea November 2008 to February 2014 Average age: 60 years 62% men	Subjective variable: SGA Anthropometric variable: BMI Metabolic variable: albumin Inflammatory variable: CRP	The changes in nutritional status evaluated by SGA during the first year of HEMO were associated with all-cause mortality
Chan et al., 2012 (34)	167 patients HD unit in Sydney (Australia) August 2000 to July 2010 Average age: 65 years 57.5% men	Subjective variable: SGA Anthropometric variable: BMI Metabolic variable: albumin	SGA Malnutrition (B and C) at the beginning of HD was associated with high mortality, regardless of BMI and serum albumin
Beberashvili et al., 2010 (35)	81 patients HD Centre in Israel 27 months Average age: 64 years 65% men	Subjective Variable: OSND Anthropometric variables: BMI, TSF, MAC Metabolic variable: albumin, transferrin and cholesterol	The OSND based on anthropometric and metabolic variables, proved to be a broader marker of all aspects of nutrition and a strong predictor of morbidity and mortality in chronic hemodialysis patients

AC: arm circumference; BMI: body mass index; HD: hemodialysis; ISRNM: International Society of Nutrition and Metabolism Renal; MAC: mid-arm circumference; MIS: malnutrition-inflammation score; OSND: Objective Score of Nutrition on Dialysis; SGA: subjective global assessment; TSF: triceps skinfold.

Table III. Comparative studies of oxidative stress predictors in the mortality of hemodialysis patients (cohort studies, 2010-2016)

Author/Year	Sample	Method/Studied variables	Main results
Rusu et al., 2016 (48)	44 patients 01 HD unit in Romania 108 months (beginning in 2005) Average age: 59.79 years 44% men	Oxidative stress variables: MDA, PC, nitric oxide Metabolic variables: ceruloplasmin, albumin, creatinine, uric acid, iron profile (iron, transferrin and ferritin), lipid profile (total cholesterol, triglycerides and HDL-cholesterol), alkaline phosphatase, (iPTH) and transaminases. pre urea and post-dialysis, Kt/V, cCA inflammatory variable: CRP Anthropometric variable: BMI	MDA is a strong predictor of mortality in hemodialysis patients. It is associated with greater amount of cCA as a predictor of mortality
Park et al., 2015 (49)	1634 patients 31 HD units in Korea April 2009 to July 2014 Average age: 58 years 61.3% men	Oxidative stress variables: gammaGT Metabolic variables: AST, ALT, alkaline phosphatase, creatinine, urea, calcium ferritin, phosphorus, albumin, triglycerides, cholesterol	The highest concentration of Gamma GT in serum was an independent risk factor for mortality from all causes and in HD patients

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CRP: C-reactive protein; Cca: corrected calcium/albumin; GGT: gamma-glutamyltransferase; HD: hemodialysis; MDA: malondialdehyde; PC: protein carbonyls; iPTH: intact parathyroid hormone.

Other anthropometric and body composition indicators do not qualify as common practices. TBF and simple anthropometric measures, such as MAC, AC and triceps skinfold thickness (TSF) are generally used (25,26). Stosovic et al. (27) found that the TBF, TSF, AC and MAC were independent predictors of mortality for

individuals in HD. The predictive values of all these anthropometric indicators for mortality were similar, except for BMI. When these indicators were altogether tested, the AC was the indicator with the greatest power to predict mortality and showed an average reduction of 8.0% in the proportional mortality risk.

Table IV. Comparative studies of inflammatory predictors in the mortality of hemodialysis patients (cohort studies, 2010-2016)

Author/year	Sample	Method/Studied variables	Main results
Carlsson et al., 2015 (65)	207 patients 01 unit of HD in Stockholm October 2003 to March 2004 Average age: 66 years 56% men	Inflammatory variables: CRP, IL-6, pentraxin 3, TNF- α and TNFR1 and 2 Subjective variable: SGA Anthropometric variable: BMI Metabolic variable: albumin	sTNFRs values seem limited when associated with anthropometric, subjective and inflammatory indicators in mortality prediction
Nakagawa et al., 2015 (64)	218 patients 01 HD unit in Sapporo (Japan) March 2006 to March 2012 Average age: 59 years 57.9% men	Inflammatory variables: adiponectin, CRP and TNF- α Subjective variables: GNRI Variable body fat distribution: VFA, SFA, BMI	TNF- α and CRP levels during the 6-year study showed strong predictive power for all-cause mortality dependent on the nutritional status of Japanese HD
Faria et al., 2013 (58)	189 patients 01 HD unit in Portugal April 2009 to 2011 Average age: 66 years 55% men	Inflammatory variables: CRP, IL-6 and adiponectin Metabolic variables: albumin, iron, ferritin, transferrin, cholesterol, triglycerides, phosphorus, potassium, calcium, creatinine, K/tv and sodium	High levels of CRP and low triglyceride levels can predict mortality risk in individuals in HD
Bazeley et al., 2011 (60)	5061 patients HD 140 units in 10 countries 2005-2008 Average age: 62 years 59.7% men in Europe 59.8% men in Japan	Inflammatory variable: CRP Anthropometric variables: BMI Metabolic variables: albumin, ferritin,	CRP when measured with other markers (albumin, and ferritin BMI) improves the prediction of mortality

BMI: body mass index; CRP: C-reactive protein; GNRI: geriatric nutritional risk index; HD: hemodialysis; IL-6: interleukin-6; TNF- α : tumor necrosis factor- α ; sTNFR1 and 2: tumor necrosis factor receptors 1 and 2; VFA: visceral fat area; SFA: subcutaneous fat area; SGA: Subjective Global Assessment.

Furthermore, the reduction of muscle mass in this population (28) is associated with hypoalbuminemia and PEM, which indicate inflammatory conditions (29). Su et al. (24) have reported that the decline in lean body mass over time, estimated by MAC and skinfold measurements were associated with higher risk of all specific causes of mortality in HD individuals. These relationships were particularly strong in those with BMI < 25 kg/m².

It is noteworthy that BMI values for individuals in HD are usually higher than for general population, although many of them may present LTI values below percentile 10 (30), suggesting that body composition related to lean tissue is more important than BMI isolated. In addition, interventions to keep lean and fat mass suitable are favorable for survival in population with ESRD. Thus, AC measure and the body fat distribution (as LTI and FTI) were altogether promissory predictors of morbidity and mortality in HD, reinforcing the importance of lean and fatty tissues in evaluating the survival of HD patients independently of BMI, making them (mainly AC) good indicators in clinical practice.

SUBJECTIVE SCORES ON MORTALITY IN HD INDIVIDUALS

In this sense, SGA is a simple method for assessing the nutritional status in many patients, including those with ESRD. Vogt

and Caramori (31) had presented prevalence of malnutrition of 26.3% by SGA, 25.2% for MIS (MIS > 8) and 28.8% by criteria based on ISRN, and malnutrition evaluated by SGA and MIS was able to predict mortality in a period of 15.5 ± 5.4 months. The study of Zuidewijnet et al. (32) highlighted the SGA and MIS, after comparing eight evaluation tests of nutritional risk, as better predictors of mortality. As results, these studies show the impact of changes in scores of SGA and MIS on clinical outcomes and mortality risk. Another study has shown that an 1-point increase in SGA, 12 months after dialysis, was independently associated with an increase of 34% in all-cause mortality risk when tested with albumin, CRP, and BMI (33). The same finding was discussed by Chan et al. (34), after adjusting for all variables including age, sex, HD time, serum albumin, body mass index and smoking. In addition, they observed that the SGA, considering mild malnutrition (B) and moderate (C) independently predicts mortality.

The study of Beberashvili et al. (35) has found significant associations with hospitalization and mortality in individuals in HD through a comprehensive OSND scoring system. Both variables were significantly correlated with inpatient days and frequency, as well as lean and fat body mass, MIS, blood pressure and IL-6 values (35,36). The results found by Beberashvili et al. (37) indicate that MIS had reliability and good concurrent and predictive validity (37).

Even so, these scoring systems should be considered as complementary clinical markers of malnutrition state, while application

of SGA and MIS could result in early detection of malnutrition compared to metabolic and inflammatory markers, or classic anthropometric indicators (38). Therefore, SGA and MIS may represent good tools for application in clinical practice, as they may contribute to an early identification of malnutrition.

OXIDATIVE STRESS MARKERS ON MORTALITY IN HD

The presence of oxidative stress, as well as anthropometric and subjective evaluation, has been related to the increase in morbidity and mortality in cardiac surgical patients, critically ill and renal patients requiring HD (39,40).

In HD individuals, increased oxidative stress results from an imbalance between pro-oxidant activity and anti-oxidant systems, more intensely, contributing to increased morbidity and mortality (41,42). Diabetes *mellitus*, advanced age, inflammation, excess of uremic toxins, bio-incompatibility of dialysis membranes (43) and intravenous iron therapy (44) are the main causes of increased pro-oxidant activity in these individuals (42).

Excess of oxygen reactive species (ROS) can produce cellular damage, interacting with biomolecules (proteins, lipids and nucleic acids) and, thus, have negative effects on tissue function and structure. ROS can react with polyunsaturated fatty acids that produce lipid hydro peroxides. MDA, a linolenic acid product of decomposition of the main final oxidation reactions of polyunsaturated fatty acids, is a useful indicator to evaluate oxidative damage (45,46). MDA can still interact with DNA and proteins, and can lead to mutagenic and cytotoxic effects and, possibly, is involved in the pathogenesis of various diseases, such as atherosclerosis (47). Low MDA values, which suggest a lower intensity of oxidative stress, are associated with better survival (45).

Rusu et al. (48) observed that the increase in MDA is associated with a higher ratio of albumin corrected calcium (cCA). It is known that elevated cCA is a predictor of mortality, since hypercalcemia and increased ROS can act synergistically in aggravating the severe vascular lesions found in HD individuals. MDA has a high predictive value for the mortality of these individuals and is related to the survival of this population, especially when associated with cardiovascular diseases.

GGT (49), a recognized biomarker for liver disease, was another marker of oxidative stress presented as a predictor of mortality in HD individuals. It is an enzyme with important role in the extracellular catabolism of glutathione, a representative intracellular antioxidant (50). GGT-mediated oxidative stress may be involved in the formation of coronary atherosclerotic plaques and endothelial dysfunction (51-53).

In this sense, oxidative stress may play an important role in the pathogenesis of atherosclerosis and cardiovascular risk in ESRD, thus contributing to the increase in mortality. More studies are necessary to identify potential biomarkers in these people. Still, an early evaluation through GGT and MDA may contribute to a better monitoring of oxidative stress presence, which is common among individuals with chronic kidney disease.

INFLAMMATORY MARKERS ON MORTALITY IN HD INDIVIDUALS

Inflammation has recently been recognized as an essential component in ESRD in HD, playing a unique role in its pathophysiology and is responsible, in part, by CVD mortality and all other causes (54). Moreover, inflammation is related to the development of PEM and other comorbidities. In fact, the increase in release or activation of pro-inflammatory cytokines such as IL-6 or TNF- α , as well as acute phase protein CRP, may suppress appetite, cause muscle proteolysis and hypoalbuminemia (55). Furthermore, PEM and inflammation contribute independently to hypoalbuminemia and thus increase the risk for mortality in ESRD in HD (56).

Inflammation is often present in individuals in HD, and the use of central venous catheter has been linked to chronic inflammatory state (57). Faria et al. (58) have found that its use as vascular access for HD procedure was independently associated with mortality in patients with high concentrations of CRP and low triglycerides.

In this context, the inflammation as assessed by CRP is present between 30% and 60% of American north and Europeans individuals in dialysis (59). In addition, values of CRP higher than 5 mg/L (60) or 10 mg/L (61,62) have been positively associated to cardiovascular mortality. Inflammatory markers such as TNF- α and CRP are powerful independent predictors of risk for atherosclerosis, cardiovascular disease and mortality in HD individuals (63). The study of Nakagawa et al. (64) has shown that TNF- α and CRP were positively associated with the causes of cardiovascular mortality, after adjusting for age and sex. When stratified by GNRI, TNF- α and CRP were positively associated with all-cause mortality, only in malnourished individuals. This is supported by the finding of Carlsson et al. (65), concerning the slightly higher values of TNFR 1 and 2 in subjects with malnutrition. However, inflammation can elevate risk of mortality in patients with ESRD in HD by increasing cardiovascular risk and malnutrition.

Thus, the inflammation in individuals in HD, particularly evaluated by the CRP, is not only related to the cardiovascular alterations, including atherosclerosis, but it is also one of the key points in the development of PEM, stimulated by the oxidative stress. This fact can be reversed through a better follow-up of these individuals through PCR, TNF- α , IL-6, identifying the evolution of inflammation and providing better nutritional support, aiming to improve the clinical picture of the individual with ESRD in HD.

CONCLUSIONS

In the absence of a gold standard to assess the mortality risk of HD individuals, application of one of the subjective methods together with adiposity and lean mass indicators, and CRP concentration in the clinical-nutritional practice could offer more accurate mortality risk in this population. Although oxidative stress biomarkers in ESRD are important, more studies are necessary to identify a recognized oxidative stress marker as a mortality predictor in HD.

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Revisión

Disruptores endocrinos en nutrición artificial

Endocrine disruptors in artificial nutrition

Maria B. Badia Tahull, Elisabet Leiva Badosa, Montserrat Colls González y Josep Llop Talaverón

Servicio de Farmacia. Hospital Universitari Bellvitge. L'Hospitalet de Llobregat, Barcelona

Resumen

Los ftalatos son unos compuestos químicos clasificados como disruptores endocrinos que están presentes en prácticamente todos los entornos de la vida cotidiana. En el campo de la nutrición artificial son relevantes porque se encuentran como plastificantes en las líneas de infusión elaboradas con PVC. Son moléculas lipófilas que se unen débilmente al PVC y, por lo tanto, se extraen fácilmente por los compuestos lipídicos que forman parte de la nutrición tanto parenteral como enteral, tal y como demuestran diversos estudios. Como disruptores endocrinos, afectan directamente a los órganos reproductivos debido a sus efectos antiandrogénicos y estrogénicos. Favorecen la inflamación y el estrés oxidativo y también se relacionan con el desarrollo de obesidad, asma, alteraciones neurológicas y oftalmológicas, colestasis y otras alteraciones gastrointestinales. La legislación establece unos rangos máximos de exposición que están pensados para la exposición diaria; sin embargo, en el entorno médico la exposición sigue un patrón diferente, más puntual y con picos muy altos, para los cuales no hay márgenes descritos, por lo que se recomienda evitar la exposición siempre que sea posible. La industria trabaja en el desarrollo de plastificantes alternativos para los cuales la experiencia de uso es todavía limitada. Actualmente, en el campo de la nutrición artificial se recomienda utilizar líneas de infusión tanto intravenosa como enteral libres de ftalatos.

Palabras clave:

Ftalato. Nutrición artificial. Plastificantes. Disruptores endocrinos. DEHP. PVC.

Abstract

Phthalates are chemical compounds classified as endocrine disruptors which are present in practically every environment of daily life. In the field of artificial nutrition, they are relevant because they are found as plasticizers in infusion lines made with PVC. They are lipophilic molecules which weakly pair with PVC and, therefore, they are easily extracted by the fatty compounds that are part of both the parenteral and enteral nutrition, as various studies show. As endocrine disruptors, they directly affect the reproductive organs because of their antiandrogenic and estrogenic effects. They promote inflammation and oxidative stress and they are also related to the development of obesity, asthma, neurological and ophthalmic disorders, cholestasis and other gastrointestinal disorders. The legislation establishes the highest recommended exposure level for daily exposure; however, in the medical environment the exposure follows a different pattern, more occasional with very high peaks, for which there are no established thresholds, that is why it is recommended to avoid exposure whenever possible. The industry is working on the development of alternative plasticizers, for which the use experience is still limited. Currently, in the field of artificial nutrition it is recommended to use phthalate-free intravenous and enteral infusion lines.

Key words:

Phthalate. Artificial nutrition. Plasticizers. Endocrine disruptors. DEHP. PVC.

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Correspondencia:

Maria B. Badia Tahull. Servicio de Farmacia. Hospital Universitari Bellvitge. Carrer de la Feixa Llarga, s/n, 08907 L'Hospitalet de Llobregat, Barcelona
e-mail: mbadia@bellvitgehospital.cat

DISRUPTORES ENDOCRINOS

Los disruptores endocrinos son compuestos que interfieren con la producción, liberación, transporte, metabolismo, unión, acción o eliminación de las hormonas naturales responsables del mantenimiento de la homeostasis y de la regulación de los procesos de desarrollo (1).

Pueden tener origen natural, derivados de animales, de humanos o de plantas (fitoestrógenos), pero la mayor preocupación la generan los disruptores que tienen origen químico, conocidos por su acrónimo en inglés EDC (*endocrine-disrupting chemical*). La mayoría de ellos son pequeñas moléculas lipófilas que incluyen una amplia variedad de clases químicas (2) como pesticidas, componentes de la industria del plástico y otros subproductos industriales y contaminantes. Los EDC más frecuentes dentro de la industria de los plásticos incluyen compuestos polifluoroalquilados, los retardantes bromados de llama, los alquilfenoles, el bisfenol A y los ftalatos (2). Son estos últimos, los ftalatos, los que tienen mayor interés en el campo de la nutrición artificial.

¿QUÉ SON LOS FTALATOS?

Químicamente, son diésteres sintéticos del ácido dialquil ftálico o alquil aril ésteres del ácido 1,2 bencenodicarboxílico (3) y se pueden agrupar en función de su peso molecular. Los de bajo peso molecular son el dimetilftalato (DMP), el dietilftalato (EDP) y el dibutylftalato (DBP), y los de alto peso molecular son el dietil hexil ftalato (DEHP), el diisononil ftalato (DINP), el didisodecil ftalato (DIDP) y el benzil butil ftalato (BBzP) (4). Todos ellos se utilizan como plastificantes. Los de bajo peso molecular se utilizan principalmente en cosméticos y productos de cuidado personal, mientras que los de alto peso molecular se asocian más con lo que comúnmente denominamos plásticos, principalmente el PVC (policloruro de vinilo) (5-7). Producidos en grandes cantidades desde los años 30, prácticamente todos los productos de consumo industrial contienen ftalatos o trazas de ellos. Se encuentran tanto en pinturas y solventes industriales como en juguetes, productos de cuidado personal y equipamientos médicos.

Los ftalatos se caracterizan por no estar unidos covalentemente a la matriz del polímero, por lo que resultan muy fáciles de extraer y son cedidos fácilmente, contaminando desde la comida a prácticamente todos los entornos cerrados (8). Se ingieren con la dieta, vía inhalada, vía dérmica, vía transplacentaria, durante la lactancia y por contacto directo de los dispositivos médicos con los fluidos biológicos (9-11).

Ya hemos comentado que se utilizan como plastificantes del PVC, que es el plástico que posee la mayor cuota del mercado de los productos sanitarios. Las ventajas del PVC son la estabilidad química, la biocompatibilidad, la claridad, la transparencia, la flexibilidad, la duración, la resistencia química, la resistencia mecánica, la facilidad para la esterilización y el bajo coste (12). El plastificante más frecuentemente utilizado es el DEHP, que da al PVC flexibilidad, fuerza, claridad óptica y resistencia a la variación de un amplio margen de temperaturas (13). El PVC puede contener entre el 20% y el 40% de DEHP en peso.

Cuando el PVC entra en contacto directo con la sangre o con fluidos que contienen lípidos (nutrición enteral [NE], nutrición parenteral [NP] o fármacos lipófilos), el DEHP puede migrar muy fácilmente y entrar en el torrente sanguíneo. Una vez en el organismo, los ftalatos tienen una vida media corta y se metabolizan rápidamente en dos fases. En la primera, los diésteres de ftalato se hidrolizan a sus formas de monoéster (forma utilizada para la monitorización de la exposición) y otros metabolitos a través de una gran variedad de conversiones enzimáticas. En la segunda fase, los monoésteres conjugados se excretan en la orina (4). La presencia de ftalatos en orina es generalizada. El metabolito más importante es el mono(2-etilhexil)ftalato (MEHP), que se piensa que es responsable de la mayor parte de la toxicidad del DEHP (14).

¿DÓNDE SE ENCUENTRAN?

En medicina, los ftalatos están presentes principalmente en los hemoderivados (las bolsas de almacenamiento son de PVC), en los tubos endotraqueales y torácicos, en los equipos de infusión intravenosa y en las líneas de administración de nutrición enteral (15). El grado de la exposición depende de la frecuencia y la duración del procedimiento y del tipo de dispositivo médico (16-18). Algunas técnicas presentan un alto grado de exposición (hemodiálisis, diálisis peritoneal, trasplante de corazón o cirugía de revascularización coronaria, membrana de oxigenación extracorpórea, transfusiones, nutrición parenteral, nutrición enteral).

En el caso de la NP, Baget y cols. (19) confirmaron la migración de DEHP desde la línea de infusión al torrente sanguíneo y que la cantidad migrada depende del tipo de lípido utilizado en la emulsión. Estudiaron seis emulsiones lipídicas (EL) a tres tiempos distintos (inicial, una hora después de iniciar la infusión y a las 24 horas) y analizaron también muestras originales de cada uno de los aceites utilizados para la fabricación de las EL (soja, coco, oliva y bacalao). Confirmaron que la extracción mayor correspondía al aceite de oliva, aunque también era alta en el aceite de pescado. En este último (pescado) lo atribuyeron a las características fisicoquímicas correspondientes a una formulación al 10% (menos triglicéridos y más fosfolípidos). Concluyeron estos autores que la NP es capaz de extraer los ftalatos de las líneas de infusión en unos ratios de amplio margen y que los factores que influyen en esta extracción son el tipo de EL, la longitud del tubo, el contenido de DEHP en el sistema, la velocidad de infusión y la temperatura ambiente.

Kambia y cols. (20) administraron durante 24 horas, utilizando equipos de PVC, cuatro formulaciones distintas de NP preparadas en bolsas EVA (etilvinilacetato). Las administraron en dos tiempos, el primero inmediatamente después de la preparación o el segundo tras el almacenamiento durante una semana a una temperatura de 4 °C. Confirmaron que había extracción de DEHP y que esta dependía tanto de la concentración del contenido lipídico como de la velocidad de infusión, así como que el grado de extracción del ftalato permanecía estable tras una semana de almacenamiento a 4 °C. La extracción era mayor a mayor concentración lipídica y

a menor flujo de administración, es decir, que el tiempo total de contacto entre la preparación y el equipo aumenta la extracción.

En el caso de la NE, también se confirma la extracción del ftalato cuando se utilizan líneas de PVC. Ni la silicona ni el poliuretano, con un coste superior al PVC, contienen ftalatos. Subotic y cols. (21) estudiaron la extracción de DEHP administrando una mezcla con una parte de jugo gástrico y dos partes de NE durante 28 días, y cuantificaron la liberación de ftalatos comprobando que el pico máximo de extracción se producía en la segunda semana.

¿QUÉ EFECTOS PRODUCEN?

DEHP y MEHP son tóxicos tanto testiculares como ováricos y afectan a la reproducción (1). Pueden producir alteraciones morfológicas gonadales y/o alteraciones funcionales en ambos sexos. Tienen efecto antiandrogénico y estrogénico en el periodo perinatal. Inhiben directamente la síntesis de testosterona en las células de Leydig y también pueden interferir con la expresión génica de los reguladores del colesterol y la homeostasis de los lípidos o las señales de insulina disminuyendo la síntesis de testosterona (22). En ratones machos, los estudios experimentales muestran una sutil toxicidad en la reproducción con alteraciones confirmadas por diversos estudios en humanos. Estos síntomas se conocen como el "síndrome del ftalato". Se aprecian signos de feminización, siendo la reducción de la distancia anogenital la primera indicación de una desmasculinización general (23,24). Criptorquidia e hypospadias, bajo tamaño de pene y testículos y ginecomastia en la pubertad son otros de los signos, así como una disminución de la calidad del esperma relacionada con una alteración de las mitocondrias testiculares por el estrés oxidativo que induce la apoptosis de los espermatozoides causando la atrofia orgánica (25). Algunos estudios los relacionan con cáncer testicular (25,26). La toxicidad ovárica se manifiesta más tarde en forma de endometriosis o pubertad precoz. Los estudios *in vivo* demuestran que las concentraciones urinarias maternas de metabolitos de ftalato se asocian con una edad gestacional más corta y fetos con menor distancia anogenital (27). La concentración de ftalatos en leche materna y el ratio de LH/esteroides libres en los niños amamantados indican un posible efecto adverso en las células de Leydig o en el eje pituitario-gonadal (28). La menor movilidad de los espermatozoides, que llega a citotoxicidad en incubación prolongada (96 horas), se ha corroborado en estudios epidemiológicos que correlacionan la exposición a ftalatos y la baja concentración y motilidad del esperma (29).

Además de los problemas de desarrollo y reproductivos, se incrementa la preocupación por los problemas metabólicos ligados a los EDC (2). Se clasifican como obesógenos porque pueden alterar críticamente las vías de la adipogénesis, el metabolismo lipídico o el balance energético, pudiendo iniciar una exacerbación de la obesidad (8). En humanos la concentración de algunos metabolitos de los ftalatos correlaciona positivamente con la obesidad abdominal (30).

Sobre la inmunidad, inducen la inflamación e inhiben su resolución favoreciendo el estrés oxidativo (3,31,32). Kambia y cols. (33),

en pacientes con NP, relacionan la elevación de los niveles plasmáticos de DEHP con incrementos plasmáticos de malondialdehído, un parámetro indicativo del aumento del estrés oxidativo.

Afectan al desarrollo pulmonar (3,11). El alargamiento de los espacios aéreos terminales junto con una reducción del número de espacios y de la superficie total disponible para el intercambio gaseoso, observado en ratones, se asemeja a la displasia broncopulmonar de neonatos pretérmino (34). Por otra parte, cada vez son más los estudios que relacionan la exposición a ftalatos con lesiones conducentes a asma (9,35).

Se relacionan con alteraciones gastrointestinales (15). Se les atribuye algún papel en la enterocolitis necrotizante ya que en conejos, tras tres semanas de exposición, se observaron fibrosis, necrosis celular, proliferación de ducto biliar y otras alteraciones características de estrés oxidativo (36). En cuanto a la toxicidad hepática, se postula que el DEHP y algunos compuestos de estructuras similares aumentan el estrés oxidativo como la peroxidación lipídica. En ratones se ha observado tanto un agrandamiento del hígado acompañado de la alteración de las enzimas hepáticas como la aparición de cáncer hepático relacionado con el estrés oxidativo mediado por H_2O_2 (2). Por otra parte, la alteración directa de actividades enzimáticas del metabolismo hepático puede resultar en un aumento de la toxicidad de agentes tóxicos endógenos y exógenos como fármacos. En monos, ya que compiten por el sistema de excreción, se ha visto una reducción en la excreción canalicular de bilirrubina y, por lo tanto, una asociación con la colestasis (37). Von Rettbert y cols. (38) seleccionaron niños de una unidad de críticos, menores de dos años y tratados con NP con lípidos durante más de 14 días. Compararon casos similares de la época en la que los equipos de infusión contenían ftalatos con otros en los que las líneas ya eran libres de ftalatos. Concluyeron que el riesgo de desarrollar colestasis se incrementa 5,6 veces cuando se utiliza un sistema de infusión de NP con PVC y que este es uno de los factores con significación estadística asociados al desarrollo de colestasis. Los otros dos factores estadísticamente significativos fueron la inflamación sistémica y la cirugía.

En relación con las alteraciones neurológicas (15), en ratones se observa una reducción de la innervación y de la densidad de las células neuronales en regiones específicas del hipocampo (39,40). Y finalmente, el último sistema afectado es el oftalmológico, ya que en la experimentación con ratas preñadas se observó que los fetos mostraban alteraciones en el desarrollo vascular que compartían características con la retinopatía de los prematuros (41).

¿CUÁL ES EL MARCO LEGAL?

La Agencia Internacional para la Investigación del Cáncer (IARC) acepta la carcinogenicidad del DEHP en animales de experimentación y desde 2008 clasifica el DEHP como "posiblemente cancerígeno para seres humanos" (grupo 2B). En cuanto a la reproducción, el DEHP se clasifica en la categoría 1B para toxicidad reproductiva (14).

El rango de la carga corporal proveniente de todas las fuentes, excluyendo exposición ocupacional, se estima en 1-30 µg/kg/d, aunque recientes investigaciones en biomonitorización sugieren que la exposición mediana actual es de 2-5 µg/kg/d (42).

El valor de ingesta diaria tolerable (TDI) de DEHP se ha fijado en 48 µg/kg/d, basado en el NOAEL (nivel de efectos adversos no observados) de toxicidad reproductiva en ratas (4,8 mg/kg/d con el factor de corrección 100) (15). El TDI es un valor establecido considerando una exposición continua, pero la exposición a través de dispositivos médicos es transitoria y puede llegar a ser puntualmente muy elevada. En pacientes dializados se puede superar entre dos y 12 veces con valores pico 40 veces más altos que el TDI. Además de los pacientes dializados, otros grupos de riesgo identificados son los neonatos prematuros en unidades de cuidados intensivos (42).

La directiva europea 2007/47/EC, efectiva desde marzo de 2010, regula la utilización de dispositivos médicos que contienen ftalatos. Por su parte, en julio de 2015 Francia emitió una prohibición que obliga a que el material sanitario utilizado en neonatos, pediatría y unidades de maternidad no contenga DEHP (43).

AL ADMINISTRAR NUTRICIÓN PARENTERAL ¿PASAN Y SE ACUMULAN LOS FTALATOS EN SANGRE?

Kambia y cols. (44) estudiaron una población pediátrica con parenteral cíclica de como mínimo un mes de duración. Cuantificaron el contenido de ftalatos plasmáticos antes de iniciar la infusión y al finalizar la misma (12 horas). Obtuvieron que, en el momento de inicio de la administración, el DEHP no fue cuantificable en cuatro pacientes (18%). En un paciente (5%) los niveles no fueron cuantificables ni al inicio ni al final de la NP. En 17 pacientes (77%) fueron cuantificables al inicio de la NP, con mucha variabilidad interindividual. Estos resultados indican que los niveles residuales de DEHP no se eliminan totalmente durante el periodo de descanso de la NP. Asimismo, como era esperable, tras la administración de la NP, las concentraciones plasmáticas aumentaban significativamente, aunque de forma muy variable tanto inter como intraindividualmente. Los autores, atribuyen estas variaciones encontradas al diferente grado de madurez metabólica. Por otra parte, la detección de DEHP en sangre en 20 muestras de controles sanos sin tratamiento con NP dio resultados negativos.

¿HAY PLASTIFICANTES ALTERNATIVOS?

Bernard y cols. (13), en un artículo de revisión, concluyen que el proceso metabólico para muchos de los plastificantes alternativos es similar entre ellos. En líneas generales, se metabolizan rápidamente y no se acumulan, lo cual conduce a bajas dosis remanentes a las 48 horas. Sin embargo, a pesar de compartir la ruta de excreción, el perfil toxicológico de cada plastificante es diferente. Centrándonos en los tres más utilizados en los equipos de nutrición artificial:

- El DINCH (di-isononil ciclohexanos-1,2-dicarboxilato) no es tóxico para la reproducción ni es un disruptor endocrino y aunque no se ha visto que induzca mutagenicidad o genotoxicidad, sí que produce toxicidad renal e hiperplasia tiroidea en ratas.
- El TOTM (tri [2-etilhexil] benceno - 1,2,4 - tricarboxílico) muestra una toxicidad hepática más débil que la del DEHP debido a su baja capacidad de transformación metabólica. El 75% de la dosis oral se elimina por las heces de forma primaria como un compuesto no alterado.
- El ATBC (acetil tri-n-butil citrato), aun cuando muestra mucha menor toxicidad que el DEHP debido principalmente a su rápida absorción y excreción, es un compuesto que preocupa por la facilidad con la que se libera del PVC.

El SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks) recomienda que los investigadores sigan reemplazando el DEHP de todos los productos. Se necesita más información sobre los materiales alternativos, su perfil toxicológico y propiedades de liberación en condiciones reales de uso para desarrollar materiales alternativos que sean eficientes y seguros (14,45).

CONCLUSIÓN

La administración de nutrición artificial puede ir acompañada de la administración de ftalatos que actúan como disruptores endocrinos y metabólicos, cuya toxicidad está claramente demostrada en animales. En humanos, hay indicios que han llevado a que las agencias reguladoras los clasifiquen como cancerígenos y como tóxicos para la reproducción en humanos. Por lo tanto, se recomienda evitar su uso y, en nutrición artificial, tenemos alternativas para no utilizarlos. En cuanto a los nuevos plastificantes, en el momento actual falta información y experiencia de uso.

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Revisión

Sugar-sweetened beverage consumption and obesity in children's meta-analyses: wrong answers to right questions

Consumo de bebidas azucaradas y obesidad en metaanálisis de estudios realizados en niños: respuestas equivocadas para preguntas correctas

Mariela Nissensohn^{1,2,3}, Daniel Fuentes Lugo⁴ and Lluís Serra-Majem^{1,2,3}

¹International Chair for Advanced Studies on Hydration (CIEAH). Universidad de Las Palmas de Gran Canaria. Las Palmas, Spain. ²Research Institute of Biomedical and Health Sciences. Universidad de Las Palmas de Gran Canaria. Las Palmas, Spain. ³CIBER OBN. Biomedical Research Networking Center for Physiopathology of Obesity and Nutrition. Carlos III Health Institute. Madrid, Spain. ⁴Faculty of Health Sciences. Universidad Autónoma del Carmen. Ciudad del Carmen, Mexico

Abstract

Background: recent studies assert that sugar-containing drinks may play a key role in the etiology of obesity. However, scientific reviews show contradictory results. Whether there is just association or clear causation still is a matter of debate. It is also subject to discussion whether the quality/adequacy of the different studies may influence their outcome.

Objective: the aim of this study is to explore the most recent scientific evidence focused on sugar-sweetened beverages (SSB) and child obesity and to further analyze the adequacy of the meta-analyses in terms of their results, with special emphasis in the methodology, clarity and transparency of their procedures.

Methods: only meta-analyses of randomized control trial studies were selected. The search was performed on PubMed and Cochrane Website until January, 2016. Adherence to PRISMA statement was assessed.

Results: six meta-analyses were included. All of them showed some degree of evidence of heterogeneity in their pool estimates. Two of them showed a positive association between SSB and obesity but the other four found no association. The adherence to the PRISMA criteria was higher in two of the meta-analyses that showed opposite conclusions regarding the association or non-association of SSB and obesity in children. Thus, there is no relation between the adequacy of the meta-analyses to the PRISMA criteria and the results obtained.

Conclusion: the use of meta-analysis as a scientific tool still demands more polishing, agreement and spread out use by researchers. SSB are being accused of being the main cause of the existing obesity, and obviously they are part of the problem, but this subject requires a broader approach that includes a thorough analysis of diet and lifestyle and a stronger body of scientific evidence based on data from epidemiological studies conducted in different populations.

Key words:

Sugar-sweetened beverage. Obesity. Children. Meta-analyses.

Resumen

Antecedentes: estudios recientes afirman que las bebidas azucaradas desempeñan un papel clave en la etiología de la obesidad. Sin embargo, las revisiones científicas muestran resultados contradictorios. Si es solo una asociación o es claramente una causa continúa siendo un tema de debate. También se discute si la calidad/adequación de los diferentes estudios puede influir en sus resultados.

Objetivo: el objetivo de este estudio fue explorar la evidencia científica más reciente enfocada a las bebidas azucaradas y a la obesidad infantil y analizar la adecuación de los metaanálisis en términos de sus resultados, con especial énfasis en la metodología, claridad y transparencia de sus procedimientos.

Método: se seleccionaron metaanálisis realizados con estudios de ensayos aleatorios controlados. La búsqueda se realizó en PubMed y en Cochrane hasta enero de 2016. Se evaluó la adherencia a los criterios PRISMA.

Resultados: se incluyeron seis metaanálisis. Todos ellos mostraron cierto grado de heterogeneidad en sus estimaciones ponderadas. Dos de ellos mostraron asociación positiva entre bebidas azucaradas y obesidad, pero los otros cuatro no encontraron asociación. La adhesión a los criterios PRISMA fue mayor en dos metaanálisis que mostraron conclusiones opuestas sobre la asociación o no asociación de las bebidas azucaradas y la obesidad en niños. Por lo tanto, no existe relación entre la adecuación de los metaanálisis a los criterios PRISMA y los resultados obtenidos.

Conclusión: el uso del metaanálisis como herramienta científica todavía requiere un mayor refinamiento, consenso y difusión por parte de los investigadores. Las bebidas azucaradas están siendo acusadas de ser la causa principal de la obesidad existente, y es obvio que son parte del problema, pero este tema requiere un enfoque más amplio que incluya un análisis exhaustivo de la dieta y del estilo de vida y una evidencia científica más sólida fundamentada en datos de estudios epidemiológicos realizados en diferentes poblaciones.

Palabras clave:

Bebidas azucaradas. Obesidad. Niños. Metaanálisis.

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Correspondence:

Mariela Nissensohn. Research Institute of Biomedical and Health Sciences. Universidad de Las Palmas de Gran Canaria. Paseo Blas Cabrera Felipe "Físico", s/n. 35016 Las Palmas, Spain
e-mail: mnissensohn@acciones.ulpgc.es

INTRODUCTION

Although obesity is the result of an imbalance of energy homeostasis, the true mechanisms underlying this process and effective strategies for prevention and treatment remain unknown. In general, obesity reflects complex interactions of genetic, metabolic, cultural, environmental, socioeconomic, and behavioral factors (1). It has been suggested that the intake of sugar-sweetened beverages (SSB) may promote weight gain and obesity by increasing overall energy intake (2).

There are some studies asserting that sugar-containing drinks may play a key role in the etiology of overweight and obesity in children and adults. In Europe, epidemiological studies focusing on beverage intake and obesity are rather scarce (3). Regarding children and adolescents, there are few studies addressing this subject. However, recent scientific reviews show contradictory findings, highlighting the weaknesses of many studies, which describe the current evidence as "not conclusive" (4), "equivocal" (5), "probable" (6) and "strong" (2,7,8).

Although the relation between SSB and obesity exists, whether this is a mere association or a real causation effect still remains controversial if based on current available scientific evidence. Thinking that the raise in childhood obesity occurs due to a single dietary factor, sugary drinks in this case, is a very simplistic approach that underestimates the real problem. Dietary elements work together with a lot of others factors like computer use less physical activity, higher portions sizes, etc. that lead to obesity. Most studies fail to detect how SSD or other aspects of diet and lifestyle have contributed to excess body weight. Whether the effect of sugar and calories from SSBs is worse than the effect of some other food is unclear (9). As Hu (2013) wrote in his article (10), from a public health point of view, identifying dietary determinants of long-term weight gain is critical for reducing the prevalence of obesity in the population. However, for many other scientists dietary determinants are not enough. It is really important to clarify the overall lifestyle involved. As it is well known, obesity is a multifactorial condition. Then, the magnitude of effects depends on the amount and length of exposure. Furthermore, according to Gibson (8), most of the evidence is dominated by American studies where SSD consumption tends to be higher. That may be less applicable to the European context, where consumption is substantially lower.

On the other hand, it is well known that the use of review articles and meta-analysis has become an important method employed in epidemiological research. However, the analysis of published papers in a meta-analysis has several considerable limitations (11). One of those is that studies may differ considerably in their designs, data collection methods and the definition of the exposure and confounder variables. A special dilemma arises when separate studies adjust for different confounding factors. Sometimes, the pooled estimate from a group of studies is published even if strong statistically significant heterogeneity between studies results was found (12).

It is also subject to debate whether the quality and adequacy of the different studies may influence the outcome. It is logical that

when the study is conducted within a rigorous methodological frame, publishing clear results will positively influence the generation of new knowledge and, in consequence, the reliability of reached conclusions will increase. In this sense, there is a new trend of using different tools to assess the methodological aspects of each study to legitimize the quality of the scientific information. Some of these tools are AMSTAR, A Measurement Tool to Assess Systematic Reviews; GRADE, Grading of Recommendations Assessment, Development and Evaluation; and PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (13). These are scales and verification of data quality lists, which differ among one another in terms of their items, validity and scoring system. Most of them are a valuable resource for readers, reviewers and journal editors, but they are in constant update. Then, we must be especially careful when considering their use and when interpreting the resulted information that arises from them.

For all the above reasons, the aim of this study is to explore the most recent scientific evidence focused on SSB and child obesity and to analyze the adequacy of the meta-analyses in terms of their results, with special emphasis on the applied methodology and the clarity/transparency of their procedures. Furthermore, to analyze the possible causes for which a consensus has not yet been found in the scientific evidence available on this topic and why it still remains a source of intense debate.

MATERIALS AND METHODS

SYSTEMATIC SEARCH AND SELECTION CRITERIA

We searched the literature for published meta-analyses of epidemiologic studies, whose primary aim was to describe the relation between SSB intake and obesity in children. Only meta-analyses including Random Control Trials (RCTs) were selected. The search was performed accessing PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed>) and Cochrane Collaborative Website (<http://www.cochrane.org>) between January, 2001 and January, 2016, using the following search terms: "beverage(s)" or "soft drink(s)" or "soda" AND "obesity" or "weight", including MESH-terms. In addition, reference lists of the retrieved articles were searched to find other additional relevant reviews.

Articles were considered as eligible for inclusion if they were: a) systematic reviews and meta-analyses that include at least two RCTs in their study selection; b) studies with a primary focus oriented towards SSB intake and obesity in children. Exclusion criteria were: a) reviews of dietary behaviors or patterns that identified SSB intake as one of many of the factors, but did not study exclusively their impact on body weight; b) systematic reviews and meta-analyses which did not include any RCT study in their analysis; c) articles published prior to the past decade (not earlier) because the discussion regarding the need for a systematic approach to reviewing the literature has evolved, and also a consensus has emerged by which a systematic approach is to be preferred over other more subjective approaches (14).

DATA ABSTRACTION

A data extraction form was designed to obtain descriptive information of each meta-analysis evaluated, including information of the study population, the RCTs included in each one, specific details of database searches, inclusion and exclusion criteria, heterogeneity of the pooled analyses and conclusions (the final statement on the association between SSB consumption and obesity/weight gain or not), adherence to PRISMA (13), data regarding the journal in which the reviews were published (the impact factor of each one, the year of publication of the article) and industry funding. Those studies which did not specify industry funding of any sort were considered by default as “not supported by the industry”. Authors that received funding for different activities were not taken into account.

In addition, the data obtained from the primary studies included in each review (RCTs) in terms of relation to the outcomes, population studied, type of intervention, conclusions as well as funding were gathered.

ADEQUACY ASSESSMENT

Among all the assessment tools that have been elaborated during the last few years to assess the adequacy of systematic reviews and meta-analyses, we employed PRISMA (13) adherence. This tool was not designed to become an instrument for evaluating the quality of the articles. It was conceived for enhancing clarity and transparency of published systematic reviews and meta-analyses. It allow to assess whether a step has been completed or not, but not necessarily whether it has been done in the correct way (<http://www.prisma-statement.org>). It comprises 27 items; each of them has an assigned value of 1 for “yes”, 0 for “no” and 0.5 for cases in which the answer is “partial”.

RESULTS

In total, six meta-analyses were included in our study. The main characteristics of the reviews are presented in table I. Malik et al., Forshee et al., Vartanian et al. and Mattes et al. (7,15-17) documented their search strategies and the inclusion and exclusion criteria. All meta-analyses performed their searches in more than one database, with at least one of them being in either Medline or PubMed, and a second source was also searched (either a database or hand-searched reference lists). Three meta-analyses (15,17,18) included a flowchart of the “study search and selection process” as recommended by PRISMA. A test of heterogeneity was developed in all the studies. The I^2 index, which measures the extent of the heterogeneity following with a p-value for this statistic, was showed in most of the studies. Substantial heterogeneity was present in most of the cases (it means a high I^2 index and a p-value for this I^2 lower than 0.05). When the I^2 Index was low, the p-value did not show statistical significance. This situation indicated the presence of heterogeneity, which somewhat compromises the validity of the

pooled estimates (19). Only Vartanian study (7) showed heterogeneity as a Q statistics value, and in this case it was low.

Table II depicts adherence to PRISMA (11) percentages. Similarly to the results obtained by Bes Rastrollo et al. study (20), only two systematic reviews (15,18) which specifically used PRISMA guidelines to report their data were identified. Adherence to PRISMA guidelines (13) was 85% and 94%, respectively. In other studies, such as Mattes et al., Kaiser et al., Forshee et al. or Vartanian et al. (7,16,17,21), adherence to PRISMA was 83%, 74%, 72% and 50%, respectively. The last two papers were published before PRISMA (13) was routinely used, but back then, there was a similar available tool called QUORUM.

Two of the articles included found a positive association between SSB and obesity (7,15). On the other hand, four articles found no association between SSB and obesity (16-18,21).

Table III shows the data obtained from the primary studies (RCTs) included in each review. Of all RCTs, only two authors were included in all six meta-analyses (22,23) and one author was included in four meta-analyses (24). Three meta-analyses (7,18,21) included RCTs which were not considered in any other meta-analysis (25-32). In some of these RCTs, authors studied different variables, conducted different interventions in different populations, and also some of them did not include a study-drop-outs analysis, nor did assessed compliance among other sources of heterogeneity. Most of the included studies lacked long term follow-up, keeping usually less than ten weeks long, suggesting the need of longer term data to conduct further analysis.

QUALITY OF META-ANALYSIS

Some authors recently reviewed the quality of SR on SSB and some health outcomes using the validated instrument AMSTAR, which is a one-page tool with eleven questions. Weed et al. (33) concluded that “the comprehensive reporting of epidemiologic evidence and use of systematic methodologies to interpret evidence was underused in published reviews on SSB and health”. They suggest a dubious quality in the currently available scientific evidence in this area with the exception of a few studies. Massougboji et al. (34) concluded that “there is no consensus on the strength of the evidence on causality, and that available quality-assessment tools have limitations, and many contextual factors beyond the intrinsic characteristics of the reviews may influence their conclusions”.

According to the analyses of Keller et al., the quality of the original papers or RCTs included in the reviews or meta-analyses could have suffered from some bias that may hence also introduce some errors (35).

DISCUSSION

Our findings indicated that, opposed to our expectations, there is no clear relation between the adequacy of the meta-analyses (using PRISMA criteria) and the results reached.

Table I. Sugar-sweetened beverages and obesity in children and adolescents: characteristics of meta-analyses evaluated

SR and year of publication	Population group	Databases searched, RCTs included, and inclusion and exclusion criteria	Heterogeneity, some details of methodology and conclusions (meta-analysis estimates)	PRISMA adherence and some others considerations	Journal published, impact factor	Industry funding and conflict of interest
Kaiser et al. 2013 (21)	Children/ adolescents and adults	Databases searched: PubMed, PsycINFO, the Cochrane Collaborative Website, SCOPUS, and Dissertation Abstracts (PROQUEST) RCTs included: James et al. 2004 Ebbeling et al. 2006 Muñoz 2006 (unpublished data) Albala et al. 2008 Sichieri et al. 2009 Tate et al. 2012 De Ruyter et al. 2012 Ebbeling et al. 2012 Inclusion and exclusion: Included: a) human trials; b) ≥ 3 weeks duration; c) random assignment to conditions differing only in consumption of SSBs; and d) including a body weight/composition indices (BMI) outcome	Heterogeneity: Effect size: 0.06; (95% CI: -0.01, 0.13) $I^2 = 59\%$ ($p = 0.02$) in all weight categories Effect size: 0.25; (95% CI: 0.13, 0.38) $I^2 = 49\%$ ($p = 0.07$) only in subjects with overweight / obese at baseline No positive association between consumption of SSB and obesity or overweight indicators Reducing consumption of SSBs in individuals of all weight categories explains 0.09% of the variance in body weight or BMI change. Among individuals who are overweight or obese at baseline, reducing the consumption of SSBs explains 1.54% of the variance in body weight or BMI change The current evidence for the effects of reducing SSB intake on obesity is equivocal. Well-designed studies are required. Even if statistical significance is ignored, the point estimates of effects on BMI reduction are small, accounting for only 1.5% of the variance observed in those who were overweight at baseline	Yes	Obesity reviews Impact factor 2013: 6.87	No and yes

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Table 1 (Cont.). Sugar-sweetened beverages and obesity in children and adolescents: characteristics of meta-analyses evaluated

SR and year of publication	Population group	Databases searched, RCTs included, and inclusion and exclusion criteria	Heterogeneity, some details of methodology and conclusions (meta-analysis estimates)	PRISMA adherence and some others considerations	Journal published, impact factor	Industry funding and conflict of interest
Malik et al. 2013 (15)	Children/ adolescents	Databases searched: PubMed (since 1966), EMBASE (since 1947), and the Cochrane library since 1951) databases RCTs included: James et al. 2004 Ebbeling et al. 2006 Sichieri et al. 2009 De Ruyter et al. 2012 Ebbeling et al. 2012 Inclusion and exclusion: Included: a) were original research (not review, abstract, editorial, letter, or commentary); b) were prospective cohort studies or clinical trials conducted in children or adults; c) reported multivariable-adjusted coefficients for the association between SSBs and body weight from prospective cohort studies or the difference in changes in body weight between intervention and control groups from clinical trials; d) did not combine SSBs with other beverages, foods, or lifestyle factors as a composite exposure; and e) had a control group and intervened for at least two weeks in clinical trials Excluded: did not consider cross-sectional or ecologic studies	Heterogeneity: $I^2 = 74.6\%$ ($p = 0.003$) Positive association in children as well as in adults Non-significant difference in change in BMI from reducing SSB consumption (weighted mean difference [WMD]: -0.17; 95% CI: -0.39, 0.05; $I^2 = 74.6\%$; $p = 0.003$) in the random-effects model From the fixed-effects model results were significant (WMD: -0.12; 95% CI: -0.22, -0.02). This difference is likely a result of the random-effects model giving greater statistical weight to smaller studies and having wider CI in the presence of heterogeneity compared with the fixed-effects model Meta-regressions and sensitive analyses were performed: when stratified by intervention modality, they observed a significant weight reduction among the three RCTs that provided non-caloric beverages as substitutes for SSBs: -0.34 (95% CI: -0.50, -0.18; $I^2 = 0\%$). In contrast, they did not find a significant intervention effect in the two RCTs that used focused school-based education to discourage SSB consumption: 0.01 (95% CI: -0.19, 0.20; $I^2 = 59.6\%$)	Yes	American Journal of Clinical Nutrition Impact Factor 2013: 6.50	No

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Table 1 (Cont.). Sugar-sweetened beverages and obesity in children and adolescents: characteristics of meta-analyses evaluated

SR and year of publication	Population group	Databases searched, RCTs included, and inclusion and exclusion criteria	Heterogeneity, some details of methodology and conclusions (meta-analysis estimates)	PRISMA adherence and some others considerations	Journal published, impact factor	Industry funding and conflict of interest
Te Morenga et al. 2012 (18)	Children/ adolescents	<i>Databases searched:</i> OVID Medline, Embase, PubMed, Cumulative Index to Nursing and Allied Health Literature, Scopus and Web of Science electronic databases <i>RCTs included:</i> Davis et al. 2009 Ebbeling et al. 2006 James et al. 2004 Paineau et al. 2008 Sichieri et al. 2009 <i>Inclusion and exclusion:</i> <i>Included:</i> English language studies were required to report intake of total sugars, component of total sugars (expressed in absolute amounts or as a % of total energy), or intake of sugar containing foods or beverages, assessed by continuous or categorical variables; and at least one measure of body fatness Adults and children free from acute illness (those with diabetes or other non-communicable diseases in which conditions were regarded as stable could be included) RCT required being of at least two weeks duration, and prospective cohort studies were required to be of at least one year duration <i>Excluded:</i> Animal studies, cross sectional studies, and case-control studies	Used a random effects model for the analysis <i>Heterogeneity:</i> $I^2 = 82\%$ ($p = 0.001$) in all studies included <i>No positive association</i> Trials conducted in children with recommendations to reduce intake of SSB and food showed no overall change in body weight They found no association between the advice to reduce intake of dietary sugars and change in BMI or BMI z-score in children (0.09, 95% CI -0.14 to 0.32). Significant heterogeneity was observed ($I^2 = 82\%$, $p = 0.001$). Excluding the study by Davis et al. (34), which showed a high risk of bias for two or more validity criteria, it did not alter the effect estimate	Yes	British Medical Journal Impact factor 2012: 1.58	No

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Table I (Cont.). Sugar-sweetened beverages and obesity in children and adolescents: characteristics of meta-analyses evaluated

SR and year of publication	Population group	Databases searched, RCTs included, and inclusion and exclusion criteria	Heterogeneity, some details of methodology and conclusions (meta-analysis estimates)	PRISMA adherence and some other considerations	Journal published, impact factor	Industry funding and conflict of interest
Mattes et al. 2011 (17)	Adults and children/adolescents	<i>Databases searched:</i> PubMed, hand-searched references plus four other databases <i>RCTs included</i> (this study only included RCT): James et al. 2004 Ebbeling et al. 2006 James et al. 2007 Sichieri et al. 2009 Albala et al. 2008 Muñoz 2006 (unpublished data) <i>Inclusion and exclusion:</i> <i>Included:</i> randomized controlled trial, ≥ 3-wk duration, in humans. An outcome as weight, BMI, obesity, % body fat or some other indicator of adiposity. No language restriction was applied <i>Excluded:</i> subjects were not pregnant, acutely ill or under severely stressed conditions (e.g., soldiers in field exercises, sugar cane harvesters in intense heat, etc.)	Fixed effects meta-analysis <i>Heterogeneity:</i> $I^2 = 0\%$ ($p = 0.643$) all studies except James et al. 2007 $I^2 = 22.36\%$ ($p = 0.266$) all studies $I^2 = 31.23\%$ ($p = 0.213$) all studies except Muñoz et al. 2006 $I^2 = 0\%$ ($p = 0.522$) all studies except Muñoz et al. 2006 and James et al. 2007 $I^2 = 0\%$ ($p = 0.529$) all studies except Albala et al. 2008 and James et al. 2007 <i>No positive association.</i> Data are not conclusive. Six of the trials included in their study showed significant dose-dependent increase in weight among studies that added SSB to the diet but also found no effect on BMI in other six studies which intended to reduce SSB “Current evidence does not support conclusively that consumption of nutritive sweetened beverage (NSB) uniquely contributed to obesity or that reducing their consumption decreases BMI levels in general” The overall estimate of standardized mean difference in BMI was extremely close to zero (-0.037; $SE = 0.042$; $p = 0.378$). The CI 95% was -0.120 to 0.046, indicating that the overall effect estimate was not significant. Heterogeneity $I^2 = 0.00\%$ not significant ($p = 0.643$). As a sensitivity analysis, they repeated the meta-analysis in four different ways, but the results were not noticeably different from that of the primary analysis.	Partially Limitations: - Data from adults and children were not taken into account as separate groups The author excluded three RCTs that were included in other of the meta-analyses (Vartanian et al. 2007) because “they were not experiments related to the effects of SSBs on weight or obesity”.	Obesity reviews Impact factor 2011: 6.87	Yes and yes

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Table I (Cont.). Sugar-sweetened beverages and obesity in children and adolescents: characteristics of meta-analyses evaluated

SR and year of publication	Population group	Databases searched, RCTs included, and inclusion and exclusion criteria	Heterogeneity, some details of methodology and conclusions (meta-analysis estimates)	PRISMA adherence and some others considerations	Journal published, impact factor	Industry funding and conflict of interest
Forshee et al. 2009 (16)	Children/ adolescents	<i>Databases searched:</i> Medline hand-searched references, plus six others databases that contain unpublished scientific studies <i>RCTs included:</i> Ebbeling et al. 2006 James et al. 2004 <i>Inclusion and exclusion:</i> <i>Included:</i> English language with human subjects < 19 y of age, developed between 1966-2006 <i>Excluded:</i> ecologic and cross-sectional designs	Used both fixed-effects and random-effects models and included both longitudinal and RCT studies without performing a sensitivity analysis excluding longitudinal studies <i>Heterogeneity:</i> $I^2 = 73.9\%$ ($p = 0.001$) in all studies included (highly significant) <i>No positive association</i> between consumption of SSB and BMI: "The level of association between SSB intake and BMI in other studies, even that showing statistical significance, was rather small" "The meta-analysis found that the association between SSB intake and BMI was <i>near zero</i>, based on the current body of scientific evidence" (BMI change per one serving of SSB increase: 0.03, 95% CI: -0.01 to 0.07)	Partially Limitations - No flow chart - Use of different instruments to assess SSB intake and body weight gain, and to estimate effect sizes - Different units of time were used among the studies	American Journal of Clinical Nutrition Impact factor 2008: 6.74	Yes (American Beverage Assoc.) and no
Vartanian et al. 2007 (7)	Adults and children/ adolescents	<i>Databases searched:</i> MEDLINE, PsycINFO, Web of Science, and hand-searched references <i>RCTs included:</i> Tordoff et al. 1990 DiMeglio et al. 2000 Grandjean et al. 2000 Raben et al. 2002 James et al. 2004 Van Wymelbeke et al. 2004 Ebbeling et al. 2006 <i>Inclusion and exclusion:</i> Studies and reviews published up to 2007	<i>Heterogeneity:</i> no I^2 data. They use the value of $q = 24.57$, $p = 0.001$ <i>Positive and strong association</i> "Recommendations to reduce soft drink consumption are strongly supported by the available science" (overall average body weight effect size: 0.24, 95% CI: 0.18-0.29) ($p < 0.001$; $q = 24.57$, $p = 0.001$) "We found clear associations of soft drink intake with increased energy intake and body weight". This association was, surprisingly, more present in studies that were not funded by the industry than in those that were They postulate that "future research with a more uniform methodology (ideally experimental designs) would help to clarify the impact of soft-drink consumption on nutrition and health outcomes" and that "intake of SSB was associated with poor nutrition, increased body weight and displacement of more healthy beverages"	No Limitations: - No forest or funnel plot - No sensitivity analysis or meta-regression	American Journal of Public Health Impact factor 2007: 3.56	No and no mention

Table II. PRISMA checklist in %

PRISMA Checklist	Malik et al. 2013 (15)	Te Morenga et al. 2012 (18)	Mattes et al. 2011 (17)	Kaiser et al. 2013 (Update of Mattes et al. 2011) (21)	Forshee et al. 2009 (16)	Vartanian et al. 2007 (7)
Yes %	25.5 (94%)	23.5 (85%)	23 (83%)	20 (74%)	19.5 (72%)	13.5 (50%)
No %	1.5 (6%)	3.5 (15%)	4 (17%)	7 (26%)	7.5 (28%)	13.5 (50%)
Grading of association between SSB and Ob	+	-	-	-	-	+

We believe that controlled trials and systematic reviews with inadequate methodology are more prone to bias (36). It is clear that, in this particular issue, the analysis of the methodology developed is not enough to shed light on this task. Otherwise it is not understood how the meta-analyses with the highest and the lowest adherence to PRISMA found a positive association between SSB and obesity in both cases. This very same situation was also detected in the Keller et al. (35) analyses using the AMSTAR analysis of quality. This situation leads us to consider several points.

First of all, small sample sizes, short follow-ups and different dietary measurement tools used are linked to problems in exposure measurements that can influence the direction of the association between SSBs and weight and change research results (35).

Despite we consider that systematic reviews and meta-analyses of RCTs are the “gold standard” of evidence, and furthermore that the PRISMA checklist used for this analysis as a good tool of items guidelines, the statistical methods for pooling data from different sources have to be better implemented in order to minimize heterogeneity between studies. Our work is based on a limited group of meta-analyses and each one of them, in turn, presents a certain degree of heterogeneity, which indicates different features in each of the included studies. This heterogeneity cannot be ignored; quite the opposite, it is mandatory to find out with further research why these differences are present since they may compromise somehow the validity of the pooled estimates. Even, there are authors who claim that a pooled estimate should not be published if heterogeneity between studies is high, and that in many publications of meta-analysis the problem of heterogeneity is not sufficiently assessed (12). As far as we understand, heterogeneity is another ingredient to account for, but in no way we consider that a study with high heterogeneity should not be published. A meta-analysis should just extract a common estimate when it may truly assume that a common parameter exists; otherwise, it would be advisable to use it just to show and highlight the differences between the results of the various studies available, in order to clarify that it is not possible to combine what is so different (37). Even studies with negative results should be taken into account with the same academic value as the ones with positive results; it is important not to forget that negative findings also contribute to the improvement of science.

Another relevant aspect to consider in our analysis is the possible existence of economic interests and their consequent bias when reaching conclusions. The debate over the influences

of corporate sponsorship on research findings has been always highly thrashed out. However, the issue of “funding source” has recently taken on a special interest, particularly in the realm of obesity research. Addressing this issue is of paramount importance especially in the nutrition field, because inexact data may have negative repercussions in general public health. Bes Rastrollo et al. (20) published a survey where financial conflicts of interest and reporting bias regarding the association between SSB and weight gain were analyzed in a series of studies. Their results show that those systematic reviews with stated sponsorship or conflicts of interest with food or beverage companies were five times more likely to report conclusions of negative association between SSB intake and weight gain (or obesity) than those which reported no industry sponsorship nor conflict of interest. Nonetheless, this study did not consider the methodological quality of the meta-analyses, but focused mainly on sponsor influence. To add more confusion to the subject, other authors such as Kaiser et al. (38) states that, “in general, the quality of industry-funded studies seems better than non-industry funded research; there is evidence that shows that industry-funding was associated with higher quality reporting”. Scientific research must always pursue the truth, regardless of financial or other interests. The consequences of reaching biased conclusions may affect directly from health care practitioners to the process of decision-making by health policy institutions, posing a threat for public health. Industry and science need to work together in order to achieve worthwhile goals, especially nowadays when research resources are scarce. Kaiser et al. (38) underline that efforts to increase the overall quality of the scientific literature can be achieved through activities that support high quality in reporting and create transparency. Approaching questions from different perspectives with diverse methods but with a strong ethical commitment may be on the one hand appealing to the industry and, on the other hand, able to produce solid outcomes free of sponsor bias (39). Research funding is beneficial and necessary, and scientist should remain aware of potential bias of all types (38,40). In addition, conflicts of interest are not always related to financial relationships, but can also occur because of personal relationships, academic competition, intellectual passion, or political engagement (41). It is very difficult to identify these types of influences, and we cannot exclude their presence in reviews not funded by industry.

Table III. Characteristics of the RCTs included in the meta-analysis

RCT author	Year of publication	Outcome analyzed	Population group	Type of intervention	Conclusion	Funding
DiMeglio and Mattes (29)	2000	Body weight change	7 males and 8 females Age: 22.8 ± 2.73 years	Carbohydrate dietary loads of 1,880 kJ/day were consumed as liquid (soda) or solid (jelly beans) during two four-week periods separated by a four-week washout	Clear positive effect of load of calorically sweetened beverages on subsequent changes in body weight - given soft drinks to consume gained weight over the course of the experiment	Supported by USDA HATCH project (U.S. Department of Agriculture)
Raben et al. (31)	2002	Body weight, fat mass, and blood pressure in overweight subjects	41 subjects (35 women and 6 men; n = 21 for sucrose group and n = 20 for sweetener group) Age: 20-50 y, overweight	For ten weeks, one group received supplemental drinks and foods containing sucrose, while the other group received similar drinks and foods containing artificial sweeteners	Clear positive effect of load of calorically sweetened beverages on subsequent changes in body weight Given soft drinks to consume gained weight over the course of the experiment	Supported by the Danish Research and Development Programme for Food Technology 1990-1994 and Danisco Sugar. Coca Cola (Nordic and Eurasia Divisions), which provided soft drinks for the study
Tordoff and Allewa (28)	1990	Body weight	21 males aged 22.9 ± 0.8 y and 9 females aged 28.2 ± 2.7 y Normal weight	For three weeks, one group received 1,150 g soda sweetened with aspartame or high-fructose corn syrup per day	Positive effect of load of calorically sweetened beverages on subsequent changes in body weight	Supported by the US Department of Agriculture's Competitive Research Grants Program grant 87-CRGR 1-2316
Ebbeling et al. (45)	2006	Body weight: change in BMI (in kg/m ²)	103 adolescents, aged 13-18 y	For 25 weeks, replacing SSBs with non-caloric beverages + instructions and motivation (decreased consumption)	The beneficial effect on body weight of reducing SSB consumption increased with increasing baseline body weight, offering additional support for American Academy of Paediatrics guidelines to limit SSB consumption	Supported by grants from the National Inst. of Diabetes and Digestive Kidney Diseases, the Charles H. Hood Found., and awarded by the National Inst. of Health to support the General Clinical Research Centre at the Children's Hospital Boston No funding from the food industry
James et al. (22)	2004	Body weight: overweight and obesity (BMI)	644 children, aged 7-11 y	One-year educational intervention program focused on decreasing consumption of carbonated drinks and overweight and obesity	School-based education programme produced a modest reduction in the number of carbonated drinks consumed, which was associated with a reduction in the number of overweight and obese children	Funded from unrestricted educational grants from GlaxoSmithKline, Aventis, and Pfizer and from internal resources within Boumemouth Diabetes and Endocrine Centre. JJ received a research scholarship from the Florence Nightingale Foundation No funding from the food industry

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Table III (Cont.). Characteristics of the RCTs included in the meta-analysis

RCT author	Year of publication	Outcome analyzed	Population group	Type of intervention	Conclusion	Funding
Van Wymelbeke et al. (32)	2004	Energy balance and hunger ratings	12 men and 12 women, aged 20-25 y	4 beverages contained either sucrose (100 g/l, 1,672 kJ) or intense sweeteners (null energy content) and were flavored with either orange (O) or raspberry (R). Food intake (FI) was measured in the lab during 2-consecutive-day periods, carried out on 10 successive weeks	No statistically significant effect of soft drink consumption on weight gain	Sponsored by SEV, Bourg la Reine, France; the French Ministry of Research and Technology (AGROBIO-Aliments Demail Programme) and the Regional Council of Burgundy (Dijon, France)
Grandjean et al. (30)	2000	Hydration status (body weight, urine and blood)	18 healthy adult males, aged 24-39 y	During 1 week treatment, on four separate occasions, subjects consumed water or water plus varying combinations of beverages Clinical guidelines were used to determine the fluid allowance for each subject Beverages were carbonated, caffeinated caloric and non-caloric colas and coffee Body weight, urine and blood assays were measured before and after each treatment	No statistically significant effect of soft drink consumption on weight gain	Supported by a grant from The Coca-Cola Company
Sichieri et al. (24)	2009	Body weight (BMI)	1,140 children, aged 9-12 y	Educational intervention program focused on decreasing consumption of carbonated drink from March to December 2005	BMI increased slightly in both groups, with no significant difference Only in a subgroup analysis, girls who were overweight at baseline showed a statistically significant reduction in BMI	Supported by the Brazilian National Research Council-CNPq
De Ruyter et al. (46)	2012	Body weight	641 children, aged 7-9 y	During 18-month a double-blind design was used Replacing SSBs with non-caloric beverages (reducing consumption) It was the most rigorous to date	Masked replacement of sugar-containing beverages with non-caloric beverages could reduce weight gain and fat accumulation in normal-weight children	Supported by grants from the Netherlands Organization for Health Research and Development, the Netherlands Heart Foundation, and the Royal Netherlands Academy of Arts and Sciences

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Table III (Cont.). Characteristics of the RCTs included in the meta-analysis

RCT author	Year of publication	Outcome analyzed	Population group	Type of intervention	Conclusion	Funding
Ebbeling et al. (23)	2012	Body weight	244 adolescents, aged 14-16 y, conducted exclusively in overweight adolescents	Replacing SSBs with non-caloric beverages during 1 year (reducing consumption)	Examined the sustained effects of their interventions on body weight at 1 year post-intervention The beneficial effects of the interventions dissipated after the interventions had ended	Supported by grants from the National Inst. of Diabetes and Digestive and Kidney Diseases and from the National Center for Research Resources to the Boston Children's Hospital General Clinical Research Center, the Harvard Catalyst Clinical and Translational Science Center, and the New Balance Foundation
Sichieri et al. (47)	2013	BMI, height, weight	1,134 students, aged 10-11 y	Secondary analysis of a randomized trial of fourth graders followed over 1 year	An adverse effect of SSBs on body weight was found It confirmed that consumption of SSBs is a significant risk factor for BMI gain It is a duplicate study population	Funded by a grant from the Brazilian National Research Institute (CNPq) and by a scholarship from the Foundation of Research from Rio de Janeiro State (FAPERJ)
James et al. (48)	2007	BMI, height, weight, and waist circumference	434 children, aged 10-14 y	Educational intervention program focused on decrease consumption of SSB and diet carbonated drink It was a follow-up analysis of a previous school based intervention (James et al. 2004) The sustained effects of their interventions on body weight at 2 y post-intervention were examined	No significant effects were found It showed that the beneficial effects of the interventions dissipated after the interventions had ended	Funded by internal resources within the Bournemouth Diabetes and Endocrine Centre JJ received a research scholarship from the Florence Nightingale Foundation (Band Trust Scholarship)
Albala et al. (49)	2008	Body fat and BMI	98 children, aged 8-10 y	During a 16-week intervention, SSBs were replaced with flavored milk beverages providing 80 kcal and 11 g carbohydrate/serving	No beneficial intervention effect on body weight was found	Supported by a grant from the Fogarty International Center, National Institutes of Health
Muñoz (unpublished data) (50)	2006	BMI	303 university undergraduate students	During 1 month, one group received information on the health risks associated with soda consumption, and the other group, on the obesity risks associated with soda consumption	The intervention program did not affect SSB consumption, so no effect on adiposity would be expected	Doctoral dissertation

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Table III (Cont.). Characteristics of the RCTs included in the meta-analysis

RCT author	Year of publication	Outcome analyzed	Population group	Type of intervention	Conclusion	Funding
Davis et al. (26)	2009	Body composition	68 adolescents, aged 14-18 y	Educational intervention program focused on decrease consumption of carbohydrate during 16 weeks	No significant intervention effects on measured risk factors, with the exception of a beneficial effect on glycemic response to oral glucose, were found	Supported by the National Inst. of Cancer (NCI), University of Southern California Center for Transdisciplinary Research on Energetics and Cancer, the National Inst. of Child Health and Human Development, the Dr Robert C. and Veronica Atkins Found., the National Cancer Inst. (Cancer Control and Epidemiology Research Training Grant), and from NCI/NIH
Paineau et al. (27)	2008	Body weight: change in BMI	1,013 children, mean age 7.7 y	Educational intervention program focused on decreasing consumption of sugar intake for 8 months	Family dietary coaching improves nutritional intake in free-living children and parents, with beneficial effects on weight control in parents	Funded by the French Ministry of Research (2002 Reseau Alimentation Reference Europe 31), and by the ELPAS study's private partners (Avenance Enseignement, the Centre d'Etudes et de Documentation du Sucre, and the Louis Bonduelle Foundation)

Another important element to consider, as mentioned above, is that consumption of SSB is usually associated with an unhealthy lifestyle characterized by a higher caloric intake, less practice of exercise, smoking habit and presence of a poorly balanced dietary pattern. According to Khan et al. (42), sugar content should not be the sole determinant of a healthy diet. There are many other factors in the diet. Rather than just focusing on one energy source, the whole diet should be considered for health benefits (42).

Lastly, unintentional or inadvertent omissions or unclear or misleading statements in research reporting are another source of bias in health research. In this sense, there is now a tendency to reject studies that produce non-significant results. Many authors do not publish their data when it shows negative results to avoid rejection by editors of scientific literature, thus creating a vicious circle. Therefore, a great number of trials have not been published yet. Including all data, regardless of their results (either positive or negative), is imperative in order to increase reliability and, in turn, produce a solid foundation which will support conclusions with more scientific strength. Lack of information may lead to questioning the validity and adequacy of an entire analysis. It is imperative to avoid this kind of publication bias.

In this sense, the lack of a statistically significant result (p -value > 0.05) does not mean that there was no underlying effect: it means that no effect was detected. A small study may not have the power to detect a real difference. As opposite, small responses are less likely to be detected. A study with many replicates might result in a statistically significant result but have a small effect size (and so, perhaps, be unimportant). The importance of an effect size is a biological, physical or social question, and not a statistical one (43).

Evidently, available adherence or quality-assessment tools have limitations, and many contextual factors beyond the intrinsic characteristics of the reviews may influence their results (34). The meta-analysis area still requires more refining, consensus and widespread use by the scientific community (12).

From another point of view, it seems that lowering SSB intake as an isolated measure will not produce a decrease in obesity prevalence (44). The suggestion that SSB consumption is the main cause of obesity cannot explain why overweight and diabetes have also increased in regions with limited intakes of SSB such as Asia and Africa. Therefore, current evidence alone is insufficient to demonstrate such a role in the global obesity epidemic. Many other causal factors should be taken into account as well. The confusing message as several nutrition researchers stand in opposite to others about the available evidence of SSB has turned a purely scientific dialogue into an intensely emotional one (42).

Summarizing, scientists need to practice good science, sponsors must commit to transparency and no influence, media needs to practice responsible scientific journalism, and we all need to base our evaluations on scientific data and not on predetermined opinions rooted in our own emotion-laden bias for or against specific funding sources (40).

Why do we remain incapable of reaching a true consensus regarding this issue? Are there so huge interests that can mask the results so treacherously that could lead us to the other side

of the street? The first step is to firmly underline that funding should not lead to conclusions that are either for or against the industry. To finance must imply to generate a better service and to guarantee the continuity of that service, especially in times of economic crisis as the one that science crosses in the last times. The ethics and professionalism of scientists have nothing to do with financial aid. Ethics and professionalism must always exist with or without funding.

In conclusion, to formally accuse SSB of causing the current obesity pandemic is a narrow approach of this subject. At this point, the evidence currently available is not capable of supporting with strength this relationship. The limited data and the heterogeneity of methods employed make it impossible to reach any conclusion. They surely may contribute to a certain degree. However, better-designed, best quality and longer-term studies and a broader approach that includes a thorough analysis of diet and lifestyle with a stronger body of scientific evidence based on data from epidemiological studies conducted in different populations are needed in order to reach real science-based conclusions to establish this relationship properly.

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DECLARATION OF INTEREST

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Nutrición Hospitalaria



Grupo de Trabajo SENPE

Consenso sobre la evaluación y el tratamiento nutricional de los trastornos de la conducta alimentaria: anorexia nerviosa, bulimia nerviosa, trastorno por atracón y otros. Resumen ejecutivo

Consensus document about the nutritional evaluation and management of eating disorders: anorexia nervosa, bulimia nervosa, binge eating disorder, and others. Executive abstract

Carmen Gómez-Candela¹, Samara Palma Milla¹, Alberto Miján-de-la-Torre², Pilar Rodríguez Ortega³, Pilar Matía Martín⁴, Viviana Loria Kohen⁵, Rocío Campos del Portillo⁶, M.^a Nuria Virgili Casas⁷, Miguel Á. Martínez Olmos⁸, María Teresa Mories Álvarez⁹, María José Castro Alija¹⁰ y Ángela Martín-Palmero¹¹

¹Unidad de Nutrición Clínica y Dietética. Servicio de Endocrinología y Nutrición. Hospital Universitario La Paz. IdiPAZ. Universidad Autónoma de Madrid. Madrid. ²Unidad de Nutrición Clínica. Servicio de Medicina Interna. Hospital Universitario de Burgos. Burgos. ³Servicio de Endocrinología y Nutrición. Complejo Hospitalario de Huelva. Hospital Juan Ramón Jiménez. Huelva. ⁴Servicio de Endocrinología y Nutrición. Hospital Clínico San Carlos. Madrid. ⁵Unidad de Nutrición y Ensayos Clínicos. Instituto Madrileño de Estudios Avanzados en Alimentación (IMDEA-Alimentación). Madrid. ⁶Servicio de Endocrinología y Nutrición. Hospital Universitario Puerta de Hierro Majadahonda. Majadahonda, Madrid. ⁷Unidad de Nutrición y Dietética. Servicio de Endocrinología y Nutrición. Hospital Universitario de Bellvitge. L'Hospitalet de Llobregat, Barcelona. ⁸Unidad de Nutrición Clínica y Dietética. Servicio Endocrinología y Nutrición. Complejo Hospitalario Universitario de Santiago de Compostela, A Coruña. ⁹Servicio de Endocrinología y Nutrición. Complejo Asistencial Universitario de Salamanca. Salamanca. ¹⁰Centro de Investigación de Endocrinología y Nutrición Clínica. Universidad de Valladolid. Valladolid. ¹¹Servicio de Endocrinología y Nutrición. Hospital San Pedro. Logroño

Los trastornos de la conducta alimentaria (TCA) se caracterizan por una alteración persistente de la conducta relacionada con el hecho de alimentarse que impacta negativamente sobre la salud y las capacidades psicosociales de aquellos que los padecen. Se consideran enfermedades psiquiátricas con una gran variabilidad en su presentación y gravedad, con gran repercusión nutricional, lo que condiciona diferentes planteamientos terapéuticos, haciéndose indispensable un enfoque multidisciplinar.

Expertos en nutrición hemos decidido crear un grupo de trabajo adscrito a la Sociedad Española de Nutrición Parenteral y Enteral (SENPE), que ha asumido entre sus objetivos el elaborar un documento de consenso que genere un protocolo basado en la mejor evidencia científica posible y en la experiencia profesional, con la finalidad de mejorar la práctica asistencial en este campo.

DIAGNÓSTICO

La anorexia nerviosa (AN), la bulimia nerviosa (BN) y el trastorno por atracón (TA) constituyen entidades nosológicas diagnósticas diferenciadas en la última edición del *Manual de diagnóstico y estadístico de los desórdenes mentales* (DSM-5). El DSM-5 define la AN en base a tres criterios, siendo el primero de estos la restricción excesiva de la

ingesta en relación a los requerimientos nutricionales, lo que determina un peso corporal significativamente bajo para la edad, sexo y estado de salud. El segundo criterio es el miedo intenso a ganar peso o a convertirse en obeso, incluso estando por debajo del peso normal. La última premisa es la alteración de la percepción del peso o la imagen corporal, exageración de la importancia en la autoevaluación o negación del peligro que comporta el bajo peso corporal.

En la BN existen 3 características fundamentales según el DSM-5: episodios recurrentes de atracones, comportamientos compensatorios inapropiados y recurrentes para evitar un aumento de peso y la autoevaluación influenciada indebidamente por el peso y la constitución corporal. Los episodios de atracones y conductas compensatorias tienen lugar como promedio una vez por semana (en lugar de dos como se definía en el DSM-IV), mantenidos durante un periodo de al menos 3 meses. La definición de atracón se caracteriza por una ingesta excesiva de alimentos durante un corto periodo de tiempo, de al menos 2 horas, en cantidad superior a la que la mayoría de las personas ingerirían en un tiempo similar y en las mismas circunstancias, existiendo una sensación de pérdida de control sobre la ingesta de alimentos. El TA se caracteriza por episodios recurrentes de atracones sin comportamientos compensatorios inapropiados asociados. Se revisan también otros cuadros clínicos emergentes (1-4).

Este Resumen Ejecutivo forma parte del número extraordinario Consenso sobre la evaluación y el tratamiento nutricional de los trastornos de la conducta alimentaria: anorexia nerviosa, bulimia nerviosa, trastorno por atracón y otros que ha sido publicado en Nutr Hosp 2018;35(Nº Extraordinario):1-97.

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EPIDEMIOLOGÍA Y ETIOPATOGENIA

El interés por estas enfermedades ha experimentado un repunte importante en los últimos años, quizás motivado por la percepción de que se trata de trastornos emergentes y en expansión. Los TCA son más frecuentes en mujeres y en la adolescencia, y sin el tratamiento adecuado, adquieren un curso clínico de carácter crónico e incapacitante. Actualmente, se estima una prevalencia combinada del 13% para todos los TCA. El TA representa el TCA más prevalente en adultos. La AN es la enfermedad psiquiátrica más frecuente en las mujeres jóvenes y la tercera enfermedad crónica tras la obesidad y el asma en las adolescentes.

Aunque la etiopatogenia de los TCA no se conoce bien a día de hoy, se asume de carácter multifactorial, con participación de factores genéticos, psicológicos, biológicos, sociofamiliares y culturales entre los más importantes. Algunos antecedentes comunes a los TCA son la preocupación excesiva por el peso, la obsesión por un cuerpo delgado, el distrés sociofamiliar, el antecedente de realización de una dieta y el de abuso sexual en la infancia (5-8).

EL EQUIPO TERAPÉUTICO

Los TCA muestran una gran variabilidad en su presentación y en su gravedad, lo que va a condicionar diferentes consideraciones terapéuticas y la individualización del tratamiento. Por ello, se hace indispensable un enfoque multidisciplinar y altamente especializado. En el equipo participan: psiquiatras, psicólogos, médicos de familia, médicos nutriólogos (o endocrinólogos), dietistas, enfermeros y terapeutas ocupacionales, y cada profesional contribuye de forma incuestionable desde su especialidad.

La coordinación de las unidades de TCA corre generalmente a cargo del psiquiatra, que suele ser el responsable de establecer las líneas generales del tratamiento y coordina al resto del equipo. El médico de familia, además de participar en los programas de prevención primaria y de intentar realizar un diagnóstico lo más precoz posible, participará, siempre que haya sido entrenado, en el programa de prevención de recaídas.

El paciente ha de estar bajo la supervisión y tratamiento del médico nutriólogo, encargado de valorar su estado nutricional y las posibles complicaciones somáticas asociadas. El dietista es la persona más indicada para llevar a cabo la educación nutricional (EN), aunque el personal de enfermería con un alto nivel de entrenamiento y experiencia en esta materia también puede ser capaz de realizar esta función (9-13).

VALORACIÓN CLÍNICA Y NUTRICIONAL

Se debe realizar una historia clínica orientada tanto al diagnóstico específico de un TCA como al estado nutricional del paciente y la presencia de síntomas que revelen organicidad del proceso o comorbilidad, efectuando el diagnóstico diferencial con otras

enfermedades. Con frecuencia, el paciente no tiene conciencia de enfermedad y puede ocultar síntomas orientativos de su proceso. La anamnesis debe dirigirse a indagar en el comportamiento ante el acto de comer, la posibilidad de restricción alimentaria, su duración temporal, cantidad y calidad de alimentos ingeridos, así como en la existencia de cuadros de atracones, conductas purgativas y otros mecanismos compensatorios, siendo recomendable el contrastar la información que aporta el paciente con la que ofrezcan familiares y personas próximas al mismo.

Los hallazgos en la exploración física dependerán del tipo de TCA, pudiendo encontrarse signos de depleción de compartimentos corporales, carenciales, de adaptación hemodinámica al ayuno prolongado o de hábitos purgativos. No debe faltar la medición del peso, la talla, el índice de masa corporal (IMC), su relación respecto al peso ideal y su evolución en el tiempo. En niños y adolescentes es obligado ajustar los datos antropométricos según curvas con percentiles de acuerdo a su edad, sexo y altura.

La valoración de análisis clínicos al inicio no debe ser diferente a un protocolo habitual. Usualmente, salvo complicaciones, estará dentro de la normalidad. Se debe realizar un electrocardiograma de forma rutinaria. Es conveniente practicar una evaluación nutricional y de la composición corporal, en función de los recursos disponibles. El gasto energético en reposo se puede calcular mediante ecuaciones predictivas tipo Harris-Benedict, siendo más adecuado medirlo a través de calorimetría indirecta (14-18).

COMPLICACIONES ASOCIADAS

Los TCA se asocian a numerosas complicaciones médicas, que se relacionan con la intensidad del trastorno, la duración del mismo y el predominio del patrón alimentario restrictivo, compulsivo y/o purgativo.

En los pacientes que presentan desnutrición, se origina una atrofia de numerosos órganos vitales y sistemas que viene condicionada por el grado de pérdida de peso y la cronicidad de la enfermedad. Pueden presentar fatigabilidad, disminución de la capacidad funcional, dolor torácico, palpitaciones, hipotensión, ortostatismo y mayor riesgo de insuficiencia cardíaca. Dentro de los trastornos hormonales, el que tiene una mayor trascendencia clínica si se prolonga en el tiempo es el hipogonadismo, con su efecto deletéreo sobre la densidad mineral ósea. Desde el punto de vista metabólico, pueden aparecer hipoglucemias y niveles elevados de colesterol en más del 50% de los pacientes. Es común el enlentecimiento del vaciamiento gástrico, el estreñimiento y la alteración del perfil de enzimas hepáticas. A nivel renal, los pacientes desnutridos presentan una reducción del filtrado glomerular y alteraciones en la capacidad de concentración de la orina. Desde el punto de vista pulmonar, la debilidad de la musculatura respiratoria y diafragmática conlleva una disminución de la capacidad funcional e incrementa el riesgo de neumotórax espontáneo y neumomediastino. A nivel hematológico, pueden aparecer diferentes citopenias, siendo las más frecuentes la anemia y la leucopenia. Los pacientes pueden manifestar deterioro cognitivo y disfunciones neuropsicológicas que afectan fundamentalmente

a la atención, la memoria y las funciones ejecutivas y, en menor medida, al procesamiento visual y a las aptitudes verbales. El déficit de micronutrientes puede condicionar neuropatías.

La obesidad, presente en hasta un 30% de los pacientes con TA, condiciona un mayor riesgo de patologías metabólicas como la diabetes mellitus tipo 2, la hipertensión, la dislipemia, la enfermedad cardiovascular y otras patologías secundarias (hernia de hiato, colelitiasis, esteatosis, insuficiencia respiratoria, apnea del sueño, insuficiencia cardíaca, insuficiencia venosa, hipertensión endocraneal y patología osteoarticular), y una mayor incidencia de algunos tipos de tumores.

Las conductas compensatorias purgativas pueden condicionar complicaciones locales (caries, gingivitis, enfermedad periodontal, patología temporomandibular, sialoadenosis, reflujo laringo-faríngeo, broncoaspiración, reflujo gastroesofágico, esofagitis, síndrome de Mallory-Weiss, síndrome de Boerhaave, colon catártico, prolapso rectal, hemorroides y signo de Russell) y sistémicas (trastornos hidroelectrolíticos y del equilibrio ácido-base, manifestaciones neurológicas, cardíacas o renales) (19-25).

HERRAMIENTAS TERAPÉUTICAS GENERALES

Los objetivos del tratamiento en los pacientes con TCA deben ser individualizados, realistas y adaptados al contexto y situación clínica del paciente:

- Restaurar o normalizar el peso y el estado nutricional.
- Reducir o eliminar los atracones y los comportamientos purgativos que existan, así como minimizar la restricción alimentaria.
- Proporcionar educación sobre patrones alimentarios saludables.
- Promover la realización de un ejercicio físico saludable.
- Tratar las complicaciones médicas intercurrentes.
- Conseguir un mejor ajuste social y confianza personal.
- Tratar las alteraciones conductuales y la comorbilidad psiquiátrica.
- Prevenir las recaídas.

El tratamiento de los pacientes con TCA puede realizarse en distintos niveles asistenciales y debe ser siempre multidisciplinar, siendo los pilares fundamentales la psicoterapia, el soporte médico y el abordaje nutricional.

La terapia psicológica que se recomienda en TA y BN es la terapia cognitivo-conductual. Los aspectos médicos incluyen el tratamiento de las comorbilidades que acompañan al TCA, de las complicaciones derivadas de la malnutrición (tanto desnutrición como obesidad) y de las conductas compensatorias.

El plan nutricional debe contemplar no solo el consejo dietético individualizado que garantice un adecuado estado nutricional, sino que debe buscar educar al paciente, proporcionándole la información necesaria que le permita la modificación a largo plazo de los hábitos alimentarios y el cese de las conductas purgantes y atracones. Existen particularidades en este plan nutricional según el TCA y la situación clínica en que se encuentre el paciente. Así, en pacientes con bajo peso, como ocurre en la AN y en ocasiones en la BN, se

debe promover la recuperación de un peso y situación nutricional adecuados, teniendo especial precaución con la aparición del síndrome de realimentación en pacientes severamente desnutridos. Puede ser necesario el empleo de nutrición artificial (NA), sobre todo suplementos nutricionales orales. En pacientes con exceso de peso, como puede ocurrir en el TA y BN, se debe fomentar una modificación saludable del estilo de vida. El empleo de fármacos "antiobesidad" puede ser de utilidad en el TA, aunque su uso es controvertido y deben contraindicarse en pacientes con BN por el potencial mal uso o abuso.

La cirugía bariátrica (CB) puede emplearse en pacientes seleccionados con TA, siendo la BN una contraindicación. Los criterios de inclusión son los mismos que para la población obesa candidata a CB sin TCA. La pérdida de peso a corto-medio plazo en los pacientes sometidos a CB con TA preoperatorio no se diferencia a la experimentada por pacientes sin TA. Es fundamental llevar a cabo un adecuado programa de educación nutricional, así como un soporte psicológico en los pacientes obesos mórbidos con TA, tanto antes como después de la cirugía.

El tratamiento farmacológico no es imprescindible, pero puede ser de utilidad. La mayor evidencia se encuentra en la indicación de fluoxetina en BN, considerado el mejor fármaco en términos de aceptabilidad, tolerancia y reducción de síntomas (14,26-28).

EDUCACIÓN NUTRICIONAL

La educación nutricional (EN) debe formar parte del tratamiento de los TCA y estar orientada a la acción y centrada en la práctica. Su objetivo principal es facilitar la adopción voluntaria de comportamientos alimentarios que fomenten la salud y el bienestar. Debe plantearse no solo de acuerdo al diagnóstico del trastorno, sino también debe tener en cuenta el patrón alimentario del paciente y sus conocimientos nutricionales.

En lo que respecta a la AN, la EN persigue mejorar la actitud y comportamiento en relación a la comida; alcanzar una mejora en el patrón alimentario, aclarar mitos y favorecer con todos estos cambios la recuperación del estado nutricional. En la BN el primer paso será conseguir una razonable organización de las comidas, centrándose en marcar tiempos y horarios, evitando en todo caso periodos largos de ayuno. En una etapa posterior, se trabajará sobre la calidad de los alimentos, siempre con cambios pequeños y graduales, priorizando la incorporación de los alimentos más saludables para, en una etapa final, trabajar sobre el aspecto cuantitativo con el fin de alcanzar el equilibrio nutricional buscado. En el TA se enfatizará en la adecuada selección de alimentos, priorizando aquellos con menor densidad energética y que promueven una mayor saciedad, y sobre el control y el tamaño de las raciones. En el paciente obeso se fomentarán los cambios de conducta a largo plazo, tendentes a favorecer el mantenimiento de un peso razonable a partir de la incorporación de elecciones más saludables de alimentos, en relación con la adquisición de nuevos hábitos alimentarios y un patrón más saludable de actividad física.

En muchos casos, la EN debe hacerse extensiva a las familias, ya que mejora la eficacia de las intervenciones educativas al facilitar la aplicación práctica y la adhesión de todos los miembros a los nuevos modelos conductuales propuestos (29-33).

INDICACIONES DE LA NUTRICIÓN ARTIFICIAL

La nutrición artificial (NA) engloba aquellas modalidades de nutrición (oral, enteral y parenteral) cuyo objetivo es cubrir las necesidades del organismo cuando no es posible o se hace de forma insuficiente a través de alimentos de consumo ordinario. La NA disminuye la morbilidad y mortalidad en pacientes malnutridos. Se debe indicar de forma escalonada, iniciando con las herramientas más sencillas como los suplementos nutricionales orales (SNO) y, posteriormente, las más complejas, nutrición enteral (NE) y, excepcionalmente, la nutrición parenteral (NP).

Existen escasos estudios sobre la utilización de SNO en TCA. Sin embargo, en la práctica clínica son una herramienta fundamental para la recuperación de muchos pacientes con AN, sobre todo cuando se emplean en periodos cortos de tiempo y siempre bajo supervisión médica.

En pacientes con TCA y bajo peso que se encuentran hospitalizados, los SNO permiten una ganancia de peso más rápida y, en algunos casos, acortan el tiempo necesario de tratamiento y la estancia hospitalaria. También son necesarios en mujeres con TCA embarazadas con desnutrición o en riesgo. En el ámbito ambulatorio, los SNO pueden estar indicados tras la retirada de la NE para continuar el proceso de recuperación nutricional y evitar o atenuar una nueva pérdida de peso al alta hospitalaria. También son útiles en pacientes ambulatorios desnutridos como alternativa al ingreso hospitalario, siempre que no exista riesgo vital. El empleo de SNO debe estar apoyado sobre un tratamiento psicoterapéutico y nutricional completo y la duración debe ser aclarada y pactada con el paciente previamente. La NE por sonda nasogástrica se emplea casi de forma exclusiva en pacientes ingresados, donde la gravedad o la falta de colaboración hacen preciso su empleo. Excepcionalmente, si la vía enteral no está disponible o si está contraindicada por una enfermedad intercurrente, puede ser necesaria la NP (34-39).

TRATAMIENTO Y SEGUIMIENTO DEL PACIENTE EN CONSULTA EXTERNA

El nivel asistencial ambulatorio es el marco del tratamiento más habitual y más prolongado en los TCA, siempre con un enfoque multidisciplinar. Requiere estabilidad clínica, ausencia de riesgo autolítico y adecuada capacidad del paciente para la vida familiar, académica o laboral. En todos los pacientes debe realizarse una valoración nutricional estructurada. La evaluación clínica tiene que efectuarse siempre al inicio, en todos los trastornos y, posteriormente, con una frecuencia variable en función de la gravedad del cuadro. En ella han de contemplarse aspectos referentes a purgas (vómitos y consumo de laxantes o de diuréticos), salud bucodental, constantes vitales, crecimiento y desarrollo en niños y adolescentes, ciclo ovárico en mujeres jóvenes o síntomas de hipogonadismo en varones, una exploración física y una valoración analítica.

El tratamiento médico debe sumarse al psicoterápico, restaurando los déficits nutricionales y electrolíticos. No hay un consen-

so definido en el aporte de kcal diarias en las diferentes guías, pero sí en el objetivo de aumento ponderal de 0,5 kg/semana en desnutrición grave. Se deben considerar los problemas derivados de la obesidad en el TA (sin evitar en este último caso la restricción calórica y planteando, en casos determinados, incluso la cirugía bariátrica).

Con un nivel de evidencia aún bajo, la telemedicina ha mostrado algunos resultados prometedores en TCA. Algunas situaciones especiales como la coexistencia de diabetes mellitus tipo 1, el embarazo o la lactancia, requieren planteamientos específicos e individualizados (40-50).

SOPORTE NUTRICIONAL EN EL PACIENTE HOSPITALIZADO

No existen criterios basados en la evidencia que establezcan qué pacientes con TCA necesitarán hospitalización, por lo que tanto los signos y síntomas médicos como los psiquiátricos o la propia evolución de la enfermedad deben ser tenidos en cuenta como criterios de ingreso. En general, se indicará el ingreso hospitalario ante las complicaciones médicas agudas o la presencia de situaciones psiquiátricas agudas o el intento de autolisis. También puede ser criterio de ingreso la pérdida del control de la situación en el entorno familiar y social del paciente o el fracaso del tratamiento de forma ambulatoria.

El ingreso hospitalario en los TCA puede ser voluntario o involuntario, pero siempre con un enfoque multidisciplinar. Habitualmente durante el ingreso hospitalario, el tipo de alimentación será oral y excepcionalmente se utilizará la NA.

Los criterios de alta hospitalaria serán: mantener una situación médica estable, la resolución de las complicaciones agudas tanto médicas como psicopatológicas y un control significativo de las alteraciones conductuales, asegurando el cumplimiento y seguimiento de los objetivos posteriormente al alta hospitalaria.

A diferencia de la AN, en la BN los ingresos hospitalarios tienden a ser cortos, con el objetivo de contención y de ruptura con el círculo vicioso en que se encuentra el paciente (51-55).

TRATAMIENTO NUTRICIONAL EN EL HOSPITAL DE DÍA

El hospital de día para TCA (HDTCA) surge como una alternativa potencialmente útil en el manejo de pacientes con TCA, a medio camino entre el tratamiento ambulatorio tradicional (consultas, terapia individual y grupal) y la hospitalización completa. En él, los pacientes reciben tratamiento médico, terapia nutricional (comidas acompañadas/vigiladas), educación nutricional, atención psiquiátrica y psicológica en modalidad individual y/o grupal, terapia ocupacional y apoyo social, siempre con un enfoque multidisciplinar e intensivo.

Algunos modelos de HDTCA se orientan a tratamientos de corta duración (semanas) para el control de los síntomas del trastorno y la estabilización ponderal; y otras veces se intenta el trata-

miento integral del paciente, trabajando aspectos psicodinámicos, habilidades interpersonales y psicosociales, conocimiento de los síntomas y con un objetivo de recuperación del estado nutricional más gradual (varios meses).

Los criterios habituales de ingreso en HDTCA suelen ser: diagnóstico de TCA, fracaso de tratamiento ambulatorio, transición hacia el manejo ambulatorio tras ingreso hospitalario, ausencia de un peso de riesgo o de complicaciones graves que aconsejen hospitalización completa (médica o psiquiátrica), motivación y compromiso. El funcionamiento de los HDTCA debe seguir un protocolo definido y consensuado con un programa estructurado y se suele negociar un contrato terapéutico donde se señalen todas las condiciones del ingreso.

Para el alta, desde el HDTCA habitualmente se requiere conseguir y mantener el objetivo ponderal establecido, corregir los comportamientos alimentarios inadecuados, los pensamientos irracionales, y asegurar un soporte sociofamiliar adecuado para el pertinente seguimiento ambulatorio. Si en algún momento se constata que no se está siguiendo correctamente lo establecido para el programa del HDTCA o que surgen complicaciones, el paciente debería ser transferido a otra modalidad terapéutica más apropiada a su caso (56,57).

EVALUACIÓN DE RESULTADOS

La evidencia para evaluar los resultados tanto clínicos como en costes de la eficacia de los distintos tratamientos en los TCA es escasa. La mayoría de las recomendaciones en las distintas guías están basadas en consenso de expertos.

Las tasas de curación completa no superan el 50-60%, con tendencia a cronificarse el 20-30% en el caso de la AN y BN, y en los TA el 70% de los casos remite de forma completa. Los pacientes con TCA tienen un aumento de riesgo de morbilidad y mortalidad. Las tasas de mortalidad son 10-12 veces más elevadas que las de la población general y aumentan en el transcurso de la enfermedad.

Existe un elevado coste social y familiar, y un importante impacto en la calidad de vida. Serían necesarios estudios a gran escala que permitan valorar el impacto económico de los TCA y sus comorbilidades, así como su repercusión en el entorno familiar y la calidad de vida (40,58,59).

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Nota Clínica

Tratamiento dietético con fructosa en una niña de 5 años con acidosis D-láctica recurrente

Dietetic treatment with fructose in a 5-year-old girl with recurrent D-lactic acidosis

Lourdes Travieso-Suárez¹, Pilar Quijada Fraile² y Consuelo Pedrón Giner³

¹Servicio de Pediatría. Hospital Infantil Universitario Niño Jesús. Madrid. ²Unidad Pediátrica de Enfermedades Raras. Servicio de Pediatría. Hospital Universitario 12 de Octubre. Madrid. ³Sección de Gastroenterología y Nutrición. Hospital Infantil Universitario Niño Jesús. Madrid

Resumen

La acidosis D-láctica es una patología infrecuente, habitualmente descrita en pacientes con síndrome de intestino corto. Se caracteriza por episodios recurrentes de encefalopatía con D-lactato sérico elevado y, generalmente, acidosis metabólica. Para su desarrollo es necesario el sobrecrecimiento de bacterias productoras de D-lactato en el colon. Otros factores, como la ingesta abundante de carbohidratos o la disminución de la motilidad intestinal, pueden favorecer una acidosis D-láctica. Presentamos un caso clínico de acidosis D-láctica recurrente en una niña de cinco años con síndrome de intestino corto secundario a un vólvulo de intestino medio. Recibió tratamiento antibiótico para el sobrecrecimiento bacteriano y restricción de carbohidratos enterales, pese a lo cual presentó recurrencias. Posteriormente, se sustituyó un 25% de su fórmula de nutrición enteral por otra con aporte exclusivo de fructosa, y se restringieron los aportes de otros azúcares fermentables. La evolución a los 16 años ha sido satisfactoria, sin presentar nuevas recurrencias.

Palabras clave:

Acidosis D-láctica.
D-lactato. Intestino corto.

Abstract

D-lactic acidosis is an infrequent complication, mainly reported in patients with short bowel syndrome. It is characterized by recurrent episodes of encephalopathy with elevated serum D-lactic acid, usually associating metabolic acidosis. The presence of D-lactate-producing bacteria is necessary for the development of this complication. Other factors, such as the ingestion of large amounts of carbohydrates or reduced intestinal motility, contribute to D-lactic acidosis. We report a case of recurrent D-lactic acidosis in a 5-year-old girl with short bowel syndrome, due to a midgut volvulus. She initially received oral antibiotics in order to treat bacterial overgrowth, together with oral carbohydrates restriction. Nevertheless, recurrences did occur. Subsequently, 25% of the enteral nutrition was replaced for a formula containing fructose exclusively, while other fermentable sugars were restricted from the diet. After 16 years of follow up, further recurrences of D-lactic acidosis were not observed.

Key words:

D-lactic acidosis.
D-lactate. Short bowel.

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Correspondencia:

Lourdes Travieso Suárez. Servicio de Pediatría.
Hospital Infantil Universitario Niño Jesús. Av. Menéndez
Pelayo, 65. 28009 Madrid
e-mail: ltravieso721@gmail.com

INTRODUCCIÓN

El síndrome de intestino corto (SIC) se define como la insuficiencia del intestino para mantener la correcta absorción de macronutrientes, micronutrientes, agua y electrolitos, cuando dicha situación es secundaria a una resección intestinal (1,2). La causa más frecuente de intestino corto es la enterocolitis necrosante. También ocurre por defectos de la pared abdominal, íleo meconial, atresia intestinal, vólvulos, enfermedad de Hirschprung y enfermedad de Crohn (3). A consecuencia de la malabsorción crónica, suele manifestarse con diarrea, pudiendo aparecer secundariamente deficiencias nutricionales, alteraciones hidroelectrolíticas, retraso ponderoestatural, etc.

La acidosis D-láctica (ADL) es una entidad infrecuente, descrita habitualmente en pacientes con SIC (4-9), aunque también puede presentarse tras un *bypass* yeyuno-ileal (1,4).

Se caracteriza por un cuadro neurológico de rápida instauración, que se acompaña de niveles elevados de D-lactato en sangre y, con frecuencia, acidosis metabólica. La clínica es habitualmente superponible a una intoxicación alcohólica, en tanto que suele cursar con ataxia, disartria, agresividad, dificultad en la concentración, alteraciones de la memoria y la coordinación, confusión, disminución del nivel de conciencia e incluso coma (3-5). Pueden aparecer recurrencias, durando cada episodio desde horas hasta varios días.

Para el desarrollo de una ADL, es necesaria la presencia del colon, pues la fisiopatología de esta entidad comienza con la instauración de un sobrecrecimiento de bacterias productoras de L y D-lactato. Así, en los pacientes con SIC, los carbohidratos no absorbidos en el intestino delgado llegan al colon, donde son metabolizados por las bacterias en diferentes ácidos orgánicos (como lactato y ácidos grasos de cadena corta). Estos reducen el pH del colon, favoreciendo la proliferación anómala de bacterias ácido-resistentes, como *Lactobacillus*, que a su vez producen más lactato a partir de azúcares, generándose así un círculo vicioso (1,4). Esta disbacteriosis también puede instaurarse tras un tratamiento antibiótico oral o la ingesta de probióticos, ya que pueden alterar la flora colónica habitual (4,11). Cuando el paciente realiza una comida rica en carbohidratos, especialmente azúcares simples, estas bacterias los fermentan a L-lactato y D-lactato, que pasan a la circulación sanguínea en cantidades elevadas, dando lugar a acidosis metabólica con anión gap elevado, e iniciándose la clínica neurológica (4).

Dada la escasa incidencia de esta complicación, en la actualidad el tratamiento está poco estandarizado y se basa en la antibioterapia oral y la restricción de carbohidratos simples, desconociéndose tanto en qué medida se debe realizar dicha restricción como la duración óptima del tratamiento.

CASO CLÍNICO

Presentamos el caso de una niña de cinco años, con antecedente de SIC secundario a una resección desde yeyuno proximal a íleon distal realizada a los cuatro años de edad por un vólvulo de

intestino medio y malrotación intestinal. La longitud del segmento yeyuno-ileal remanente era de 21 cm, con válvula ileocecal y colon íntegros. Recibía nutrición parenteral y enteral a través de gastrostomía en su domicilio. En el tránsito digestivo, presentaba dilatación del intestino delgado tras la última porción duodenal y gran antiperistaltismo. El vaciamiento del íleon estaba retrasado. El colon no presentaba alteraciones (Fig. 1)

Consultó en cuatro ocasiones en un periodo de cinco meses por aumento del número de deposiciones diarreicas y clínica neurológica, coincidentes con aumento de la nutrición enteral. A la exploración presentaba decaimiento, deshidratación leve, cutis marmorata, disartria y ataxia. Se realizó analítica sanguínea con bioquímica y gasometría, donde se objetivó acidosis metabólica hiperclorémica con anión gap elevado. Ante la sospecha de acidosis D-láctica, se demostraron niveles de D-lactato en suero, orina y en heces claramente elevados (Tabla I), con L-lactato normal. En el coprocultivo se evidenció crecimiento prácticamente puro de bacilos grampositivos. Mediante técnica de MALDI-TOF se constató que se trataba de *Lactobacillus* spp.

En todos los episodios, se corrigió la acidosis metabólica con sueroterapia intravenosa con bicarbonato, y se suspendió la nutrición enteral (NE), manteniendo todo el aporte calórico con nutrición parenteral. En un intento de prevenir las recurrencias, inicialmente se combatió la disbacteriosis con metronidazol (30 mg/kg/día en tres dosis) y solución de descontaminación (nistatina, colistina sulfato y tobramicina sulfato) en ciclos de cinco días cada dos semanas. Tras la tercera recaída, se cambió la antibioterapia por una solución con vancomicina (100 mg cada 8h) y trimetoprim/sulfametoxazol (20/100 mg cada 8h) la primera semana de cada mes. En todos los casos, el progresivo aumento de la NE desencadenó un nuevo episodio de ADL. Por ello, se decidió restringir los aportes de NE de sacarosa y glucosa, sustituyendo un 25% de su fórmula habitual (Nieda Plus®, Abbott Laboratories SA) por una fórmula con aporte exclusivo de fructosa (Galactomin 19 fórmula®, SHS España SA, actualmente Nutricia SRL). Más tarde, al diversificar la alimentación, se le dieron reco-

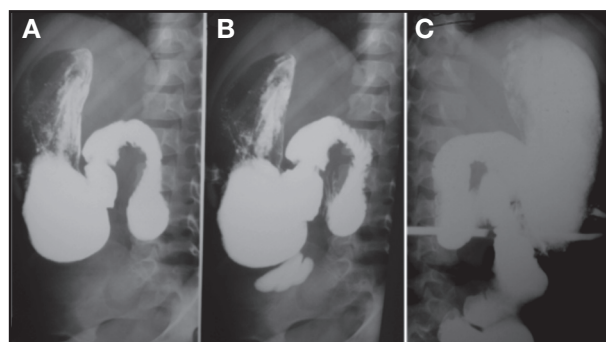


Figura 1.

A. Buen vaciamiento gástrico con relleno del duodeno y dilatación ileal en la que se observa antiperistaltismo previa a la anastomosis del colon. B. El vaciamiento ileal está enlentecido, y se realiza a través de una anastomosis de pequeño calibre que permite la repleción total del colon (C).

Tabla I. Valores analíticos durante los episodios de acidosis metabólica

	1º ingreso	2º ingreso	3º ingreso	4º ingreso
PH	7,16	7,24	7,16	7,23
Bicarbonato mEq/l	15,6	12,6	5,2	13,7
Exceso de bases mEq/l	-13,2	-12,6	-20,2	-12
Anión gap	19,5	19,5	38,7	
Láctico (suero) mg/dl			8,33	
D-láctico (suero) mg/dl			73,8	
D-láctico (orina) mg/dl			890	
D-láctico (heces) mg/dl			21,3	

mendaciones para realizar una dieta baja en sacarosa y glucosa y se mantuvo el aporte de NE con la misma pauta, sustituyendo, en función de su disponibilidad en el comercio, la fórmula con aporte exclusivo de fructosa por una fórmula con bajo aporte de carbohidratos (almidón) (3232 A®, Mead Johnson Nutrition) suplementada con fructosa.

La paciente recibió varios ciclos de antibióticos durante nueve meses, y se mantuvieron los aportes descritos de NE durante dos años y nueve meses. Posteriormente, se sustituyó de forma progresiva por fórmula polimérica pediátrica con aportes normales de carbohidratos. No volvió a presentar ningún nuevo episodio de ADL.

Precisó nutrición parenteral domiciliaria durante un total de dos años y un mes y NE por gastrostomía durante cinco años y diez meses. La evolución a los 16 años ha sido satisfactoria: ha mantenido una curva ponderoestatural adecuada, alcanzando una talla adulta en el momento del alta a los 20 años de edad de 154,1 cm (P8, -1,38 DE), e índice de masa corporal de 19,4 kg/m² (p23, -0,73 DE), según patrón de la Organización Mundial de la Salud (OMS) ajustado a la edad. Recibe suplementos de vitaminas liposolubles, ácido fólico y calcio por vía oral y vitamina B₁₂ intramuscular.

DISCUSIÓN

Son varias las circunstancias que pueden favorecer el desarrollo de una acidosis D-láctica: en primer lugar, el desarrollo de bacterias ácido-resistentes productoras de lactato en el colon secundario a la malabsorción de carbohidratos (4,5,9). Este hecho puede favorecerse por la ingesta de probióticos o de un antibiótico oral (2,11). Por otra parte, la dismotilidad intestinal puede aumentar el sobrecrecimiento bacteriano, y una ingesta rica en carbohidratos, en especial azúcares simples, supone un aporte del sustrato necesario para la síntesis de lactato (4,12).

Varios de estos factores estaban presentes en nuestra paciente: la malabsorción por su intestino corto, que aumenta el paso de nutrientes no digeridos al colon; la existencia de un asa dilatada, que produce sobrecrecimiento bacteriano; el tratamiento con volúmenes crecientes de nutrición enteral con la intención de retirar la nutrición parenteral; y la existencia de disbacteriosis a

expensas de *Lactobacillus*, como está descrito en la literatura.

El lactato existe en forma de dos isómeros, L-lactato y D-lactato, que pueden ser metabolizados a piruvato o producidos a partir de él, mediante la L-lactato deshidrogenasa (LDH) y la D-LDH, respectivamente. En el hombre, el L-lactato, que se produce a partir de piruvato durante el metabolismo anaerobio de los carbohidratos, es el isómero predominante, mientras que el D-lactato se sintetiza en la vía del metilglicoxal en cantidades prácticamente despreciables; por ello, en condiciones fisiológicas, los niveles de D-lactato son indetectables. Además, como el ser humano carece de D-LDH, se creía que durante la acidosis D-láctica, el L-lactato producido por las bacterias colónicas era rápidamente metabolizado por la L-LDH, mientras que el D-lactato permanecía elevado al carecer de un enzima capaz de eliminarlo. Sin embargo, se ha demostrado la existencia de un enzima con esta actividad, la D-2-hidroxi ácido deshidrogenasa, presente en abundancia en hígado y riñón (5). El exceso de D-lactato (se consideran niveles tóxicos aquellos superiores a 3 mmol/l) podría explicarse, entonces, por la inhibición de esta enzima en situación de acidosis, como se ha observado en estudios *in vitro* (4,5).

Es preciso puntualizar que, actualmente, se sospecha que el exceso de D-lactato *per se* no explica la encefalopatía que presentan los pacientes con acidosis D-láctica, ya que no parece existir correlación entre sus niveles y la intensidad de los síntomas (4,5). Se propone que la neurotoxicidad puede deberse a la producción de otros ácidos orgánicos en el colon (mercaptanos, aldehídos, aminas, etc.), que pasarían a la sangre y al líquido cefalorraquídeo (LCR) junto con el D-lactato, y que se comportarían como falsos neurotransmisores (4,5).

Los pacientes con ADL suelen presentar, además de altos niveles de ácido D-láctico en sangre, orina y heces, acidosis metabólica con anión gap elevado en sangre y orina (3,4). Sin embargo, se han descrito casos aislados de ADL con encefalopatía y ácido D-láctico elevado, y ausencia de acidosis metabólica (4). El electroencefalograma, en los casos en los que se ha realizado, muestra signos de encefalopatía durante la fase aguda, aunque no parece aportar datos específicos que sean útiles como herramienta diagnóstica (4).

El tratamiento inicial consiste en la corrección de la acidosis metabólica mediante sueroterapia intravenosa con bicarbonato.

Se debe evitar el Ringer lactato por su contenido en L-lactato y D-lactato. Asimismo, se deben restringir o suspender los aportes enterales de carbohidratos, para reducir los sustratos fermentables por las bacterias productoras de lactato (1,4,5).

Para prevenir posibles recurrencias, es preciso tratar la disbiosis mediante ciclos de antibióticos orales con escasa absorción entérica (neomicina, vancomicina, metronidazol, clindamicina) y restricción de carbohidratos en la dieta (especialmente azúcares simples) (4,5). Dada la infrecuencia de la ADL, se desconoce la duración óptima del tratamiento (2). Los síntomas pueden reaparecer pocos días después de finalizar el antibiótico, o no presentarse durante años (2,9). En cuanto al uso de probióticos con bacterias productoras exclusivamente de L-lactato, no está clara su efectividad en el tratamiento de la ADL, por lo que no existe evidencia suficiente para recomendarlos como parte de la terapia de estos pacientes (3-5,10).

Las modificaciones dietéticas han sido propuestas en la literatura como parte del tratamiento de la ADL. Mayne sostiene que es posible prevenir las recurrencias proporcionando los carbohidratos con el siguiente perfil: monosacáridos 1%, disacáridos 6%, trisacáridos 8%, tetrasacáridos 7% y pentasacáridos y el resto 78% (12). Ramakrishnan recomienda una dieta baja en carbohidratos (10%) como alternativa a los antibióticos en algunos pacientes (13) y Bongaerts propone dieta baja en carbohidratos y rica en grasas (14). En nuestra paciente, la dieta con aportes de fructosa y restricción de glucosa y sacarosa fue eficaz en el control de las recidivas. Nuestra hipótesis se basa en el mecanismo de absorción intestinal de los distintos monosacáridos: mientras que la glucosa y otros monosacáridos se absorben por transporte activo, la fructosa es el único que lo hace por difusión facilitada. En los pacientes con SIC suele existir sobrecrecimiento bacteriano a nivel de intestino delgado, que deconjugue los ácidos y sales biliares provocando inflamación de la mucosa intestinal, de modo que fallan los mecanismos de transporte activo. De esta forma, la glucosa y la sacarosa no se absorben correctamente y llegan al colon, donde pueden ser fermentadas a lactato por las bacterias. Esto no ocurre así con la fructosa, ya que se absorbe por difusión facilitada.

Para confirmar la correcta absorción de la fructosa, hubiera sido óptimo verificar nuestra hipótesis mediante pruebas complementarias. Sin embargo, la respuesta clínica tras el tratamiento dietético con aporte enteral parcial de fórmula con fructosa fue radical: no se produjeron recaídas posteriores, mientras que previamente se documentaron cuatro episodios en cinco meses a pesar de una correcta adherencia a la antibioterapia de escasa absorción entérica y restricción de carbohidratos simples (disminución de la cantidad de NE con la fórmula habitual que recibía la paciente y aumento de la nutrición parenteral), lo cual sugiere que la modificación de la dieta fue eficaz.

En el momento en que tuvieron lugar los episodios, hubiera sido atractivo estudiar la absorción de fructosa mediante un test de hidrógeno espirado tras sobrecarga oral con dicho monosacárido. Sin embargo, por entonces dicha prueba no se realizaba de rutina en nuestro medio. Por otra parte, en documentos de consenso recientes en pacientes adultos se concluye la falta de estandarización de esta prueba, sin que se hayan establecido la dosis de fructosa a administrar para realizar el test, así como los puntos de corte para establecer el diagnóstico de malabsorción de dicho monosacárido (15). En cualquier caso, la interpretación de estas pruebas en nuestra paciente hubiese sido poco esclarecedora, dado que la presencia de sobrecrecimiento bacteriano se traduce en un aumento de la detección basal del hidrógeno espirado superior a diez partes por millón.

Los autores exponemos el presente caso para que las modificaciones dietéticas realizadas con buen resultado en nuestra paciente sean tenidas en cuenta como opción terapéutica en otros pacientes con SIC.

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Nota Clínica

Can pediatricians recognize eating disorders? A case study of early-onset anorexia nervosa in a male child

¿Puede un pediatra sospechar un trastorno de la conducta alimentaria? Un caso de comienzo precoz de anorexia nerviosa en un varón

Emel Ataş Berksoy¹, Gonca Özyurt², Murat Anıl¹, Özlem Üzümlü³ and Yeliz Çağan Appak⁴

¹Pediatric Emergency Clinic. Tepecik Training Hospital. Health Science University. İzmir. ²Pediatric Psychiatry. Katip Çelebi University. İzmir. ³Pediatric Clinic. Tepecik Training Hospital. Health Science University. İzmir. ⁴Pediatric Clinic. Tepecik Training Hospital. Health Science University. İzmir

Abstract

Introduction: this article examines a boy who was diagnosed with anorexia nervosa at eight years old. Pediatricians and family physicians encountered difficulties during the diagnosis and treatment stages due to the fact that early onset of the disease is rare.

Case report: a boy aged eight years and four months presented with bradycardia, malnutrition and dehydration as far away from the preliminary diagnosis of anorexia nervosa investigated for possible organic pathologies at the pediatric ward. Finally, he was diagnosed with early-onset anorexia nervosa and anxiety disorder based on the Diagnostic and Statistical Manual of Mental Disorders 5.

Discussion: the case highlights two important points. First, this case report demonstrates a limited awareness of anorexia nervosa and of a psychosomatic or psychiatric origin of weight loss in children among physicians. Second, disrupted eating behaviors and mood changes may be predicting factors for the development of full-blown anorexia nervosa.

Key words:

Anorexia nervosa.
Child. Eating disorder.

Resumen

Introducción: se presenta el caso clínico de un niño diagnosticado de anorexia nerviosa a los 8 años. Tanto los pediatras como los médicos de familia tuvieron problemas durante el diagnóstico y en el tratamiento debido a que su aparición a tan corta edad es poco frecuente.

Caso clínico: un varón de ocho años y cuatro meses ingresó por bradicardia, desnutrición y deshidratación en un hospital pediátrico. Tras el despistaje de un origen orgánico, se diagnosticó de anorexia nerviosa y trastorno de ansiedad según DSM-5.

Discusión: el caso pone de relieve dos aspectos. El primero, demuestra la atención limitada que prestan los médicos a un origen psicósomático o psiquiátrico, incluyendo la anorexia nerviosa, en una pérdida de peso en un niño. El segundo, que una alteración en la conducta alimentaria acompañada de cambios de carácter pueden ser factores predictores del desarrollo de un cuadro de anorexia nerviosa florida.

Palabras clave:

Anorexia nerviosa.
Niños. Trastorno de la conducta alimentaria.

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Correspondence:

Emel Ataş Berksoy. Pediatric Emergency Clinic. Tepecik Training Hospital. Health Science University. İzmir
e-mail: emelberksoy@hotmail.com

INTRODUCTION

Anorexia nervosa (AN) is an eating disorder (ED) that is associated with distorted body image and is characterized by excessive weight loss and an intent to lose weight by not eating enough (1). The main problem for AN is that even though patients have a body weight below the normal values, they refuse to eat because of an intense fear of being fat (2). AN has a 5% mortality rate and typically begins during adolescence and early adulthood (10-29 years). It primarily affects young girls; only one in ten of AN cases are men (3,4). The reported prevalence of AN is 0.1-1% in girls aged 15-19 years and 0.02% in boys aged 15-19 years (5).

This article will discuss the case study of a prepubertal boy who was diagnosed with early-onset AN. Physicians encountered problems during diagnosis and treatment due to the early onset.

CASE REPORT

A boy aged eight years and four months was admitted to the Pediatric Gastroenterology Polyclinic due to a lack of appetite and fatigue. He was directed to the Emergency Department because he was extremely exhausted and cachectic and required intravenous fluid. He did not have any systemic or chronic diseases. It was discovered that he had refused to eat solid food for four months and that he had neither eaten nor drunk anything for almost 15 days. During this period, his weight dropped from 20 kg to 16 kg, and he had become withdrawn from his favorite activities and refused to eat even his favorite foods. The symptoms could not be diagnosed by family physicians or pediatricians. Birth and developmental history were normal. There was no ongoing physical or psychological illness in his family.

At admission to the Emergency Department, he was exhausted, sluggish and cachectic enough not to stand up. He did not communicate verbally, did not answer questions, and avoided eye contact (Fig. 1). On physical examination, heart rate was 55 beats/min (bradycardic), respiratory rate was 16/min (normal), blood pressure was 85/65 mmHg (normal), oxygen saturation was 99% (on room air), Glasgow Coma Scale (GCS) score was 15 (normal), and capillary refilling time was below two seconds (normal). In addition, mucous membranes were dry and skin turgor was reduced. Systemic physical examination and neurological examination findings were normal. No physical examination finding suggested child abuse.

In laboratory tests, complete blood count, serum electrolytes, and liver and kidney function tests were normal. Serum uric acid level was 10 mg/dl (high), blood glucose level was 44 mg/dl, and complete urinalysis was normal except for 2+ ketones. In peripheral blood smear, there were 48% polymorphonuclear neutrophils, 46% lymphocytes, and 6% monocytes. Platelets and erythrocytes were normal. There were a few atypical lymphocytes, no abnormal findings on the ECG other than sinus bradycardia were found, and chest X-ray was normal.



Figure 1.

At admission to the Emergency Department, the patient was exhausted, sluggish and cachectic enough not to stand up. He did not communicate verbally, did not answer questions, and avoided eye contact.

CLINICAL APPROACH AND DIAGNOSTIC PHASE IN THE EMERGENCY DEPARTMENT

Blood glucose level was found to be 40 mg/dl. This was interpreted as ketotic hypoglycemia due to prolonged hunger. The patient was given 5 cc/kg of 10% dextrose intravenously. Maintenance and replacement fluid therapy was initiated to provide a glucose infusion rate at 8 mg/kg/min. Oxygen therapy was started with a mask at a flow rate of 6 l/min. Follow-up blood glucose level was 80 mg/dl. Because of personality and behavioral changes, loss of weight, and bradycardia, the primary differential diagnosis was an intracranial tumor. Cranial magnetic resonance imaging was normal. No medical treatment for bradycardia was given because there was no evidence of increased intracranial pressure and the patient was hemodynamically stable. Lymphoma was considered in the second rank in the differential diagnosis; however, there were no organomegaly and night sweats. He had no family history that might support a tuberculosis diagnosis, and the chest X-ray was normal. Because atypical lymphocytes were seen on peripheral blood smear, he was referred to the Children's Ward for further examination and treatment with the preliminary diagnoses of leukemia and lymphoma.

CLINICAL APPROACH AND DIAGNOSTIC PHASE IN THE CHILDREN'S WARD

At admission to the Children's Ward, he was exhausted and agitated, but could stand up. Body weight was 16.8 kg (< 3 p; SDS: -4.01).

Height was 122 cm (10 p). His weight-to-height ratio was 74%. His body mass index (BMI) was 11.2 (SDS: -4.75). When the vital findings were examined, heart rate was 60 beats/min, respiratory rate was 20/min, blood pressure was 90/65 mmHg, and body temperature was 37 °C.

Physical examination revealed mild dehydration. Neurological examination was not performed due to patient incompatibility. Intravenous fluid/electrolyte therapy was continued. Bone marrow aspiration was performed at the recommendation of the Department of Hematology/Oncology and was found to be normal. Thyroid function measurements were normal. Coeliac disease-related antibodies were negative. Thoracic and abdominal computed tomography was requested to exclude other possible oncologic pathologies; however, his family rejected this suggestion. The patient reacted violently to nasogastric tube feeding and had angry outbursts before every feeding attempt.

During follow-up treatment, he exhibited agitation and anger in refusal of a variety of nutrients and fluids to be administered either orally or nasogastrically. On the third day of hospitalization, he was evaluated by the Child and Adolescent Psychiatry Clinic. The psychiatric assessment indicated that he was depressed, that it was impossible to communicate with him, and that he did not provide clear answers to questions. In addition, it was reported that the patient's perception of his body was distorted, and 10 mg of fluoxetine and 2.5 mg of olanzapine per day were recommended for the preliminary diagnoses of AN and psychotic depression. However, on the fifth day of hospitalization, despite the insistence of the medical staff, the patient and his family refused the treatment and indicated that they would continue with it only after getting another physician's opinion. A week later, the father contacted the hospital to indicate that the boy's general condition was getting worse, and that they would administer the medication at home and would cooperate with the Child and Adolescent Psychiatry Clinic only if this condition was agreed to. In the second week of treatment, the patient was again evaluated by the Child and Adolescent Psychiatry Clinic.

A SECOND PSYCHIATRIC ASSESSMENT PERFORMED BY THE CHILD AND ADOLESCENT PSYCHIATRY CLINIC

According to the assessment, the patient had an elevated anxiety level, did not want to leave his mother, gave short answers to questions, and did not speak without being prompted. The mother was depressed and afraid of losing her son as the result of AN. She was observed to be over-controlling. The patient continued to struggle with his body image, did not eat in the evenings to avoid weight gain, and still felt fat. His Children's Depression Inventory (CDI) score was 22, and his State-Trait Anxiety Inventory for Children (STAIC) score was 43. His weight had dropped from 20 kg to 15 kg over the previous four months, and his perception of his body had become distorted.

Based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the patient was diagnosed with anorexia nervosa,

childhood depression and separation anxiety disorder. It was recommended that he continue to receive 10 mg of fluoxetine and 2.5 mg of olanzapine per day. Individual and parental interviews were scheduled; however, the patient and his family did not come to the appointment. Information about whether the medicines were given regularly and his eating habits was obtained via telephone. It was recommended that he continued to receive 10 mg of fluoxetine and 2.5 mg of olanzapine per day. Individual and parental interviews were scheduled. These updates indicated that he took both medicines regularly and started consuming liquid foods again. At the end of the first month of regular eating and medication, he was admitted to the Pediatric Emergency Department, and his body weight was recorded as 18 kg. He showed a better general condition and was active and interested in his surroundings and gave clear answers to questions (Fig. 2). It was reported that he had started attending school and playing the games he had previously enjoyed.

DISCUSSION

The rate of children with EDs who are identified by Primary Health Care physicians is very low (6). Since AN typically occurs after normal-weight or overweight adolescents make the decision to start a diet, early-onset AN can be easily overlooked by family physicians and pediatricians.



Figure 2.

At the end of the first month, body weight was 18 kg. He also had a better general condition, was active and interested in his surroundings and gave clear answers to the questions. Written informed consent from the parents was obtained.

It has been reported that EDs which do not meet the full diagnostic criteria are seen in 5-8% of boys and in 9-14% of girls among primary school children (7). It was clear that the patient had a disruption in eating behaviors before he met the full diagnostic criteria, but it could not be recognized by family physicians and pediatricians because there was no physical deterioration. AN can also present as a failure to gain weight rather than a loss of weight. For this reason, it can be misleading to evaluate patients on the basis of their BMI alone. Lask et al. reported that thoughts of patients about weight and body shape can be a good predictor for the development of AN in those admitted to the family physician for EDs (5). It is important that family physicians and pediatricians are able to recognize that disrupted eating behaviors, including food refusal, may reflect a patient's mental status. The authors of this report conclude that selective eating behaviors (one of the predictors of AN) accompanied by a reduced awareness of surroundings and mood changes could be factors that signal AN to physicians. For our patient, bradycardia, behavioral changes, and loss of weight pointed to central nervous system malignancies in the differential diagnosis. However, bradycardia can also occur due to the activation of the parasympathetic nervous system in patients with AN. Further examinations were performed in accordance with other differential diagnoses, including lymphoma and leukemia. AN was not initially considered.

A psychiatric consultation was requested for the patient because he exhibited agitation and aggressive behavior toward orogastric tube feeding. The detection of his distorted body perception during the first meeting suggested the final diagnosis. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) lists the following criteria for the diagnosis of AN: body weight of less than 85% of the normal range, disruption of judgment regarding weight or body image, and pathological fear of weight gain despite a body weight below the normal values (2). In our patient, the diagnosis of AN was based on his refusal to eat due to intense fear of gaining weight and his self-perception as fat,

despite being too weak to walk and having a body weight of less than 85% of normal values. Between 25-75% of patients with AN have also experienced childhood-onset anxiety disorders (8). In our patient, AN was accompanied with separation anxiety disorder and depression.

The delay in diagnosis damaged the family's trust in the doctors and led to a lack of cooperation with their approaches to treatment and follow-up.

This case reveals the importance of pediatricians' consideration of AN as a potential diagnosis in prepubertal children. Disrupted eating behaviors and mood changes may be predictive factors for the development of AN. An increased awareness of AN in family physicians and pediatricians is important for facilitating early diagnosis and treatment of the disease and preventing unnecessary deaths.

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