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Editorial

Trabajos Originales

Paciente crítico

Nutrición artificial

Pediatría

Nutrición anciano

Obesidad y síndrome metabólico

Valoración nutricional

Epidemiología y dietética

Otros

Revisiones

Crítica de libros

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Sumario

Vol. 40 Marzo-Abril N.º 2

sumario

Nutrición Hospitalaria

Sumario

Vol. 40 Marzo-Abril N.º 2

sumario

Nutrición Hospitalaria

Sumario

Vol. 40 Marzo-Abril N.º 2

sumario

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Summary

Vol. 40 March-April No. 2

summary

Nutrición Hospitalaria

Summary

Vol. 40 March-April No. 2

summary

Nutrición Hospitalaria

Summary

Vol. 40 March-April No. 2

summary

ISSN (electrónico): 1699-5198 - ISSN (papel): 0212-1611 - CODEN NUHOEQ S.V.R. 318

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Características organolépticas en la suplementación artificial, ¿prescribimos o servimos?

Organoleptic properties in oral nutritional supplementation, do we prescribe or do we serve?

La desnutrición relacionada con la enfermedad (DRE) tiene una fisiopatología variada en función de la enfermedad de base. Un factor común a la mayor parte de pacientes con DRE es la pérdida de apetito y la base del tratamiento médico nutricional es la adaptación de la dieta hacia alimentos que el paciente consuma y en el enriquecimiento de esta. No obstante, cuando se plantea el inicio de suplementación artificial, no siempre se trata de algo apetecible para el paciente.

El uso de suplementación artificial es un tratamiento médico nutricional y debe equipararse a cualquier otro tipo de prescripción farmacológica. Por lo tanto, es necesario consumir la dosis prescrita de dicho suplemento para poder obtener el beneficio deseado. La diferencia con la mayor parte de tratamientos farmacológicos es que tiene un volumen mayor y, habitualmente, depende de los gustos y la tolerancia del paciente para conseguir una adherencia adecuada, y, por tanto, el efecto deseado. Esta doble condición del suplemento oral nutricional como tratamiento médico y alimento conlleva que, en su prescripción, debamos tener en cuenta otro tipo de factores como el sabor, la textura, el olor o, incluso el color de este; pero sin olvidarnos de que es un tratamiento médico que debe tener en cuenta el contenido en tipo y cantidad de los macro y micronutrientes y su efecto sobre un paciente con unas características determinadas.

El prototipo de paciente con Desnutrición Relacionada con la Enfermedad y alteración del apetito es el paciente con patología oncológica. En este tipo de patologías, por una parte, la propia enfermedad causa un síndrome constitucional asociado a anorexia más o menos intensa. Esta situación puede potenciarse en relación con los tratamientos dirigidos al tratamiento de la enfermedad de base con síntomas como sequedad de boca, disgeusia, disfagia, o mucositis. En estos pacientes se recomienda el uso de suplementación oral nutricional para alcanzar los requerimientos necesarios a través del aporte de una cantidad específica de macro y micronutrientes contenidos en el suplemento. Además, en algunos casos, puede estar recomendado el aporte de determinados inmunonutrientes (arginina, glutamina, omega-3…) que pueden cambiar el sabor del suplemento pero que tienen evidencia para su uso en la mejoría de la evolución de la enfermedad (1,2).

En estos casos se nos puede plantear la disyuntiva de utilizar la suplementación más adecuada a su enfermedad, o la suplementación artificial que más le guste al paciente para conseguir la adherencia. Este planteamiento puede hacernos incurrir en errores en la prescripción y alejarnos de los objetivos terapéuticos planteados para el paciente. Es importante, por tanto, en primer lugar, explicar al paciente la importancia del consumo de la suplementación artificial para la evolución de la enfermedad y equipararlo a cualquier otro tratamiento médico que se le prescribe, pero, por otra parte, también es importante conseguir que, dentro de la suplementación pautada podamos adaptarnos a los gustos del paciente para intentar mejorar la adherencia.

Por esta razón, el desarrollo de las fórmulas de nutrición enteral oral debe tener en cuenta la saborización, no sólo testeada en los departamentos de I+D de las empresas dedicadas a la nutrición clínica, sino realizarla en base a investigación reglada en el tipo de paciente que va a ser beneficiario de esta suplementación de la misma manera que se realiza en la investigación clínica de la farmacoterapia en los ensayos clínicos de desarrollo de fármacos (fase II principalmente). Al fin y al cabo, estamos desarrollando un tratamiento médico y debería seguir las pautas relacionadas con cualquier tratamiento médico y no ser considerada únicamente como un alimento.

editorial

El artículo publicado por Morato y cols. en el presente número de la revista *Nutrición Hospitalaria* plantea este tipo de intervención en pacientes con patología oncológica y demuestra con datos que ciertas características organolépticas (en este caso el sabor) son mejor toleradas por paciente con patología oncológica que otras, y, por tanto, pueden conseguir una mejor adherencia por parte de este (3). Como se menciona en dicho artículo se han realizado distintos estudios en la evaluación de texturas y sabores en función de la base de la suplementación (zumo, yogur o leche). Incluso características como el frescor o el picante en pacientes con determinadas complicaciones asociadas al tratamiento. No obstante, estos estudios siguen siendo escasos y, habitualmente, en práctica clínica real postcomercialización y en poblaciones muy amplias con características variables (4,5).

Por muy básica que parezca la propuesta, se debe plantear el desarrollo de fórmulas en características organolépticas y de adherencia desde un punto de vista científico, al igual que se evalúan otros factores como su contenido nutricional o el efecto farmacoterápico de sus nutrientes. La evaluación de todos estos aspectos del desarrollo de las fórmulas con las garantías asociadas a la investigación clínica, pero con su idiosincrasia especial, nos permitirá apoyarnos en la evidencia a la hora de prescribir la suplementación y aportará un valor añadido al tratamiento médico nutricional en la DRE.

En resumen, la prescripción de suplementación artificial y la adherencia a esta debe enfocarse desde una base científica para poder aplicar el efecto nutricional y de modificación de la enfermedad deseado para ser considerado el tratamiento médico que nosotros sabemos que es.

Conflictos de interés: los autores declaran no tener conflicto de interés.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Paciente crítico

Assessment of dietary nutrient intake and its relationship to the nutritional status of patients with Crohn's Disease in Guangdong Province of China

Evaluación de la ingesta de nutrientes y su relación con el estado nutricional de los pacientes con enfermedad de Crohn en la provincia de Guangdong de China

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Abstract

Background and objectives: to investigate the association between the dietary nutrient intake and nutritional status of patients with Crohn's disease (CD).

Methods: sixty CD patients who had been diagnosed but had not begun treatment were enrolled. The dietary nutrient intake was recorded after three days of 24-hour recall and was calculated using NCCW2006 software. The nutrition levels were assessed using the Patient-Generated Subjective Global Assessment (PG-SGA). Indicators included body mass index (BMI), mid-arm circumference, the circumference of the upper-arm muscle, triceps skinfold thickness, handgrip strength, and the circumference of both calves.

Results: eighty-five per cent of CD patients did not meet the necessary energy requirements. Of these, the protein and dietary fiber intake in 63.33 % and 100 %, respectively, were below the standard of the Chinese dietary reference. Many patients had insufficient intake of vitamins, as well as other macro- and micronutrients. An inverse association was observed between the risk of malnutrition and higher levels of energy (1,590.0-2,070.6 kcal/d, OR = 0.050, 95 % CI: 0.009-0.279) and protein (55.6-70.5 g/d, OR = 0.150, 95 % CI: 0.029-0.773). Appropriate supplementation of vitamin E, calcium, and other dietary nutrients helped to reduce the risk of malnutrition.

Conclusions: significant deficiencies in dietary nutrient intake were found in CD patients, and dietary intake was associated with the nutritional status of the patient. Appropriate adjustment and supplementation of nutrient intake may reduce malnutrition risk in CD patients. The gap between actual consumption and recommendation indicates a need for improved nutritional counseling and monitoring. Early relevant advice for the dietary guidance of CD patients may be beneficial for long-term effects associated with nutritional status.

Keywords:

Crohn's disease. Dietary intake. Malnutrition. 24-hour recall.

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

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Hong Zheng and Xinbin Chen contributed equally to this work and are the co-first authors for this article.

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Resumen

Antecedentes y objetivos: investigar la asociación entre la ingesta de nutrientes y el estado nutricional de los pacientes con enfermedad de Crohn (EC).

Métodos: se reclutaron 60 pacientes de EC que habían sido diagnosticados, pero no habían iniciado ningún tratamiento. La ingesta de nutrientes se registró tras 3 días de recordatorio de 24 horas y se calculó utilizando el *software* NCCW2006. El estado nutricional se evaluó mediante la valoración global subjetiva generada por el paciente (PG-SGA). Los indicadores incluyeron el índice de masa corporal, la circunferencia media del brazo, la circunferencia del músculo de la parte superior del brazo, el grosor del pliegue cutáneo del tríceps, la fuerza de agarre y la circunferencia de la pantorrilla.

Resultados: el 85 % de los pacientes de EC no cubrieron las necesidades energéticas necesarias. De estos, las ingestas de proteína y fibra dietética en el 63,33 % y el 100 %, respectivamente, era más baja que lo que recominenda la norma de referencia dietética china. Muchos pacientes tuvieron una ingesta insuficiente de vitaminas, así como de otros macronutrientes y micronutrientes. Se observó una asociación inversa entre el riesgo de desnutrición y niveles más altos de energía (1590,0-2070,6 kcal/d, OR = 0,050, IC 95 % = 0,009-0,279) y proteínas (55,6-70,5 g/d, OR = 0,150, IC 95 % = 0,029-0,773). La suplementación adecuada de vitamina E, calcio y otros nutrientes dietéticos ayudó a reducir el riesgo de desnutrición.

Conclusiones: se observaron deficiencias significativas en la ingesta de nutrientes en los pacientes con EC, y la ingesta dietética se asoció con el estado nutricional del paciente. El ajuste y la suplementación adecuados de la ingesta de nutrientes pueden reducir el riesgo de malnutrición de los pacientes con EC. La diferencia entre el consumo real y la recomendación indica la necesidad de mejorar el asesoramiento y el seguimiento nutricional. El consejo temprano pertinente para la orientación dietética de los pacientes con EC puede ser beneficioso para los efectos a largo plazo asociados al estado nutricional.

Palabras clave:

Enfermedad de Crohn. Ingesta dietética. Malnutrición. Recordatorio de 24 horas.

INTRODUCTION

Crohn's disease (CD) is a relapsing systemic inflammatory disease, mainly affecting the gastrointestinal tract with extraintestinal manifestations and associated immune dysfunction. In terms of etiology, CD is currently believed to be caused by both genetic and environmental factors. The environmental factors mainly include smoking and poor dietary habits and lifestyle (1). As economic and living standards have improved, the incidence and prevalence of CD have gradually increased. In Asia, studies have reported annual prevalence rates in Hong Kong and mainland China of 21.0/100,000 and 2.29/100,000, respectively (2,3). Inflammation of the digestive tract leads to pain, diarrhea, and nausea that, in turn, result in reduced food consumption together with erratic eating habits, eventually affecting the nutritional status of the patient; malnutrition is thus a common challenge in CD patients. The incidence of malnutrition varies with different nutritional screening tools and diagnostic criteria, with several studies suggesting that the incidence ranges from 20 % to 85 % in patients with CD (4-7). The European Society for Parenteral and Enteral Nutrition (ESPN) defines malnutrition as a condition in which a lack of or insufficient intake of nutrients leads to changes in body composition that result in physical and mental dysfunction and affect the clinical outcome of the disease (8).

Several studies have shown that dietary fiber, vitamin C, vitamin D, and vitamin E, amongst other factors, may have protective effects against the development of CD (9,10). However, there are few studies that have investigated the intake of different nutrients in patients with CD and there is also a lack of comprehensive analysis. Some foreign researchers have reported that, compared with the recommended dietary intake (RDI) of Canada, 18.7 % and 86.5 % of CD patients did not reach the daily recommended intake of protein and dietary fiber (9,11). In addition, over 40 % of the CD patients consumed less than optimal levels of vitamins A, E, C, folic acid, calcium, and zinc (11). Furthermore, other studies have reported that the adult average intake of calcium, magnesium, and zinc is lower than the RDI (12). In China, there are no reports on the comparative analysis of the diets and dietary components of CD patients compared with the recommended dietary intake for Chinese residents, and the relationship between the nutritional status of CD patients and the dietary components remained unknown. The assessment of nutrient intake may provide dietary guidance to CD patients to assess their nutritional status and lead to improvements in clinical outcomes. The purpose of this study was to assess the dietary nutrient intake of CD patients and explore the association between dietary nutrient intake and nutritional status, to provide evidence for proper nutritional support.

MATERIALS AND METHODS

STUDY DESIGN

A cross-sectional study was conducted at the Guangdong Provincial People's Hospital in Guangzhou, Guangdong Province, China. Sixty adult patients (ranging from 18 to 60 years) who had been diagnosed but had not yet begun treatment were selected between May 2018 and January 2021. The CD diagnosis was based on standard clinical, endoscopic, histological, and cross-sectional imaging criteria (13).

ETHICS AND PATIENT CONSENT

Permission from the Ethics Committee of the Guangdong Provincial People's Hospital was obtained before the study (No. GDREC2018091H). The clinical trial registration number was ChiCTR1800015174. The study was conducted according to the principles of the Declaration of Helsinki and the participants provided written informed consent.

MEASUREMENTS

Anthropometric assessments were performed in the morning after an 8-12 hour fast, and the same times of assessment were used for each participant. All assessments were conducted by the same investigator. Anthropometric measurements included height, weight, body mass index (BMI), mid-arm circumference (MAC), triceps skinfold thickness (TSF), mid-arm muscle circumference (MACM), handgrip strength of the non-dominant hand, and the left calf circumference (LCC) and right calf circumference (RCC). Body weights were taken to the nearest 100 g with an electronic scale; participants were barefoot and wore minimum clothing. A stadiometer was used to measure height to the closest 0.1 cm, and the BMI was determined as weight (kg)/height^2 (m). BMI values less than 18.5 kg/m^2 indicated malnutrition. The MAC and MACM were measured with a measuring tape at the mid-point between the olecranon process and acromion on the right side. TSF measurements were taken at the same position using Holtain skinfold calipers. Leg measurements included the circumferences of the thickest and thinnest parts of the calf, and the calf average measurement was calculated from three measurements. Nutritional status was determined by Patient-Generated Subjective Global Assessment (PG-SGA) with scores ≥ 4 indicating malnutrition.

Dietary recall (three days of 24 hours) was performed to record the nutrient intake of each person via face-to-face interviews. The patients were asked to describe the time, type, and amounts of all foods and beverages consumed over the previous three days. The interviewer used the food models to help the interviewee estimate the amounts of each food and beverage. The dietary information was recorded using a 24-h dietary review questionnaire. The date and the time of consumption of each food item were entered into the Nccw2006 Nutrient Analysis Software program. Macro- and micronutrients were calculated using the software, and the result was compared with the Chinese dietary reference intakes (DRIs). For energy, protein, zinc, vitamin A, thiamine, riboflavin, vitamin C, and niacin, intake values < 80 % of the recommended nutrient intake (RNI) were considered as not meeting the requirement. For calcium, phosphorus, magnesium, iron, and vitamin E, intake values less than the adequate intake (AI) value were considered to not meet the requirement.

STATISTICAL ANALYSIS

SPSS version 26.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. For quantitative data, the Shapiro-Wilk method (W test) was used to assess the normality of the data distribution. Normally distributed data were described as means with standard deviations ($\overline{\chi} \pm s$), while if the data did not follow the normal distribution, the interval between the median and quantile [M(P25, P75)] was used for description. The form of the qualitative data adoption rate is described. Correlation analysis was used to analyze the relationship between nutritional status and various nutrients in patients with CD. All dietary nutrients were categorized into quartiles based on the distribution of the dietary intake of patients. Logistic regression analysis was used to calculate the odds ratios for the association between various nutrients and malnutrition risk-adjusted for age and sex. For analysis, the lowest intake of dietary nutrients was considered as the reference and the odds ratios in other quartiles were computed. All test level α values were 0.05, and bilateral probability was taken.

RESULTS

The anthropometric parameters of the study subjects are listed in table I. Forty-three males, accounting for 71.67 % of the total, and 17 females, accounting for 28.33 % of the total, were included. Twenty-eight patients had BMIs in the normal and underweight range, accounting for 46.67 % of the total number of patients, while there were two overweight and two obese patients, accounting for 3.33 % of the total number of patients. Nutritional status assessed by MAC, MACM, TSF, LCC, and RCC were all below the reference range of China. The average total score of the PG-SGA was 9.30 ± 4.77. Twenty-four patients had normal nutrition, accounting for 40 %. The number of participants with moderate and severe malnutrition was six and 30, respectively, accounting for 10 % and 50 %, respectively, of the total. Thus, in this survey, most patients exhibited severe malnutrition.

The dietary nutrient intake of the CD patients is shown in table II. Overall, 85 % of CD patients did not meet their energy requirements, and 63.33 %, 13.33 %, 11.67 %, and 100 % of CD patients had intakes of protein, fat, carbohydrate, and dietary fiber, respectively, that were lower than the Chinese dietary reference standards. The insufficient intake prevalence was 88.33 % for vitamin A, 90.0 % for vitamin B1, 91.67 % for vitamin B2, 76.67 % for vitamins C and E, and 50 % for vitamin PP. Overall, 21-100 % of CD patients did not meet their mineral requirements and 100 % and 50 % of them did not meet their requirements for calcium and phosphorus, respectively. The sufficient intake prevalence was 95 % for potassium, 55 % for sodium, 96.67 % for magnesium, 36.67 % for iron, 53.33 % for zinc, 91.67 % for selenium, 21.67 % for copper, and 65.00 % for manganese.

The results in table III show the relationship between the total score of the patients' PG-SGA evaluation scale and the intake of various nutrients. The statistically significant nutritional factors were energy, protein, carbohydrate, vitamin A, vitamin B1, vitamin B2, vitamin E, vitamin PP, and all minerals. In addition, the correlation analysis indicated that the total score of the PG-SGA evaluation scale was negatively correlated with the intake of each nutrient, that is, the higher the intake of each nutrient, the lower the total score of the PG-SGA evaluation scale, which represented better nutritional status.

Table IV presents the odds ratios and 95 % CIs for the risk of malnutrition associated with energy, protein, fat, carbohydrate, and dietary fiber. For all patients combined, there was a significant decrease in the malnutrition risk among patients with CD in the third quartile (1,590.0-2,070.6 kcal/d for energy and 55.6-70.5 g/d for protein) intake of energy (OR = 0.050, 95 %

CI: 0.009-0.279), and protein (OR = 0.150, 95 % CI: 0.029-0.773). We next examined the risk of malnutrition associated with the intake of individual vitamins, as shown in table V. In these patients with CD, inverse associations were observed for vitamin B-2, vitamin E, and vitamin PP, with evidence of significant dose response for vitamin B-2 (p trend = 0.002), vitamin E (p trend = 0.013), and vitamin PP (p trend = 0.002). For example, patients in the highest quartile of vitamin E intake had a significant 87 % reduction in risk when compared with those in the lowest quartile (OR = 0.125, 95 % CI: 0.024-0.640). Table VI presents the odds ratios and 95 % CIs for the risk of malnutrition associated with individual minerals. Comparing the highest to the lowest quartile of mineral intake, the odds ratios were lower for potassium (OR = 0.227, 95 % CI: 0.052-0.986; p trend = 0.048), calcium (OR = 0.188, 95 % CI: 0.042-0.848; p trend = 0.030), magnesium (OR = 0.186, 95 % CI: 0.040-0.875; p trend = 0.033), iron (OR = 0.101, 95 % CI: 0.018-0.566; p trend = 0.009), zinc (OR = 0.144, 95 % CI: 0.026-0.800; p trend = 0.027), and selenium (OR = 0.152, 95 % CI = 0.030-0.770; p trend = 0.023), whereas manganese was unrelated to the risk of malnutrition even at extreme levels of intake (OR = 0.411, 95 % CI = 0.092-1.847; p trend = 0.246).

Table I. Characteristics of participants (n = 60)

Group	n (%)/($\bar{\chi} \pm s$)/*M* (P_{25}, P_{75})	Reference range
Sex		
Male	43 (71.67 %)	-
Female	17 (28.33 %)	-
Age	36.53 ± 8.21 (20-47)	
BMI (kg/m²)		
Lean	28 (46.67 %)	< 18.5
Normal	28 (46.67 %)	18.5-23.9
Overweight	2 (3.33 %)	24-27.9
Obesity	2 (3.33 %)	≥ 28
MAC (cm)		
Male	22.41 ± 3.81	30.5~32.7
Female	21.98 ± 4.31	27~30.7
MACM (cm)		
Male	20.35 (17.68, 21.69)	26.8~28.8
Female	18.99 ± 3.96	20.9~22.8
TSF (mm)		
Male	7.80 (5.10, 10.50)	11.2~12.6
Female	9.37 ± 3.96	19.4~25.4
Handgrip strength (kg)		
Male	32.00 ± 7.39	29.2~40.4
Female	19.78 ± 4.60	16.8~20.9
LCC (cm)		
Male	31.74 ± 4.12	Male: ≥ 34 Female: ≥ 33
Female	29.90 (27.95, 32.90)	
RCC (cm)		
Male	32.03 ± 4.20	
Female	31.10 (28.50, 32.95)	
Results of total score of PG-SGA evaluation scale		
Normal nutrition	24 (40 %)	0-3
Moderate malnutrition	6 (10 %)	4-8
Severe malnutrition	30 (50 %)	≥ 9

BMI: body mass index; MAC: mid-arm circumference; TSF: triceps skinfold thickness; MACM: mid-arm muscle circumference; LCC: left calf circumference; RCC: right calf circumference; PG-SGA: Patient-Generated Subjective Global Assessment.

Table II. Dietary intake of patients with CD (n = 60)

Nutrients	$(\bar{\chi} \pm s)/M\ (P_{25}, P_{75})$	n* (%)
Energy (kcal/d)	1,667.42 ± 630.15	51 (85.00)
Protein (g/d)	55.58 (38.45, 70.45)	38 (63.33)
Fat (g/d)	53.93 (38.85, 69.55)	8 (13.33)
Carbohydrate (g/d)	220.6 (149.39, 291.18)	7 (11.67)
Dietary fiber (g/d)	3.93 (2.00, 5.80)	60 (100.00)
Vitamin A (ugRAE/d)	153.75 (103.20, 280.50)	53 (88.33)
Vitamin B1 (mg/d)	0.78 (0.52, 1.07)	54 (90.00)
Vitamin B2 (mg/d)	0.65 (0.44, 0.87)	55 (91.67)
Vitamin C (mg/d)	28.50 (6.68, 89.24)	46 (76.67)
Vitamin E (mg-αTE/d)	11.33 (9.21, 13.94)	46 (76.67)
Vitamin PP (mg NE/d)	14.08 (9.22, 17.88)	30 (50.00)
Calcium (mg/d)	166.65 (83.60, 316.25)	60 (100.00)
Phosphorus (mg/d)	733.15 (549.23, 940.28)	30 (50.00)
Potassium (mg/d)	1,027.82 (628.23, 1,422.98)	57 (95.00)
Sodium (mg/d)	1,463.94 (1,380.11, 1,554.60)	33 (55.00)
Magnesium (mg/d)	170.80 (116.55, 235.33)	58 (96.67)
Iron (mg/d)	15.46 (11.12, 19.96)	22 (36.67)
Zinc (mg/d)	10.31 (7.83, 13.36)	32 (53.33)
Selenium (ug/d)	38.00 (25.65, 50.23)	55 (91.67)
Copper (mg/d)	1.12 (0.86, 1.56)	13 (21.67)
Manganese (ug/d)	3.68 (2.68, 5.31)	39 (65.00)

*CD: Crohn's disease. *n (%) denotes numbers and percentages lower than the standard of Chinese dietary reference intake (2013 edition).*

Table III. Relationship between dietary intake and the PG-SGA scores of patients (n = 60)

Nutrients	r/r_s	*p*	Nutrients	r/r_s	*p*
Energy	-0.370	0.004*	Vitamin PP	-0.402	0.001*
Protein	-0.420	0.001*	Calcium	-0.265	0.040*
Fat	-0.232	0.083	Phosphorus	-0.423	0.001*
Carbohydrate	-0.384	0.002*	Potassium	-0.354	0.005*
Dietary fiber	-0.244	0.060	Sodium	-0.309	0.016*
Cholesterol	-0.315	0.014*	Magnesium	-0.406	0.001*
Vitamin A	-0.338	0.008*	Iron	-0.350	0.006*
Vitamin B-1	-0.322	0.012*	Zinc	-0.403	0.001*
Vitamin B-2	-0.506	< 0.001*	Selenium	-0.381	0.003*
Vitamin C	-0.210	0.108	Copper	-0.358	0.005*
Vitamin E	-0.364	0.004*	Manganese	-0.296	0.022*

*PG-SGA: Patient-Generated Subjective Global Assessment. *p < 0.05.*

Table IV. Logistic regression analysis of energy, protein, fat, carbohydrate, dietary fiber, cholesterol, and nutritional status in patients with CD

	Model *OR (95 % CI)	p trend
Energy (kcal/d)		
Q_1 (< 1,134.9)	1.00 (reference)	-
Q_2 (1,134.9-1,590.0)	0.832 (0.151, 4.578)	0.833
Q_3 (1,590.0-2,070.6)	0.050 (0.009, 0.279)	0.001†
Q_4 (> 2,070.6)	0.718 (0.131, 3.947)	0.703
Protein (g/d)		
Q_1 (< 38.5)	1.00 (reference)	-
Q_2 (38.5-55.6)	0.479 (0.088, 2.613)	0.396
Q_3 (55.6-70.5)	0.150 (0.029, 0.773)	0.023†
Q_4 (> 70.5)	0.204 (0.039, 1.052)	0.057
Fat (g/d)		
Q_1 (< 38.9)	1.00 (reference)	-
Q_2 (38.9-53.9)	0.743 (0.175, 3.161)	0.687
Q_3 (53.9-69.6)	0.764 (0.171, 3.427)	0.726
Q_4 (> 69.6)	1.046 (0.226, 4.838)	0.954
Dietary fiber (g/d)		
Q_1 (< 2.00)	1.00 (reference)	-
Q_2 (2.00-3.93)	0.819 (0.175, 3.824)	0.800
Q_3 (3.93-5.80)	0.553 (0.126, 2.421)	0.432
Q_4 (> 5.80)	0.397 (0.093, 1.701)	0.214
Carbohydrate (g/d)		
Q_1 (< 149.4)	1.00 (reference)	-
Q_2 (149.4-220.6)	0.444 (0.092, 2.148)	0.113
Q_3 (220.6-291.2)	0.258 (0.049, 1.354)	0.109
Q_4 (> 291.2)	0.284 (0.060, 1.347)	0.313

*CD: Crohn's disease. *Adjusted for age and sex; †p < 0.05.*

Table V. Logistic regression analysis of vitamins and nutritional status in patients with CD

	Model †OR (95 % CI)	p trend
Vitamin A (ugRAE/d)		
Q_1 (< 103.2)	1.00 (reference)	-
Q_2 (103.2-153.8)	0.719 (0.135, 3.820)	0.699
Q_3 (153.8-280.5)	0.219 (0.046, 1.038)	0.056
Q_4 (> 280.5)	0.355 (0.078, 1.610)	0.179
Vitamin B-1 (mg/d)		
Q_1 (< 0.52)	1.00 (reference)	-
Q_2 (0.52-0.78)	1.188 (0.203, 6.959)	0.849
Q_3 (0.78-1.07)	0.239 (0.055, 1.038)	0.056
Q_4 (> 1.07)	0.313 (0.070, 1.399)	0.128

(Continue in the next column)

Table V (Cont.). Logistic regression analysis of vitamins and nutritional status in patients with CD

	Model †OR (95 % CI)	p trend
Vitamin B-2 (mg/d)		
Q_1 (< 0.44)	1.00 (reference)	-
Q_2 (0.44-0.65)	0.653 (0.086, 4.937)	0.680
Q_3 (0.65-0.87)	0.082 (0.013, 0.522)	0.008†
Q_4 (> 0.87)	0.055 (0.009, 0.350)	0.002†
Vitamin C (mg/d)		
Q_1 (< 6.68)	1.00 (reference)	-
Q_2 (6.68-28.5)	0.393 (0.082, 1.878)	0.242
Q_3 (28.5-89.2)	0.298 (0.067, 1.322)	0.111
Q_4 (> 89.2)	0.530 (0.110, 2.545)	0.427
Vitamin E (mgα-TE/d)		
Q_1 (< 9.21)	1.00 (reference)	-
Q_2 (9.21-11.3)	0.475 (0.088, 2.552)	0.385
Q_3 (11.3-13.9)	0.346 (0.067, 1.790)	0.206
Q_4 (> 13.9)	0.125 (0.024, 0.640)	0.013†
Vitamin PP (mgNE/d)		
Q_1 (< 9.22)	1.00 (reference)	-
Q_2 (9.22-14.1)	0.155 (0.024, 1.006)	0.051
Q_3 (14.1-17.9)	0.047 (0.007, 0.316)	0.002*
Q_4 (> 17.9)	0.165 (0.025, 1.086)	0.061

*CD: Crohn's disease. *Adjusted for age and sex. †p < 0.05.*

Table VI. Logistic regression analysis of minerals and nutritional status in patients with CD

	Model *OR (95 % CI)	p trend
Potassium (mg/d)		
Q_1 (< 628.2)	1.00 (reference)	-
Q_2 (628.2-1,027.8)	1.167 (0.234, 5.806)	0.851
Q_3 (1,027.8-1,423.0)	0.628 (0.137, 2.882)	0.549
Q_4 (> 1,423.0)	0.227 (0.052, 0.986)	0.048†
Sodium (mg/d)		
Q_1 (< 1,380.1)	1.00 (reference)	-
Q_2 (1,380.1-1,463.9)	0.991 (0.181, 5.418)	0.991
Q_3 (1,463.9-1,554.6)	0.163 (0.033, 0.811)	0.027†
Q_4 (> 1,554.6)	0.290 (0.063, 1.336)	0.112
Calcium (mg/d)		
Q_1 (< 83.6)	1.00 (reference)	-
Q_2 (83.6-166.7)	1.361 (0.262, 7.075)	0.714
Q_3 (166.7-316.3)	0.597 (0.131, 2.716)	0.504
Q_4 (> 316.3)	0.188 (0.042, 0.848)	0.030†

(Continues on next page)

Table VI (Cont.). Logistic regression analysis of minerals and nutritional status in patients with CD

	Model *OR (95 % CI)	p trend
Magnesium (mg/d)		
Q_1 (< 116.6)	1.00 (reference)	-
Q_2 (116.6-170.8)	0.887 (0.156, 5.048)	0.892
Q_3 (170.8-235.3)	0.180 (0.037, 0.873)	0.033†
Q_4 (> 235.3)	0.186 (0.040, 0.875)	0.033†
Iron (mg/d)		
Q_1 (< 11.1)	1.00 (reference)	-
Q_2 (11.1-15.5)	0.286 (0.051, 1.597)	0.154
Q_3 (15.5-20.0)	0.205 (0.038, 1.089)	0.063
Q_4 (> 20.0)	0.101 (0.018, 0.566)	0.009†
Manganese (ug/d)		
Q_1 (< 2.68)	1.00 (reference)	-
Q_2 (2.68-3.68)	1.365 (0.260, 7.171)	0.713
Q_3 (3.68-5.31)	0.238 (0.051, 1.114)	0.068
Q_4 (> 5.31)	0.411 (0.092, 1.847)	0.246
Zinc (mg/d)		
Q_1 (< 7.83)	1.00 (reference)	-
Q_2 (7.83-10.3)	0.438 (0.075, 2.561)	0.360
Q_3 (10.3-13.4)	0.089 (0.016, 0.494)	0.006†
Q_4 (> 13.4)	0.144 (0.026, 0.800)	0.027†
Copper (mg/d)		
Q_1 (< 0.86)	1.00 (reference)	-
Q_2 (0.86-1.12)	0.346 (0.065, 1.849)	0.214
Q_3 (1.12-1.56)	0.157 (0.031, 0.803)	0.026†
Q_4 (> 1.56)	0.294 (0.059, 1.457)	0.134
Phosphorus (mg/d)		
Q_1 (< 549.2)	1.00 (reference)	-
Q_2 (549.2-733.2)	3.335 (0.509, 21.856)	0.209
Q_3 (733.2-940.3)	0.293 (0.067, 1.291)	0.105
Q_4 (> 940.3)	0.219 (0.048, 0.999)	0.050
Selenium (ug/d)		
Q_1 (< 25.7)	1.00 (reference)	-
Q_2 (25.7-38.0)	0.231 (0.046, 1.174)	0.077
Q_3 (38.0-50.2)	0.347 (0.066, 1.831)	0.212
Q_4 (> 50.2)	0.152 (0.030, 0.770)	0.023†

**Adjusted for age and sex. †$p < 0.05$.*

DISCUSSION

This study analyzed the nutritional status of patients with CD, finding an association between nutritional status and dietary intake. The PG-SGA evaluation scale was used to evaluate the nutritional status of CD patients. The results showed that the patients suffered from malnutrition to different degrees, with the incidence of moderate and severe malnutrition reaching 60.0 %, which is close to the results reported by Bian D (14). In addition, a systematic review concluded that close to one-third of CD patients have altered body compositions, seen as reductions in the BMI (15). The American Society of Parenteral and Enteral Nutrition (ASPEN) has proposed the use of specific parameters, including loss of weight, muscle mass, and subcutaneous fat, as well as handgrip strength, for diagnosing malnutrition (16). As shown by a recent systematic review, reduced muscle mass occurs in approximately 60 % of inflammatory bowel disease (IBD) patients (17). Body composition indicators such as reduced BMI and upper-arm circumference, amongst others, have been described in CD patients (18) who were also found to have reduced circumferences of the leg and mid-arm, as well as reduced mid-arm muscle (19). The results of our study showed that the mean BMI, MAC, MACM, TSF, LCC, and RCC values in CD patients were all lower than the corresponding reference values of normal Chinese adults. Altogether, malnutrition is a prevalent problem in CD patients and Coqueiro et al. concluded that deficiencies in nutritional factors in CD patients could lead to a risk of developing osteopenia and other complications in the long term (20).

In general, the incidence of malnutrition in patients with CD remains high, which may be caused by various factors (21,22). CD patients often experience abdominal pain, loss of appetite, nausea, vomiting, diarrhea, and other common gastrointestinal symptoms, which may lead to restricted diets and a reduction in food intake. In addition, reduced dietary intake can also lead to deficiencies in trace elements such as zinc and copper, which affect taste and will thus further affect their appetite. Furthermore, when the patient experiences active disease, although there may be increased nutrient consumption, the nutrient supplementation may be insufficient, further aggravating the occurrence of malnutrition. A study in Shanghai reported that people with CD did not receive sufficient energy, protein, calcium, and iron (21). Another study suggested that the intake of dietary fiber, as well as macro- and micronutrients, did not meet World Health Organization/Food and Agriculture Organization of the United Nations (WHO/FAO, 2003 edition) recommendations in most patients (23). However, there have been no reports of comparisons with the DRI standards for Chinese residents (24). The current study addressed the dietary intake of patients with CD. It was obvious that the dietary intake of most of these patients was far below the standard of the Chinese DRIs, and this, together with their low average food intake, may lead to further deteriorations in the nutritional status of patients with CD.

We found that the PG-SGA scale evaluations were negatively correlated with the intake of different nutrients. Similarly, a cross-sectional study (25) and an ambulatory study (14) also demonstrated a negative association between the PG-SGA and the dietary intake of energy and protein. These results indicated that CD patients having lower energy and protein intake may experience more severe malnutrition (reflected as higher PG-SGA scores). Thus, our research showed that an inverse association between dietary energy and protein intakes of 1,590.0-2,070.6 kcal/d and 55.6-70.5 g/d, respectively, may reduce the risk of malnutrition in patients with CD. This, together with

the findings that the energy and protein intakes in CD patients fell far below the DRIs, suggests that energy and protein should be increased appropriately to prevent malnutrition and to prevent disease progression.

In addition, vitamin deficiencies are often seen in patients with CD (26,27). Sufficient micronutrient intake is essential for improving the clinical outcome. Studies have shown that antioxidants such as vitamins A, C, and E can reduce oxidative stress, retard inflammation and delay the occurrence and development of diseases to a certain extent (10). B vitamins function as cofactors for essential metabolic enzymes and mediate fat, protein, and carbohydrate metabolism. B vitamins also play roles in both dietary and gut microbiome-mediated immune modulation. Moreover, B-vitamin supplementation in the diet in CD patients produces various anti-inflammatory effects and reductions in systemic oxidative stress and clinical symptoms, as shown by a clinical study (28). The results of this survey also showed that patients did not experience deficiencies in single vitamins but lacked multiple vitamins. The results of the current study suggested that higher intakes of vitamins B2, PP, and E from food were associated with a statistically significant reduction in the risk of malnutrition among patients. Therefore, attention should be paid to the supplementation of multiple vitamins in CD patients, such as at least 0.87 mg of vitamin B-2 and 13.9 mg-αTE of vitamin E daily, which may improve the body status of patients with malnutrition. At the same time, mineral deficiencies are also common in CD (27). Calcium and phosphorus play important roles in bone growth and development and CD patients have severe deficiencies in these minerals (100 % deficiency), which may increase the risk of osteoporosis in patients (29). Other minerals play important roles in tissue regeneration and protect cells from free radical damage, thus influencing the healing and prognosis of various diseases (30,31). In this study, we observed an association between the intake of individual minerals and the nutritional status of CD patients, with higher mineral intake reducing the incidence of malnutrition. Therefore, we speculate that appropriate supplementation of various minerals may be effective in improving patient nutritional status or delaying disease progression. Above all, we found that the average micronutrient intake was below the DRIs and, as dietary intake and nutritional status are correlated, clinicians should focus on micronutrient intake to ensure good nutritional status.

In this study, we analyzed the relationship between nutritional status and dietary intake in patients with CD, and found correlations between nutritional status and dietary intake, together with providing useful quantitative data that may reduce the risk of malnutrition among CD patients. Few studies have addressed this issue. Based on the results of this survey, we have several dietary recommendations for CD patients (32,33). It is recommended to take an appropriate vitamin and mineral supplement daily under the guidance of a doctor, including vitamins and minerals such as vitamins A, B-2, C, and E, and calcium, iron, and zinc, amongst others. In addition, if the patient is unable to improve their nutritional status from diet alone, enteral and parenteral nutrition could be used to provide supportive treatment.

The limitations to this study include the relatively small sample size, which precluded investigation of the relationships with sex and age using these as subgroups. Dietary recall, which was supposed to be three 24-h days, was not always accurate as, if a weekend intervened, some patients had difficulty in remembering food types due to the extended time. While we used PG-SGA for the assessment of nutritional status, we did not compare it with the ESPEN definition or the GLIM criteria. In addition, the lack of available equipment, such as dual-energy X-ray absorptiometry (DEXA) or bioelectrical impedance analysis (BIA), as well as nurses with professional training, was a non-negligible problem. Furthermore, the study was not able to assess causal relationships as it was not an intervention trial; cross-sectional surveys are unable to clarify cause and effect and can only suggest clinical significance. Future studies should use appropriately increased sample sizes for further analysis and provide detailed dietary guidelines for interventions.

CONCLUSION

In this study, the results showed incidence of moderate to severe malnutrition (reaching 60 %) in CD patients. The dietary survey found the intake of various nutrients by these patients fell far below the Chinese DRI standard, and there was a correlation between nutritional status and dietary intake. Appropriate intake of energy, protein, vitamin E, calcium, and other dietary nutrients may relate to malnutrition in CD patients. Therefore, early individualized nutritional guidance and suggestions may be beneficial for long-term improvements in nutritional status and may thus alleviate disease progression.

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Trabajo Original

Paciente crítico

Feeding intolerance during prolonged prone position in overweight and obese patients with severe COVID-19

Intolerancia a la alimentación durante el prono prolongado en pacientes con COVID-19 y sobrepeso y obesidad

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Abstract

Objective: the aim of this study was to compare the incidence rate of feeding intolerance (FI) during supine (SP) or prone positioning (PP) in critically ill COVID-19 patients.

Methods: this was a retrospective cohort study of critically ill patients with overweight or obesity who received enteral nutrition (EN) in prone or supine positioning continuously during the first five days of mechanical ventilation. Nutritional risk, anthropometric measurements and body composition were assessed at the first 24 hours upon Intensive Care Unit (ICU) admission. Biochemical and clinical variables (Sequential Organ Failure Assessment [SOFA], Acute Physiology and Chronic Health Evaluation II [APACHE II], Acute Kidney Injury [AKI] or comorbidities diagnosis) were collected. Pharmacotherapy (prokinetics, sedatives or neuromuscular blocking agents) and FI incidence (gastric residual volume [GRV] ≥ 200 ml or ≥ 500 ml, vomiting or diarrhea) were daily recorded. Constipation was defined as the absence of evacuation for five consecutive days.

Results: eighty-two patients were included. Higher rate of prophylactic prokinetic prescription was observed in PP (42.8 *vs* 12.5 %, p = 0.002). GRV ≥ 200 in supine position was not different when compared to PP (p = 0.47). Vomiting episodes in supine compared to PP showed no difference between groups (15 % *vs* 24 %, p = 0.31). No differences in diarrhea events were detected (10 % *vs* 4.7 %, p = 0.36). Constipation was common in both groups (95 % *vs* 82 %, p = 0.06).

Conclusion: FI during prone position was not different in comparison to supine position. Routinely use of prokinetics in continuous prone position may help to prevent FI incidence. Algorithm development is necessary for FI prevention and treatment so to avoid EN interruptions and adverse clinical outcomes.

Keywords:

Enteral nutrition. Nutrition assessment. Critically ill. Prone position. Gastrointestinal dysfunction.

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Resumen

Objetivo: comparar la incidencia de intolerancia a la alimentación entre pacientes críticos en posición supino (PS) o prono (PP).
Métodos: cohorte retrospectiva de pacientes bajo ventilación mecánica por distrés respiratorio por COVID-19 y sobrepeso y obesidad, quienes recibieron nutrición enteral (NE) en PP o PS. Se evaluaron riesgo nutricional, mediciones antropométricas y composición corporal en las primeras 24 horas de ingreso a la Unidad de Cuidados Intensivos (UCI). Se recolectaron variables bioquímicas y clínicas (Sequential Organ Failure Assessment [SOFA], Acute Physiology and Chronic Health Evaluation II [APACHE II], lesión renal aguda y otras comorbilidades). Se registró el esquema de farmacoterapia prescrita durante los primeros cinco días (procinéticos, sedantes y bloqueadores neuromusculares). Se evaluó la incidencia de intolerancia a la alimentación, definida como la presencia de residuo gástrico (RG) ≥ 200 o ≥ 500 ml, vómito, diarrea o estreñimiento.

Resultados: fueron incluidos 82 pacientes. Se observó una mayor prescripción de procinéticos como terapia profiláctica en PP (42,8 *vs.* 12,5 %, p = 0,002). No se observaron diferencias en RG ≥ 200 ml (p = 0,47) ni vómito (p = 0,31) entre ambos grupos. No se observaron diferencias en episodios de diarrea (10 % en PS *vs.* 4,7 % en PP, p = 0,36). El estreñimiento fue común en ambos grupos de estudio (95 *vs.* 82 %, p = 0,06).

Conclusiones: la PP no se relaciona con una mayor incidencia de intolerancias a la alimentación. El uso rutinario de procinéticos durante la PP continua puede ayudar a prevenir la incidencia de dichas intolerancias. Es necesario el desarrollo de algoritmos para la prevención y tratamiento de las intolerancias a la alimentación para evitar interrupciones en la NE y desenlaces no deseables.

Palabras clave:

Nutrición enteral. Valoración nutricional. Paciente crítico. Posición prono. Disfunción gastrointestinal.

INTRODUCTION

Enteral nutrition (EN) is the preferred feeding route for critically ill patients on mechanical ventilation (MV) (1), and it is associated with better immunological and clinical outcomes when started within 48 hours after admission (2). EN interruption is common during ICU stay due to procedural-related fasting, vasopressors doses, and other potentially avoidable causes (3). Feeding intolerance (FI), defined as gastrointestinal (GI) dysfunction resulting in a reduction in the delivery of enteral feeding, regardless of the underlying cause, is another common cause of EN interruption (4). Different definitions of GI symptoms are currently used in studies (5), and include vomiting, regurgitation, abdominal distension, gastric residual volume, absent/abnormal bowel sounds, abdominal pain, absence/presence of stool, diarrhea, high intra-abdominal pressure and GI bleeding (6).

Prone positioning (PP) is commonly used in acute respiratory distress syndrome (ARDS) patients (7,8), and may be a cause of EN interruptions due to higher episodes of vomiting and gastric residual volume (GRV) (9), intra-abdominal hypertension (IAH), and gut dysmotility, which can also be exacerbated by pharmacotherapy (7,10,11). Furthermore, the incidence of ARDS is higher in obese patients, and could be beneficiated by PP (12,13). Since obesity has been associated with a higher risk of impaired gastric motility and EN intolerance, due to IAH (14,15) and comorbidities such as diabetes (16), there is a lack of knowledge about the safety of EN provision in overweight and obese patients in PP. The aim of this study is to compare the incidence of FI during the supine or prone position in overweight and obese patients on MV.

METHODS

This was a retrospective cohort of consecutive patients that were admitted to the Intensive Care Unit (ICU) from November 2020 to December 2021. COVID-19 patients (confirmed by SARS-CoV-2 real-time polymerase chain reaction) on MV due to ARDS were included (17). Patients were categorized as PP if they required this management during the first five days of EN, or supine positioning (SP) if not required during that same period. PP was considered when PaO_2/FiO_2 was below 150 according to current treatment guidelines (18). Patients were excluded if they did not have overweight/obesity (body mass index [BMI] < 25 kg/m^2), or if their management required either MV or PP for less than five days, or position changed during the same period. This study was reviewed and approved by the Institutional Review Board (Register #C51-29).

DATA COLLECTION

Demographic information including sex and age was collected from patient records. Prescribed drugs with nutritional implications (steroids, benzodiazepines, opioids, neuromuscular blocking agents [NBA], sedatives, dexmedetomidine, prokinetics and vasopressors) along with medical history of non-communicable diseases were also registered. According to our unit standard, PP was achieved with foam wedges and pillows, alternating head, and neck rotation every four hours. Duration of PP cycle is continuous (24 hours) without cycles SP changed.

NUTRITIONAL ASSESSMENT

Nutritional assessment was performed on all patients during the first 24-48 hours after ICU admission. Body weight and height were estimated by means of validated equations using anthropometric measurements (19). BMI was calculated and classified using the World Health Organization (WHO) criteria (20). Waist circumference was measured at the midpoint of the line between the rib or costal margin and the iliac crest; measurements were made using a tape graduated in centimeters with 0.1 cm precision (SECA® 201, Germany). Body composition was assessed by bioelectrical impedance (BIA) using a multi-frequency device (InBody S10®, InBody Co., Ltd., Seoul, Korea). Fat mass in kg and phase angle were recorded from the machine output. The nutritional risk of each patient was calculated using a modified NUTRIC-Score due to the unavailability of the IL-6 determinations. High nutritional risk was established with a score ≥ 5 (21).

ENTERAL NUTRITION PRESCRIPTION

Orogastric tube placement was used over other short-term accesses as a common institutional practice to avoid epistaxis and sinus infection. Following radiographic confirmation of the correct tip position, EN was initiated. Calories and protein were prescribed according to recommendations by the American Society of Parenteral and Enteral Nutrition (ASPEN) and European Society for Clinical Nutrition and Metabolism (ESPEN), with a general target of 25 kcal/kg and 1.3 g/kg, respectively (22,23). Adjusted body weight was used in patients with a BMI > 30 kg/m^2 and was calculated using Hamwi equations. An algorithm for EN progression was used: 10 kcal/kg, 15 kcal/kg, and 20 kcal/kg on days 1, 2 and 3, respectively. Next, 25 kcal/kg on day 4 was prescribed in patients with high nutritional risk, and 20 kcal/kg during the first 4-7 days on low nutritional risk. Calories derived from non-nutritional sources were factored into the nutrition prescriptions to avoid overfeeding. In case of FI and interruption during EN advancement, prokinetics were administered and same nutritional support prescription from the previous day was maintained.

MAIN OUTCOME DEFINITION

FI incidence was defined as the presence of any of the following clinical conditions: diarrhea (frequency of bowel movement > 3 times/day Bristol 6 or liquid stools), vomiting, constipation (no evacuation during five consecutive days) and gastroparesis (gastric residual volume ≥ 200 and ≥ 500 ml, because there are common cut-off values used in hospital setting) (24,25). GRV was measured one time at day before EN initiation by aspirating the orogastric tube with a 50-ml syringe.

STATISTICAL ANALYSIS

Data were analyzed using Stata Intercooled (version 14, Stata Corporation, College Station, TX, USA). The normality of the distribution of quantitative variables was verified by the Shapiro-Wilk test. Descriptive statistics were used for the analysis of categorical variables (absolute and relative frequency) and quantitative variables (mean and standard deviation [SD] or median and interquartile range [IQR]). Clinical data between PP and SP were compared using the Student's t-test, Mann-Whitney U test or the χ^2 test. Statistical significance was defined as $p < 0.05$. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

RESULTS

A total of 180 patients were admitted to the ICU. Only 82 patients were included in this analysis (mean age ± SD: 45.3 ± 12.1; 70 % males) (Fig. 1). Overweight was identified in 59 % and obesity in 41 % according to BMI, with higher fat mass (%) in PP males (35 ± 10.8 *vs* 29.1 ± 8.9, p = 0.02) but not in females.

Statistical toward of low phase angle was observed in PP males (6.2 ± 1.4 *vs* 5.6 ± 0.9, p = 0.06), but not in females (Table I). Differences in FI were reported in table II; constipation was common in both groups (92 % *vs* 97 %, p = 0.11). GRV ≥ 200 (18 % *vs* 12 %, p = 0.38) and ≥ 500 ml (5 % *vs* 5 %, p = 0.92), vomiting (8 % *vs* 16 %, p = 0.23) and diarrhea events (8 % *vs* 2.3 %, p = 0.26) were similar in SP and PP groups (Fig. 2).

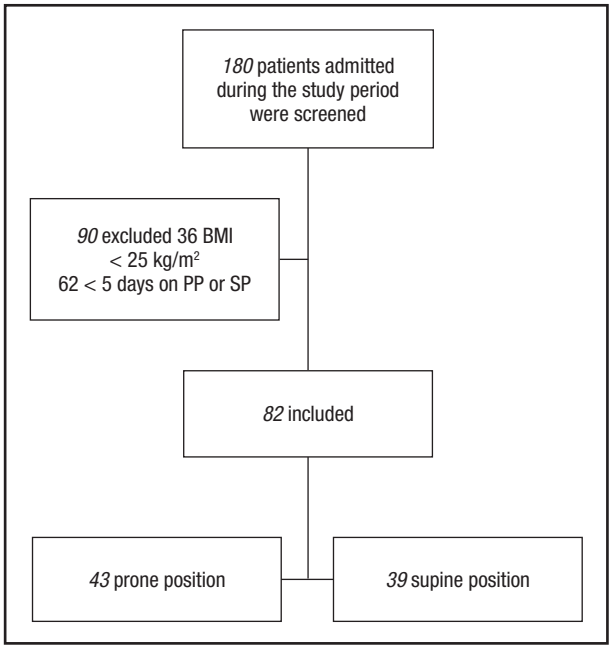

Figure 1.

Patients included in this analysis. BMI: body mass index; PP: prone position; SP: supine position.

Table I. Demographical characteristics of critically ill COVID-19 patients

	Supine (n = 39)	Prone (n = 43)	p value
Age	45.3 ± 13	45.3 ± 11.6	0.97
Sex Female (%)	7 (18 %)	17 (40 %)	0.03
Diabetes (%)	11 (28 %)	11 (26 %)	0.78
Hypertension (%)	11 (28 %)	14 (33 %)	0.66

(Continues on next page)

Table I (Cont.). Demographical characteristics of critically ill COVID-19 patients

	Supine (n = 39)	Prone (n = 43)	p value
AKI (%)	18 (47 %)	11 (27 %)	0.06
SOFA scale	9 ± 2	10 ± 2	0.24
APACHE II	19 ± 4	19 ± 5	0.77
Nutric-score	4 ± 2	4 ± 1	0.78
Benzodiazepines Days	36 (92 %) 3.9 ± 1.4	34 (79 %) 4.3 ± 1.0	0.09 0.25
Opioids Days	39 (100 %) 4.6 ± 0.8	42 (98 %) 4.6 ± 0.7	0.33 0.65
Propofol Days	9 (23 %) 4.1 ± 1.0	16 (37 %) 3.8 ± 1.5	0.16 0.53
Neuromuscular blocking agents Days	30 (77 %) 3 ± 1.4	36 (84 %) 4 ± 1.2	0.43 0.009*
PEEP cmH_2O > 10 cmH_2O	11 ± 3 31 (79 %)	12 ± 2 41 (98 %)	0.18 0.009*
PCR baseline (mg/dl)	13.1 (8.8-18)	13.8 (6.7-25.5)	0.95
Waist circumference (cm)	109.7 ± 12	111.3 ± 11.5	0.54
Weight (kg)	86.1 ± 17.9	88 ± 18.6	0.64
BMI (kg/m^2) Overweight Obesity	30.5 ± 6.6 25 (68 %) 12 (32 %)	31.1 ± 5.3 21 (51 %) 20 (49 %)	0.63 0.14
Fat mass (%) Male Female	 29.1 ± 8.9 40.7 ± 6.9	 35 ± 10.8 41.2 ± 9.0	 0.02* 0.92
Phase angle (°) Males Females	 6.2 ± 1.4 4.7 ± 0.4	 5.6 ± 0.9 4.9 ± 0.9	 0.06 0.66
Prokinetic use Day 1 Day 2 Day 3 Day 4 Day 5	5 (12.5 %) 3 (8 %) 3 (8 %) 2 (5 %) 2 (5 %) 1 (3 %)	18 (42.8 %) 4 (9 %) 11 (26 %) 13 (30 %) 12 (28 %) 14 (33 %)	0.002* 0.79 0.03* 0.003* 0.006* < 0.001*
Vasopressors use Day 1 Day 2 Day 3 Day 4 Day 5	 21 (54 %) 22 (56 %) 18 (46 %) 20 (51 %) 16 (41 %)	 19 (45 %) 17 (40 %) 11 (27 %) 12 (29 %) 14 (34 %)	 0.43 0.15 0.07 0.04* 0.52
Norephinefrine dose (mcg/min) Day 1 Day 2 Day 3 Day 4 Day 5	 2.6 (1.3-7.9) 2.3 (0.6-5.3) 1.9 (1.3-2.9) 2.3 (1.3-6.3) 1.4 (0.6-3.3)	 2.3 (0.6-5.3) 3.9 (1.3-6.6) 3.3 (1.0-7.9) 2.8 (1.0-6.3) 3.9 (1.8-6.6)	 0.57 0.34 0.71 0.65 0.02*
Antibiotic use Day 1 Day 2 Day 3 Day 4 Day 5	 7 (17 %) 13 (33 %) 14 (36 %) 16 (41 %) 18 (46 %)	 8 (19 %) 8 (19 %) 10 (23%) 14 (32 %) 11 (26 %)	 0.60 0.33 0.59 0.22 0.25
Clinical outcomes Mortality Days on mechanical ventilation	 5 (13 %) 16 (10-28)	 13 (30 %) 15 (10-26)	 0.06 0.87

AKI: Acute Kidney Injury; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation II; PEEP: positive end-expiratory pressure; BMI: body mass index.

Table II. Differences in feeding intolerance according to prone or supine positioning

Postural positioning	Day 1		Day 2		Day 3		Day 4		Day 5	
	SP	PP	SP	PP	SP	PP	SP	PP	SP	PP
GRV ≥ 200 ml	0	2 (5 %)	1 (2 %)	2 (5 %)	3 (8 %)	0	0	0	4 (10 %)	0
GRV ≥ 500 ml	0	2 (5 %)	0	0	0	0	1 (2.5 %)	0	1 (2.5 %)	0
Vomiting	2 (5 %)	1 (2.3 %)	1 (2.5 %)	2 (5 %)	1 (2.5 %)	3 (7 %)	0	3 (7.0 %)	0	3 (7 %)
Diarrhea	0	0	0	0	1 (2.6 %)	1 (2.3 %)	2 (5.1 %)	1 (2.3 %)	1 (2.5 %)	0
Absence of evacuations	38 (97 %)	43 (100 %)	38 (97 %)	43 (100 %)	37 (95 %)	42 (98 %)	36 (92 %)	42 (98 %)	35 (90 %)	43 (100 %)

n (%). SP: supine position; PP: prone position; GRV: gastric residual volume.

Figure 2.

Differences in patients/events of feeding intolerances during study period. GRV: gastric residual volume.

DISCUSSION

This study found no differences in FI incidence between PP and SP patients on MV due to COVID-19 ARDS. In this cohort we included only patients with BMI ≥ 25 kg/m^2 (59 % overweight and 41 % obesity) receiving EN in PP o SP continuously during the first five days of MV. No differences in BMI (p = 0.63) and phase angle by sex were observed between individuals at the SP or PP. Similar prevalence of overweight and obesity were observed by Savio R et al. in critically-ill patients with non-COVID related ARDS (49.2 % and 30.2 %, respectively) (26). Both studies showed no significant differences in FI despite SP or PP. This suggests that EN during PP is safe and does not represent a higher risk for GI dysfunction in overweight or obese individuals (27).

The use of certain drugs such as sedatives, opioids and vasopressors has also been related to FI (7). In our cohort, we found no differences in the use of benzodiazepines (p = 0.09), opioids (p = 0.33), propofol (p = 0.16) or antibiotics in SP compared to PP during the study period. The number of individuals receiving vasopressors in the SP group and the PP group was also similar, except for day 4 (51 % *vs* 29 %, p = 0.04); however, no significant differences were observed in FI events. Individuals in PP do not seem to have different or higher drug requirements compared to SP, which can be related to the fact that both groups reported a similar incidence of FI.

According to the guidelines and practice recommendations for nutritional care of critically-ill patients with COVID-19, it has been established that prokinetics use can be considered to promote gastric motility in high risk aspiration patients (28,29). In a systematic review from Lewis et al. prokinetics were associated with reduced FI; defined as GRV ≥ 150 ml, vomiting or abdominal distention (RR 0.73, 95 % CI: 0.55-0.97; p = 0.03), and high gastric residual volumes reduction (RR 0.69; 95 % CI: 0.52-0.91; p = 0.009). Nevertheless, there was no significant improvement

in the risk of vomiting, diarrhea, ICU length of stay or mortality (30). In a recent meta-analysis from Peng et al. an updated definition of FI (GRV ≥ 500 ml, presence of vomiting, diarrhea, gastrointestinal bleeding or inadequate delivery of EN < 60 % of the target or < 20 kcal/kg after 72 hours of feeding attempts) was proposed. According to this, ten of 13 studies showed that prokinetics were beneficial on FI in critically-ill patients with gastric EN, with a reduction in ICU length of stay (MD -2.03, 95 % CI: -3.96, -0.10; p = 0.04; low certainty) and hospital length of stay (MD -3.21, 95 % CI: -5.35, -1.06; p = 0.003; low certainty) (31). However, prokinetics effect on other clinical outcomes related to ICU mortality such as pneumonia, remains unclear.

In our cohort, prokinetics were used routinely by some members of physician's staff in continuous PP as prevention or initiated after FI episodes; we observed that a higher frequency of individuals in our PP group received prokinetics, compared to the SP group (42.8 % *vs* 12.5 %, p = 0.002). In our cohort, constipation was common in both groups (97 % *vs* 92 %, p = 0.11). GRV ≥ 200, vomiting and diarrhea events were similar in SP and PP groups. Considering this, the initiation of prokinetics agents should be considered simultaneously at PP (7), to avoid fasting prescription previous to PP or the reduction of the rate infusion of EN as strategies for FI prevention.

Higher prevalence of obesity grade 1 (BMI ≥ 35 kg/m^2) was observed in males on PP group (31 % *vs* 13 %, p = 0.26). This explain the higher amount of adipose tissue in males between groups. Obese patients have an increased risk of ARDS and were the group of patients that may benefit from PP. No differences were observed for phase angle between groups, which is a marker of low muscle mass and is associated with higher mortality and length of stay (32-34).

Similar to our results, other authors report no differences between positions in GRV and vomiting episodes in non-COVID-19 critically-ill patients with ARDS (26), however, BMI was not reported (35,36). Reignier et al. report that patients on PP and nasogastric tube had a higher GRV and had more vomiting episodes, however, nutritional status and BMI was not reported (37). Similarly, L'Her et al. report an incidence of high GRV in 14 % and vomiting in 12 % of patients on PP, but enteral access and BMI were not reported (38). Contrary to what can be expected, Liu et al. report that BMI ≥ 40 kg/m^2 is associated with decreased risk of FI, but differences between PP and SP were not analyzed. The incidence rate variation between reports may be influenced by PP, BMI and enteral access (39).

Our study offers data in COVID-19 critically-ill patients with overweight and obesity, showing that EN during PP is not different from SP and might be considered as a safe intervention, but it also has the following limitations: a) our cohort was enrolled at a single center; d) no data of interruptions or caloric debt associated with reported FI during prone were available; c) no data of the timing of the initiation of prokinetics agents as prophylactic or treatment of FI was gathered, and this may have an impact on FI rate; d) infectious complications or the incidence of ventilator-associated pneumonia (VAP) were not assessed; and e) although the follow-up period in our study was limited to the first five days of MV, it includes the time of initiation and advancement of EN, where the deficit in its supply due to FI interruptions has been associated with adverse clinical outcomes.

CONCLUSION

FI in terms of GRV, vomiting or diarrhea during PP was not different in comparison with SP. To prevent adverse effects, a multidisciplinary intervention in critically-ill patients undergoing prone positioning is required.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

Suplementación de proteína de suero de leche y caseinato en pacientes oncológicos sometidos a cirugía electiva para la modificación de la capacidad funcional

Whey protein and caseinate supplementation in oncological patients undergoing elective surgery for the modification of functional capacity

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Resumen

Introducción: la intervención nutricia se ha convertido en un punto crítico para lograr la disminución de la morbimortalidad perioperatoria en el paciente oncológico. Existen distintos factores que jugarán un papel fundamental en la evolución y el pronóstico de esta patología, siendo el estado de nutrición y la dieta una piedra angular en estos aspectos.

Objetivos: evaluar el efecto perioperatorio de la proteína aislada de suero de leche (WPI) y el caseinato de calcio (CaCNT) en pacientes oncológicos sometidos a cirugía electiva.

Métodos: ensayo clínico controlado aleatorizado con tres grupos: grupo control (n = 15), que consistió en manejo convencional por parte de los servicios de cirugía oncológica, y dos grupos de intervención, uno con suplementación de caseinato de calcio (n = 15) y otro con suplementación con proteína aislada de suero de leche (n = 15) durante seis semanas de forma perioperatoria. Se evaluaron en tiempos preoperatorio y postoperatorio la fuerza de prensión de mano, la caminata de seis minutos y la composición corporal.

Resultados: aquellos que fueron suplementados con WPI mantuvieron la fuerza de prensión y mostraron menor cantidad de agua extracelular ($p < 0,02$); se mostró un incremento en la masa visceral ($p < 0,02$). Finalmente, se encontró correlación con variables asociadas a la composición corporal y variables de evolución del paciente en comparación con el grupo control.

Conclusiones: la suplementación nutricional requiere ser abordada desde el punto de vista funcional y metabólico para identificar factores que impacten favorablemente, así como la distinción entre carcinoma y el tipo de suplementación a implementar.

Palabras clave:

Proteína de suero de leche. Caseinato. Suplementación dietética. Servicio oncológico hospitalario. Fuerza de prensión. Bioimpedancia eléctrica.

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Abstract

Introduction: the nutritional intervention has become a critical point to achieve the reduction of perioperative morbidity and mortality in cancer patients. There are different factors that will play a fundamental role in the evolution and prognosis of this pathology, being the state of nutrition and diet a cornerstone in these aspects.

Objective: to evaluate the perioperative effect of whey protein isolate (WPI) and calcium caseinate (CaCNT) in cancer patients undergoing elective surgery.

Methods: randomized controlled clinical trial with three groups: the control group (n = 15), consisting in conventional management by the oncology surgery services, and two intervention groups, one with calcium caseinate supplementation (n = 15) and another one with whey protein isolate supplementation (n = 15) for six weeks perioperatively. Handgrip strength, six-minute walk, and body composition were assessed pre and postoperatively.

Results: those who were supplemented with WPI maintained their handgrip strength and showed less extracellular water ($p < 0.02$); also an increase in visceral mass was shown ($p < 0.02$). Finally, a correlation was found with variables associated with body composition and patient evolution when compared to the control group.

Conclusions: nutritional supplementation needs to be approached from the functional and metabolic point of view to identify factors that have a favorable impact, as well as the distinction between carcinoma and the type of supplementation to be implemented.

Keywords:

Whey protein. Casein. Dietary supplement. Hospital oncology service. Hand strength. Bioelectrical impedance.

INTRODUCCIÓN

La disminución en la ingesta de alimentos en los pacientes oncológicos es uno de los principales obstáculos para mantener un correcto estado nutricio. Además de esto, existen otras anomalías que contribuyen a la desnutrición, como es el caso de la posible malabsorción de los nutrimentos debido a cambios estructurales y funcionales del tracto digestivo. Por otra parte, la misma patología subyacente induce cambios metabólicos, como resistencia a la insulina, intolerancia a la glucosa, lipólisis incrementada y un exacerbado catabolismo proteico (1). La pérdida de la masa magra y grasa, la debilidad, la anorexia y el edema en pacientes con cáncer se conoce como caquexia y se presenta hasta en el 50 % de estos casos. Esta ha sido relacionada con el incremento de complicaciones de la propia enfermedad, así como de los efectos adversos asociados a la terapéutica, lo cual se debe a los mecanismos sistémicos inflamatorios derivados de la propia caquexia a causa de alteraciones hormonales y la presencia de citocinas inflamatorias, que llega a complicar la respuesta anabólica del paciente (1-3).

Asimismo, el músculo esquelético se encuentra en un estado de hiperactivación debido a los factores de transcripción, como el factor nuclear κB (NFκB), el factor de necrosis tumoral α (TNF-α), las interleucinas (IL-1β e IL- 6) (3,4) y la sobreexpresión de miostatina, proteína perteneciente a la familia del factor de crecimiento transformante β (TGF- β), limitando de esta manera el crecimiento de la masa muscular (4). Lo anterior, en conjunto con una baja actividad física y una dieta ineficiente, generará un aumento en la debilidad muscular y una alteración en la realización de actividades de la vida diaria (2).

Ante el contexto señalado, la evaluación e intervención nutricia se ha convertido en un punto crítico para lograr la disminución de la morbimortalidad perioperatoria (5). Algunas de las estrategias terapéuticas implican el uso de suplementación con aminoácidos de cadena ramificada (AACR), particularmente de la leucina (0,2-0,4 g/kg de peso) y sus metabolitos (6). Este aminoácido tiene un impacto positivo en la síntesis proteica, subsanando en parte el catabolismo, independientemente de la vía de administración (7). Por otra parte, los pacientes geriátricos podrían representar el grupo etario mayormente beneficiado ante el incremento de la ingesta proteica. Es por ello que los suplementos como la proteína de suero de leche con alto contenido de AACR han sido utilizados en diversos estudios, en los que han mostrado mejoría en la evolución de estos pacientes (7).

La implementación de proteína de suero de leche en conjunto con terapia de rehabilitación física ha sido estudiada previamente y se han encontrado efectos positivos en indicadores de fuerza de extensión muscular y en funcionalidad valorada por el índice de Barthel (8). La evidencia emergente se dirige a la mejoría de las complicaciones perioperatorias en pacientes con apoyo de suplementación por vía oral (9), reportando resultados favorables en pacientes quirúrgicos con diversas patologías que tomaron proteína de suero de leche en conjunto con el tratamiento médico. Algunos de los beneficios documentados fueron la mejora en los efectos de rehabilitación posterior a resección colorrectal por carcinoma (10) o la mejora del estado nutricional en pacientes sometidos a cirugía bariátrica (11). Resulta fundamental comprender las alternativas que puedan mejorar el panorama del paciente oncológico, por lo cual el objetivo planteado para este estudio fue evaluar el efecto perioperatorio de la proteína de suero de leche y del caseinato de calcio (CaCNT) en pacientes con cáncer sometidos a cirugía electiva.

MATERIAL Y MÉTODOS

PARTICIPANTES

Se realizó un estudio clínico aleatorizado en el periodo de marzo a octubre de 2021, en el Departamento de Cirugía de un hospital de Seguridad Social de segundo nivel de atención hospitalaria. Se incluyeron pacientes adultos de ambos sexos de 18 a 65 años de edad con diagnóstico de cáncer y que requirieron intervención quirúrgica por parte de los servicios de Oncología Quirúrgica, Coloproctología y Oncología Ginecológica. Se excluyeron pacientes con embarazo, falla renal o hepática o con contraindicación para utilizar la vía oral. El estudio fue aprobado por el Comité de Investigación y de Ética en Investigación

Hospitalaria con número de registro (R-2021-101-006). A los pacientes candidatos a manejo quirúrgico que aceptaron participar en el estudio se les presentó consentimiento informado para la obtención de firma. Posteriormente, la aleatorización de los grupos se generó por medio de números generados en el software Excel. Los participantes fueron distribuidos en tres grupos de 15 participantes cada uno: el grupo control, el grupo de intervención con CaCNT y el grupo de intervención con proteína aislada de suero de leche (WPI).

ANÁLISIS DE LA COMPOSICIÓN CORPORAL

Se realizaron mediciones de composición corporal y funcionalidad dos semanas antes del procedimiento quirúrgico, así como cuatro semanas después del mismo. La evaluación se llevó a cabo por medio de la técnica de bioimpedancia eléctrica con el equipo Medical Body Composition Analyzer modelo mBCA 525, marca SECA. La talla y el peso fueron evaluados con un estadímetro y báscula marca SECA® modelo 217 y se determinó el índice de masa corporal (IMC) de acuerdo a los criterios de la Organización Mundial de la Salud (OMS). Las variables consideradas para la composición corporal fueron: masa muscular y grasa, agua extracelular (AEC) e intracelular (AIC) y la relación de estas, ángulo de fase, ángulo de fase estandarizado y grasa visceral. Todos los pacientes fueron evaluados bajo las mismas condiciones, marco de tiempo y periodo de ayuno de cuatro horas. Todas las medidas realizadas se basaron en las técnicas y los estándares establecidos por la Sociedad Internacional para el Avance de la Cineantropometría (ISAK) para la toma de las mediciones antropométricas.

EVALUACIÓN DE LA FUNCIONALIDAD

Para la funcionalidad se aplicaron pruebas de fuerza de prensión de mano para evaluar la fuerza muscular, el rendimiento se evaluó a través de la prueba de caminata de seis minutos (P6CM) y para evaluar la masa magra se midió la longitud del recto femoral (LRF) de ambas piernas.

La fuerza de la prensión de mano se realizó con el dinamómetro Medequip Depot® modelo FE-120241. La medición se hizo con el paciente sentado, con los hombros aducidos, el codo flexionado en 90°, el antebrazo colocado neutralmente y la muñeca dorsiflexionada entre 0 y 30°; posteriormente, se le solicitó al participante presionar el mango tan fuerte como le fuese posible. En dicha posición se realizan tres mediciones con un intervalo de un minuto; la medición reportada fue el valor máximo de los tres eventos.

Por otro lado, previo a la evaluación de la P6CM, se le solicitó al participante permanecer descansando por un lapso de 15 minutos. A continuación, se le explicó que caminaría a lo largo de un pasillo de ida y regreso tantas veces fuera posible por un periodo de seis minutos. Se permitía disminuir velocidad o detenerse durante la prueba y continuar posteriormente, de ser posible. Al finalizar los seis minutos, se realizó la medición de acuerdo con la marca de inicio y fin para calcular la distancia por medio de un flexómetro, y al concluir la prueba se realizó medición de signos vitales y oximetría.

Finalmente, para la LRF se utilizó el ultrasonido Esaote MyLab® con sonda lineal (AC2541) en modalidad para músculo esquelético. Para realizar la medición se colocó al paciente en decúbito supino, obteniendo la medición a dos tercios de la distancia existente entre la espina iliaca anterosuperior y el polo superior de la patela en un plano sagital.

SUPLEMENTACIÓN CON PROTEÍNA

Dos grupos recibieron suplementación con proteína (25 g), uno de ellos con CaCNT (n = 15). El caseinato de calcio fue disuelto en ocho onzas de agua purificada cada 24 horas dos semanas previo al evento quirúrgico y cuatro semanas posterior al mismo; la toma de proteína se realizó en el mismo marco temporal en condición de ayuno por las mañanas. En relación con el grupo con WPI (n = 15), la proteína fue otorgada siguiendo los mismos criterios anteriormente mencionados.

REVISIÓN CLÍNICA DEL PACIENTE

Como parte de las medidas de control del estudio, se llevó a cabo un seguimiento del paciente desde el momento del ingreso hospitalario hasta cuatro semanas posterior al mismo para monitorizar la presencia de complicaciones perioperatorias (clasificación de Clavien-Dindo). Previo a la suplementación, se evaluó la ingesta dietética del paciente para complementar el análisis de este. Se registraron el día de ingreso y el de egreso para contabilizar la estancia intrahospitalaria.

ANÁLISIS ESTADÍSTICO

Se analizaron los datos demográficos de manera descriptiva y fueron representados en media y desviación estándar. En el análisis inferencial para el cálculo de la normalidad se utilizó la prueba de Shapiro-Wilk; respecto la evaluación de las diferencias intergrupos, se analizaron por medio de ANOVA y una prueba *post hoc* de Dunnett; y para diferencias intragrupos se utilizó la prueba de t de Student pareada. Por otro lado, la posible asociación entre variables se analizó a través del test de correlación de Pearson. Los datos fueron analizados con el paquete estadístico SPSS versión 20 (IL, Estados Unidos) y se consideraron un intervalo de confianza del 95 % y una diferencia estadística con un valor de p menor a 0,05 ($^{*}p < 0,05$, $^{\dagger}p < 0,01$, $^{\ddagger}p < 0,001$).

RESULTADOS

Se evaluaron 45 pacientes de entre 21 y 65 años de edad, con un promedio de 47,62 ± 13,45 años de edad; el 66,7 % de los

pacientes fueron mujeres (n = 30) y el 33,3 % fueron hombres (n = 15). La mayoría de los pacientes fueron tratados por parte del Servicio de Oncología Quirúrgica (53,3 %) y la patología más frecuente fue carcinoma mamario (26,7 %), seguida de carcinoma rectal y tiroideo (17,8 %); la información se puede verificar en la tabla I. Respecto a la evolución perioperatoria entre grupos, no se mostraron diferencias de acuerdo a la clasificación Clavien-Dindo para complicaciones quirúrgicas, siendo constante la prevalencia de complicaciones posquirúrgicas no graves. En relación a la estancia intrahospitalaria, el uso de CaCNT o de WPI no mostró una modificación en los días de internamiento respecto al control (3,11 ± 2,7 días, p = 0,19). De igual manera, el sangrado registrado durante la operación mostró un promedio de 279 ± 203,4 ml (p= 0,54) y un tiempo quirúrgico de 2,6 ± 0,8 horas (p = 0,89), sin llegar a ser diferente estadísticamente en ninguno de los grupos.

Por otro lado, el análisis de las medidas antropométricas fue determinado previamente a la cirugía y posterior a un mes de esta. El IMC predominante entre los grupos fue sobrepeso, con una media de 26,6 ± 4,9 kg/m^2 de acuerdo a los criterios de la OMS, sin existir diferencias entre grupos. Respecto al peso corporal, en todos los grupos se presentó una disminución de peso del 0,88 % (0,627 kg); no obstante, es importante mencionar que el grupo con WPI mantuvo su peso posterior a la cirugía (70,4 ± 14 kg *vs.* 70,4 ± 15 kg). En cuanto a la evaluación de la dieta, los participantes registraron una dieta isocalórica (1.680,18 ± 387,75 Kcal), con una distribución promedio del 56,4 % de hidratos de carbono, 18,3 % de proteínas y 25,3 % de lípidos. No se encontraron diferencias entre los grupos (en la tabla II se puede ver en detalle la distribución de cada grupo).

La funcionalidad o recuperación de los pacientes se evaluó por medio de la prueba de caminata de seis minutos, la fuerza de prensión de brazos y la LRF. El rendimiento de los metros reportados en la P6CM (pre: 396,5 ± 104,6 m *vs.* post: 394,1 ± 97,4 m) entre los grupos no mostró ser diferente en aquellos con suplementación respecto al control. No obstante, en referencia con la fuerza de prensión, el grupo control mostró una disminución de fuerza posterior a la cirugía (-4,4 kg, p = 0,02) (Fig. 1A) en comparación con los grupos suplementados con proteína, que mantuvieron la fuerza inicial registrada. Asimismo, se identificó un aumento en la LRF de ambas piernas en el grupo control posterior a la cirugía, que se incrementó un 32,8 % (pre: 16,35 ± 9,84 mm *vs.* post: 21,72 ± 11,97 mm; p = 0,005), comparado con los grupos con proteína suplementada, que no registraron cambios.

La evaluación de la composición corporal no mostró diferencias significativas entre el grupo control y los grupos de intervención (Tabla III). Sin embargo, en la comparación intragrupal se identificó un incremento posquirúrgico de la grasa visceral en el grupo de proteína de suero de leche (2,5 kg *vs.* 2,9 kg, p = 0,02). De igual manera, el agua extracelular fue mayor tanto en el grupo control como en el grupo de CaCNT (2,6 %, p = 0,04, y 3,3 %, p = 0,001, respectivamente); este último aumentó también su relación de agua en los espacios celulares (AEC/AIC) (p = 0,03). El ángulo de fase y el ángulo de fase estandarizado en el grupo con CaCNT fueron diferentes respecto al control y el grupo con WPI, siendo menor posterior al procedimiento quirúrgico (6,3 ± 1,2 *vs.* 5,6 ± 1,0, p = 0,002). Los cambios posquirúrgicos pueden ser valorados a detalle en la figura 1B-F.

Finalmente, se analizó la correlación entre diversas variables, destacando un mejor resultado en la P6CM con puntajes altos en el ángulo de fase (r = 0,358, p = 0,01) y peores resultados en aquellos con mayores niveles de AEC (r = -0,322, p = 03). Por otro lado, variables de interés perioperatorio como el sangrado durante la operación y la estancia intrahospitalaria se relacionaron de manera inversa con la LRF, el IMC y el ángulo de fase y se asociaron con un mayor sangrado quirúrgico y un mayor número de días de hospitalización cuando los valores de estas características fueron bajos (Fig. 2).

Tabla I. Características del paciente y relacionadas con el padecimiento

Variable poblacional	Frecuencia (f)	Porcentaje (%)
Servicio		
Oncología Ginecológica	18	40
Oncología	24	53,3
Coloproctología	3	6,7
Tipo de tumor		
Renal	2	4,4
Rectal	8	17,8
Colon	3	6,7
Tiroides	8	17,8
Sarcoma	3	6,7
Seminoma	1	2,2
Carcinoma de mama	12	26,7
Cervicouterino	3	6,7
Ovario	4	8,9
Epidermoide	1	2,2
Tratamiento neo y adyuvante		
Quimioterapia PC (Sí)	19	42,2
Quimioterapia PC (No)	26	57,8
Radioterapia PC (Sí)	6	13,3
Radioterapia PC (No)	39	86,7

Los datos son representados en frecuencias y porcentajes (n = 45).
PC: previo a cirugía.

Tabla II. Características antropométricas y dietéticas por grupo

Características	Control (n = 15)	CaCNT (n = 15)	WPI (n = 15)	p
Talla (m)	1,61 ± 0,07	1,62 ± 0,10	1,61 ± 0,0	0,91
Peso precirugía (kg)	69,9 ± 15,3	69,1 ± 14,9	70,4 ± 14,0	0,97
Peso poscirugía (kg)	68,4 ± 14,6	68,9 ± 15,1	70,4 ± 15,0	0,92
IMC precirugía (kg/m^2)	26,7 ± 4,9	26,0 ± 4,5	27,1 ± 5,6	0,83
IMC poscirugía (kg/m^2)	26,2 ± 5,7	25,9 ± 4,5	27,2 ± 6,1	0,77
Energía (Kcal)	1.579,5 ± 349,4	1.719,9 ± 431,1	1.741,0 ± 384,7	0,71
HC (%)	57,5 ± 7,7	55,4 ± 6,5	56,0 ± 7,2	0,95
Proteínas (%)	18,0 ± 4,5	18,4 ± 4,5	18,3 ± 4,3	0,89
Lípidos (%)	24,6 ± 5,7	25,4 ± 6,6	25,7 ± 7,6	0,47

Los datos se representan en media ± DE (n= 45). Prueba estadística utilizada ANOVA post hoc: *prueba de Dunnett. CaCNT: caseinato de calcio; WPI: proteína aislada de suero de leche; IMC: índice de masa corporal; HC: hidratos de carbono.*

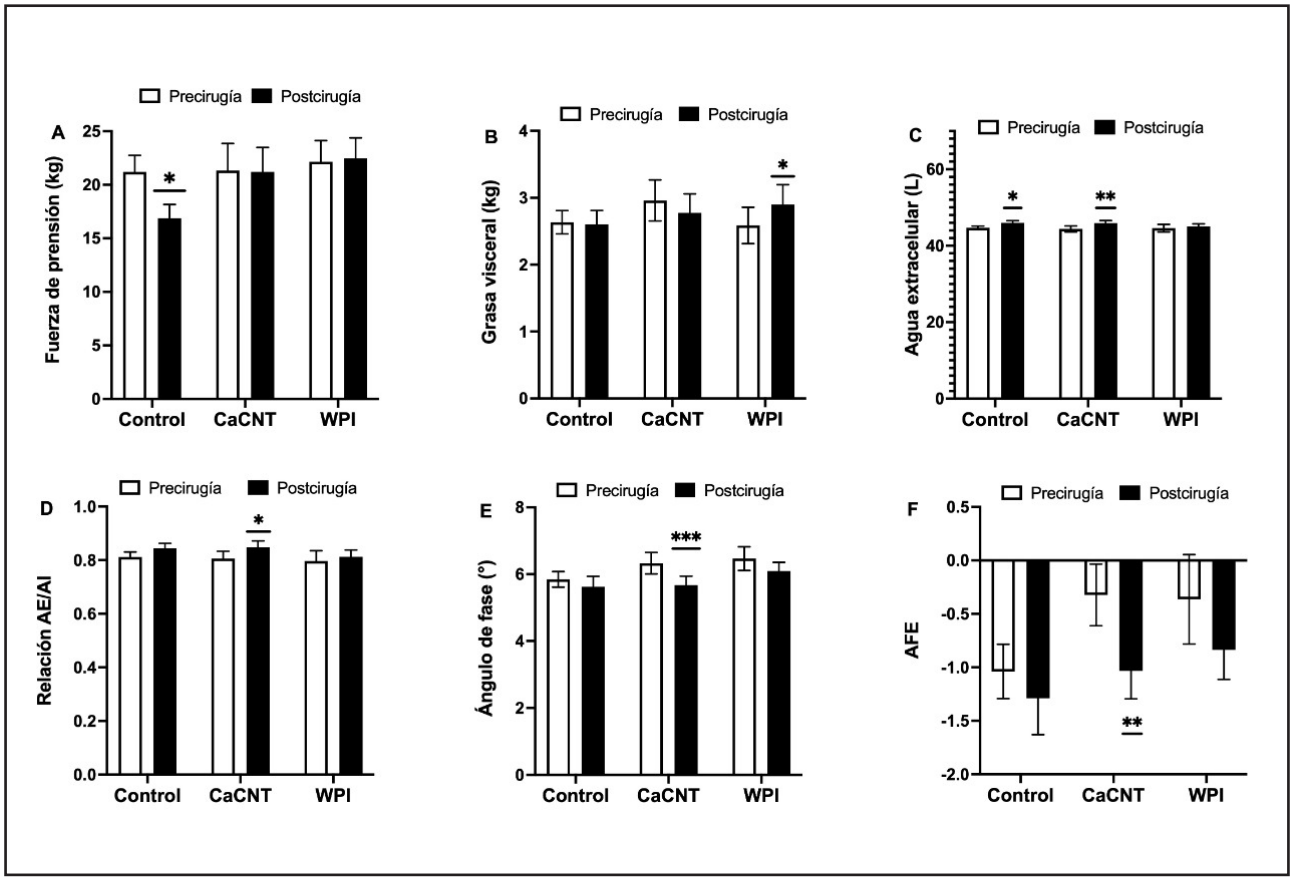

Figura 1.

Análisis intragrupos de pruebas de funcionalidad y composición corporal (n = 45). A. Fuerza de prensión precirugía y poscirugía. B. Grasa visceral precirugía y poscirugía. C. Agua extracelular precirugía y poscirugía. D. Relación entre agua extracelular e intracelular precirugía y poscirugía. E. Ángulo de fase precirugía y poscirugía. F. Ángulo de fase estandarizado precirugía y poscirugía (CaCNT: caseinato de calcio; WPI: proteína aislada de suero de leche; AFE: ángulo de fase estandarizado. Prueba estadística utilizada: t de Student pareada. *p < 0,05. **p < 0,01. ***p < 0,001).

Tabla III. Análisis de la composición corporal por grupo

Características	Control (n = 15)	CaCNT (n = 15)	WPI (n = 15)	p
MMT precirugía (kg)	45,4 ± 7,6	45,5 ± 8,8	43,9 ± 10,3	0,86
MMT poscirugía (kg)	44,4 ± 7,4	44,3 ± 9,1	44,0 ± 7,3	0,99
MG precirugía (kg)	24,5 ± 11,4	23,6 ± 10,0	26,4 ± 11,9	0,78
MG poscirugía (kg)	24,5 ± 12,4	24,7 ± 10,3	26,3 ± 13,9	0,90
Grasa visceral precirugía (kg)	2,6 ± 0,6	2,9 ± 1,1	2,5 ± 1,0	0,54
Grasa visceral poscirugía (kg)	2,6 ± 0,8	2,7 ± 1,0	2,9 ± 1,1	0,72
AF precirugía (°)	5,8 ± 0,9	6,3 ± 1,2	6,4 ± 13	0,33
AF poscirugía (°)	5,6 ± 1,1	5,6 ± 1,0	6,0 ± 1,0	0,43
ACT precirugía (%)	47,8 ± 8,1	48,9 ± 5,7	46,9 ± 6,7	0,73
ACT poscirugía (%)	47,0 ± 8,5	48,1 ± 6,6	45,4 ± 8,4	0,66
LRFD (mm)	16,3 ± 11,9	20,7 ± 5,2	20,4 ± 8,3	0,26
LRFI (mm)	21,7 ± 11,0	21,1 ± 6,9	23,0 ± 10,0	0,87

Los datos se representan en media ± DE (n = 45). Prueba estadística utilizada ANOVA post hoc: *prueba de Dunnett. CaCNT: caseinato de calcio; WPI: proteína aislada de suero de leche; BIE: bioimpedancia eléctrica; MMT: masa muscular total; MG: masa grasa; AF: ángulo de fase; ACT: agua corporal total; LRFD: longitud del recto femoral derecho; LRFI: longitud del recto femoral izquierdo.*

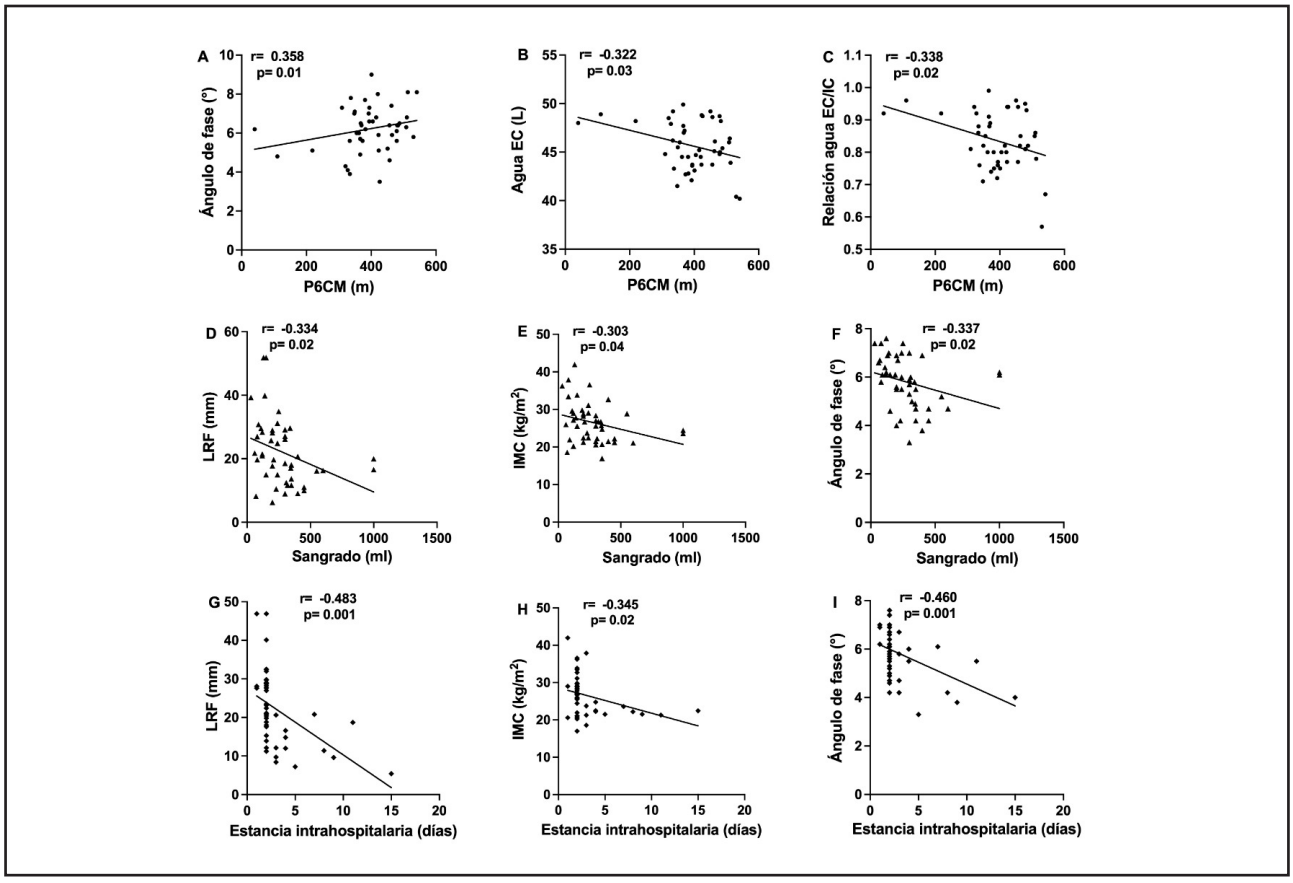

Figura 2. Análisis de correlación (n = 45). A. Ángulo de fase y P6CM. B. Agua extracelular y P6CM. C. Relación de agua extra e intracelular y P6CM. D. Longitud de recto femoral y cantidad de sangrado. E. Índice de masa corporal y cantidad de sangrado. F. Ángulo de fase y cantidad de sangrado. G. Longitud de recto femoral y días de hospitalización. H. Índice de masa corporal y días de hospitalización. I. Ángulo de fase y días de hospitalización (P6CM: prueba de caminata de seis minutos; LRF: longitud de recto femoral; IMC: índice de masa corporal. Prueba estadística utilizada: coeficiente de correlación de Pearson).

DISCUSIÓN

La cirugía en el paciente oncológico continúa siendo el pilar del tratamiento médico (12), sin embargo, el tratamiento tanto nutricional como multidisciplinario se lleva a cabo en pocos pacientes (13). De acuerdo con Bargetzi y cols., (14) la terapia nutricional individualizada permite mejorar la capacidad funcional, así como la calidad de vida de los pacientes oncológicos. Particularmente en el caso de la proteína de suero de leche, sus componentes biológicos, como la lactoferrina, la beta lactoglobulina, la alfa lactoalbúmina y las inmunoglobulinas, contribuyen con los efectos antioxidantes, antitumorales, antivirales y antibacteriales (15).

En este estudio se pretendió evaluar los posibles beneficios posquirúrgicos de la suplementación de proteína en pacientes con cáncer de diferentes parámetros como composición corporal, antropometrías, funcionalidad, tiempo de hospitalización y complicaciones postoperatorias. La estancia intrahospitalaria en la población estudiada no se vio disminuida con el uso de suplementos proteicos. Mientras que Gillis y cols. (13), en su estudio, reportan una disminución en los días de hospitalización, sin embargo, se aprecia una tendencia de disminución en el grupo de proteína de suero de leche, ya que se observa una reducción en promedio de cuatro días, lo cual, en cuestión de costos, podría tener implicaciones positivas en el área administrativa. Esto puede explicarse, en parte, por la variabilidad de los tipos de cáncer entre los grupos de pacientes, así como del tiempo de evolución de los mismos.

Las complicaciones posteriores a la cirugía fueron similares entre grupos, sin denotar diferencias de acuerdo con la clasificación de Clavien-Dindo, lo cual difiere con lo reportado por Srinivasaraghavan y cols., que muestran una disminución de complicaciones en su grupo de intervención con proteína de suero de leche (17). Dicha diferencia puede deberse a factores como la edad, ya que, a mayor edad, será mayor el riesgo de aparición de complicaciones. Asimismo, niveles bajos de hemoglobina y albúmina (18) pueden condicionar la morbimortalidad de estos pacientes, esto sin considerar la progresión de acuerdo al tipo de neoplasia, que es un foco de estudio para elucidar la posible respuesta de la suplementación de proteína ante cada tipo de cáncer.

La fuerza de prensión se considera un marcador de la capacidad funcional. En nuestro estudio no pudo ser incrementada en los grupos de intervención, pero sí mantenida. Yacong Bo y cols. (16) reportan una mejora en la fuerza de prensión de mano posterior a la suplementación en paciente adulto mayor con sarcopenia, sin embargo, además de la proteína de suero de leche, su dieta fue complementada con vitaminas D y E. Otro aspecto que se debe considerar es la presencia del catabolismo proteico que se genera en el paciente oncológico, que por sí solo ha demostrado disminuir la fuerza de prensión de mano en estos pacientes (19), lo que se suma al estrés posquirúrgico. La presencia de citocinas proinflamatorias (IL-6, TNF-α, TGF-β, interferón-γ) (20) puede empeorar este panorama, lo cual podría explicar que, si bien no se presenta un aumento, la fuerza no se pierde y se mantiene, asociándose a una mejor evolución entre los pacientes con suplementación de proteína antes y después de la cirugía.

Por otra parte, la actividad física como terapia de rehabilitación ha demostrado un efecto positivo para incrementar la masa libre de grasa en conjunto con la proteína de suero de leche en pacientes con sarcopenia, lo que parece indicar un efecto sinérgico. En nuestra población, se encontró un aumento en la fuerza muscular en el grupo suplementado con proteína de suero de leche, lo que concuerda con lo reportado en otros estudios (21). Sin embargo, en nuestros grupos de estudio no fue posible implementar el programa de rehabilitación para paciente posquirúrgico dado el periodo de pandemia y la saturación del Servicio de Rehabilitación a favor de pacientes postinfectados de COVID-19.

Se ha documentado un mejor rendimiento en la distancia de la caminata de seis minutos posterior a la suplementación con proteína de suero de leche (17). No obstante, en nuestra población no se pudo observar esa mejora debido, posiblemente, a las diferencias entre grupos en cuanto al tipo y el tiempo de evolución del cáncer, aunque se muestra una tendencia hacia el incremento en metros caminados en ambos grupos de intervención, que es mayor en el grupo suplementado con proteína de suero de leche.

En cuanto a la diferencia en la LRF, su modificación no corresponde con los incrementos de fuerza de prensión de mano o de la distancia de caminata observados en los diversos grupos. Sin embargo, la LRF puede modificarse de manera aguda y está relacionada con la composición corporal. Esto concuerda con las conclusiones de Battaglia y cols. (21), quienes reportaron una reducción en el recto femoral en aquellos pacientes con composición corporal con parámetros por debajo de lo deseable, incluidos la masa muscular y el aumento de agua extracelular, lo que se asocia a mayor edematización y menor rendimiento en las pruebas de funcionalidad, como es el caso de lo reportado en nuestros resultados. Esto representa una ventana de oportunidad para la intervención temprana para el mantenimiento de la masa muscular, considerando el uso de suplementación de proteína posterior a un análisis pertinente de la función renal de los pacientes que pueden ser candidatos a su uso.

A pesar de que se ha documentado que la ingesta de proteína de suero de leche favorece la disminución de la composición corporal a favor de una pérdida de grasa (22-24), en nuestro estudio se observó un incremento de la grasa visceral en el grupo de proteína de suero de leche. Dicho resultado corresponde con revisiones en las cuales se concluye que el efecto de la suplementación con proteína de suero de leche en la grasa corporal es poco claro (25). La disminución de la grasa visceral se ha asociado con la suplementación de dicha proteína en conjunto con actividad física anaeróbica (26). Otra posible explicación es la velocidad de absorción de la proteína de suero de leche en comparación con otro tipo de proteína, lo cual podría favorecer mecanismos anabólicos en estos pacientes. Sin embargo, esto no aún no se comprende en su totalidad (27,28), por lo que es recomendable ahondar en este efecto y en el posible acompañamiento de rehabilitación muscular, que podrían esclarecer este resultado.

En relación con el ángulo de fase y el ángulo de fase estandarizado, ambos presentaron una disminución en el grupo de CaCNT, lo que puede considerarse un marcador de mal pronós-

tico de acuerdo con diversos autores (29,30), ya que se traduce en una disminución de la calidad de los tejidos secundaria a la afectación de la membrana plasmática (31,32); con ello, además, se genera un incremento tanto del agua extracelular como de la razón de agua extracelular con el agua intracelular. Además de esto, Trommelen y cols. describen la cinética y absorción del CaCNT (33), que tiende a precipitarse en el estómago retrasando el vaciado gástrico, generando sensación de plenitud y disminuyendo su digestión y, por ende, absorción (34). Esto puede generar en los participantes una ingesta menor respecto a los otros grupos que impactaría en su composición corporal, pudiendo explicar dicha relación en nuestros resultados.

La evaluación del estado nutricional requiere ser abordada de manera integral con diversas herramientas desde el punto de vista antropométrico, funcional y metabólico, debido a los múltiples factores que logran repercutir en el mismo, por ejemplo, el periodo de ayuno y el estrés por patología y la terapia implementada. Por lo tanto, es recomendable que la valoración sea multiinstrumental y dinámica en el periodo de tiempo durante el cual se le otorgue la atención médica al paciente. Asimismo, las pruebas de funcionalidad deben ser implementadas como objetivos de desenlace del paciente posquirúrgico con la finalidad de tener parámetros que se vinculen con las actividades de la vida diaria y la independencia del paciente. Dichos parámetros se ven afectados por el ayuno y las alteraciones en el metabolismo proteico de manera sistémica. Por lo anterior, se deben seguir buscando estrategias de suplementación proteica que coadyuven en el mantenimiento de la masa muscular y su funcionamiento.

En relación con las pruebas de análisis de bioimpedancia, no mostraron cambios favorables para el grupo de CaCNT. No obstante, en el grupo de proteína de suero de leche, por los hallazgos relacionados en el mantenimiento del agua celular y el ángulo de fase, se asoció a mejores expectativas en cuanto a complicaciones perioperatorias, cantidad en el sangrado y días de hospitalización, lo que abre la opción a futuras investigaciones para conocer a nivel metabólico el efecto de estos suplementos en pacientes oncológicos. Finalmente, no se encontraron mejoras en pruebas de funcionalidad como la caminata de seis minutos. La cantidad reducida de pacientes reclutados durante el periodo del estudio, correspondiente a las olas de la pandemia por SARS-CoV-2, fue una limitante importante. Otra fue la diversidad de tipos de cáncer entre grupos y, por otro lado, el abordaje quirúrgico de acuerdo con el tipo de tumor podría afectar en mayor o menor grado el efecto de la intervención, por lo que será importante indagar en este tipo de estudios estratificando de acuerdo a estas características y el estadio del cáncer presente en el paciente.

CONCLUSIONES

La proteína aislada de suero de leche mantiene los parámetros de composición corporal como la fuerza de prensión, la masa muscular y el agua celular, lo cual puede generar mejores expectativas y evolución en en pacientes oncológicos sometidos a cirugía electiva. La suplementación nutricional requiere ser abordada desde el punto de vista funcional y metabólico para identificar factores que impacten favorablemente.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

Evaluación de las características organolépticas de un suplemento nutricional oral diseñado específicamente para el paciente oncológico

Evaluation of the organoleptic characteristics of an oral nutritional supplement designed specifically for the cancer patient

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Resumen

Introducción: los suplementos nutricionales orales (SNO) son una de las terapias nutricionales más utilizadas para tratar la desnutrición en los pacientes oncológicos. Por ello, es de gran importancia contar con la innovación en estos tratamientos, desde los nutrientes hasta la calidad sensorial, para asegurar su consumo.

Objetivos: evaluar las características organolépticas de diferentes prototipos de SNO diseñados específicamente para pacientes oncológicos.

Métodos: estudio clínico piloto transversal, aleatorizado, cruzado y doble ciego en pacientes con cualquier tipo de cáncer, con o sin tratamiento oncológico, a los que se les realizó una cata de cinco prototipos de SNO con distintos sabores (*brownie,* tropical, piña, tomate y jamón) y distintas cualidades sensoriales para evaluar sus características organolépticas (color, olor, sabor, gusto residual, textura y densidad) a través de un cuestionario específico.

Resultados: treinta pacientes de 67,5 ± 11,2 años y con un índice de masa corporal (IMC) de 22,3 ± 3,52 kg/m^2 fueron evaluados. Los tumores más prevalentes fueron cabeza y cuello (30 %), páncreas (20 %) y colorrectal (17 %). El 65 % de los pacientes había perdido ≥ 10 % del peso corporal en seis meses. Los SNO mejor valorados fueron los sabores *brownie* (23,67 ± 3,91 puntos) y tropical (20,33 ± 3,37 puntos) mientras que los menos valorados fueron los SNO con sabor tomate (16,33 ± 5,44 puntos) y jamón (13,97 ± 4,64 puntos).

Conclusión: los pacientes oncológicos valoran de forma mucho más positiva las características organolépticas de los SNO con sabores dulces, como el *brownie,* y los sabores afrutados, como el tropical. Menos apreciados por este colectivo son aquellos con un sabor salado, como el sabor jamón y tomate.

Palabras clave:

Suplementos nutricionales orales. Cáncer. Desnutrición. Características organolépticas.

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Abstract

Introduction: oral nutritional supplements (ONS) are nutritional therapies used to treat malnutrition in cancer patients, therefore, innovation in these treatments, from nutrients to sensory quality, is essential to ensure their consumption.

Objectives: to evaluate the organoleptic characteristic of different prototypes of oral nutritional supplements specifically designed for cancer patients.

Method: cross-sectional, randomized, double-blind pilot clinical study in patients with any type of cancer, with or without oncological treatment, who tasted five ONS prototypes with different flavors (brownie, tropical, pineapple, tomato and ham) and different sensory qualities in order to evaluate their organoleptic characteristics (color, smell, taste, residual taste, texture and density) through a specific questionnaire.

Results: thirty patients aged 67.5 ± 11.2 years and body mass index (BMI) of 22.3 ± 3.52 kg/m^2 were evaluated. The most prevalent tumors were head and neck (30 %), pancreas (20 %) and colon (17 %); 65 % of the patients had lost ≥ 10 % of their body weight in six months. The best rated supplements by the cancer population were those with brownie flavor (23.67 ± 3.91 points) and tropical (20.33 ± 3.37 points), while the least valued were tomato (16.33 ± 5.44 points) and ham flavor (13.97 ± 4.64 points).

Conclusions: cancer patients value the organoleptic characteristics of ONS with sweet flavors, such as brownie, and fruity flavors, such as tropical, much more positively. Less appreciated by these patients are those with a salty taste, such as ham and tomato flavor.

Keywords:

Oral nutritional supplement. Cancer. Malnutrition. Organoleptic characteristics.

INTRODUCCIÓN

El cáncer es la segunda causa de mortalidad en el mundo, y en España es una de las principales causas de morbimortalidad. Es una enfermedad multifactorial en la cual el estado nutricional previo puede influir sobre la calidad de vida de los pacientes y, una vez establecida la enfermedad, influye directamente sobre su pronóstico (1).

Comparado con otras enfermedades, los enfermos de cáncer tienen una probabilidad mayor de padecer desnutrición relacionada con la enfermedad (DRE) por diferentes motivos (factores del propio paciente, factores del propio tumor y factores del tratamiento administrado). En este sentido, está descrito que entre el 30 y el 50 % de los pacientes con cáncer presentan desnutrición, hasta alcanzar más del 80 % en estadios avanzados (2).

Se conoce bien cómo la DRE en el paciente oncológico está directamente relacionada con un incremento de la morbilidad, la mortalidad y los costes sanitarios asociados (3), por ello, su detección y tratamiento temprano son de gran importancia.

En este sentido, las guías internacionales de práctica clínica recomiendan que el primer escalón para tratar la DRE en el paciente oncológico sea realizar un consejo dietético individualizado. Sin embargo, cuando con las medidas dietéticas no se consiga cubrir el 75 % de los requerimientos nutricionales, se deberá optar por completar la dieta con suplementos nutricionales orales (SNO) (4).

Los SNO son preparados nutricionales que complementan una ingesta oral insuficiente y que han demostrado que, en los pacientes oncológicos, aumentan la calidad de vida, la ingesta energética y el peso corporal (5).

Los SNO son de prescripción médica y esto debe basarse en la composición nutricional, las características físicas, la enfermedad de base, etc. Sin embargo, aunque son muchos los SNO que existen en el mercado actualmente, el impulso hacia la práctica médica basada en la evidencia nos debe obligar a que consideremos la investigación de fórmulas específicas que prestan atención a la calidad nutricional y a la población a la que va dirigida, y entre estas premisas también es importante considerar las características organolépticas. En este sentido, la European Society for Clinical Nutrition and Metabolism (ESPEN) recomienda que, como parte de la intervención nutricional para aumentar la ingesta oral de pacientes oncológicos desnutridos o en riesgo de desnutrición se prescriban SNO. En aquellos con cáncer avanzado que reciben quimioterapia, además, se sugieren SNO con ácidos grasos omega-3 para estabilizar o mejorar el apetito, la ingesta de alimentos, la masa corporal magra y el peso corporal. Además, en pacientes que pierden peso con resistencia a la insulina se sugiere aumentar la densidad de la dieta y reducir la carga glucémica (4).

En este sentido, los pacientes oncológicos tienen una mala adherencia en el consumo de los SNO derivada de diferentes factores. Estos incluyen la percepción de las necesidades y los beneficios, el impacto de la enfermedad y/o los tratamientos administrados, la tolerancia a los SNO o la preferencia personal de las cualidades sensoriales, entendiendo que los tratamientos oncológicos pueden afectar estas preferencias (6). En este sentido, además de valorar cuantitativamente y cualitativamente los nutrientes que aportan, se deben tener en cuenta sus características organolépticas. Esto es debido a que los pacientes oncológicos son un grupo de población en el cual las alteraciones en el gusto y en el olfato son muy prevalentes como consecuencia de las terapias antitumorales (7), lo que puede acentuar aún más la desnutrición favoreciendo una mala calidad de vida y peor función física y socioemocional (8).

Por ello, el objetivo de este estudio fue evaluar las características organolépticas de diferentes prototipos de SNO específicos en pacientes oncológicos y seleccionar aquellos productos finales con mayor aceptación por la población diana.

MATERIAL Y MÉTODOS

SUJETOS DEL ESTUDIO

Un total de 30 pacientes oncológicos, hombres y mujeres, fueron reclutados por la Unidad de Nutrición y Dietética del Hospital Universitario La Paz (HULP). Los criterios de inclusión incluyeron pacientes oncológicos mayores de 18 años y menores de 65 años que hubiesen iniciado o estuviesen a punto de iniciar tratamiento de quimioterapia y/o radioterapia con o sin cirugía,

con un adecuado nivel cultural y de comprensión del estudio clínico y que estuviesen de acuerdo en participar voluntariamente dando su consentimiento por escrito. Los criterios de exclusión fueron: infección severa, cirugía mayor en los tres meses previos, proceso infeccioso activo en el momento de la realización del estudio, sujetos con diabetes insulinodependientes, sujetos con demencia, enfermedades mentales o disminución de la función cognitiva, sujetos que rechacen los SNO, sujetos con nutrición enteral y/o parenteral y sujetos que presenten obesidad mórbida (índice de masa corporal [IMC] ≥ 40 kg/m^2).

Por otra parte, los sujetos seleccionados fueron informados acerca de las cualidades organolépticas del estudio, así como de la manera de evaluarlos.

El protocolo de investigación fue aprobado por el Comité Ético de Investigación Clínica del HULP (Código 5254) bajo la normativa descrita en la Declaración de Helsinki (9).

DISEÑO DEL ESTUDIO Y ALEATORIZACIÓN

Se llevó a cabo un estudio clínico piloto transversal, aleatorizado, cruzado y doble ciego. La aleatorización de la valoración organoléptica de los SNO se realizó a través de un sistema validado SMSS, proporcionado por la Unidad de Bioestadística del Hospital La Paz, que determina aleatoriamente y de forma automática el orden de consumo de los diferentes SNO. A cada sujeto que entrase en el estudio le correspondía un número de participante y, en función del número asignado, consumió los cinco prototipos del suplemento en estudio en un orden diferente dividido en cinco grupos. Los 30 participantes del estudio se dividieron en cinco grupos de estudio con seis individuos cada uno según el método de aleatorización (Tabla I).

PRODUCTO DEL ESTUDIO Y ENMASCARAMIENTO

La empresa Adventia Pharma S.L. elaboró, envasó, etiquetó y suministró los distintos SNO. Estos consistían en una dieta enteral nutricionalmente completa (Bi1 Alisenoc) hipercalórica, hiperproteica, con fibra, aceite de oliva virgen extra, omega-3 (ácido eicosapentaenoico [EPA] y ácido docosahexaenoico [DHA]), betaglucanos, triglicéridos de cadena media y enriquecida con L-leucina. El SNO diseñado, con independencia de las cualidades organolépticas, aportaba 400 kcal, 20 g de proteínas, 39,70 g de hidratos de carbono, 17,10 g de grasas, 3,60 g de fibra, 3,3 g de leucina y 1,5 g de EPA y DHA, en 200 ml (Tabla II).

Los sabores elegidos para el estudio fueron: tropical, jamón, tomate, piña y *brownie.* Para el proceso de saborización de las dietas, en las cinco variedades, se utilizaron aromas y sustancias compuestas por sustancias aromáticas, preparaciones aromáticas naturales y sustancias naturales aromáticas.

Esta selección de sabores se llevó a cabo tras la realización de una encuesta previa a pacientes oncológicos que se encontraban en el Hospital de Día de Oncología del Hospital Universitario La Paz, con el objetivo de conocer qué sabores para un SNO resultaban más atractivos para el paciente oncológico con tratamiento antineoplásico activo.

Los cinco prototipos de suplementos estaban envasados en el mismo Tetra Pak Edge blanco totalmente opaco, con el mismo tipo de tapa de rosca (HeliCap™), y solo se diferenciaban por el número de lote, asegurando así el enmascaramiento.

EVALUACIÓN SENSORIAL Y TOLERANCIA

La valoración de las características organolépticas de cada suplemento se realizó a través de un cuestionario subjetivo (10) con seis ítems. El color fue evaluado según la apariencia, el olor se evaluó acercando el producto a las fosas nasales para realizar una inspiración y, seguidamente, se consumió una parte del producto reteniéndolo unos segundos en la cavidad bucal y acabando con una espiración. El sabor, el gusto residual, la textura y la densidad se evaluaron directamente en la boca. Se otorgó una puntuación de 1 a 5 de la siguiente manera: me disgusta mucho = 1 punto, me disgusta moderadamente = 2 puntos, ni me gusta ni me disgusta = 3 puntos, me gusta moderadamente = 4 puntos, y me gusta mucho = 5 puntos.

Para calcular la percepción total de la aceptación de los productos se realizó el sumatorio de todas las puntuaciones obtenidas, con un máximo puntuable de 30 puntos.

Asimismo, la tolerancia gastrointestinal fue evaluada tras 24 horas preguntando a cada individuo por la aparición de los síntomas gastrointestinales más probables, como náuseas, vómitos, dolor abdominal, diarrea, estreñimiento y mal aliento.

Tabla I. Aleatorización del consumo de los prototipos de los suplementos del estudio

Grupo 1	Prototipo 1	Prototipo 2	Prototipo 3	Prototipo 4	Prototipo 5
Grupo 2	Prototipo 2	Prototipo 1	Prototipo 3	Prototipo 5	Prototipo 4
Grupo 3	Prototipo 3	Prototipo 4	Prototipo 1	Prototipo 2	Prototipo 5
Grupo 4	Prototipo 4	Prototipo 5	Prototipo 1	Prototipo 3	Prototipo 2
Grupo 5	Prototipo 5	Prototipo 4	Prototipo 3	Prototipo 2	Prototipo 1

Tabla II. Composición del producto Bi1 Alisenoc por 100 ml y 200 ml

Información nutricional	100 ml	200 ml
Energía (kcal)	200	400
Proteínas (g)	10	20
L-leucina (g)	1,68	3,37
Grasa (g), de las cuales	8,56	17,11
Ácidos grasos saturados (g)	2,42	4,84
TCM	0,86	1,71
Ácidos grasos monoinsaturados (g)	4,13	8,26
Ácidos grasos poliinsaturados (g)	2,01	4,02
EPA (mg)	462	923
DHA (mg)	288	577
Hidratos de carbono (g), de los cuales	*19,9*	*39,7*
Azúcares (g)	1,73	3,45
Fibra alimentaria (g)	*1,80*	*3,60*
Betaglucanos (g)	0,08	0,16
Sal (g)	0,15	0,30
Vitamina A (µg-RE)	117	234
Vitamina D (µg)	2	4
Vitamina K (µg)	20	40
Vitamina C (mg)	12	24
Vitamina B1 (mg)	0,20	0,40
Vitamina B2 (mg)	0,30	0,60
Vitamina B6 (mg)	0,30	0,60
Niacina (mg-NE)	3	6
Ácido fólico (µg)	50	100
Vitamina B12 (µg)	0,33	0,66
Ácido Pantoténico (mg)	0,83	1,66
Biotina (mg)	5	10
Vitamina E (mg-αTE)	3,50	7
Sodio (mg)	60	120
Cloruro (mg)	60	120
Potasio (mg)	120	334
Calcio (mg)	117	234
Fósforo (mg)	117	234
Magnesio (mg)	35	70
Hierro (mg)	1,80	6,30
Zinc (mg)	1,80	3,60
Cobre (µg)	120	240
Yodo (µg)	20	40
Selenio (µg)	8	16
Manganeso (mg)	0,30	0,60
Cromo (µg)	3,50	7
Molibdeno (µg)	4,50	9
Fluoruro (mg)	0,98	1,06
Colina (mg)	40	80
Taurina (mg)	20	40
Osmolaridad (mOsmol/l)	210	420

TCM: triglicéridos de cadena media; EPA: ácido eicosapentaenoico; DHA: ácido docosahexaenoico.

DESARROLLO DEL ESTUDIO

Las catas se llevaron a cabo en dos áreas separadas entre sí: por un lado, el área de preparación de la muestra, una zona separada de la zona de prueba para evitar que los participantes observasen la preparación de las muestras; y por otro, el área de cata, una zona tranquila y bien ventilada donde los participantes llevaron a cabo la cata de los productos a evaluar.

En la Unidad de Nutrición se recogieron datos sociodemográficos, antropométricos (peso, talla, IMC y porcentaje de pérdida de peso en los últimos seis meses) y de la enfermedad (tipo de tumor y tratamiento). Posteriormente, los participantes pasaban al área de cata.

Cada suplemento se presentó al participante en un vaso de plástico opaco con 20 ml del producto y con una temperatura de 8 °C.

Para evitar el sesgo por agotamiento de las papilas gustativas, los participantes debían enjuagarse la boca con agua a temperatura ambiente entre cada producto para minimizar el riesgo de que la anterior valoración influyese sobre el nuevo producto a catar.

ANÁLISIS ESTADÍSTICO

La recogida de todos los resultados se realizó en una base de datos creada específicamente para el estudio cumpliendo la normativa vigente de protección de datos. Todos ellos fueron codificados y procesados con el paquete estadístico SPSS® (versión 25.0 para Windows).

Los resultados cualitativos se muestran en forma de frecuencias absolutas y porcentajes y los datos cuantitativos, mediante media y desviación típica.

Todas las variables fueron sometidas a las pruebas de distribución de normalidad y homogeneidad de la varianza, usando los test de Kolmogorov-Smirnov y Levene, respectivamente. Para establecer diferencias entre las medias de más de dos grupos se aplicó la prueba de ANOVA de un factor, el test *post hoc* Newman-Keuls para varianzas homogéneas y el test *post hoc* de Tamhane cuando las varianzas no fueron homogéneas. Para comprobar diferencias intergrupo se utilizó el test de Mann-Whitney y se emplearon el método de Bonferroni para varianzas homogéneas y el test *post hoc* de Tamhane cuando estas no fueron homogéneas. Para asociar diferentes datos cualitativos se utilizaron tablas de contingencia.

Por último, se consideraron significativas aquellas diferencias cuya probabilidad fue inferior al 5 % ($p < 0,05$).

RESULTADOS

Fueron evaluados 30 pacientes, 57 % hombres y 43 % mujeres, con una edad media de 67,5 ± 11,2 años. Los tumores más prevalentes fueron los de cabeza y cuello (30 %), páncreas (20 %) y colorrectal (17 %), seguidos de pulmón (13 %),

ginecológicos (7 %), linfoma no Hodgkin (7 %), gástricos (3 %), unión gastroesofágica (3 %) y hepatobiliar (3 %).

La mayoría de los participantes estaban en tratamiento activo con quimioterapia (67 %) y los fármacos más utilizados fueron los agentes alquilantes (31,7 %), los anticuerpos monoclonales (18 %) y los alcaloides vegetales (16,7 %). Un 30 % se encontraba en tratamiento combinado de quimio-radioterapia, siendo el fármaco quimioterápico un agente alquilante, y una minoría, en radioterapia (7 %).

En cuanto a los resultados antropométricos, la media resultante del IMC fue de 22,30 ± 3,52 kg/m^2, y el 65 % de los participantes presentaba una pérdida superior al 10 % en los últimos seis meses.

Con respecto a la evaluación de las características organolépticas de cada suplemento, la puntuación total más alta la obtuvo el SNO con sabor *brownie* (23,67 ± 3,91 puntos). Esta puntuación fue estadísticamente significativa en comparación con el resto de los suplementos (Tabla III). La siguiente puntuación total más alta la obtuvo el SNO con sabor tropical (20,33 ± 3,37 puntos), y en tercer lugar quedó el SNO con sabor piña (18,90 ± 3,93 puntos).

La puntuación total más baja fue para los SNO con sabores a tomate (16,33 ± 5,44 puntos) y jamón (13,97 ± 4,64 puntos), con diferencias significativas con respecto al sabor *brownie* y al sabor tropical (Tabla III).

Las puntuaciones individuales de cada SNO referentes a color, olor, sabor, gusto residual, textura y densidad se muestran en la tabla III.

Con respecto a la asociación entre las características organolépticas, en el color no se encontraron diferencias significativas entre productos, sin embargo, en el olor, el sabor, el gusto residual, la textura y la densidad se encontraron diferencias significativas entre el SNO con sabor a *brownie* y los SNO con sabores a jamón, piña y tomate, así como entre el SNO con sabor tropical y los SNO con sabores a jamón y tomate (Tabla III).

Por último, no se detectaron síntomas gastrointestinales adversos relacionados con el consumo de los productos.

DISCUSIÓN

Está claramente demostrado que la desnutrición relacionada con la enfermedad en el paciente oncológico es muy prevalente (2); que se asocia con una alta tasa de morbilidad, peor tolerancia a las terapias antitumorales y mayor mortalidad (11,12); y que se confirma que es un problema urgente de salud pública (13). Esta situación descrita concuerda con los resultados obtenidos, pues más de la mitad de la población estudiada presentaba una pérdida de peso superior al 10 % en los últimos seis meses, lo que se clasifica, según los nuevos criterios diagnósticos, como desnutrición severa (14).

Las guías internacionales de práctica clínica indican que el consejo dietético es el primer escalón a la hora de tratar un estado nutricional deficiente. Sin embargo, en muchas ocasiones, los factores que implican los tratamientos oncológicos (efectos secundarios, interferencia en la absorción/metabolismo de los nutrientes, etc.), así como las necesidades energéticas y proteicas aumentadas, impiden que se puedan cubrir los requerimientos únicamente con la dieta. En esos casos, las guías clínicas aconsejan utilizar nutrición enteral, siendo la primera elección los suplementos nutricionales orales (SNO) (4).

En el paciente oncológico, la prescripción de los suplementos se debe ajustar a los requerimientos nutricionales, a las comorbilidades asociadas a la propia enfermedad y a las características individuales del paciente.

Este estudio pretende completar los limitados trabajos publicados que existen en cuanto a evaluación de las características organolépticas de suplementos específicos para oncología. A este respecto, se conoce bien que las diferentes sensaciones, temperatura y cantidad de saliva producida, así como la composición nutricional de los productos pueden influir en la palatabilidad de los alimentos. En este sentido, los suplementos específicos para oncología tienen la recomendación de llevar en su composición ácidos grasos poliinsaturados procedentes del pescado (4) debido a su efecto demostrado frente a la toxicidad

Tabla III. Puntuación de las características organolépticas de cada SNO

	Jamón	Brownie	Tropical	Piña	Tomate	ANOVA
Color	3,27 ± 0,98	3,83 ± 0,95	3,53 ± 0,90	3,40 ± 0,77	3,30 ± 0,84	NS
Olor	2,07 ± 1,05*,†	3,70 ± 1,09$^{*,\|\|,\P}$	2,93 ± 1,17†	2,67 ± 1,32$^{\|\|}$	2,23 ± 0,93¶	0,001
Sabor	1,50 ± 0,82*,†,‡	4,40 ± 0,81$^{*,\|\|,\P}$	3,83 ± 0,87†,**	3,13 ± 1,20$^{\ddagger,\|\|}$	2,40 ± 1,50¶,**	0,001
Gusto residual	2,20 ± 1,24*,†,‡	4,03 ± 0,96$^{*,\|\|}$	3,60 ± 0,93†,**	3,30 ± 1,12‡	2,60 ± 1,40¶,**	0,001
Textura	2,63 ± 1,38*,‡	4,00 ± 0,59$^{*,\|\|}$	3,40 ± 0,97	3,47 ± 1,11‡	3,13 ± 1,31¶	0,001
Densidad	2,30 ± 1,29*	3,70 ± 0,99$^{*,\|\|}$	3,03 ± 1,03	2,93 ± 1,23	2,67 ± 1,21¶	0,001
Total	13,97 ± 4,64*,†,‡	23,67 ± 3,91$^{*,\S,\|\|,\P}$	20,33 ± 3,37†,§,**	18,90 ± 3,93$^{\ddagger,\|\|}$	16,33 ± 5,44¶,**	0,001

Símbolos iguales indican diferencias significativas entre los sabores.

inducida por la quimioterapia (15), pero también por la mejora del apetito, el peso corporal y la calidad de vida (16,17). Sin embargo, su inclusión también puede provocar aversiones debido al sabor si no están bien tratados y enmascarados.

En el presente estudio, se evalúan nuevos sabores elegidos específicamente por los pacientes oncológicos y diferentes de los habitualmente preferidos y comercializados vainilla y fresa. En este sentido, otros autores han comparado la palatabilidad de SNO a base de leche (vainilla y fresa) con otros SNO a base de jugo (manzana y naranja) o a base de yogur (vainilla-limón y melocotón-naranja) en pacientes con cáncer de testículo sometidos a quimioterapia de primera línea basada en cisplatino. Estos encontraron que los SNO a base de leche, principalmente la fresa, resultaron ser los preferidos, aunque la palatabilidad fue variando en función de los ciclos de quimioterapia (18). Si bien este estudio reforzó la utilización de sabores tradicionalmente aceptados, el presente estudio demuestra gran aceptabilidad por parte de los pacientes oncológicos a nuevos sabores.

Una de las limitaciones del estudio es que no se ha evaluado el estadio del tumor o cómo el tipo de tratamiento pueden interferir y afectar sobre las preferencias gustativas (19), debido principalmente al carácter exploratorio del estudio. Sin embargo, que un SNO específico en oncología, altamente energético y con presencia de ácidos grasos poliinsaturados (Tabla II), tenga una buena aceptabilidad en todas sus características organolépticas (Tabla III), como pasa en este estudio con los sabores *brownie* y tropical, puede mejorar el cumplimiento de la pauta de consumo y paliar potencialmente la DRE.

Por otro lado, es bien sabido que los receptores gustativos están distribuidos por toda la cavidad bucal. En este sentido, se hipotetiza que el mecanismo de preferencia gustativa se encuentra a nivel central y en relación con las necesidades del organismo respecto a determinadas sustancias (20). De hecho, uno de los estudios pioneros en mostrar tal aspecto fue el realizado por Nachman en 1962, donde se observó cómo ratas suprarrenalectomizadas tenían preferencia por agua rica en cloruro sódico (21). Este aspecto podría haber influido en estos pacientes dado que un gran porcentaje presentaba déficits nutricionales.

Asimismo, se sabe que las preferencias alimentarias pueden estar influidas por una serie de factores, como experiencias personales, adaptaciones culturales, genes, edad, etc. (22), lo que pone de manifiesto el carácter complejo de la predilección por los sabores.

La lucha contra la DRE ha impulsado el desarrollo de nuevas estrategias para mejorar la adherencia al consumo de los SNO en pacientes oncológicos, y una de ellas es la mejora de la estimulación sensorial (19). En este sentido, Hann y cols. administraron a 50 pacientes con diversos tipos de cáncer y tratamientos cinco sabores de SNO, de los cuales dos proporcionaban una sensación de calor por contener derivados del pimiento y cuyo objetivo era desencadenar sensaciones cálidas/picantes que activan el nervio trigémino; dos SNO proporcionaban una sensación refrescante por contener derivados de mentol para tener la sensación de boca fresca, que activa el nervio trigémino; y un SNO era neutro. Esto se tradujo en una apreciación sensorial por parte de los pacientes (23).

En conclusión, en el presente estudio se pone de manifiesto que los pacientes oncológicos valoran de forma mucho más positiva las características organolépticas de los SNO con sabores dulces y ácidos debido, posiblemente, a la interacción de los múltiples factores que engloban a este tipo de enfermos (tratamientos antineoplásicos, déficits nutricionales, factores personales, etc.). Conocer las preferencias sensoriales de los SNO en los pacientes oncológicos podría tener resultados positivos con respecto a la adherencia a su consumo y, por tanto, puede repercutir positivamente sobre las altas tasas de DRE.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Pediatría

Risk of vitamin D deficit in asthmatic children hospitalized in the north area of Santiago

Riesgo de déficit de vitamina D en niños asmáticos hospitalizados en el área norte de Santiago

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Abstract

Introduction: in recent years asthma hospitalization rate in Chilean children has doubled. Numerous studies have shown an association between hypovitaminosis D and frequent, severe asthmatic exacerbations in children.

Objective: to estimate the risk of vitamin D (vitD) deficiency and insufficiency in hospitalized asthmatic children compared with patients who are monitored on an outpatient basis and do not have records of hospitalization in one year.

Material and methods: an observational, analytic, and case-control study carried out in one calendar year including asthmatic children between 5 and 15 years of age. This study registered: sociodemographic and clinical data, asthma control test, severity score of hospitalization and measurements of vitD blood levels. Associations between variables were analyzed using the t-test and chi-squared test. The risk for hypovitaminosis D and deficiency was calculated through logistic regression. The data was fed into the Stata 14 software.

Results: a total of 117 patients, 9 ± 2.7 years old, were admitted, 64 % were male and 51 % presented with malnutrition by excess. Six out of ten children presented moderate asthma and 55 % had a poor control of their pathology; 73.5 % presented hypovitaminosis D (insufficiency and deficiency), hospitalized patients had 2.8 times more risk of presenting vitD deficiency, adjusted according to seasonality and age (95 %CI, 1.07-7.5, $p < 0.05$) without being associated with a higher severity score of hospitalization.

Conclusion: most of the asthmatic children in the sample presented with hypovitaminosis D, with a higher percentage of deficiency in hospitalized patients, which is not associated with greater severity of hospitalization.

Keywords:

Asthma. Vitamin D. Vitamin D deficiency. Children.

Resumen

Introducción: la tasa de hospitalización por asma se ha duplicado en los últimos años en Chile. Numerosos estudios demuestran una asociación entre la hipovitaminosis D y la presencia de exacerbaciones frecuentes y severas.

Objetivo: comparar el riesgo de déficit e insuficiencia de vitamina D (vitD) en niños asmáticos que se hospitalizan en relación con los que se tratan ambulatoriamente.

Material y métodos: estudio observacional, analítico, de casos y controles realizado durante 1 año calendario. Se incluyó a pacientes asmáticos de 5 a 15 años. Se registraron datos sociodemográficos, clínicos, nivel de control de asma, puntaje de severidad de hospitalización y se midió la concentración sanguínea de vitD. Se analizó la asociación entre las variables mediante la prueba de la t y la del chi cuadrado. Mediante regresión logística se calculó el riesgo de hipovitaminosis D y déficit de vitD en los sujetos. Los datos se analizaron con el software Stata 14.

Resultados: se enrolaron 117 pacientes de 9 ± 2,7 años, 64 % de varones y 51 % con malnutrición por exceso. Seis de cada diez niños presentaban asma moderada y el 55 % tenían mal control de su enfermedad. El 73,5 % de los sujetos presentaban hipovitaminosis D (déficit o insuficiencia). Los hospitalizados tuvieron 2,8 veces más riesgo de presentar déficit de vitD (IC 95 %: 1,07-7,5), ajustado según estacionalidad y edad, sin asociarse a mayor puntaje de severidad de la hospitalización.

Conclusión: la mayoría de los niños asmáticos de la muestra presentan hipovitaminosis D, siendo mayor el porcentaje de déficit en los hospitalizados, lo que no se asocia a mayor severidad de la hospitalización.

Palabras clave

Asma. Vitamina D. Deficiencia de vitamina D. Niños.

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INTRODUCTION

Bronchial asthma is one of the most common chronic diseases in childhood, ranking among the top 20 conditions worldwide for disability-adjusted life years in children (1). In Chile, a significant increase in the rate of hospitalization for asthma in children has been observed, reaching a figure of 7.8 per 10,000 in 2014 (2). On the other hand, hypovitaminosis D is a major health problem that affects more than 2 billion children and adults worldwide (3). Vitamin D (vitD) has multiple functions in the health of children and adolescents. In addition to its importance for the metabolism of calcium and phosphorus, it is an important immunomodulator and has effects on the development of autoimmune diseases, some cancers, insulin resistance, and cardiovascular health, respiratory tract infections and wheezings (4-6).

In recent years, numerous prospective and retrospective studies have been published that demonstrate an increased risk of exacerbations and hospitalizations for asthma in children with hypovitaminosis D (7,8). This is probably due to an immunomodulatory effect of vitD on T helper 1, 2 lymphocyte function and on regulatory T cells (9).

In a pilot study carried out 2 years ago at Hospital Clínico Universidad de Chile (HCUCH), we were able to verify that 62 % of asthmatic children who were hospitalized had hypovitaminosis D (deficit or insufficiency of vitD) and that this deficit was associated with poor control of the disease (10).

The objective of the present study was to evaluate the risk of hypovitaminosis (vitD < 30 ng/ml) and vitD deficiency (< 20 ng/ml) in a group of asthmatic children of similar socioeconomic status who were hospitalized at the HCUCH University Hospital and at the Roberto del Río Public Hospital (HRRIO), in relation to the same number of asthmatic schoolchildren who were controlled at the outpatient level in these hospitals, and who did not underwent hospitalization in the last 12 months prior to the study. Sociodemographic and clinical characteristics were analyzed and the association between hypovitaminosis D and nutritional status and severity of hospitalization was evaluated.

MATERIAL AND METHODS

A descriptive, analytical, case-control study was carried out between May 2017 and May 2018. The sample size of 54 patients was calculated for each group considering a power of 80 % with a significance level of 0.05, and a difference of 27 percentage points in the frequency of hypovitaminosis D in hospitalized asthmatics (H) versus those treated as outpatients (A). The project was approved by the ethics committee of both hospitals.

Patients between 5 and 15 years of age were recruited, who were treated consecutively either as inpatients or as outpatients at the bronchopulmonary clinic of HCUCH and HRRIO. After signing an assent or informed consent form, a sociodemographic data survey and asthma control questionnaire were applied using the Asthma Control Test (ACT) (11,12). A complete physical examination and calculation of BMI (body mass index) was performed to then make a diagnosis of nutritional status according to the WHO 2007 curve (13). A blood sample was taken from the patients to measure the serum concentrations of vitD. Aliquots were processed in the HCUCH Endocrinology laboratory using the electro-chemiluminescence technique (14). Patients with hypovitaminosis D (vitD < 30 ng/ml) were treated, administering vitamin D3 cholecalciferol 2,000 IU per day for 2 months, as indicated by expert recommendation (15). Calcium intake and supplementation was not evaluated in this study.

A severity score was recorded for those children who required hospitalization due to an asthmatic crisis. The score included: total number of days of hospitalization, total number of days with oxygen requirement, maximum inspiratory fraction of oxygen (FiO_2max) reached, and need to transfer to the critical patient unit (mild score: 0-3, moderate: 4-6, severe: 7-14) (16).

Statistical calculations were performed using the Stata 14 package. The association between quantitative variables was assessed through the t-test and using the chi-squared test for categorical variables. Logistic regression was used to estimate the risk of deficiency and hypovitaminosis D, with a significance of $p < 0.05$.

This protocol was approved by the research ethics committee of HCUCH (Acceptance number, 874/17)

RESULTS

A total of 117 subjects entered the study, 64 % male and 9 years old on average; 67 % of the patients were hospitalized during the months with the lowest exposure to UVB radiation (May to November). More than half of the patients presented excess malnutrition without significant differences according to group (H/A) or sex. In all, 55 % had poor control of their disease (ACT ≤ 19), with no differences in average score according to group. The majority had a diagnosis of allergic rhinitis, the highest percentage in A patients ($p < 0.05$). The high frequency of underdiagnosis of the disease stands out, which was higher in group H ($p < 0.05$). Most of the patients had moderate asthma at the time of recruitment, this percentage being significantly higher in group H.

We found a high frequency of hypovitaminosis D in the patients studied (vitD < 30 ng/ml). Although we did not find any differences in the frequency of hypovitaminosis D (deficiency and insufficiency) between the groups, the deficit (vitD < 20 ng/ml) in H patients was significantly higher, and the average level of vitD was significantly lower in this group of children (Table I). When performing the analysis separately according to UVB exposure, there were no differences in the mean concentration of vitD, nor in the percentages of hypovitaminosis according to group; however, in months with lower UVB light levels, the deficit of vitD in hospitalized patients triples the deficit in patients A ($p < 0.05$) (Table II). We did not find any significant differences in the percentage of hypovitaminosis D according to sex; however, the mean concentration of vitD was lower and the percentage of deficit was higher in men (Table III).

The characteristics of hospitalization can be seen in table IV. The average severity score achieved during hospitalization was 7 (moderate), with 48 % of the sample scoring severe. There were no differences in the mean concentration of vitD according to the severity score and according to each of its components (Fig. 1).

The risk of hypovitaminosis and vitD deficiency in hospitalized asthmatic children was determined in comparison with those who were controlled and did not undergo hospitalization in the previous year through 2 logistic regression models (Table IV). In the first model, adjusted according to age, sex, presence of obesity and lower UVB; and in the second model, adjusted according to age and UVB (variables that were statistically significant). No risk of hypovitaminosis D was found in hospitalized children in either of the 2 models; however, the deficit of vitD was 2.8 times higher in patients who were hospitalized (OR, 2.8; 95 % CI, 1.08-7.6, $p < 0.05$) adjusted according to sex, obesity, UVB and age. In the second model, the risk of vitD deficiency is also higher in H subjects compared to A subjects (OR, 2.8; 95 % CI, 1.07-7.5, $p < 0.05$). The risk of vitD deficiency increases by 20 % for each year that the age of the subjects increases (OR, 1.2; 95 % CI, 1.02-1.45, $p < 0.05$).

In the second model, the odds of vitD deficiency persists, it being higher in H subjects compared to A subjects (OR, 2.8; 95 % CI, 1.07-7.5, $p < 0.05$). In both models, a lower UVB implies a 3.3 to 3.7 times greater risk of having vitD deficiency.

Table I. Characterization of children with asthma treated at the Clinical University of Chile and Roberto del Río hospitals

	Total	Hospitalized	Outpatients	*p*
n	117	58	59	
Age (years) X ± sd	9.0 ± 2.7	*8.5 ± 2.6*	*9.5 ± 2.7*	< 0.05
Male gender (%)	64.0	69.5	62.7	ns
Hospital U. de Chile (%)	43.5	*64.7*	*35.2*	< 0.05
Vitamin D (ng/ml) X ± sd	25.0 ± 9.3	*22.7 ± 8.6*	*27.2 ± 9.5*	< 0.05
Hypovitaminosis D (%) (< 30 ng/ml)	73.5	79.3	67.8	NS
VitD deficiency (%) (< 20 ng/ml)	27.3	*27.9*	16.9	< 0.05
Samples in months with lower UVB (%)	53	*67.3*	*37.3*	< 0.05
Malnutrition due to excess (%)	51.7	48.2	55.1	ns
Overweight	29	27.6	30.5	ns
Obesity	22.2	20.6	23.7	ns
Asthma severity (%) Mild Moderate Severe	 30.0 65.5 4.5	 *0* *91.4* *8.6*	 *60.0* *39.0* *0*	< 0.05
Asthma score (ACT)	18.0 ± 3.8	18.0 ± 3.6	18.0 ± 4.0	ns
Poor asthma control (%) (ACT ≤ 19)	55.5	62.7	49.0	ns
Allergic rhnitis (%)	77.0	*67.2*	*87.9*	< 0.05
Passive smoking (%)	51.0	48.2	53.4	ns
Undiagnosed asthma (%)	24.7	*41.0*	*6.0*	0.01

Table II. Serum concentration and percentage of deficit and hypovitaminosis D according to seasonality. Hypovitaminosis D < 30 ng/ml; deficiency < 20 ng/mL

	Greater UVB Exposure (December-April)			Lower UVB Exposure (May-November)		
	Total	**H**	**O**	**Total**	**H**	**O**
VitD (ng/ml)	*28.5 ± 9.2**	27.5 ± 6.8	28.9 ± 10.3	*21.8 ± 8.2**	20.5 ± 8.5	24.2 ± 7.3
Hypovitaminosis D (%)	*63.6**	74.1	65.2	*82.2**	85.1	76.9
Deficiency (%)	*14.5**	22.5	17.3	*38.7**	*55.5**	*15.3**

*UVB: ultraviolet B radiation; H: hospitalized patients; O: outpatients. *p < 0.05.*

Table III. Distribution of nutritional status and VitD according to sex in schools with asthmatic children

	Boys	**Girls**	***p***
n	75	42	
Malnutrition by excess (%)	50.6	53.6	Ns + jhy'y
Obesity (%)	25.0	17.0	ns
VitD (ng/ml)	*23.2*	*28.4*	< 0.01
Hypovitaminosis D (%)	78.6	64.2	ns
VitD deficciency (%)	*33.3*	*16.6*	< 0.05

Table IV. Risk of hypovitaminosis D (< 30 ng/ml) and VitD deficit (< 20 ng/ml) in hospitalized asthmatic children

Risk of hipovitaminosis D	**Model 1**			**Model 2**			
	OR	**95 % CI**	**p**		**OR**	**95 % CI**	**p**
Hospitalized	1.7	0.6-4.5	ns	Hospitalized	1.4	0.5-3.4	ns
Age	1.1	0.9-1.4	ns	Lower UVB	2.3	0.9-5.8	ns
Male sex	2	0.8-5.2	ns				
Obesity	3.6	0.9-14	Ns				
UVB	3.2	1.2-8.5	p < 0.05				
Risk of vitamin D deficiency	OR	95 % CI			OR	95 % CI	
Hospitalized	*2.8**	1.08-7.6	< 0.05	Hospitalized	*2.8**	1.07-7.5	< 0.05
Age	*1.2**	1.02-1.45	< 0.05	Age	*1.2**	1.05-1.4	< 0.05
Male sex	2.5	0.88-7.1	ns	Lower UVB	*3.3**	1.2-9.0	< 0.05
Obesity	1.56	0.53-4.53	ns				
UVB	3.7	1.38-10.14	< 0.05				

**p < 0.05. Hosmer-Lemeshow > 0.05 (appropriate goodness of fit). OR: odds ratio; CI: confidence interval; UVB: ultraviolet B radiation.*

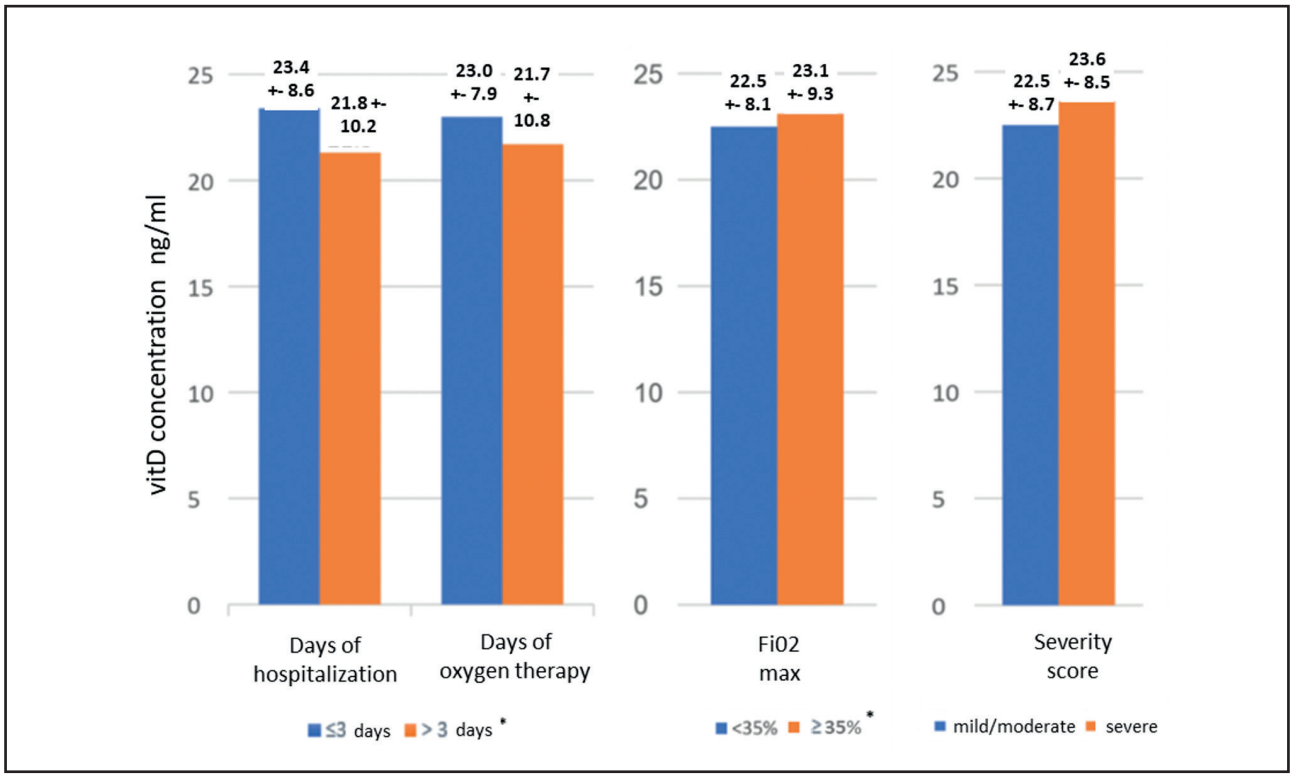

Figure 1.

Vitamin D according to hospitalization characteristics ($p > 0.05$).

DISCUSSION

The main finding of our study was that hospitalized asthmatic subjects have a higher frequency of vitD deficiency, an association that disappears in the months of greater exposure to UVB radiation and increases in the months of less exposure. In inpatients the risk of having vitD deficiency is higher than that of outpatients, even after adjusting for seasonality and age. Few studies evaluate the frequency of deficiency and insufficiency of vitD in asthmatic patients who are hospitalized, and there are numerous studies that evaluate the concentration of vitD according to level of control, severity of asthma, and response to treatment. Bugadze, for example, found in a group of 50 Russian asthmatic schoolchildren a higher frequency of vitD deficiency in those with frequent and severe exacerbations compared to those with good control of the disease ($p < 0.05$) (17).

We found a high frequency of hypovitaminosis D (< 30 ng/ml) in the children studied (73.5 %). This result differs from that described in Costa Rica and Puerto Rico, where there is a much lower frequency than ours (28 % and 44 %, respectively), while the hypovitaminosis D rate found in Italian asthmatic children was 90.6 % (18,19). These differences could be explained by the different UVB exposures in these countries.

The high frequency of hypovitaminosis D found in our patients could be due to a low exposure to UVB light and/or a low intake of milk and fortified cereals, frequent conditions in the age group to which they belong (20,21). Numerous publications describe the relationship between vitD deficiency and increased risk of hospitalization for asthma. Brehm in Costa Rica finds that, as the concentration of vitD increases, a decrease in the risk of hospitalization is observed, after adjusting for age, sex, BMI-z and parental education (OR, 0.05; 95 % CI, 0.004-0.71; $p = 0.03$). This study also detected a decrease in the need for anti-inflammatory medication and bronchial hyperresponsiveness, variables that were not evaluated in our study (4). Other prospective cohort publications carried out in North American asthmatic children show that 35 % of them had hypovitaminosis D. After adjusting for age, sex, BMI, income, treatment received, and seasonality, it was observed that both deficit and insufficiency of vitD were associated with a higher risk of hospitalization or emergency service consultation (OR, 1.5; 95 % CI, 1.2-2.1; $p = 0.004$) (22).

In our study, the high prevalence of allergic rhinitis in H and A subjects stands out, a figure higher than that found in a study carried out in Japan (23) and in a multicenter study recently carried out in our country (24). Proper management of allergic rhinitis is very important, observing that this improves asthma control and exacerbations decrease (25).

Most of the asthmatic children in our study presented excess malnutrition, without differences between the group of hospitalized patients and that of outpatients, and without differences

according to sex. We did not find any association between obesity and a higher frequency of hospitalization; however, it is described that excess malnutrition is a factor that may worsen the clinical management of asthma. Tashiro observed that obesity was associated with an increase in the incidence and prevalence of asthma, and that the more overweight, the more severity increased (26). This association could be due to the fact that asthmatic children with malnutrition due to excess have a lower response to corticosteroids, have a higher degree of airway inflammation, alteration of the intestinal and pulmonary microbiome and often vitD deficiency.

In our work, we did not find any association between nutritional status and vitD concentration. This could be explained by poor asthma control in these patients, which could be associated with a short time spent in outdoor activities, with the consequent low sunlight exposure.

In contrast to these results, in a study carried out in Costa Rica it was verified that as BMI increases, the average concentration of vitD decreases (5).

The average days of hospitalization and the concentration of O_2 administered in our patients agrees with that described in the literature (27,8). Lastly, we found that serum VitD concentration was not associated with in-hospital evolution or with severity score in hospitalized subjects. In agreement with our findings, Iqbal found that in pediatric patients hospitalized for respiratory causes (66.7 % asthmatics) the concentration of vitD was not associated with severity of the disease (28). On the contrary, a study carried out in Concepción shows that vitD deficiency is frequent in children hospitalized in the Pediatric Critical Patient Unit (UPCP), and that this is associated with a greater probability of requiring mechanical ventilation, fluids and inotropic drugs (29).

Regarding the limitations of our work, it seems important to highlight that the power (72 %) to detect differences between the subjects with vitD deficiency was lower than expected. Furthermore, most of the hospitalized patients were recruited during the months of lower UVB exposure, which may have influenced the concentration of vitD. On the other hand, one of the centers participating in this study does not have a UPCP, which could have limited the admission of patients with greater severity. An element to be highlighted is that this study is the first in Chile to compare the serum concentration of vitD with associated factors in pediatric, hospitalized and outpatient asthmatic patients. Given the results obtained, it seems important to consider the systematic measurement of vitD in all asthmatic patients, especially in those who are hospitalized. We recommended the systematic supervision of intake and measurements of vitD blood levels before supplementing it. More clinical trials and cohort studies in asthmatic children are still needed to determine the optimal dose to be supplemented, the cut-off point to define the deficiency of vitD, as well as the clinical role it produces in asthmatic patients with hypovitaminosis when supplemented with this vitamin. On the other hand, it seems important to us to insist that asthmatic children perform physical activity outdoors to allow greater exposure to UVB light.

CONCLUSIONS

In all, 73.5 % of asthmatic children who are controlled in HCUCH and HRRio have vitD deficiency or insufficiency. VitD deficiency is 2.8 times higher in hospitalized patients than in outpatients. This risk increases with age and in the months with less UVB exposure. Clinical trials and cohort studies are needed to evaluate the optimal doses required by asthmatic children to achieve vitD concentrations and determine the clinical changes associated with vitamin supplementation.

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Trabajo Original

Pediatría

Vitamin D levels and their association with oxidative stress and inflammation markers in patients with cystic fibrosis

Niveles de vitamina D y su asociación con marcadores de estrés oxidativo e inflamatorios en pacientes con fibrosis quística

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Abstract

Introduction: cystic fibrosis is a disease that causes inflammation, oxidative stress and metabolic changes that lead to nutrient deficiency, such as vitamin D deficiency. On the other hand, it is suggested that vitamin D has anti-inflammatory and antioxidant actions.

Objective: to evaluate the prevalence of hypovitaminosis D and the association between serum 25 hydroxyvitamin D levels with markers of oxidative stress and inflammation in patients with cystic fibrosis.

Method: a cross-sectional study was carried out with 48 patients with cystic fibrosis including children, adolescents and adults in the northeast region of Brazil. Blood collection was performed for analysis of 25-hydroxyvitamin D, calcium, parathyroid hormone, inflammatory process (C-reactive protein [CRP] and alpha-1-acid glycoprotein-A1 [A1GPA]) and oxidative stress (malondialdehyde (MDA) and total antioxidant capacity [CAOT]). The statistical analysis was performed using the "Statistical Package for the Social Sciences", adopting a significance level of $p < 0.05$.

Results: vitamin D insufficiency/deficiency was found in 64.6 % of patients. After multiple linear regression analysis, MDA showed an inverse association with blood values of 25-hydroxyvitamin D ($p < 0.05$) conditioned by the presence of inflammatory process markers. When only oxidative stress was evaluated, this association disappeared.

Conclusion: in conclusion, there was a high prevalence of hypovitaminosis D, with 25(OH)D levels associated with greater oxidative stress when combined with inflammatory markers. Improved vitamin D levels may be an alternative to reduce the damage caused by excess oxidative stress and inflammation in CF patients.

Keywords:

Vitamin D. Cystic fibrosis. Oxidative stress.

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Resumen

Introducción: la fibrosis quística es una enfermedad que cursa con inflamación, estrés oxidativo y cambios metabólicos que conducen a deficiencia de nutrientes como la vitamina D. Por otro lado, se sugiere que la vitamina D tiene acción antiinflamatoria y antioxidante.

Objetivo: evaluar la prevalencia de hipovitaminosis D y la asociación entre los niveles séricos de 25 hidroxivitamina D con los marcadores de estrés oxidativo e inflamación en pacientes con fibrosis quística.

Método: estudio transversal realizado con 48 pacientes con fibrosis quística, niños, adolescentes y adultos, de la región nordeste de Brasil. Se realizó una extracción de sangre para el análisis de 25-hidroxivitamina D, calcio, hormona paratiroidea, proceso inflamatorio (proteína C-reactiva [PCR] y alfa-1-glucoproteína ácida-A1 [A1GPA]) y estrés oxidativo (malondialdehído [MDA] y capacidad antioxidante total [CAOT]). El análisis estadístico se realizó utilizando el "Paquete Estadístico para las Ciencias Sociales", adoptando un nivel de significancia de $p < 0,05$.

Resultados: se encontró insuficiencia/deficiencia de vitamina D en el 64,6 % de los pacientes. Después de un análisis de regresión lineal múltiple, la MDA mostró una asociación inversa con los valores sanguíneos de 25-hidroxivitamina D ($p < 0,05$) condicionado a la presencia de marcadores de proceso inflamatorio; cuando solo se evalúa el estrés oxidativo, esta asociación desaparece.

Conclusión: en conclusión, hubo una alta prevalencia de hipovitaminosis D, con niveles de 25(OH)D asociados a mayor estrés oxidativo cuando se combina con marcadores inflamatorios. La mejora de los niveles de vitamina D puede ser una alternativa para reducir el daño causado por el exceso de estrés oxidativo y la inflamación en pacientes con FQ.

Palabras clave:

Vitamina D. Fibrosis quística. Estrés oxidativo.

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disease characterized by pulmonary hyperinflammation followed by destruction of airway walls and fibrosis, resulting in a gradual decline in lung function, high oxidative stress, and impaired antioxidant/oxidant balance, among other systemic alterations (1-2). It is caused by mutations in the Cystic Fibrosis Transmembrane Regulatory Protein (CFTR), leading to absent or diminished CFTR protein function on the cell surface (2). Dysfunction in this protein affects the respiratory, gastrointestinal, hepatobiliary and immune systems (2,3,17).

The inflammatory process in CF behaves chronically, promoting an imbalance between pro- and anti-inflammatory mediators (3,4). It is believed that the inflammatory response and excess oxidative stress play a decisive role in the progression of lung damage and CF severity (5,6). Some studies have already demonstrated a relationship between HR and oxidative stress, and the role of antioxidants (2-6). However, the role of vitamin D has not yet been investigated in CF patients.

Most CF patients are at risk for vitamin D deficiency due to poor nutrient absorption, caused by pancreatic insufficiency, impaired metabolism, and lack of sun exposure (6,7). The prevalence of vitamin D deficiency/insufficiency in the CF population ranges from 23 % to up to 95 % (3,8,26). Vitamin D is a fat-soluble vitamin that has a known role in the development and maintenance of calcium and bone health (7). In addition to its known bone role, vitamin D may have anti-inflammatory properties, immune function and immune system actions with an antioxidant role (8,9,10).

In view of the immunomodulating role of vitamin D, it is relevant to assess the status of vitamin D in these patients and the possible association of serum levels with markers of oxidative stress and inflammation. Thus, the aim of the study was to assess the prevalence of vitamin D insufficiency/deficiency and to verify its association with markers of inflammatory status and oxidative stress in patients with cystic fibrosis.

METHODS

TYPE OF STUDY AND CASUISTRY

A cross-sectional study with a sample of patients diagnosed according to the criteria of the Cystic Fibrosis Foundation (11). Two important centers of reference in the treatment and monitoring of patients with CF were part of this research: the University Hospital Lauro Wanderey (HULW), located in João Pessoa, PB, the largest of the two centers located in the state of Paraíba, and the Integral Medicine Institute Professor Fernando Figueira (IMIP), located in Recife, PE, the only center of its type located in the state of Pernambuco.

A probabilistic sample value was obtained by the allocation method proportional to the stratum size (12), identifying two strata with different finite populations for the calculation: João Pessoa-PB and Recife-PE. The percentages, as well as the population size of the extracts, were chosen taking into account the population of CF patients in Brazil in 2016, and the distribution by regions listed until the beginning of the study in the latest edition of the document (13). The chosen margin of error was 4.5 %. In order to correct any losses, an increase by 10 % was made, resulting in a sample size calculation of at least 38 patients for a significant representation of this population.

Patients older than 5 years of age with a diagnosis of CF who were under outpatient follow-up at the two hospitals were invited. Patients with indication for or undergoing lung transplantation, with pulmonary exacerbation and/or with renal or hepatic dysfunction were not included. After inclusion and exclusion criteria, data from 48 patients were collected.

Data were collected between August 2018 and December 2019 after the parents or guardians of children and adolescents and the adults signed the Informed Consent Form (FICF) and the Informed Consent Term (TALE, in Portuguese), in compliance with Resolution 466, of December 12, 2012 of the National Health Council (14). The study was previously approved by the ethics committee of the two institutions with the CAE number 87354018.1.0000.5183 and CAE number 12994619.6.1001.5201, respectively.

ASSESSMENT OF CLINICAL, SOCIAL AND NUTRITIONAL FACTORS

The patients were interviewed through a previously structured questionnaire for clinical and nutritional evaluation, through an interview using a previously elaborated form.

The skin phototype was classified from I to VI, as proposed by Fitzpatrick (15), where the patient was asked about the description of their skin, whether it burns easily, rarely, or never, and also about its sensitivity to the sun, ranging from slightly sensitive to very sensitive. With this information, the skin phototype was classified ranging from white (I) to black (VI).

Participants were weighed on a digital anthropometric scale, with the patient standing upright in the center of the equipment, with his back to the scale, feet together, barefooted, wearing light clothing, and arms extended along the body. To measure the height of the patients they were placed in an orthostatic position, in respiratory apnea, barefooted, with no head decorations. The measurement was read by touching the cursor to the highest point of the head at the end of an inspiration. Ideally, they had to touch the heels, calves, buttocks, scapulae, and back of the head to the stadiometer. When it was not possible to touch these five points, they had to place at least three of them against the stadiometer (16). The classification of nutritional status was performed using the indicators weight/age, BMI/age and height/age, evaluated according to the WHO-2006/2007 curves for patients aged 5 to 18 years (17). For the classification of adult patients (over 18 years and under 60 years), the values proposed by the World Health Organization were used (18).

Vitamin D intake was assessed by applying a 24-hour recall with all participants and a second recall with 40 % of the population studied (19), keeping a minimum period of 30 and a maximum of 45 days between the application of a recall and the next one. Vitamin D intake was calculated using the Virtual Nutri plus software. The residual nutrients method (MSM) (20) was used to control the effect of intrapersonal energy consumption in the evaluation of micronutrients.

BIOCHEMICAL COLLECTION AND ASSESSMENT

Approximately 20 ml of blood were collected from patients fasting for 8 to 12 hours, informed in advance by a trained team at each pole. Serum levels of 25-hydroxyvitamin D (25(OH)D), parathyroid hormone (PTH) and calcium were measured by chemiluminescent immunoassay (Liaison XL Diasorin). The classification of vitamin D levels was performed based on the reference values used by the Cystic Fibrosis Foundation (12) — sufficient levels above 30.0 ng/mL, insufficient 25(OH)D levels below 30.0 ng/mL, and deficiency below 20.0 ng/mL.

Inflammatory markers (ultra-sensitive C-Reactive Protein (US-CRP), alpha-1-acid glycoprotein [A1GPA]) were analyzed by the immunochemical method of turbidinomotry. For oxidative stress, the analysis was through the evaluation of an oxidizing marker, malondialdehyde (MDA), analyzed by the thiobarbituric acid reaction method (TBARS) (21), and total antioxidant capacity (CAOT), analyzed by the DPPH method (22). Tests were also performed to assess liver function (alanine transaminase [ALT], aspartate transaminase [AST]), renal function (urea, creatinine, uric acid), in order to evaluate patients regarding inclusion criteria.

STATISTICAL ANALYSIS

A descriptive analysis of all study variables was performed, data were analyzed using the Statistical Package for Social Sciences for Windows, version 22.0 (SPSS Inc., Chicago, IL). All data were checked for normal distribution using the Kolmogorov-Smirnov test. To assess the existence of possible differences between the means of patients according to vitamin D status, Student's T-test or the Mann-Whitney test were used.

Simple linear regression analyses were performed to identify the variables associated with serum 25(OH)D levels to develop the multiple linear regression model, which also included variables that, despite not having associations, have an association already reported in the literature (8,9). The existence of colinearity between the explanatory variables was assessed. Throughout the study, tests whose p-value was less than 0.05 were considered significant.

RESULTS

This study evaluated 48 patients who met all the inclusion criteria, 26 of whom were male (54.2 %). Among these individuals, 56.4 % were adolescents, followed by 27.1 % of children between 5 and 10 years of age and 16.7 % of adults between 20 and 45 years old. The mean age of the studied group was 14.85 ± 7.04 years and 62.5 % reported < 30 minutes of sun exposure per day. The majority of the research population (54%) declared themselves to be of mixed race (n = 26) or (31 %) white (n = 15) (Table I). As for the use of vitamin supplementation, only 35.4 % (n = 17) reported using some vitamin supplementation according to medical prescription, and 3 participants used vitamin D daily (800 to 2000 IU/day). Regarding nutritional status, more than 40 % of patients were considered to have a low-weight nutritional status.

Vitamin D insufficiency/deficiency was observed in 64.6 % (n = 31) of patients, and there was no statistically significant difference between genders and age groups. As for the dietary intake of vitamin D, the participants consumed an average of 4.80 ± 2.15, with no difference between the sufficiency and hypovitaminosis D groups (p = 0.81). Vitamin D levels were grouped into two classes: sufficient (25(OH)D ≥ 30 ng/mL) and insufficient/deficient (25(OH)D < 30 ng/mL). Mean serum 25(OH)D levels were 33.84 ± 3.10 ng/mL in the sufficient group, and 22.41 ± 5.0 ng/mL in the vitamin D insufficiency/deficiency group. No significant differences were found between anthropometric parameters, skin phototype, exposure time, serum calcium levels and consumption, inflammatory markers and oxidative stress with nutritional status of vitamin D (insufficient/deficient or sufficient) (Tables II and III).

Table I. General characteristics of and vitamin D status in patients with cystic fibrosis in northeastern Brazil

Characteristics	Total
n (%)	
Number of patients	48
Gender	
Female	22 (45.8)
Male	26 (54.2)
Color	
Mixed race	26 (54.2)
Black	7 (14.6)
White	15 (31.3)
Others	0 (0)
Degree of education of persons responsible	
Illiterate	1 (2.1)
Elementary School	19 (40.4)
High School	18 (38.3)
≥ Graduation	9 (19.2)
Skin phototype	
Type 1	5 (10.4)
Type 2	9 (18.8)
ype 3	17 (35.4)
Type 4	8 (16.7)
Type 5	5 (10.4)
Type 6	4 (8.3)
*Status of 25 OH D**	
Sun exposure	
< 30 minutes/day	30 (62.5)
> 30 minutes/day	18 (37.5)
25 (OH) D status	
Vitamin D insufficient/deficient, < 30ng/mL	31 (64.6)
Sufficient vitamin D, ≥ 30 ng/Ml	17 (35.4)

*Data presented in number (n) and percentage (%). *Parameters adopted from Cystic Fibrosis Foundation (18). 25(OH)D: 25-hydroxyvitamin D.*

Table II. Association between 25(0H)D status and metabolic parameters in patients with cystic fibrosis treated in northeastern Brazil

Serum 25-hydroxyvitamin D concentrations				
	Total of variables n = 48	**Insufficient/Disabled† n = 31**	**Enough† n = 17**	**p***
Age (years)	14.85 ± 7.04	14.53 ± 7.89	15.03 ± 6.61	0.82
Time of sun exposure (minutes/day)	45.2 ± 57.32	48.10 ± 64.33	39.41 ± 42.89	0.54
Vitamin D consumption (mcg)	4.80 ± 2.15	4.400 ± 8.43	5.03 ± 8.74	0.81
Calcium consumption in mg	1096.80 ± 736.87	10077 ± 638.99	1107.21 ± 7995.00	0.89
Serum calcium (mg/dL)	9.52 ± 0.51	9.50 ± 0,65	9.53 ± 0.42	0.85
PTH (mg/dL)	46.17 ± 25.75	44.84 ± 30.46	46.89 ± 23.41	0.80
CRP (mg/dL)	11.25 ± 17.69	11.31 ± 16.40	11.20 ± 18.62	0.98
A1GPA (mg/dL)	115.5 ± 47.47	115.97 ± 50.66	114.21 ± 46.48	0.93
MDA (µmol/L)	3.71 ± 0.92	3.425 ± 0.60	3.870 ± 1.03	0.72
CAOT (%)	18.7 ± 8.47	18.46 ± 8.97	19.25 ± 8.32	0.77

*Data presented as mean ± standard deviation. *Significant p with $p < 0.05$. †Parameters based on Cystic Fibrosis Foundation (18). A1GPA: alpha 1 acid glycoprotein; CAOT: total antioxidant capacity; MDA: malondialdehyde; CRP: C-reactive protein; PTH: parathyroid hormone. T-test or its non-parametric Mann-Whitney match.*

Table III. Multiple linear regression model to predict serum 25(OH)D levels

Variables	Coefficient	p	r^2
Model 1			
Serum calcium	2.395	0.28	0.179
MDA	-3.318	0.14*	
CAOT	-0.150	0.23	
CRP	3.651	0.57	
Model 2			
Serum calcium	1.465	0.66	0.128
MDA	-3.019	0.04*	
CAOT	-0.109	0.40	
A1GPA	0.034	0.25	
Model 3			
Serum calcium	0.841	0.69	0.098
MDA	-2.053	0.84	
CAOT	-0.134	0.30	

*Multiple linear regression models. The variables age and gender, height and gender were inserted as confounding variables to adjust the linear regression models. *Significant value, p-value < 0.05. Dependent variable: A1GPA: alpha 1 acid glycoprotein; CAOT: total antioxidant capacity; MDA: malondialdehyde; CRP: C-reactive protein; 25(OH)D: 25-hydroxyvitamin D.*

When performing multiple regression analysis to estimate the association of variables with serum 25(OH)D levels, variables with associations reported in the literature were considered. Variables were adjusted for gender and age. The variable BMI showed multicolinearity and was removed from the model, and the variables A1GPA and CRP were analyzed in different models for also presenting multicolinearity (> 0.800). Sun exposure values were not included in the model due to the presence of outliers. MDA levels showed a negative association with serum 25(OH)D levels when associated in the model with the inflammatory process markers CRP ($p = 0.14$) and A1GPA ($p = 0.40$). When evaluated without the presence of inflammatory markers, this association did not remain ($p = 0.84$).

DISCUSSION

Individuals with CF have difficulty maintaining vitamin D status due to malabsorption induced by pancreatic insufficiency, low sun exposure, and insufficient intake of vitamin D-containing foods (23). The present study found a high prevalence of vitamin D insufficiency/deficiency. The study (11) investigated 45 patients with CF in the São Paulo region regarding the association of vitamin D levels, and observed a percentage of 43.56 % of hypovitaminosis D in children and preschool children. Similar data (24) were collected in the state of Rio Grande do Sul, where the authors evaluated 37 children and adolescents with cystic fibrosis, finding a prevalence of 54 %. They also found 59 % ($n = 35$) of adults with CF with less than ideal levels of 25 hydroxyvitamin D (25). Therefore, based on these previous data, we can classify the prevalence of the present study as HIGH.

In addition to decreased intestinal absorption, poor nutritional intake and poor adherence, other factors that contribute to vitamin D deficiency in CF include decreased outdoor activity and exposure to sunlight (23). Northeastern Brazil has a sunlight exposure for most of the year that is more accentuated than in the regions already studied, which could positively favor the maintenance of serum vitamin D concentrations, but this study showed that the fact of living in a sunny region was not enough to have adequate levels of vitamin D. Although sun exposure is an influencing variable in vitamin D status, results still diverge in studies on other populations in sunny locations (26,27). In the CF population (27) an association of vitamin D status with sun exposure was shown in the last 3 years, counteracting our results. Thus, studies are suggested to standardize the time of assessment of sun exposure and its association with characteristics such as pathophysiology, season of the year, and skin phototype.

Inflammation is an important contributor to CF disease progression, and anti-inflammatory therapies can improve clinical outcomes (4-10). The resulting chronic infection and airway inflammation can lead to progressive lung destruction, increasing the severity of the disease(28). In the present study, it was possible to observe that, although the relationship between the inflammatory character of CF and the association of inflammation with hypovitaminosis is already known, in this study patients with CF showed no differences between the group with vitamin D sufficiency and insufficiency, but it did influence the marker of oxidative stress MDA in the multivariate analysis. A study in CF respiratory epithelial cells showed that the active form of vitamin D, 1,25 dihydroxyvitamin D, significantly reduced inflammatory cytokines (IL-6 and IL-8) stimulated by antigens (29). A double-blind (12), controlled clinical trial with 30 adults with CF pulmonary exacerbation used a single vitamin D3 megadose for 12 weeks. After 12 weeks in the supplemented group there was a trend towards a reduction in IL-6 and TNF-α, but not in the other interleukins evaluated.

Chronic infection and common inflammation in CF patients generate an increase in reactive oxygen species and thus an increase in oxidative stress (2,30,31) playing a role in the progression of lung damage in these individuals (6). Our data indicate the role of inflammation in oxidative stress, since the association of MDA was significant in multivariate models, when associated with the inflammatory process markers evaluated in this study. Larger studies with a greater number of inflammatory and oxidative stress markers are needed to test this hypothesis and the anti-inflammatory and antioxidant role of vitamin D.

Only one (1) study was found evaluating MDA as a marker of lipid peroxidation in CF patients. Lezo and collaborators (2) investigated oxidative stress in 70 patients with CF aged 1 to 18 years. The study evaluated whether supplementation with antioxidant vitamins (A, C and E) can be tailored to individual needs and oxidative status. Oxidative stress markers, lipid 4-hydroxynonenal (HNE-L) and MDA, had an inverse relationship with antioxidant vitamins, particularly vitamin C. No studies were found evaluating the role of vitamin D and oxidative stress in this population.

This is a pioneering study in finding an association between vitamin D levels and markers of oxidative and inflammatory stress in CF patients. However, this claim needs to be validated through further research. The main limitation of our study is the restricted number of oxidative and inflammatory stress markers analyzed. Furthermore, the association found was weak, increasing the need for further studies. Another limitation was that the study was cross-sectional, which could infer causality for the outcome (vitamin D deficiency).

Our study has interesting implications for the scientific community and clinical practice by demonstrating a high prevalence of hypovitaminosis D in patients with CF, a treatable condition that should be better monitored and whose treatment should focus on maintaining serum vitamin D levels within normal levels. The results suggest that further studies should be carried out in order to verify whether the treatment of hypovitaminosis D is able to reduce the classic oxidative stress that normally affects patients with CF.

CONCLUSION

We conclude that most CF patients have insufficient vitamin D levels and that hypovitaminosis D was associated with greater oxidative stress when associated with inflammatory markers. We suggest greater attention should be paid to vitamin D levels and more clinical studies should be performed for a possible role of correcting vitamin D status in improving common oxidative stress in these patients.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Pediatría

Assessment of nutrient intakes of children and adolescents with recessive dystrophic epidermolysis bullosa, severe subtype

Evaluación de la ingesta de nutrientes de niños y adolescentes con epidermólisis bullosa distrófica recesiva, subtipo severo

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Abstract

background and aims: epidermolysis bullosa (EB) is a rare disease presenting with skin fragility and formation of blisters. Constant presence of skin lesions, loss of blood, wastage of heat through the open skin, increased turnover of proteins and infections, result in increased energy, protein, and micronutrient needs. This study investigated the intake adequacy of energy, protein, zinc, iron, and dietary fiber in children with epidermolysis bullosa.

Methods: this cross-sectional, analytical study was conducted with children and adolescents of up to 18 years of age with recessive dystrophic EB, severe subtype. Demographic data and clinical manifestations affecting food consumption were collected. Nutritional assessment was performed through anthropometric data. We used a formula to estimate specific energy needs for EB, and ratio of skin lesions was also evaluated to assist in estimating energy needs. A protein adequacy of 115 % to 200 % of the Recommended Dietary Allowance was considered for the adequacy of protein intake. And the Dietary Reference Intake tables according to sex and age were used as a reference for micronutrients. Intake assessment was performed using seven consecutive daily food records. Sip feed consumption was considered for intake assessment.

Results: all patients showed undernutrition and presented at least three clinical symptoms that affect food consumption: pseudosyndactyly, microstomy, and blisters in the oral cavity. Sip feed constituted between 20 % and 50 % of the patients' energy intake. Intake of iron and zinc was adequate for most patients (confidence of adequacy ≥ 0.85), while fiber intake was below the reference value.

Conclusions: this study underscores the importance of nutritional monitoring for EB patients, which is often interpreted as a skin disease but has enormous nutritional repercussions.

Keywords:

Epidermolysis bullosa. Nutrient intake. Iron. Zinc. Protein.

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Resumen

Antecedentes y objetivos: la epidermólisis bullosa (EB) es una enfermedad rara que se manifiesta con fragilidad cutánea y formación de ampollas. La presencia constante de lesiones en la piel, la pérdida de sangre, la pérdida de calor a través de la piel abierta, el aumento de la pérdidas de proteínas y las infecciones hacen que aumenten las necesidades de energía, proteínas y micronutrientes. Este estudio investigó la adecuación de la ingesta de energía, proteínas, zinc, hierro y fibra dietética en niños con EB.

Métodos: este estudio analítico transversal se llevó a cabo con niños y adolescentes de hasta 18 años de edad con el subtipo grave de la EB distrófica recesiva. Se recogieron los datos demográficos y las manifestaciones clínicas que afectan al consumo de alimentos. La evaluación nutricional se realizó mediante datos antropométricos. Se utilizó una fórmula para estimar las necesidades energéticas específicas de la EB y también se evaluó la proporción de las lesiones cutáneas para ayudar a estimar las necesidades energéticas. Para la adecuación de la ingesta de proteínas se consideró entre el 115 y el 200 % de la ingesta dietética recomendada. Y como referencia para los micronutrientes se utilizaron las tablas de ingesta dietética de referencia según el sexo y la edad. La evaluación de la ingesta se realizó mediante siete registros diarios consecutivos de alimentos. Para la evaluación de la ingesta se tuvo en cuenta el consumo de suplementos nutricionales.

Resultados: todos los pacientes mostraban desnutrición y presentaban al menos tres síntomas clínicos que afectaban al consumo de alimentos: pseudosindactilia, microstomía y ampollas en la cavidad oral. Los suplementos nutricionales constituían entre el 20 y el 50 % de la ingesta energética de los pacientes. La ingesta de hierro y zinc era adecuada para la mayoría de los pacientes (confianza de adecuación ≥ 0,85), mientras que la ingesta de fibra estuvo por debajo del valor de referencia.

Conclusiones: este estudio destaca la importancia del seguimiento nutricional de los pacientes con EB, que a menudo se interpreta como una enfermedad de la piel pero que tiene enormes repercusiones nutricionales.

Palabras clave:

Epidermólisis bullosa. Ingesta de nutrientes. Hierro. Zinc. Proteína.

INTRODUCTION

Epidermolysis bullosa (EB) is a specific group of rare disorders presenting with fragility of the skin that are characterized by the formation of blisters with disruption of the dermoepidermal junction in response to minimal mechanical trauma (1). The disease affects individuals of both sexes and all racial groups, and an estimated 500,000 people are living with EB worldwide (2). In addition to the cutaneous manifestations, some EB subtypes present extracutaneous manifestations resulting in enhanced morbidity and negative effects on the patient's nutritional status. Recessive dystrophic EB — severe subtype (RDEB-S) is one of the types with the greatest nutritional impact (3), presenting with anemia, growth retardation, and impairment of the gastrointestinal tract, including constipation (4-6).

Patients with RDEB-S present hypercatabolism due the constant presence of skin lesions that increase energy, protein and micronutrient needs (6-8). Blood loss through wounds, chronic inflammation, and iron deficiency result in anaemia in EB (9). Low levels of zinc serum are present in the second year of life and this is associated with low weight in RDEB (9). Zinc levels can be falsely low in hypalbuminaemia, and assessment of zinc intake can be a factor contributing to its interpretation.

Some studies have evaluated the biochemical status of vitamins and minerals in EB with the intention of identifying deficiencies or excesses, both of which are important aspects of nutritional status. Giuseppe et al. evaluated, among other micronutrients, the levels of vitamins B6, B12, and serum folate in 20 children and adolescents with EB (10). Another study conducted exclusively in RDEB patients evaluated plasma levels of iron, calcium, folates, vitamins C, D, B12, A, E, B1, B6, and B2, zinc, selenium, and copper in 14 patients (11). Although biochemical status assessments are essential, monitoring biochemical markers in EB is difficult due to inflammation (9); monitoring nutrient intake becomes important and complementary to identify intake deficiencies and offers the advantage of being a non-invasive approach. In this regard, a few previous studies have evaluated the adequacy of nutrient intake in EB patients. Colomb et al. (12) evaluated energy intake in patients with RDEB, and observed that it was reduced to 56 % ± 18 % of the recommended daily allowance (RDA). Regarding the use of sip feed orally or via gastrostomy, the study by Yellet et al. (13) analyzed vitamin K intake and identified that patients who did not consume at least 200 ml of sip feed/day were at significant risk for deficiency. However, to our knowledge, no study has accurately assessed dietary intake in EB. Therefore, we aimed to investigate dietary intake including sip feed in a group of children and adolescents with RDEB-S to determine their intake adequacy for energy, protein, zinc, iron, and dietary fiber. Additionally, we sought to evaluate the clinical manifestations that may potentially affect food consumption.

MATERIALS AND METHODS

This cross-sectional analytical study evaluated children and adolescents aged up to 18 years with RDEB-S who attended an EB pediatric nutrition outpatient clinic. The individuals with RDEB-S participating in this study represent all patients in the age group followed up at our referral service for EB. Persons with EB are referred to our service by other hospitals or by the Society of EB Patients and Families. Signed informed consent and assent term were obtained from all parents and patients. This study was conducted in accordance with the Declaration of Helsinki (14), and was approved by the Ethics Committee of the Faculty of Health Sciences of the University of Brasília (registration number 1202012).

DEMOGRAPHIC PROFILE AND CLINICAL MANIFESTATIONS THAT AFFECT FOOD CONSUMPTION

The following information was collected from medical records and by using a structured questionnaire: demographic data, food consistency, feeding route, frequency of bowel movements, pain/difficulty in defecating, and presence of dysphagia, odynophagia, microstomy, difficulty in chewing, blisters in the oral cavity, ankyloglossia, gas-

troesophageal reflux, and pseudosyndactyly. EB type was based on previous clinical features and laboratory diagnoses.

RATIO OF SKIN LESIONS OF BODY SURFACE AREA

The ratio of skin lesions of body surface area (%BSA) was used in a formula to estimate energy requirements and was determined by filling a form (Fig. 1) containing a representative image of a person, back and front, that was subdivided into 100 small rectangles, each of which represented 1 % of body surface area. Form filling was performed at the time of dressing change. Parents and caregivers were instructed to color the areas with infected lesions and non-infected lesions in yellow and pink, respectively. To assess if the skin lesion was infected, the presence of some of the following signs was verified (15): 1) it becomes more painful, instead of gradually improving; 2) looks red around the skin edges, this red area may feel warm or hot; 3). looks swollen; 4) secretion of yellow material (pus), which may be smelly. The calculation of %BSA was carried out by the main researcher and was based on the sum of the areas shaded yellow or pink.

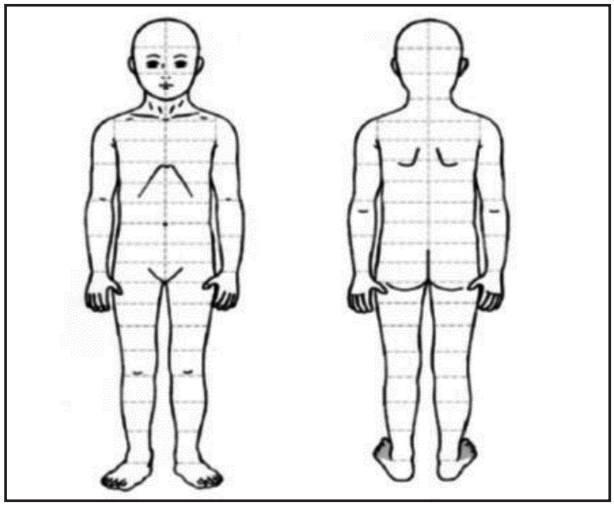

Figure 1.

Guide to calculate the percentage of body surface area with skin lesions (adapted from: Haynes L, 2007 [7]).

NUTRITIONAL ASSESSMENT AND ESTIMATION OF ENERGY AND PROTEIN REQUIREMENTS

Assessment of nutritional status was performed using anthropometric data collected according the World Health Organization (WHO) criteria (16,17). The weight and height of the patients were measured by a trained professional. Length was measured with a horizontal anthropometer 110 cm long and with a 0.1 cm precision; In those patients aged two years or older a vertical anthropometer with an accuracy of 0.1 cm was used. A digital Filizola® scale was used for children younger than 2 years, with a maximum capacity of 15 kg and 10 g of variation. A platform-type Filizola® mechanical scale with a maximum capacity of 150 kg and a variation of 0.1 kg for children with 2 years or more. Due to the conditions of the patients, the dressings were not removed for measurements. In one of the patients, measuring height and weight using conventional methods was not possible due to contractures and dystrophy. Height was obtained with an inextensible millimeter tape, graduated every 0.5 cm, with the participant in the supine position; measures included the distance between the top of the head and hip, then from the hip to the knee, and from the knee to the base of the foot, and then these measurements were added. Weight was determined by measuring the weight of the child on the caregiver's lap, then measuring the caregiver's weight and subtracting the two weights.

For assessment of undernutrition in patients, the WHO indicators for underweight, stunting, and wasting were used (18).

Weight and height measurements were also used with a specific formula for children and adolescents with severe types of EB to determine their energy requirements (Fig. 2) (19). This formula uses current weight, energy for the corrected age, and additional factors such as %BSA, sepsis, and catch-up growth requirement. For %BSA one of the options of predetermined levels was chosen to be inserted in the equation — 0.19 for up to 20 % BSA; 0.5 for up to 40% BSA, and 0.950 for over 40 % BSA. Values 0.1 or 0.2 were used to determine catch-up growth requirements. To determine the degree of sepsis, the sum of the areas colored yellow was performed, and three levels of sepsis were considered with their respective values: mild = 0.2, moderate = 0.4, and severe = 0.8. The values corresponding to each of these factors are added into the formula according to the participant's condition.

To correct age, WHO growth standards (16) were used to identify the age corresponding to height in the 25th percentile for each participant. Subsequently, the amount of calories was determined from the tables of the Food and Agriculture Organization of the United Nations (FAO) according to sex and corrected age (20).

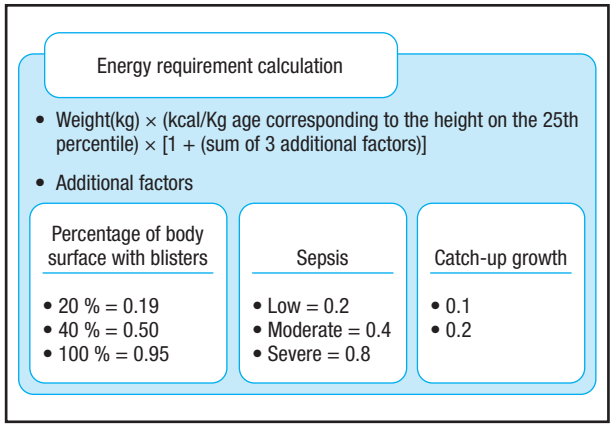

Figure 2.

Formula to estimate the energy requirements of children and adolescents who had severe types of EB or were at nutritional risk (adapted from: Birge K, 1995 [19]).

The protein requirement for patients was established within a percentage range of 115 %-200 % of the RDA according to sex and age (21). This percentage range is recommended for children and adolescents with EB (7).

INTAKE ASSESSMENT OF ENERGY, PROTEIN, ZINC, IRON, AND DIETARY FIBER

Seven consecutive daily food records (22) were used to determine the mean intake. The data were recorded by parents/caregivers. Comprehensive written instructions were given to parents/caregivers by trained professional, combined with face-to-face explanations to improve the quality of data for consumption of both solid, pasty, and liquid foods. For better control of effective food records, trained professional made telephone contacts on alternate days to clarify any doubts. Patients who used sip feeds were instructed to record them. And at the end of the registration period a trained professional reviewed the registration with parents/caregivers to clarify possible omissions and ambiguities, to probe for additional information, and to make any necessary changes. The intake of energy, protein, zinc, iron, and dietary fiber for each patient was calculated by the main researcher using the NutWin software (18). Food and sip feed that did not appear in the database were added by evaluating the food composition table (23) and food labels, respectively. Mean intake was determined by measuring the 7-day arithmetic mean.

We used the dietary reference intake (DRI) values (24) to evaluate the long-term mean nutrient intake described in the previous paragraph. For energy intake, we considered that children and adolescents with EB must consume an adequate amount of calories to facilitate healing and growth processes; thus, energy intake below the values calculated using the Birge formula was considered inadequate (19). For evaluation of protein intake, values within or above the reference range for EB patients (7) were interpreted as adequate intake, and values below the range were interpreted as deficient.

The estimated average requirement (EAR) was calculated for zinc and iron according to age and gender. For dietary fiber, we considered the adequate intake (AI) value since there is no EAR for dietary fiber. To accurately obtain the intake of iron, zinc, and dietary fiber without underestimation or overestimation, we considered a 10 % variability in the needs, and accounted for intrapersonal variability in nutrient intake based on the values provided in tables that estimate within-subject variations in intake. These values were obtained from a document issued by the Institute of Medicine, which provides guidance for application of DRIs in dietary assessment (24).

Using the variability values, the mean intake values, and the values for requirements (EAR/AI), as well as the adequacy of nutrient intake and the confidence of results, were determined. To calculate the adequacy of dietary fiber the AI was used and the 10 % variability in requirements was not considered, since AI represents the intake of a group and not a requirement. Confidence values equal to or above 0.85 were considered a low probability of inadequate intake. Notably, for dietary fiber intake values below the AI intake inadequacy could not be determined. We also determined the contribution of sip feed to the intake of energy, protein, zinc, and iron for each patient.

RESULTS

Seven patients with RDEB-S were evaluated in this study. All patients were diagnosed with undernutrition and five presented infected skin lesions. With respect to the clinical symptoms that affected food consumption, all participants presented at least three symptoms, namely, pseudosyndactyly, microstomy, and pain/difficulty in evacuation. Bowel movements were irregular in four patients, of which three patients reported defecation frequencies of 3 to 7 days whereas the fourth reported a defecation frequency over 7 days. All patients received only oral diets, and the consistency of their diets varied from liquid to normal (Table I). All patients completed the 7-day food record, and no meals were eaten away from home during the period. Due to their EB, the patients have an accompaniment at school, which could be their parents or a caregiver, which facilitated the registration. From our group of patients, the two newer ones, aged 1 year and 3 months and 3 years and 10 months, respectively, and the oldest participant were not attending school. Table II presents the individual values for energy and protein intake. To calculate energy requirement a value of 0.2 was considered for the catch-up growth item of all subjects, since all patients had low weight and/or short stature and needed a greater caloric intake to improve their nutritional status. While most patients had adequate protein intake, energy intake, in general, was inadequate. The use of sip feed, which accounted for 40 % to 50 % of their daily requirements, allowed only patients F01 and F04 to achieve adequacy of energy intake.

Most patients showed fiber intake below the AI (Table III), and only one participant showed low probability of inadequate intake (participant F03; 27.1 g). The intake of iron and zinc was adequate in most patients (confidence of adequacy: 0.98). The sip feed represented 20 % to 50 % of the patients' energy intake, 29 % to 57 % of their protein intake, 38 % to 75 % of their iron intake, and 42 % to 87 % of their zinc intake (Tables II and III). Notably, patient M02, who was the oldest participant, showed the maximal infection (%BSA, 15 %), wasting, deficient intake of energy, protein, and zinc, as well as no use of sip feed.

The adequacy of iron, zinc, and dietary fiber intake for two patients between 1 and 3 years of age was determined without considering intrapersonal variability in nutrient intake; as a result, the confidence values for this comparison could not be determined. This is because there is no variability in nutrient intake values available for this age group in DRIs.

Table I. Food consistency, clinical manifestations that affected food consumption, stool frequency, and pain/difficulty in evacuation in children and adolescents with recessive dystrophic epidermolysis bullosa, severe subtype

Patient	Age	Anthropometric nutritional assessment	% BSA with skin lesions	Total % BSA (skin lesions + infected)	Food consistency	Pseudosyndactyly	Microstomy	Difficulty in chewing	Oral cavity blisters	Ankyloglossia	GOR	Stool frequency	Pain/ difficulty in evacuation
F01	15 y, 6 m	Wasting	18 %	23 %	Liquidy-pasty	+	+	+	+	+	+	1 day	+
F02	3 y, 10 m	Stunting	14 %	17 %	Normal	+	+	-	-	-	-	2 days 3-7 days	+
F03	12 y, 10 m	Wasting	25 %	29 %	Normal	+	+	-	+	+	-	1 day	+
F04	9 y, 4 m	Stunting	19 %	19 %*	Normal	+	+	-	+	-	-	1 day	+
F05	1 y, 3 m	Stunting	10 %	13 %	Liquid	+	+	+	+	-	-	Intervals 3-7 days	+
M01	12 y	Underweight	20 %	20 %*	Pasty	+	+	-	+	+	-	2 days 3-7 days	+
M02	18 y, 11 m	Wasting	0 %	15 %	Pasty	+	+	+	+	+	-	Over 7 days	+

**All % BSA is non infected. F: female; M: male; y: years; m: months; % BSA: the ratio of skin lesion of body surface area; +: present; -: absent; GOR: gastroesophageal reflux.*

Table II. Adequacy of energy and protein intake, and the percentage provided by sip feed in children and adolescents with recessive dystrophic epidermolysis bullosa, severe subtype

Patient	Age	Energy				Protein			
		Mean intake (kcal/day)	Requirement (kcal/day)	Qualitative assessment	% Intake from sip feed	Mean intake (g/day)	Requirement† (g/day)	Qualitative assessment	% Intake from sip feed
F01	15 y, 6 m	1584	1567	Adequate	40	70	53 to 92	Adequate	35
F02*	3 y, 10 m	581	1436	Deficient	NA	32	15 to 26	Adequate	NA
F03	12 y, 10 m	2205	2307	Deficient	30	106	39 to 68	Adequate	39
F04	9 y, 4 m	2293	1899	Adequate	50	96	39 to 68	Adequate	57
F05	1 y, 3 m	886	941	Deficient	20	25	15 to 26	Adequate	29
M01	12 y	1647	2342	Deficient	44	70	39 to 68	Adequate	37
M02*	18 y, 11 m	1531	3156	Deficient	NA	52	60 to 104	Deficient	NA

*F: female; M: male; y: years; m: months; kcal: kilocalories; g: grams; NA: not applicable. *Participant did not use sip feed. †115 %-200 % of the recommended dietary allowance/DRI (EB requirement).*

Table III. Adequacy of iron, zinc, and dietary fiber intake, and quantities provided by sip feed in children and adolescents with recessive dystrophic epidermolysis bullosa, severe subtype

Patient	Age	Iron				Zinc				Dietary fiber		
		Mean intake (milligrams)	Confidence of adequacy	Qualitative assessment of intake	% Intake from sip feed	Mean intake (milligrams)	Confidence of adequacy	Qualitative assessment of intake	% Intake from sip feed	Mean intake (grams)	Confidence of adequacy	Qualitative assessment of intake
F01	15 y, 6 m	16.8	0.98	Adequate	66	12.2	0.98	Adequate	87	15.3	0.85	<AI
F02*	3 y, 10 m	2.4	NA	Inadequate	NA	3.5	NA	Adequate	NA	4.1	NA	<AI
F03	12 y, 10 m	23.4	0.98	Adequate	57	25.7	0.98	Adequate	75	27.1	0.50	Low probability of inadequate intake
F04	9 y, 4 m	25.2	0.98	Adequate	74	30	0.98	Adequate	85	8.9	0.85	<AI
F05	1 y, 3 m	5.4	NA	Adequate	38	4.8	NA	Adequate	42	8.5	NA	<AI
M01	12 y	17.1	0.98	Adequate	75	12	0.93	Adequate	69	15.1	0.85	<AI
M02*	18 y, 11 m	11.7	0.85	Adequate	NA	6.6	0.85	Inadequate	NA	12.4	0.85	<AI

*F: female; M: male; y: years; m: months; AI: adequate intake; <AI: less than the AI (adequacy of intake cannot be determined); NA: not applicable. *Participant did not use sip feed. None of the patients used fiber supplements.*

DISCUSSION

Nutritional management is an essential component of long-term treatment for children and adolescents with RDEB-S, especially due the elevated risk of nutritional compromise. Adequate intake of energy, proteins, and trace elements is essential for growth, wound healing, and optimal immunity (11,25). Our results suggest that clinical manifestations that affect food consumption have a great impact on nutrient intake, and the use of sip feed can be a key management strategy to achieve nutrient intake adequacy and the primary nutritional approach to be employed in children with RDEB-S who are at nutritional risk.

To our knowledge, this is the first study to apply seven-day food records to establish the nutrient intakes in people with EB. This method is useful since the foods are noted at the time of consumption; records are not dependent on memory; and the types of food, preparations consumed and mealtimes are identified (26). The Institute of Medicine's documentation for the use of DRIs in dietary assessment of individuals highlights that data obtained over a greater number of days will yield more reliable results (24).

The factors that were shown to principally affect food consumption in the present study were similar to those reported in other studies. Food intake has been reported to be influenced by clinical manifestations such as oral and esophageal blisters, followed by scars that result in microstomy, ankyloglossia, and esophageal stenosis (4,6,25,27). In our study, the main factors that affected food intake were pseudosyndactyly, which impaired the ability to hold food and handle cutlery; microstomy, which makes it difficult to open the mouth; and blisters in the oral cavity, which caused discomfort, pain, and bleeding when chewing food. In the present study, all patients were fed orally since well-defined protocols for gastrostomy insertion in patients with EB have not been proposed in some countries. This factor may have played a decisive role in the patients' inability to meet their nutritional needs. Notably, the feeding route to be adopted in these patients should aim to mitigate clinical symptoms and ensure an adequate supply of energy, nutrients, and dietary fiber. Haynes (28,29) reported that nutritional sip feed with high energy and high protein content can be used in EB patients when natural food does not meet their nutritional needs; however, those studies also noted that the most compromised patients may be incapable of maintaining a satisfactory nutritional status despite efforts to maximize oral intake, needing enteral feeding. A study conducted at a referral center in Paris (12) found catch-up growth in children who received an average of 180 % of the RDA for protein intake through gastrostomy. A systematic review (30) evaluated the effectiveness of gastrostomy and concluded that it is a viable and safe alternative to improve the nutritional status and quality of life of patients with EB.

Energy intake is an important variable that interferes with protein balance, since insufficient energy intake can force the body to use the protein pool as an energy source (31,32). Patients with EB have greater protein requirements than their healthy peers due to the major loss of proteins through their skin lesions, the

constant need for skin synthesis, and recurrent infections (33). Moreover, patients with RDEB-S are usually undernourished, as observed in the present study, and need more energy (7); in these patients, any deficit in energy intake in comparison with the protein-energy requirements may result in an increase in catabolism (8). The high values of %BSA with skin lesions indicate an increase in energy-protein requirements. We can raise some hypotheses with results of energy and protein intake: 1) considering that the currently protein recommendation for EB is reliable: diet (food and sip feed) ensured sufficient protein intake in these patients; however, did not provide enough energy, and protein intake is used to produce energy; 2) the protein recommendation that currently exists for children and adolescents with the most severe types of EB does not represent the real need, because these needs are difficult to establish due to variation in the extent and inflammation of lesions on a daily basis. Is a greater supply of protein necessary?

Difficulty was observed in the application of the specific formula to estimate the energy needs of patients since the interpretation of the items sepsis and catch-up growth is somewhat subjective. It is important to highlight that the term infection might be more appropriate to be used in the equation rather than the term sepsis; however, we decided to keep the name as in the original formula. Other more relevant situation is that establishing the energy and protein needs of children and adolescents with EB seems to be the biggest challenge, due to the interaction between the increase in nutritional needs, the emergence of clinical manifestations that affect food consumption, and the need for catch up growth. All these factors change constantly, and energy and protein requirements also change over a period depending on all these factors. A point that deserves further studies in EB is assessment of the individual's energy needs related to their mobility. It is well known that in some neurological diseases such as stroke, and musculoskeletal diseases such as arthritis changes in mobility occur (34). Efficient mobility is designed to minimize energy expenditure (35); however, in people with RDEB mobility difficulties are observed (36), which may be an indication of an increase in energy requirements. The formula for estimating the specific energy requirement for EB (19) does not consider mobility. Skin fragility, pain, joint contractures, fibrosis and fatigue are some of the many factors that contribute to changes in mobility in this population (37,38) and may impact energy requirements.

Iron and zinc are micronutrients that deserve special attention in EB, since their deficiency can increase susceptibility to infections and contribute to poor wound healing (39). In a study of seventy-three patients with several types of EB that included evaluations of the plasma levels of ten micronutrients, low levels of iron and zinc were found in those with junctional EB and RDEB. Ingen-Housz-Oro et al. (11) also reported iron and zinc deficiencies in a study of 14 RDEB patients. A retrospective study (9) that described the natural history of growth and anemia in children with EB identified low serum levels of iron and zinc between patients shows anemia in 91 % of RDEB patients and zinc deficiency in 55 % of RDEB patients. In this same study, significant positive correlations were found between weight in RDEB and levels of zinc and iron, which reinforces the need for monitoring nutrient intake and early intervention to minimize the impact of these deficiencies on growth.

It is known that the intestinal absorption of iron from the diet is related to the type of iron contained in the food, therefore the heme form of iron of foods such as meats is better absorbed than the inorganic form of iron found in vegetables and cereals. Children with RDEB in most cases have missing or malformed teeth, difficulty in chewing, ankyloglossia, esophageal stenosis, and fragility in the oral mucosa (40), and consequently meat is difficult or impossible to chew and swallow (28); therefore intake of heme iron from meats is scarce. In addition, malabsorption occurs as a result of severe recurrent denudation of the small intestine (4). In the present study, the intake of iron and zinc was adequate in comparison with the EAR for most patients, and this adequacy could be primarily attributed to sip feed. Thus, adequate assessment of the intake of these nutrients, as performed in the present study, is periodically recommended for show if the EAR is being reached and help establish the best supply of micronutrient to help minimize deficiencies. And must be associated with the periodic evaluation of biochemical tests.

Dietary fiber is also a prominent component for the management of RDEB-S patients (7,28,29). Constipation is a common clinical manifestation of EB and has been reported in all disease types, especially in RDEB (40 % to 75 % of cases) (6). Frequently, constipation is observed (4) in children/adolescents with different EB types that require laxatives and dietary fiber supplementation. In our study, most patients showed dietary fiber intake bellow AI, and none of them reported fiber supplement intake. In general, the consumption of fiber-rich food may be reduced because of the clinical manifestations that affect chewing and swallowing, as in the case of patients with EB. Thus, fiber supplements may be considered in these patients.

It can be difficult to obtain reliable anthropometric measurements from people with physical limitations and children with rare diseases who have inability to stand, contractures, scoliosis, lack of head and trunk control, among other reasons. An example is ankylosis and contractures of the lower limbs present in epidermolysis bullosa. We confirm in the present study that anthropometric measurements of weight and height in RDEB-S children represent an activity that requires a trained team, depending on the physical situation, and an alternative method of measurement may be necessary. In this study, to minimize potential errors in measurements, the same evaluator and the same equipment were used throughout.

At the time of data collection, our EB service was at the beginning of its structuring. Patients and family members contributed a lot to the team's learning. In this study, the form filling used to identify %BSA with skin lesions was performed by parents/caregivers. In EB and other rare diseases, many health professionals are not knowledgable of the disease and therefore, in many cases patients and their families have in-depth knowledge about their health care and treatment. According to the International Consensus on Skin and Wound Care in EB (37), people with EB and their caregivers are experts in the management of their condition and their involvement is paramount.

The present study had some limitations that require consideration. These include the small number of patients, a cross-sectional design that precluded cause-and-effect evaluations, and the non-inclusion of socioeconomic variables that may interfere with food consumption. Regarding the small number of subjects, it is important to note that EB is a rare disease and the real number of people with the disease in the world remains unknown. Only a few countries have adequate epidemiological data. In the United States, the incidence and prevalence of EB were estimated at 19.57 and 11.07 per million individuals, respectively. There are no epidemiological data about the incidence and prevalence of EB in Brazil; however, DEBRA-Brazil (Epidermolysis Bullosa Research Association of Brazil) has a record of more than 900 Brazilian patients. This number is likely to be significantly higher, considering the underdiagnosis of the disease and the lack of notification of new cases, especially in a country with continental dimensions like Brazil (41). Because our health EB service was still structuring at the time of study collection, some procedures that are currently routine for people with EB were not performed, such as wide and periodic biochemical evaluations and an esophagogram when stenosis is suspected. Regarding iron and zinc, we recognize that the absence of biochemical testing limits the assessment of micronutrient deficiencies. Therefore, we show the intake adequacy of these micronutrients by comparing to DRI. Although the method used in this study to assess nutrient intake is considered the gold standard to assess nutrient intake, some considerations must be made: the patient may change eating habits and may omit recording certain foods.

Despite the rarity of this genetic disease, and the small sample size and limitations of the services specialized in rare diseases in our country, it was possible to raise several points of discussion that suggest new studies in EB. In conclusion, the nutrient intake in RDEB-S patients in this study was characterized by adequate intake of proteins, iron, and zinc, of which a significant percentage is provided by sip feed. However, fiber and energy intake remained deficient despite the consumption of sip feeds, which could be primarily attributed to the clinical manifestations that affected food consumption. The findings of the present study underscore the importance of nutritional monitoring to assess intake and ensure sufficient nutritional support for patients with this rare disease, which is often interpreted as only a skin disease but has enormous clinical and nutritional repercussions.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Pediatría

Validación de la herramienta de tamizaje nutricional para el cáncer infantil SCAN. Versión en español

Validation of the nutritional screening tool for childhood cancer SCAN. Spanish version

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Resumen

Introducción: la prevalencia de la desnutrición en la población con cáncer infantil puede variar notablemente, elemento que influye de manera significativa en el desenlace clínico de los pacientes. No obstante, este es un factor pronóstico potencialmente modificable y para ello se requiere una identificación del riesgo nutricional oportuna que oriente el proceso de cuidado nutricional.

Objetivo: evaluar el rendimiento operativo de la versión en español de la escala de tamización nutricional para el cáncer infantil (SCAN-SP) en el marco del proceso de validación del instrumento en un hospital de alta complejidad en la ciudad de Bogotá, Colombia.

Métodos: se siguió el diseño metodológico para la validación de una escala diagnóstica. La muestra final fue de 96 pacientes entre los 0 y 17 años con cáncer y hospitalizados en el Centro de Cáncer Infantil de la Fundación HOMI en Bogotá. A cada paciente se le aplicó la SCAN-SP y también se le realizó una valoración nutricional completa (VNC) tomada como patrón de referencia para conocer su estado nutricional.

Resultados: el 82,3 % (n = 79) de los pacientes fueron clasificados como "con riesgo de desnutrición" por la SCAN-SP y el 69,8 % (n = 67) del total de la muestra estaban realmente desnutridos. La evaluación del rendimiento operativo de la SCAN-SP contra la VNC mostro excelentes resultados: sensibilidad del 100 %, especificidad del 59 %, VPP del 85 %, VPN del 100 %, RVP de 2,4 y una RVN de 0.

Conclusión: la escala SCAN-SP tiene un buen comportamiento como herramienta de tamización nutricional en el paciente pediátrico con cáncer, por lo que se recomienda su uso en la práctica clínica.

Palabras clave:

Desnutrición. Cáncer infantil. Tamizaje nutricional. Estado nutricional.

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Abstract

Introduction: the prevalence of undernutrition in the pediatric cancer population can vary considerably, an element that significantly influences the clinical outcome of patients. However, this is a potentially modifiable prognostic factor, which requires timely identification of nutritional risk to guide the nutritional care process.

Objectives: to evaluate the operational performance of the Spanish version of the nutritional screening tool for childhood cancer (SCAN) in the context of the validation process of this instrument in a high-complexity hospital in the city of Bogotá, Colombia.

Methods: the methodological design for the validation of a diagnostic scale was followed. The final sample consisted of 96 patients between 0 and 17 years with cancer and hospitalized at the Children's Cancer Center of the HOMI Foundation in Bogota. The SCAN-SP was applied to each patient and a complete nutritional assessment (CNA) was performed as a gold standard to determine nutritional status.

Results: 82.3 % (n = 79) of patients were classified "at risk of malnutrition" by SCAN-SP and 69.8 % (n = 67) of the total sample had undernutrition. The evaluation of the operative performance of SCAN-SP against CNA showed excellent results: sensitivity of 100 %, specificity of 59 %, PPV of 85 %, NPV of 100 %, positive likelihood ratio of 2.4, and negative likelihood ratio of 0.

Conclusion: the SCAN-SP scale performs well as a nutritional screening tool in pediatric cancer patients, so its use in clinical practice is recommended.

Keywords:

Undernutrition. Childhood cancer. Nutritional screening. Nutritional status.

INTRODUCCIÓN

La importancia de la nutrición en los niños con cáncer es incuestionable. A lo largo de los años se ha buscado demostrar el impacto que tiene un diagnóstico oncológico en el estado nutricional (EN) de la población infantil. Como resultado se ha encontrado que el EN no está asociado únicamente a las alteraciones metabólicas que puede inducir una neoplasia para el cuerpo de un niño con cáncer (1) sino que también tiene una fuerte relación con el tipo de diagnóstico, la modalidad de tratamiento a la cual sea sometido y las condiciones sociodemográficas y socioeconómicas del paciente y su familia (2-6).

Si bien esta enfermedad es más prevalente en los adultos, en muchos países del mundo el cáncer infantil (CI) suele ser la segunda causa de muerte en los niños y niñas mayores de 1 año, superada únicamente por los accidentes (7). De acuerdo con la Organización Mundial de la Salud (OMS), el CI se ha posicionado como un asunto de prioridad en salud pública a nivel mundial, dado que su impacto trasciende más allá del diagnóstico del paciente e implica una carga psicosocial y económica abrumadora para las familias y comunidades (2). Infortunadamente, los serios problemas de desigualdad social no son ajenos a condiciones como estas y logran reducir las tasas de supervivencia a cifras inferiores al 30 % en los niños con cáncer que viven en países de medianos y bajos ingresos, debido a las dificultades para recibir una atención multidisciplinaria que les garantice un tratamiento exitoso (2,8). Entendiendo la naturaleza de esta situación, la OMS dio a conocer en 2021 la Iniciativa Global por el Cáncer Infantil, cuyo objetivo principal es garantizar en 2030 la supervivencia de al menos el 60 % de todos los niños con cáncer (2), lo que implica mejorar la capacidad de los países para diagnosticar, tratar y hacer un adecuado seguimiento a esta población, proceso que incluye, según la misma OMS, la atención nutricional de estos pacientes.

Para tal fin, las herramientas de tamizaje nutricional se convierten en un apoyo fundamental para el personal de salud ya que, si bien no son aptas para establecer un diagnóstico determinado, sí son capaces de identificar el riesgo de manera oportuna y permiten derivar a una atención nutricional mucho más extensa, previniendo así que se establezcan cuadros de desnutrición infantil o que, si ya existen, sean correctamente evidenciados, controlados y tratados.

Actualmente, la literatura ha identificado diferentes herramientas de tamización nutricional en pediatría (9). Sin embargo, salvo contadas excepciones (10), la mayoría ellas están validadas para la población pediátrica en general (11-15) y, así, se desconocen los efectos del cáncer y su tratamiento en el estado nutricional de los pacientes. En 2016 se publica la herramienta de tamización nutricional para el cáncer infantil SCAN, como instrumento que se ha proyectado de gran utilidad en la atención nutricional en oncología pediátrica (16). Sin embargo, al ser validada y publicada en inglés, se hizo necesario contar con un adecuado proceso de validación del instrumento al español, que pueda respaldar su uso en regiones hispanohablantes, mitigando las variaciones de interpretación asociadas al contexto cultural y el idioma, y fortaleciendo así la evidencia de su utilidad en la práctica clínica, por lo que el objetivo del presente estudio es evaluar el rendimiento operativo de la versión en español de la escala de tamización nutricional para el cáncer infantil (SCAN-SP) en el marco del proceso de validación del instrumento en un hospital de alta complejidad en la ciudad de Bogotá.

MATERIAL Y MÉTODOS

Se realizó un estudio de validación de esta escala diagnóstica. El levantamiento de la información tuvo lugar entre noviembre de 2021 y mayo de 2022 en la Fundación Hospital Pediátrico La Misericordia-HOMI en Bogotá, Colombia. Se incluyeron en el estudio niños y niñas desde el nacimiento hasta los 17 años y 11 meses de edad con cáncer, hospitalizados en el Centro de Cáncer Infantil de la Fundación Hospital Pediátrico La Misericordia en Bogotá, Colombia, que contaran con el consentimiento informado debidamente diligenciado y firmado por el padre de familia o representante legal. Criterios de exclusión: pacientes con algún grado de incapacidad motora de origen cerebral, síndrome de Down o hemodinámicamente inestables o en condiciones que no permitan realizar la evaluación nutricional completa.

PROCESO DE VALIDACIÓN: PRIMERA FASE

Como parte del proceso de validación de la SCAN se realizó una primera fase en la que se llevó a cabo la adaptación transcultural, en la que, previa autorización de uso por parte de los autores originales de la herramienta, se realizó la traducción de la escala por parte de un traductor bilingüe cuya lengua materna era la de la población objetivo (español), y la retrotraducción de esta misma a través de una persona cuya lengua materna era la de la versión original (inglés). Luego, en un comité de revisión se realizó una comparación de equivalencia semántica de las 2 traducciones y se obtuvo la primera versión en español, la cual fue sometida a una prueba piloto de adaptación con 40 pacientes de la población objetivo con el fin de evaluar la comprensión del instrumento, obteniendo así la versión final de la escala en español SCAN-SP (Fig. 1). Posteriormente se analizó la validez de criterio y fiabilidad (evaluando la consistencia interna mediante el coeficiente KR20) en una muestra obtenida por conveniencia de 47 pacientes.

Pregunta	Puntaje
¿Tiene el paciente un cáncer de alto riesgo?	1
¿Está actualmente el paciente bajo tratamiento intensivo?	1
¿Presenta el paciente algunos síntomas relacionados al tracto gastrointestinal?	2
¿Ha presentado el paciente pobre ingesta la última semana?	2
¿Ha tenido el paciente pérdida de peso en el último mes?	2
¿Muestra el paciente signos de desnutrición?	2
	Total

Figura 1.

Herramienta de tamización nutricional para el cáncer infantil. Versión en español. (SCAN-SP). Un puntaje igual o mayor a 3 indica que el niño está en riesgo de desnutrición y debe ser referido a un nutricionista para una extensiva valoración. Adaptado de Murphy AJ, White M, Viani K, Mosby TT. Evaluation of the nutrition screening tool for childhood cancer (SCAN). Clin Nutr 2016;35(1):219-24. Uso autorizado por: Alexia J. Murphy, dada el 17 de marzo de 2022.

PROCESO DE EVALUACIÓN DEL RENDIMIENTO OPERATIVO: SEGUNDA FASE

En una segunda fase se evaluó el rendimiento operativo de la SCAN-SP. Usando el método de tamaño de muestra para una proporción se estimó un tamaño de muestra mínimo de 75 pacientes (proporción de la población, $p = 0,5$, $n = 352$ (de acuerdo con el censo anual de pacientes del servicio de oncohematología del hospital), nivel de significancia del 95 % y error muestral de 0,1). En cuanto al diseño metodológico, se realizó una valoración nutricional completa (VNC) a cada uno de los pacientes, la cual fue tomada como patrón de referencia o *gold standard* para conocer el estado nutricional real de los pacientes. Dichos resultados fueron contrastados con la estimación del riesgo nutricional obtenida mediante la aplicación de la escala SCAN-SP. Con ella, un paciente que tenga un puntaje total mayor o igual a 3 es clasificado como "en riesgo de desnutrición". Con estos dos resultados se estableció su correlación y se realizó el respectivo análisis estadístico de los resultados.

Respecto a los procedimientos para la recolección de información, diariamente se realizó una revisión del censo de pacientes hospitalizados en el servicio de oncohematología, realizando una primera identificación de los pacientes que cumplieran con los criterios de inclusión y exclusión. Posteriormente se llevó a cabo una valoración nutricional completa, en la que se tuvieron en cuenta los siguientes parámetros: datos generales de los pacientes, indicadores paraclínicos, examen físico centrado en la nutrición, anamnesis alimentaria y valoración antropométrica.

Los indicadores paraclínicos correspondieron a la información disponible en la historia clínica de los pacientes con relevancia en la evaluación del estado nutricional, como: hemograma, ionograma, pruebas de función renal y hepática, glucometrías y perfil lipídico, entre otros. El examen físico centrado en la nutrición se realizó por medio de un análisis de cinco componentes: evaluación de reservas grasas, evaluación de reservas musculares, evaluación de signos clínicos de deficiencia de micronutrientes, estado de hidratación y evaluación funcional. En cuanto a la anamnesis alimentaria, se recolectó información relacionada con: información general sobre la ingesta de alimentos, frecuencia de consumo por grupos de alimentos, disminución en la ingesta usual y porcentaje de consumo de la dieta hospitalaria, síntomas gastrointestinales, soporte nutricional y recordatorio de 24 horas. Finalmente, en la valoración antropométrica se realizó la medición de peso, talla, circunferencia del brazo y pliegue cutáneo del tríceps como datos necesarios para evaluar los indicadores de la clasificación antropométrica del estado nutricional, conforme a los patrones de referencia de la OMS, adoptados por Colombia a través de la resolución 2465 de 2016 del Ministerio de Salud y Protección Social; también se evaluó el porcentaje de cambio de peso (en mayores de 2 años). El diagnóstico nutricional se estableció considerando los 5 parámetros de la VNC y no exclusivamente en función de los indicadores antropométricos (17,18).

ANÁLISIS ESTADÍSTICO

En cuanto al procesamiento y análisis de la información, para la clasificación antropométrica de los pacientes se usaron los softwares Anthro para niños menores de cinco años y Anthro Plus para niños mayores de cinco años. Estos datos se complementaron con las gráficas de la OMS adoptadas por Resolución 2465 de 2016. Respecto a la información recolectada, se utilizó el software para el análisis estadístico R, versión 4.1.2., para el análisis de las variables de caracterización tanto clínica como poblacional. Para realizar el análisis del rendimiento operativo se partió de una matriz de confusión o tabla de contingencia

elaborada con los resultados de la VNC *vs.* la clasificación del riesgo nutricional de la escala de tamización SCAN-SP. Posteriormente, utilizando la librería epiR, se calcularon los parámetros para evaluar una prueba diagnóstica (sensibilidad [S], especificidad [E], valores predictivos positivo [VPP] y negativo [VPN], y las razones de verosimilitud positiva [RVP] y negativa [RVN]) junto a sus intervalos de confianza. Finalmente, mediante el análisis de la curva ROC, se realizó una valoración global del rendimiento de la herramienta.

CONSIDERACIONES ÉTICAS

La presente investigación se llevó a cabo de acuerdo con las directrices establecidas por la Asociación Médica Mundial y la Declaración de Helsinki. Así mismo se garantizó el cumplimiento de la resolución 8430 de 1993 del Ministerio de Salud y Protección Social de Colombia, por lo cual contó con la aprobación del Comité de Ética e Investigación de la Fundación Hospital Pediátrico La Misericordia - HOMI mediante el acta No. 60 474-22R.

RESULTADOS

En cuanto a los resultados de la primera fase del estudio, en la que se llevó a cabo la adaptación transcultural de la SCAN, se aplicó el cuestionario en su versión en español a un grupo de 47 pacientes del grupo poblacional objetivo, y la evaluación de las características psicométricas del instrumento demostró que la escala SCAN-SP presenta una alta fiabilidad (con un coeficiente KR20 de 0,9092) al momento de identificar el riesgo nutricional en pacientes con cáncer infantil que presentaban desnutrición. Los resultados de la segunda fase, objeto de este estudio, se presentan a continuación.

CARACTERIZACIÓN DEMOGRÁFICA Y CLÍNICA DE LA POBLACIÓN

Una vez realizado el trabajo de campo, 96 pacientes conformaron la muestra final del estudio tal como lo muestra la figura 2, de los cuales el 53 % eran mujeres (n = 51) y el 47 % eran hombres (n = 45). La edad promedio de los pacientes fue de 8 años (± 5,1 DE), incluyendo pacientes entre 1 y 17 años, con una distribución simétrica en las edades, ya que la media concuerda con la mediana (8,8 y 8,5, respectivamente). El 27 % de los pacientes pertenecen al grupo de menores de 5 (n = 26) mientras que el 73 % (n = 70) pertenecen al de 5 años o más.

Para realizar la descripción clínica de los pacientes se tuvo en cuenta la Clasificación Internacional para el Cáncer Infantil (ICCC-3, por sus siglas en inglés), en la cual se clasifican los diferentes tipos de CI en 12 grupos establecidos de acuerdo con la morfología del tumor y su localización primaria (19). En ese sentido, de acuerdo con la tabla I, se evidencia que la mitad de los pacientes (50 %, n = 48) estaban diagnosticados con patologías pertenecientes al grupo I: leucemias, enfermedades mieloproliferativas y enfermedades mielodisplásicas. De esos 48 pacientes, 45 tenían leucemia linfoblástica aguda.

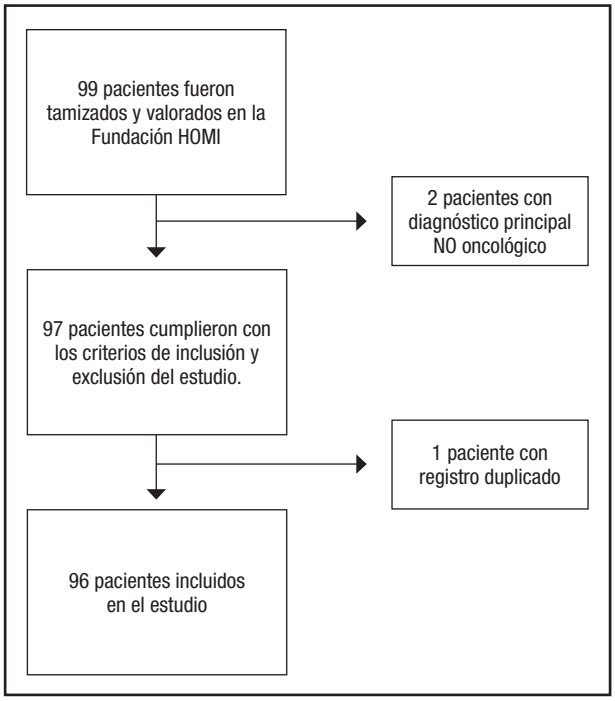

Figura 2.
Consolidación de la muestra objeto de estudio.

TAMIZACIÓN NUTRICIONAL

Los resultados de la tamización nutricional con la herramienta SCAN-SP se resumen en la tabla II, en la cual se puede ver como el 82,3 % (n = 79) de los pacientes fueron clasificados como "En riesgo de desnutrición" por obtener un puntaje total ≥ 3. Adicionalmente, el puntaje promedio de la escala fue de 5 (± 2,57 DE), con unos puntajes mínimo de 1 y máximo de 10. En relación con la información recolectada a través del tamizaje, cabe resaltar que la pregunta que tuvo la mayor cantidad de respuestas afirmativas fue aquella que indaga por la presencia de un cáncer de alto riesgo, con una 94,2 %, seguido por las preguntas que evalúan la reducción en la ingesta de alimentos y la pérdida de peso, con un 62,5 % en ambos casos.

DIAGNÓSTICO NUTRICIONAL

Una vez estudiados cada uno de los parámetros estipulados para la VNC, se realizó una evaluación integral de los mismos en relación con el estado nutricional y de salud de los pacientes y se emitió un diagnóstico nutricional, el cual fue parametrizado siguiendo la clasificación CIE-10, que se utiliza actualmente en la institución hospitalaria en la que se llevó a cabo el estudio según

muestra la tabla III. En esta se observa la distribución del diagnóstico nutricional de los pacientes y se evidencia que el 69,8 % de los pacientes (n = 67) presentan algún grado de desnutrición. De la muestra, el diagnóstico nutricional con mayor prevalencia es la desnutrición proteico-calórica moderada (36,5 %), seguido de la desnutrición proteico-calórica leve, presentada por el 26 % de los participantes. El 14,6 % de los pacientes presentan exceso de peso (espectro que incluyen el riesgo de sobrepeso, el sobrepeso y la obesidad), información que se convierte en un claro indicador de la coexistencia de una doble carga nutricional en esta población.

Tabla I. Diagnóstico de los pacientes de la muestra de acuerdo con la clasificación ICCC-3

Grupo	Nombre del grupo según ICCC-3	n	%
I	Leucemias, enfermedades mieloproliferativas y enfermedades mielodisplásicas	48	50
II	Linfomas y neoplasias reticuloendoteliales	9	9,4
III	Neoplasias del SNC y neoplasias diversas intracraneales e intraespinales	9	9,4
IV	Neuroblastoma y otros tumores de células nerviosas periféricas.	0	0
V	Retinoblastoma	1	1,0
VI	Tumores renales	0	0
VII	Tumores hepáticos	1	1,0
VIII	Tumores óseos malignos	10	10,4
IX	Tejidos blandos y otros sarcomas		
X	Tumores de células germinales, tumores trofoblásticos y neoplasias de gónadas	2	2,1
XI	Otras neoplasias epiteliales malignas y melanomas malignos	5	5,2
XII	Otras neoplasias malignas y las no especificadas	7	7,3
Total		*96*	*100*

ICCC-3: International Classification of Childhood Cancer, third edition.

Tabla II. Clasificación del riesgo de desnutrición de acuerdo con los resultados de la herramienta SCAN-SP

	n	%
Puntaje < 3 (SIN riesgo de desnutrición)	17	17,7
Puntaje ≥ 3 (CON riesgo de desnutrición)	79	82,3

Tabla III. Diagnóstico nutricional de los pacientes de la muestra establecido mediante valoración nutricional completa (VCN) y organizados de acuerdo con la clasificación CIE-10

Diagnóstico nutricional	Código CIE-10	n = 96	%
Pacientes con desnutrición		*67*	*69,8*
Desnutrición proteico-calórica leve	E44.1	35	26,0
Desnutrición proteico-calórica moderada	E44.0	25	36,5
Retraso del crecimiento debido a la desnutrición proteico-calórica	E45	7	7,3
Pacientes con exceso de peso		*14*	*14,6*
Obesidad debida a exceso de calorías	E660	2	2,1
Sobrepeso	--	6	6,3
Riesgo de sobrepeso	--	6	6,3
Pacientes eutróficos		*15*	*15,6*

CIE-10: Clasificación Internacional de Enfermedades, décima edición.

RENDIMIENTO OPERATIVO DE LA SCAN-SP

Se consideraron "positivos" o con riesgo de desnutrición aquellos valores mayores o iguales al punto de corte ≥ 3, y "negativos" o sin riesgo de desnutrición aquellos valores menores al punto de corte, y posteriormente se cruzó esta información con los diagnósticos obtenidos en la VNC para obtener la tabla IV o tabla de contingencia con las diferentes alternativas diagnósticas, donde se evidencia que 17 pacientes fueron identificados correctamente como sin riesgo de desnutrición dado que no tienen un diagnóstico de desnutrición, 67 fueron identificados correctamente con riesgo de desnutrición dado que tenían desnutrición, 12 pacientes fueron identificados con riesgo de desnutrición pero no tenían diagnóstico de desnutrición (falso positivo), y finalmente ningún paciente fue identificado sin riesgo de desnutrición que realmente tuviera un diagnóstico de desnutrición. Utilizando la librería epiR se calcularon los principales parámetros de rendimiento operativo para evaluar el desempeño de una prueba de predicción del riesgo junto a sus intervalos de confianza; sus resultados se presentan en la tabla V:

- S: la proporción de pacientes que tenían desnutrición y la prueba clasificó "con riesgo" es del 100 %, lo que significa que la SCAN-SP es capaz de detectar o clasificar los casos positivos de manera correcta.
- E: la proporción de pacientes sin diagnóstico de desnutrición que tendrán un resultado negativo en el tamizaje es del 59 %.
- VPP: la probabilidad de que un paciente tenga desnutrición dado que la SCAN-SP lo identifico con riesgo es del 85 %.
- VPN: la probabilidad de que un paciente no tenga desnutrición dado que la SCAN-SP lo identificó sin riesgo es del 100 %, comportamiento muy bueno para una prueba de tamizaje.
- RVP: La probabilidad de clasificar alguien como "con riesgo de desnutrición" es 2,4 veces mayor en los pacientes realmente desnutridos que en los que no están en desnutrición.
- RVN: la probabilidad de clasificar a un paciente como "sin riesgo de desnutrición" entre pacientes realmente desnutridos y quienes no lo están es la misma (RVN = 0).

Finalmente, mediante el análisis de curva ROC, la estimación del área bajo la curva (AUC) es igual a 0,912 (IC 95 %: 0,850 a 0,973), que es el área comprendida entre la línea de no-discriminación y la curva ROC; lo que indica que existe un 91,2 % de probabilidad de que el diagnóstico realizado a un enfermo sea más correcto que el de una persona sana escogida al azar.

Tabla IV. Tabla de contingencia SCAN-SP *vs.* valoración nutricional completa

Con desnutrición		Diagnóstico nutricional		
		Sin desnutrición	Total	
SCAN-SP	Con riesgo de desnutrición	67 (VP)	12 (FP)	79
	Sin riesgo de desnutrición	0 (FN)	17 (VN)	17
	Total	67	29	96

VP: verdaderos positivos; FP: falsos positivos; FN: falsos negativos; VN: verdaderos negativos.

Tabla V. Parámetros de rendimiento operativo de la SCAN-SP

Parámetro	Estimación	IC 95 %
Sensibilidad	100 %	95-100
Especificidad	59 %	39-76
Valor predictivo positivo (VPP)	85 %	75-92
Valor predictivo negativo (VPN)	100 %	80-100
Razón de verosimilitud positiva (RVP)	2,4	1,57-3,73
Razón de verosimilitud negativa (RVN)	0	0
Área bajo la curva (AUC)	0,912	0,850-0,973

IC: intervalo de confianza.

DISCUSIÓN

En cuanto a los resultados de la primera fase, la validez predictiva de una escala para determinar el riesgo de desnutrición está condicionada por la fiabilidad de esta (20). Para este estudio se obtuvo un valor favorable en cuanto a esta característica psicométrica (KR20 = 0,9092), lo cual indica que la SCAN-SP es un instrumento fiable, dado que existe una buena relación entre sus ítems evaluadores y una adecuada medición de las preguntas que la componen.

Respecto a la segunda fase del estudio, la OMS refiere que los tipos de CI más frecuentes son la leucemia, los tumores del SNC, el neuroblastoma, el linfoma y los tumores renales y óseos (2), información que guarda estrecha correlación con los resultados de la tabla I, la cual establece que los diagnósticos oncológicos más prevalentes en la población objeto de estudio pertenecen al grupo I de la clasificación ICCC-3 (n = 48; 50 %), seguidos por los diagnósticos clasificados en el grupo VIII (n = 10; 104 %), grupo II y grupo III (con n = 9; 9,4 % en cada uno). De esto, sin duda alguna, destaca que en el diagnóstico más prevalente es la de leucemia linfoblástica aguda con un 47 % (n = 45).

Más allá de la caracterización clínica de la población, el estudio revela un dato alarmante, debido a que la prevalencia de desnutrición en la población estudiada es del 69,8 % (n = 67). Un dato que da cuenta de la complejidad de esta situación es el registrado por Cañedo y cols. (21) en un estudio en el que evaluaban la validez y fiabilidad de la SCAN, dado que el 8 % de sus pacientes fueron diagnosticados de desnutrición moderada mientras que en este estudio la cifra es 4 veces mayor: 36,5 %. Si bien la prevalencia de esta condición en el CI es altamente variable (6,22,23), el hecho de encontrar una prevalencia tan alta en una institución que es referente y líder en oncología pediátrica y que, por tanto, recibe pacientes de todas las regiones de Colombia, da cuenta del desfavorable panorama que viven los niños con cáncer en nuestro país, más aun teniendo en cuenta que enfrentarse con estas dos condiciones de manera concomitante aumenta la probabilidad de tener resultados clínicos poco favorables (6,24,25).

Por otra parte, el 82,3 % de los pacientes fueron clasificados con riesgo de desnutrición por la SCAN-SP. Dentro de los resultados discriminados por cada pregunta, aquella que indaga por la presencia de un cáncer de alto riesgo tuvo el mayor porcentaje de respuestas positivas (94,2 %), seguida de la disminución en la ingesta y la pérdida de peso con 62,5 % cada una. Estos resultados son muy similares a los obtenidos por Murphy y cols. en el estudio original, donde estas tres preguntas, en el mismo orden citado anteriormente, son las que representan el mayor porcentaje de riesgo (16).

En cuanto al rendimiento operativo de la SCAN-SP, los resultados dan cuenta de que es capaz de detectar o clasificar de manera correcta a aquellos pacientes que tienen riesgo de desnutrición ya que es una herramienta muy sensible (sensibilidad = 100 %, IC 95 %: 95-100), pero su capacidad para clasificar correctamente a los pacientes sin riesgo de desnutrición que realmente no estén desnutridos no es la mejor dada su baja especificidad (especificidad = 59 %, IC 95 %: 39-76). Estos dos parámetros son muy comunes en este tipo de estudios dado que se convierten en un indicador de seguridad, ya que dan cuenta de la posibilidad de clasificar correctamente un paciente como enfermo (20).

Un dato importante por considerar de acuerdo con los resultados de la curva ROC es que la SCAN-SP, con su puntaje de corte establecido "≥ 3", es un buen instrumento de tamizaje, ya que la curva se acerca bastante al punto de clasificación perfecta y además está alejada de la línea de no discriminación. Adicionalmente es posible ver que la estimación de la AUC sugiere que existe un 91,2 % de probabilidad de que el diagnóstico o estimación del riesgo realizado a un paciente con desnutrición sea más correcto que el de una persona sana escogida aleatoriamente. Así mismo, dado que, en esencia, tamizar es buscar probables enfermos, lo que se espera de una herramienta de tamizaje es que sea más sensible que específica con el objetivo de detectar a todos los enfermos a pesar de que un resultado positivo incluye también falsos positivos (26,27), ya que luego de esto se harán pruebas más específicas como, en este caso, una VNC. Debido a que la SCAN-SP tiene una excelente sensibilidad, cumpliría con este criterio para ser una buena herramienta de tamizaje nutricional.

Si bien la sensibilidad y especificidad nos muestran la cercanía a la realidad, no contienen la información suficiente para tomar una decisión clínica (20,28); por tanto, vale la pena evaluar los valores predictivos positivo y negativo de la SCAN-SP. En esencia, estos dos valores indican cuál es la probabilidad de enfermar una vez conocido el resultado de la prueba (20). En este caso, la probabilidad de que un paciente tenga desnutrición dado que la SCAN-SP lo identifico con riesgo es del 85 % (VPP = 85 %, IC 95 %: 75-92) mientras que el VPN es del 100 % (IC 95 %: 80-100). Acá es importante considerar que cuanto más sensible sea la SCAN-SP, mayor será su valor predictivo negativo y, por tanto, mayor seguridad tendrá el personal de salud de que un resultado negativo descarta realmente que el paciente tenga desnutrición, comportamiento muy bueno para una herramienta de tamizaje nutricional. Algo importante a tener en cuenta respecto a los valores predictivos es que su información es válida para este estudio, ya que el objetivo es aplicar la SCAN-SP a sujetos con condiciones similares a los que se incluyeron en el estudio (pacientes con cáncer infantil); por lo tanto, el efecto de la prevalencia de la enfermedad no influirá de manera importante en la validez de los resultados (27,29,30).

Para dar un mayor alcance a la validez de los resultados y mitigar las limitaciones en la práctica clínica asociadas a los parámetros ya descritos, las razones de verosimilitud son de gran utilidad ya que, además de aportar información similar a la obtenida mediante la sensibilidad y la especificidad, también permiten conocer cuántas veces es más probable encontrar determinado resultado en personas enfermas en comparación con aquellas que no lo están (20). En ese sentido, la razón de verosimilitud positiva de la SCAN-SP muestra que en un paciente con CI que tenga desnutrición es 2,4 veces más probable (IC 95 %: 1,57-3,73) que la herramienta lo clasifique con riesgo,

en comparación con aquellos que no estén desnutridos, mientras que la razón de verosimilitud negativa es igual a 0 (la probabilidad de clasificar a un paciente como "sin riesgo de desnutrición" entre pacientes realmente desnutridos y quienes no lo están es la misma). Esta información es muy útil en la práctica clínica debido a que nos permite entender con qué fuerza de asociación el resultado positivo de las SCAN-SP indica la presencia real de desnutrición en el paciente pediátrico con cáncer (27).

Los resultados del presente estudio de validación son congruentes con los obtenidos por Murphy y cols., estudio original en el que se desarrolló la escala SCAN y en el cual se reportan una S del 100 % (IC 95 %: 76-100), una E del 39 % (IC 95 %: 17-64), un VPP del 56 % (IC 95 %: 35-76) y un VPN del 100 % (IC 95 %: 59-100) (16). Como se puede ver, la S y el VPN de ambos estudios son los mismos y las variaciones en cuanto a los demás parámetros pueden estar relacionadas con la metodología de validación, ya que en el estudio original los resultados del tamizaje realizado con la SCAN fueron contrastados con el instrumento "Subjective Global Nutrition Assessment, SGNA", una herramienta abreviada utilizada como método para diagnosticar la desnutrición pediátrica a nivel hospitalario que, entre otras diferencias, solo considera las variables antropométricas de peso y talla, y no considera los parámetros bioquímicos del estado nutricional o los signos de deficiencia de micronutrientes (13). Adicionalmente, el tamaño de muestra del estudio original fue de 32 pacientes, mientras que en la presente investigación fue de 96.

Por último, dados los buenos resultados de los indicadores de rendimiento operativo, es acertado afirmar que la interpretación que se obtiene luego de aplicar la versión en español de la SCAN tiene validez clínica y, por tanto, es de gran utilidad para identificar el riesgo de desnutrición en la población infantil con cáncer.

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ARÁN

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Trabajo Original

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Validación del instrumento Infant Malnutrition and Feeding Checklist for Congenital Heart Disease, una herramienta para identificar riesgo de desnutrición y dificultades de alimentación en lactantes con cardiopatías congénitas

Validation of the instrument "Infant Malnutrition and Feeding Checklist for Congenital Heart Disease", a tool to identify risk of malnutrition and feeding difficulties in infants with congenital heart disease

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Resumen

Introducción: actualmente, se han diseñado diversas herramientas para detectar oportunamente el riesgo de desnutrición en niños hospitalizados. En aquellos con diagnóstico de cardiopatías congénitas (CC), solo existe una herramienta desarrollada en Canadá, llamada Infant Malnutrition and Feeding Checklist for Congenital Heart Disease (IMFC:CHD), la cual fue diseñada en idioma inglés.

Objetivo: evaluar la validez y confiabilidad de la adaptación en español de la herramienta IMFC:CHD en lactantes con CC.

Métodos: estudio transversal de validación realizado en dos etapas: la primera, de traducción y adaptación transcultural de la herramienta; y la segunda, de validación de la nueva herramienta traducida, donde se obtuvieron las evidencias de confiabilidad y validez.

Resultados: en la primera etapa se obtuvo la herramienta traducida y adaptada al idioma español; para la segunda etapa se incluyeron 24 lactantes con diagnóstico de CC. Se evaluó la validez de criterio concurrente entre la herramienta de tamizaje y la evaluación antropométrica, obteniéndose un acuerdo sustancial (κ = 0,660, IC 95 %: 0,36-0,95). Para la validez de criterio predictiva, la cual fue comparada con los días de estancia hospitalaria, se obtuvo un acuerdo moderado (κ = 0,489, IC 95 %: 0,1-0,8). La confiabilidad de la herramienta se evaluó mediante consistencia externa, midiendo la concordancia interobservador, y se obtuvo un acuerdo sustancial (κ = 0,789, IC 95 %: 0,5-0,9); la reproducibilidad de la herramienta mostró un acuerdo casi perfecto (κ = 1, IC 95 %: 0,9-1,0).

Conclusiones: la herramienta IMFC:CHD mostró una adecuada validez y confiabilidad, por lo que podría considerarse un recurso útil para la identificación de desnutrición grave.

Palabras clave:

Cardiopatía congénita. Desnutrición. Evaluación nutricional. Tamizaje. Validación.

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Abstract

Introduction: currently, various tools have been designed to timely detect the risk of malnutrition in hospitalized children. In those with a diagnosis of congenital heart disease (CHD), there is only one tool developed in Canada: Infant Malnutrition and Feeding Checklist for Congenital Heart Disease (IMFC:CHD), which was designed in English.

Objective: to evaluate the validity and reliability of the Spanish adaptation of the IMFC:CHD tool in infants with CHD.

Methods: cross-sectional validation study carried out in two stages. The first, of translation and cross-cultural adaptation of the tool, and the second, of validation of the new translated tool, where evidence of reliability and validity were obtained.

Results: in the first stage, the tool was translated and adapted to the Spanish language; for the second stage, 24 infants diagnosed with CHD were included. The concurrent criterion validity between the screening tool and the anthropometric evaluation was evaluated, obtaining a substantial agreement (κ = 0.660, 95 % CI: 0.36-0.95) and for the predictive criterion validity, which was compared with the days of hospital stay, moderate agreement was obtained (κ = 0.489, 95 % CI: 0.1-0.8). The reliability of the tool was evaluated through external consistency, measuring the inter-observer agreement, obtaining a substantial agreement (κ = 0.789, 95 % CI: 0.5-0.9), and the reproducibility of the tool showed an almost perfect agreement (κ = 1, CI 95 %: 0.9-1.0).

Conclusions: the IMFC:CHD tool showed adequate validity and reliability, and could be considered as a useful resource for the identification of severe malnutrition.

Keywords:

Congenital heart disease. Malnutrition. Nutritional evaluation. Screening. Validation.

INTRODUCCIÓN

La presencia de desnutrición en niños hospitalizados tiene especial relevancia debido a que se relaciona con alteraciones en el crecimiento y el desarrollo, complicaciones clínicas, una baja respuesta al tratamiento y retraso en la recuperación, lo que conduce a mayor estancia hospitalaria, readmisión y utilización de recursos (1-3). Particularmente, los pacientes pediátricos con cardiopatías congénitas (CC) pueden presentar diversos grados de desnutrición debido a una disminución en la ingesta de energía, aumento de los requerimientos energéticos, dificultades para proporcionar una nutrición adecuada y limitaciones de líquidos, entre otras. Esto afecta a los resultados de los procedimientos quirúrgicos y ocasiona mayor duración de la ventilación mecánica y días de estancia en la Unidad de Cuidados Intensivos y mayor morbimortalidad (4-6).

Diversas organizaciones internacionales como la American Society for Parenteral and Enteral Nutrition (ASPEN) (7) y la European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recomiendan el uso de herramientas de tamizaje nutricionales dentro de las primeras 24 horas de hospitalización para determinar el riesgo nutricional (8), permitiendo así una intervención oportuna para evitar resultados clínicos negativos (1).

En la actualidad, se han desarrollado diversas herramientas de tamizaje en población pediátrica (9), sin embargo, la mayoría de ellas han sido desarrolladas en idioma inglés. También se ha documentado la adaptación transcultural, trasculturalización y validación de una de estas herramientas al idioma español, la herramienta STRONGkids, la cual mostró buenos resultados en general (1). Sin embargo, a la vez, se han estado desarrollando herramientas de tamizaje enfocadas a patologías específicas, en donde se toman en cuenta características exclusivas que impactan en el estado de nutrición dependiendo de la patología. Un ejemplo de ellas es la herramienta SCAN (Nutrition Screening Tool for Childhood Cancer), enfocada en pacientes oncológicos, que toma en cuenta el tipo de cáncer que presenta el paciente, la etapa de tratamiento en la que se encuentra, así como síntomas gastrointestinales que puedan ocurrir durante el tratamiento (10). De igual manera, existe una herramienta de tamizaje dirigida a pacientes pediátricos con CC: el tamizaje Infant Malnutrition and Feeding Checklist for Congenital Heart Diseasese (IMFC:CHD), que se utiliza para identificar el riesgo de desnutrición y las dificultades de alimentación en lactantes con CC. Esta herramienta fue diseñada y publicada en idioma inglés y toma en cuenta, dentro de las variables a evaluar, los diagnósticos cardiacos específicos con mayor riesgo de desnutrición y otras variables que pueden influir de manera directa en la presencia de desnutrición en esta población, como el tipo de alimentación, la presencia de vómito y si durante la alimentación el paciente presenta mala succión, tos o atragantamiento, entre otras (11). Sin embargo, para el uso de esta herramienta en poblaciones hispanohablantes existe la limitación del uso adecuado debido a que la herramienta está en habla inglesa, lo que representa una desventaja para utilizarla en el contexto lingüístico hispanohablante. Por ello, objetivo del presente estudio fue realizar la adaptación transcultural de la herramienta IMFC:CHD y determinar su validez y confiabilidad en una población pediátrica con CC ingresada en un hospital de tercer nivel pediátrico.

MATERIALES Y MÉTODOS

DISEÑO DEL ESTUDIO

Se realizó un estudio transversal descriptivo de validación en un hospital de tercer nivel de la Ciudad de México entre enero de 2019 y septiembre de 2021. Dicho estudio se llevó a cabo en dos etapas: la primera etapa se centró en realizar la traducción y adaptación transcultural de la herramienta y la segunda etapa consideró el proceso de validación de la adaptación de la herramienta.

ETAPA I: TRADUCCIÓN Y ADAPTACIÓN TRANSCULTURAL

La primera etapa consistió en el proceso metodológico para obtener una versión en español dialecto mexicano a partir del formato original de la herramienta IMFC:CHD. Para diseñar y llevar a cabo este proceso se siguieron los lineamientos establecidos por

tres grupos internacionales: International Society for Pharmacoeconomics and Outcomes Research (ISPOR), mediante su división dedicada a la traducción y adaptación cultural, International Test Commission Guidelines for test translation and adaptation (TCA FORCE), las directrices para la traducción y adaptación de los test (12) y los lineamientos para el proceso de adaptación transcultural de mediciones autorreportadas (13). A partir de ello, se realizó un proceso de diez pasos que consistieron en lo siguiente:

1. Se formó el equipo del proyecto y se revisó el constructo de la herramienta.
2. Se obtuvieron dos traducciones certificadas al idioma español.
3. Síntesis: se formó un panel de expertos que, de manera individual y segada, compararon las dos traducciones y se corrigieron centrándose en la equivalencia conceptual y en la consistencia del lenguaje.
4. Retrotraducción: el borrador generado en el paso anterior se tradujo de nuevo al idioma inglés (versión reconciliada).
5. Revisión de la retrotraducción, en donde se comparó la traducción de la versión reconciliada con la versión original.
6. Se revisó la redacción de la herramienta llegando a un consenso sobre la equivalencia semántica.
7. Armonización: se revisaron todas las traducciones realizadas durante el proceso para detectar y discutir todas las posibles discrepancias.
8. Prueba de usuario: la traducción propuesta se probó en cinco participantes con características similares a la población objetivo.
9. Finalización: se identificaron fallas reveladas durante el pilotaje.
10. Reporte final: se detalló un informe explícito de las acciones realizadas en cada paso, destacando cómo se abordaron las tareas y cómo se detectaron las posibles discrepancias. Con ello se llevó a cabo la traducción y adaptación transcultural, buscando tener una estructura metodológica que asegurara obtener una versión en español, dialecto mexicano derivado de la versión en inglés de la herramienta IMFC:CHD.

ETAPA II: VALIDACIÓN

En la segunda fase se incluyeron lactantes entre un mes y 24 meses de edad, femeninos y masculinos, con diagnóstico de CC, ingresados al área de Cardiología, con presencia de cuidador primario y estancia hospitalaria mayor a 24 horas. El protocolo fue aprobado por los comités de investigación y ética del Instituto Nacional de Pediatría (número de aprobación 2019/001), que están registrados oficialmente en la Oficina de Protección de la Investigación Humana del NIH (Institutos Nacionales de Salud, de sus siglas en inglés National Institutes of Health; http://ohrp.cit.nih.gov/search/search.aspx) con los números IRB00013674 e IRB00013675. La publicación y el proyecto fue financiado por Recurso Fiscal del Instituto Nacional de Pediatría. Todos los participantes fueron informados del alcance y los procedimientos del estudio y se obtuvo formalmente el consentimiento informado por escrito del padre o tutor a cargo antes de cualquier procedimiento del estudio.

En esta etapa, se obtuvieron las evidencias de validez y confiabilidad de la versión traducida al español, dialecto mexicano, de la herramienta. La validez de la herramienta se realizó mediante la obtención de las evidencias de validez de criterio, tanto de forma concurrente como predictiva. La validez concurrente se realizó comparando el riesgo nutricional dado por la nueva herramienta contra el estándar de referencia. Derivado de que no existe un estándar de referencia para la evaluación del riesgo nutricional, se utilizó la evaluación nutricional realizada por un experto en nutrición, la cual comprende: evaluación subjetiva, antropometría y valoración del estado nutricional a través de los indicadores peso para la longitud, peso para la edad y longitud para la edad.

Un nutriólogo estandarizado realizó las medidas antropométricas de peso y longitud a todos los participantes en el momento del ingreso. Los índices de peso para la edad, peso para la longitud y longitud para la edad se calcularon de acuerdo con los estándares de crecimiento de la Organización Mundial de la Salud (OMS) y las referencias de crecimiento (0-2 años) como z-puntuaciones (14). Una vez obtenida toda la información, se definió si el lactante se encontraba en alguna de estas categorías: normopeso (-1,0 a +1,0 desviación estándar [DE]), desnutrición leve (-1,0 a -2,0 DE), desnutrición moderada (-2,0 a -3,0 DE) o desnutrición grave (> -3,0 DE). La validez de criterio predictiva se determinó mediante la evaluación de las asociaciones entre las categorías de riesgo dadas por la herramienta IMFC:-CHD como: riesgo de desnutrición grave (≥ 2 elementos) como una categoría y sin riesgo de desnutrición grave (< 2 elementos) como otra categoría *vs.* la prolongación de la estancia hospitalaria de los pacientes, que se dicotomizó como estadía prolongada (≥ 15 días) y estadía normal (< 15 días), la cual se calculó a partir de la mediana de días de estancia del grupo de estudio.

La confiabilidad se determinó mediante concordancia interobservador, comparando el desempeño de calificadores con conocimientos especializados en temas de nutrición (licenciados en Nutrición) contra calificadores sin dichos conocimientos (médicos residentes de la especialidad de Cardiología). Para ello, se compararon los resultados obtenidos con el instrumento al ser aplicado a un mismo grupo de pacientes, bajo las mismas condiciones, en un mismo momento, pero por aplicadores diferentes y cegado para ambos profesionales. La reproducibilidad se determinó mediante la técnica de prueba/re-prueba, comparando los resultados arrojados por el instrumento al ser aplicado a un mismo grupo de pacientes, bajo las mismas condiciones, por un mismo aplicador, pero en dos momentos distintos. Para realizar esto se eligió a calificadores con conocimientos especializados en temas de nutrición (licenciados en Nutrición) para ser evaluados contra sí mismos, con una diferencia de 24 horas de la primera aplicación *vs.* la segunda versión.

ANÁLISIS ESTADÍSTICO

Se realizó el cálculo de tamaño de muestra con un tamaño mínimo de 23 niños, con un nivel de confianza del 95 %, calcu-

lando que la población de los niños con cardiopatía ingresados al año es de 200 individuos, y asumiendo una prevalencia mínima de desnutrición esperada del 12 %. Se determinó la normalidad de las variables usando la prueba estadística de Kolmogorov-Smirnov. En el análisis descriptivo, las variables cuantitativas continuas fueron expresadas como promedios y desviaciones estándar o como medianas y percentiles 25 y 75, dependiendo de su curva de distribución; para las variables dicotómicas se utilizaron frecuencias y porcentajes. Se utilizó el estadístico U de Mann-Whitney y Kruskall-Wallis.

La validez de criterio, tanto concurrente como predictiva, así como el nivel de acuerdo interobservadores y la reproducibilidad de la herramienta se evaluaron aplicando la prueba estadística Kappa de Cohen con sus IC al 95 %, con la siguiente escala de valores de kappa: $\kappa < 0$, acuerdo pobre; $\kappa = 0$-0,2, acuerdo leve; $\kappa = 0{,}21$-0,4, acuerdo justo; $\kappa = 0{,}41$-0,6, acuerdo moderado; $\kappa = 0{,}61$-0,8, acuerdo sustancial; y $\kappa = 0{,}81$-1, casi perfecto (15).

Los datos fueron analizados utilizando el *software* SPSS versión 25 for Macintosh (IBM Corp., Armonk, NY, USA).

RESULTADOS

ADAPTACIÓN

De acuerdo con la metodología utilizada para la traducción y adaptación transcultural, la versión final del IMFC:CHD demostró que es comprensible y fácil de usar por los clínicos (equipo de salud). Esta nueva versión tuvo diversos cambios, principalmente en cuestión de terminología de la herramienta (Tabla I). Se concluyó que la nueva versión de la herramienta de tamizaje nutricional IMFC:CHD en idioma español dialecto mexicano cumplió con los requisitos de calidad y resultó en una versión equivalente a la herramienta original (Fig. 1).

Tabla I. Modificaciones realizadas en los términos de la herramienta traducida al español dialecto mexicano

Elemento	Modificaciones realizadas
Elemento	Se cambia la palabra "ítem" por su significado en español ("elemento")
Título	Se quita el artículo "la" del título
Vía rápida	
Vía rápida	Se cambia el término "vía rápida" por "evaluación rápida"
Encabezado de la herramienta	Se cambia el término "dudoso" por "no es seguro"
Dietista	Se cambia el término "dietista" por nutriólogo y se agrega el término "nutricionista" para tener una mayor proyección en países de habla hispana
Las siguientes conocidas/sospechadas anomalías cromosómicas u otras:	Se cambia por "las siguientes alteraciones o cromosomopatías conocidas/sospechadas"
DiGeorge (22q11 del) Trisomía 18/13	Se cambia el término DiGeorge (22q11 del) por DiGeorge (deleción 22q11)
Daño cerebral	Se cambia el término "daño cerebral" por "lesión cerebral"
Paresia de las cuerdas vocales	Se cambia el término "paresia" de las cuerdas vocales por "parálisis de cuerdas vocales"
Dietista/OT	Se cambia el término "OT" por "rehabilitador"
Nutrición	
< 3.er percentil	Se cambia el término por "< percentil 3"
Ha bajado dos grupos percentiles principales desde el nacimiento	Se cambia por: "Descenso de dos percentiles desde el nacimiento"
Inicie la derivación al dietista	Se cambia el término por "referencia"
Tolerancia digestiva	Se cambia el término por "tolerancia gastrointestinal"
Dieta: leche materna fortificada o fórmula hipercalórica	Se cambia por "leche materna fortificada", "fórmula infantil" o "formula hipercalórica con módulos nutricionales"
Vómitos	Se cambia por "presencia de vómito"

(Continúa en página siguiente)

Tabla I (Cont.). Modificaciones realizadas en los términos de la herramienta traducida al español dialecto mexicano

Elemento	Modificaciones realizadas
Alimentación	
Inicie la derivación al TO	Se cambia por el término "referencia"
RR > 65 rpm	Se cambia el término "RR" por "FR" y se pone completo "respiraciones por minuto" en vez de "rpm"
Desaturaciones	Al ser un tamiz, no ponemos lo valores de desaturación
Aumento de la TR	Se cambia el término por "trabajo respiratorio"
Lugar de derivación	Se cambia el término por "lugar de referencia"
Lugar de derivación: clínica, Unidad de Cuidados Intensivos Pediátricos (UCIP), sala, otro	Se cambian los términos "clínica" por "consulta externa" y "sala" por "hospitalización"

LISTA DE VERIFICACIÓN DE LA ALIMENTACIÓN Y NUTRICIÓN INFANTIL PARA CARDIOPATÍAS CONGÉNITAS (CC)
Por favor, complete el formulario para todos los bebés con CC admitidos/transferidos a su unidad

Lugar de referencia:_____ Consulta externa_____ UCIP_____ Hospitalización Otro_____

		Sí	No es seguro	No
Vía rápida Si responde "Sí" o "No es seguro" a cualquier elemento, inicie la referencia al *nutriólogo/ nutricionista y rehabilitador*	Los siguientes diagnósticos cardiacos: – Interrupción del arco aórtico, corazón izquierdo hipoplásico, coartación de aorta, tronco arterioso			
	Las siguientes *alteraciones o cromosomopatías:* – DiGeorge (22q11 del), Trisomía 18/13, CHARGE, VACTERL			
	Lesión cerebral			
	Parálisis de las cuerdas vocales			
Nutrición Si responde "Sí" o "No es seguro" a cualquier elemento, inicie la referencia al *nutriólogo/ nutricionista*	*Peso* Cualquiera de los siguientes: – < percentil 3 – Descenso de dos percentiles desde el nacimiento			
	Dieta – Leche materna fortificada, fórmula infantil fortificada, fórmula hipercalórica y/o con módulos nutricionales			
	Sonda de alimentación			
	Tolerancia digestiva – Presencia de vómito			
Alimentación Si responde "Sí" o "No es seguro" a cualquier elemento, inicie la referencia al *rehabilitador*	*Estado fisiológico* – FR > 65 respiraciones por minuto – Aumento del TR – Taquicardia* – Desaturaciones			
	Cuerdas vocales – Estridor o voz ronca o sibilancias			
	Durante la alimentación – Tos, atragantamiento o arcadas – Congestión/sonidos de las vías aéreas superiores – Mala succión – No completa la alimentación por vía oral			

*UCIP: Unidad de Cuidados Intensivos Pediátricos; FR: frecuencia respiratoria; TR: trabajo respiratorio. *Taquicardia: de 1 a 6 meses > 145 pulsaciones por minuto (ppm); de 6 a 12 meses > 135 ppm; de 1 a 3 años: > 120 ppm).*

Nombre:_____ Firma:_____ Fecha:_____

Figura 1.

Herramienta traducida y adaptada.

CARACTERÍSTICAS DE LA POBLACIÓN

El estudio incluyó 24 lactantes (62,5 % hombres) con edad promedio de 10,7 ± 6,2 meses y una mediana de estancia hospitalaria de 15 (12-26) días. Los diagnósticos con mayor prevalencia fueron las CC acianógenas 58,3 % y de alto flujo pulmonar 54,1 % (Tabla II). De acuerdo con el estado nutricional evaluado con peso para la edad, realizado por un experto, se observó presencia de desnutrición en todos los participantes, siendo la desnutrición grave (n = 13, 54,2 %) la de mayor prevalencia, seguida de desnutrición moderada (n = 6,25 %) y, en menor presencia, desnutrición leve (n = 5, 20,8 %) (Tabla III).

Tabla II. Características basales de los participantes incluidos (n = 24)

Sexo, n (%) Hombre/Mujer	 15 (62,5)/9 (37,5)
Edad, *meses*	10,7 ± 6,2
Peso, *kg*	6,3 ± 2,2
Peso al nacimiento, *kg*	2,7 ± 0,54
Estrato diagnóstico, n (%) Alto flujo pulmonar Bajo flujo pulmonar	 13 (54,2) 11 (45,8)
Estrato diagnóstico, n (%) Cianógena Acianógena	 10 (41,7) 14 (58,3)
Estancia hospitalaria, *días*	15 (12-26)

Los datos están expresados como media ± desviación estándar o mediana (percentil 25-75).

Tabla III. Evaluación nutricional de los participantes (n = 24)

Peso para la edad, *puntuación Z*	-4,19 ± 1,54
Peso para la longitud, *puntuación Z*	-4,31 ± 0,93
Longitud para la edad, *puntuación Z*	-3,66 ± 0,021
Perímetro braquial, *puntuación Z*	-3,16 ± 0,26
Diagnóstico de peso para la edad, n (%) Desnutrición leve Desnutrición moderada Desnutrición grave	 5 (20,8) 6 (25) 13 (54,2)

VALIDEZ

Debido a que, en la evaluación de los pacientes incluidos, ninguno de ellos tenía un estado de nutrición normal, se decidió evaluar la validez con respecto al estrato de gravedad del estado de nutrición. Para ello, evaluamos el puntaje resultado de la herramienta de tamizaje nutricional IMFC:CHD con respecto al estado de nutrición evaluado por experto y encontramos que los estratos de desnutrición leve y moderada se comportaban con un puntaje similar, sin embargo, el estrato de desnutrición grave tenía un puntaje más alto al de la herramienta IMFC:CHD (Fig. 2). Por este motivo, se decidió dicotomizar el estado de nutrición y juntar el estrato de desnutrición leve + moderada y compararlo contra el estrato de desnutrición grave. Aunado a lo anterior, se realizó un análisis de curva ROC con el objetivo de evaluar el punto de corte de elementos positivos de la herramienta de tamizaje para predecir desnutrición grave en esta población con CC. En el análisis se observó un área bajo la curva de 0,766 (IC 95 %: 0,556-0,976; p = 0,047) y al analizar el mejor punto de corte con el índice de Youden (IY = 0,65), encontramos que la presencia de ≥ 2 elementos positivos tenía una sensibilidad del 92,3 % y una especificidad del 72,7 % para desnutrición grave, por lo que las evaluaciones de validez presentadas a continuación se realizaron con dicho punto de corte.

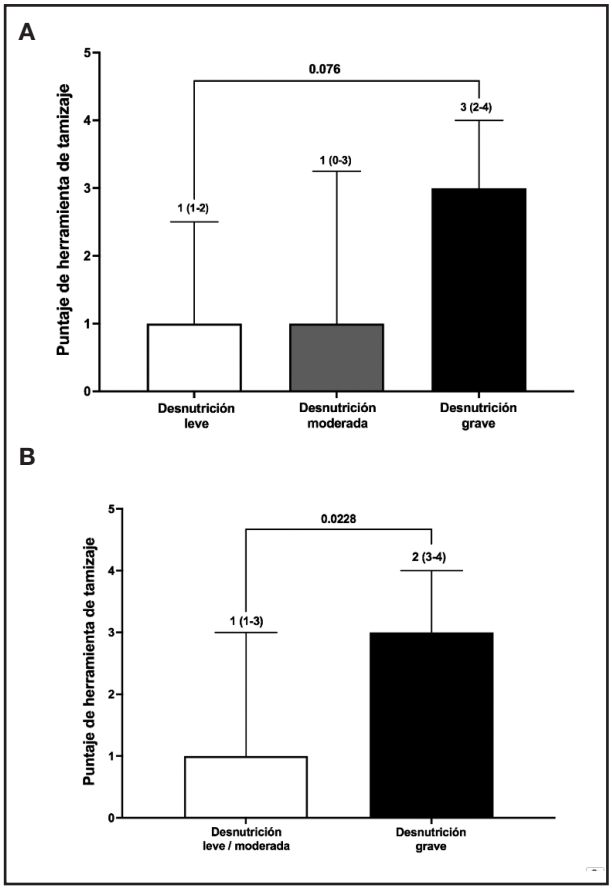

Figura 2.

Resultados de la herramienta de tamizaje estratificada por estado de nutrición. Los datos están expresados como mediana (percentil 25-75). A. Puntaje de la herramienta estratificado por desnutrición leve, moderada y grave; análisis estadístico Kruskal-Wallis. B. Puntaje de la herramienta estratificado por desnutrición leve/moderada *vs.* grave; análisis estadístico U de Mann-Whitney.

Para la validez concurrente se compararon los resultados obtenidos mediante la herramienta de tamizaje IMFC:CHD contra la valoración de características antropométricas confrontando las categorías desnutrición leve/moderada *vs.* desnutrición grave de la evaluación antropométrica comparada, con la presencia de ≥ 2 elementos positivos de la herramienta, y se halló un valor de kappa sustancial, κ = 0,660 (IC 95 %: 0,360-0,959; p = 0,001). Para la validez de criterio predictiva se compararon los resultados de la herramienta de tamizaje IMFC:CHD dicotomizada (< 2 elementos positivos *vs.* ≥ 2 elementos positivos) frente a la duración de estancia hospitalaria, que también fue dicotomizada por una estancia ≥ 15 días, que se consideró como estancia prolongada. De acuerdo a lo anterior, se obtuvo un valor de kappa moderado, κ = 0,489 (IC 95 %: 0,142-0,839) (p = 0,027). Para el total de la muestra, 15 niños tuvieron una estadía prolongada y al comparar los días de estancia hospitalaria entre aquellos que obtuvieron un puntaje de la herramienta de < 2 elementos positivos y ≥ 2 elementos positivos, se observaron 13 (3-16) días *vs.* 19 (14-28) días (p = 0,05), respectivamente (Fig. 3).

CONFIABILIDAD

El acuerdo entre evaluadores del profesional de la nutrición y los obtenidos por parte del profesional de la salud fue sustancial, con un valor de kappa de κ = 0,789 (IC 95 %: 0,5-0,9). Por otro lado, la reproducibilidad del instrumento evaluada por el mismo profesional de la nutrición con diferencia de 24 horas obtuvo un nivel de Kappa de κ = 1 (IC 95 %: 0,9-1,0) es decir, un acuerdo casi perfecto (Tabla IV).

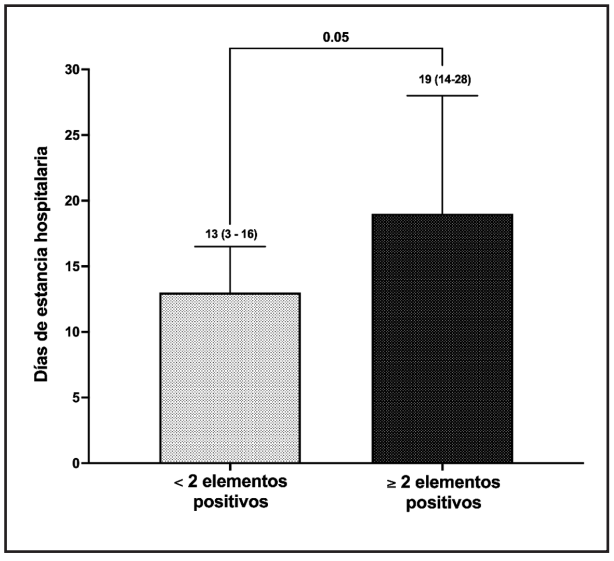

Figura 3.

Comparación de los días de estancia hospitalaria estratificada por puntaje de la herramienta. Los datos están expresados como mediana (percentil 2-75). Análisis estadístico U de Mann-Whitney.

Tabla IV. Resultados de confiabilidad de la herramienta de tamizaje

	Valor de kappa κ (IC 95 %)	Valor de p
Interobservadores	0,789 (0,5-0,9)	< 0,0001
Reproducibilidad	1,00 (0,9-1,0)	< 0,0001

DISCUSIÓN

La presencia de desnutrición en el niño con CC hospitalizado tiene un papel preponderante en el desenlace clínico, además de representar indirectamente un impacto adverso para los cuidadores primarios y para las instituciones de salud (4,16). La utilidad de las herramientas para evaluar el riesgo nutricional radica en que ayudan a detectar de forma oportuna a los niños que se verían más beneficiados de recibir una atención nutricional especializada, lo que, consecuentemente, permite una intervención adecuada y una focalización de los recursos entre aquellos niños que resultan más vulnerables (17). Por lo tanto, la implementación de una herramienta que permita detectar a los pacientes en riesgo, para tomar más y mejores decisiones al respecto, es sin lugar a dudas necesaria. En México, como en otros países, la implementación de pruebas de tamiz nutricional al ingreso de los pacientes a los servicios de hospitalización puede observarse de manera más o menos regular entre las instituciones de salud (18), ya que se encuentra como uno de los parámetros a cumplir para la certificación de hospitales (8). Pese a lo anterior, la población pediátrica con CC pocas veces es sometida a estos procesos de escrutinio. Suponemos que esto se debe a la falta de una herramienta dirigida específicamente para este grupo, ya que en el contexto nacional no hay presencia de un instrumento para evaluar riesgo nutricional que haya sido diseñado, adaptado y/o validado para los niños mexicanos hospitalizados con CC.

Para dar respuesta a la necesidad de contar con una herramienta que pudiera implementarse a la población pediátrica en idioma español, se determinó adaptar y validar el instrumento de tamizaje nutricional Infant Malnutrition and Feeding Checklist for Congenital Heart Disease (IMFC:CHD) (11). Para lograr esto, el primer paso fue realizar el proceso de traducción y adaptación transcultural de su versión en inglés al idioma español en su dialecto mexicano. El proceso seguido en el presente estudio consistió en diez pasos consecutivos y secuenciales que, en conjunto y con las evidencias obtenidas en cada paso, permitieron obtener una versión en idioma español de la herramienta de tamiz de riesgo nutricional IMFC:CHD. Dentro de los pasos seguidos, se incluyó la evaluación de la herramienta mediante su aplicación en un estudio piloto, lo que verificó que se trata de un instrumento cabalmente entendible y que no podrían generarse conflictos durante su aplicación derivados del formato, la redacción y/o la estructura. El proceso de traducción y adaptación transcultural de un instrumento de medición es de suma

relevancia cuando se busca emplear una herramienta que fue desarrollada en un lenguaje y un contexto cultural distintos del idioma y la cultura en que se pretende usar, por lo que realizar la traducción y adaptación bajo el rigor metodológico pertinente, documentando y siguiendo exhaustivamente cada parte del proceso se vuelve de gran importancia para garantizar que la nueva versión del instrumento sea equivalente a la original (12).

También se llevó a cabo la validación de esta herramienta con la finalidad de garantizar la correcta detección del riesgo nutricional de la población de lactantes con CC. Los resultados de la población mostraron la presencia de desnutrición en el 100 % de la población estudiada y, además, se mostró que uno de cada dos niños con CC que era hospitalizado tenía desnutrición grave. Asimismo, la herramienta validada demostró que la presencia de ≥ 2 elementos positivos tenía una sensibilidad del 92,3 % y una especificidad del 72,7 % para detectar desnutrición grave. Por ello, es importante implementar el tamizaje en las primeras 24 horas y tomar acciones adecuadas con el personal experto en nutrición, lo que indica que debe haber un nutriólogo encargado de este departamento o el Servicio de Cardiología Pediátrica. Por consiguiente, en el futuro, la presencia de un experto en nutrición en niños con CC hospitalizados podría disminuir costos al disminuir los días de estancia hospitalaria y las complicaciones (19-21).

Finalmente, es importante comentar las fortalezas y limitaciones de este estudio. La fortaleza es realizar la traducción y adaptación transcultural de la herramienta para tamizar el grado de desnutrición en niños con CC para población hispanohablante, ya que la herramienta estaba en habla inglesa, lo que presenta una desventaja para utilizar en el contexto lingüístico hispanohablante. Por otro lado, también se demostró que la herramienta tenía una adecuada validez y confiabilidad, por lo que podría considerarse un recurso útil para la identificación de desnutrición grave. En cuanto a las limitaciones, el tamaño de la muestra del presente estudio sigue siendo relativamente pequeño y presenta sesgos en el momento de la validación. El tamaño de la muestra fue limitado por diferentes factores, entre ellos, la pandemia, y secundario a esto, el número limitado de camas para ingreso a niños con CC , por lo que se considera en futuros estudios realizar validación de esta herramienta en otras poblaciones dentro del país de México, así como en diferentes poblaciones hispano hablantes.

CONCLUSIÓN

El uso de una herramienta específica que permita identificar el riesgo que tiene un paciente de presentar o desarrollar desnutrición grave durante su hospitalización pareciera ser una excelente estrategia para prevenir las complicaciones derivadas de dicho cuadro. El proceso de adaptación y validación del IMFC:CHD generó una versión que se presenta como la primera propuesta para emplear entre la población pediátrica con diagnóstico de CC. Sin embargo, es importante tener en consideración que no es suficiente la identificación del riesgo nutricional, la presencia de desnutrición o las dificultades de alimentación mediante la aplicación de herramientas de tamiz. Para hacer un cambio en la manera en que impacta la desnutrición al paciente hospitalizado, es necesario incidir en la creación de equipos inter y transdiciplinarios para lograr el diseño de un programa que no solo identifique a los pacientes a su ingreso o durante su estancia, sino que también realice intervenciones de forma oportuna y adecuadas a las necesidades de cada paciente, para finalmente evaluar su impacto.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Nutrición en el anciano

Validity and reliability of SCREEN II (Seniors in the Community: Risk Evaluation for Eating and Nutrition) search in Turkish society

Validez y fiabilidad de la escala de evaluación de riesgos para la alimentación y la nutrición (SCREEN II) en la sociedad turca

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Abstract

Objective: the aim of this study is to determine the reliability and the validity of the Seniors in the Community: Risk Evaluation for Eating and Nutrition (SCREEN II) scale, which has been developed with the aim of evaluating eating and nutrition risks.

Methods: a total of 207 elderly were included in the study. The Standardized Mini Mental Test (SMMT) was applied to individuals for mental adequacy assessment and then SCREEN II scale was applied. For the selection of scale items, main components factor analysis and Varimaks conversion has been applied to the data and it has been decided to use the components which have 0.40 and bigger factor loading.

Results: in accordance with the validity and reliability analyzes, it was determined that the 3 subscales and 12-item adaptation of the screen scale were suitable for Turkish society. These subscales are "Food intake and eating habits", "Conditions and difficulties affecting food intake" and "Weight change and food restriction". When the Cronbach alpha internal consistency values were evaluated for the reliability of the SCREEN II scale, the obtained values indicated that the items in each subscale were consistent with each other and formed a whole.

Conclusion: the findings have shown that SCREEN II is a reliable and valid scale for the elderly people living in Turkey.

Keywords:

Nutrition of elderly. Malnutrition. Nutritional assessments. Free-living elderly. Nutritional screening tools.

Resumen

Objetivo: el objetivo de este estudio es determinar la fiabilidad y la validez de la escala de evaluación de riesgos para la alimentación y la nutrición en adultos mayores en la comunidad (SCREEN II, por sus siglas en inglés), que se ha desarrollado con el objetivo de evaluar los riesgos alimentarios y nutricionales de las personas mayores.

Métodos: se incluyeron en el estudio un total de 207 personas mayores. Se aplicó el SMMT (Standardized Mini-Mental Test) para la evaluación de función cognitiva y luego se aplicó la escala SCREEN II. Para la selección de ítems de la escala, se han aplicado a los datos el análisis factorial de componentes principales y la conversión de Varimaks, y se ha decidido utilizar los componentes que tienen una carga factorial de 0,40 y mayor.

Resultados: el estudio mostró que las tres subescalas y la adaptación de los 12 ítems de la herramienta fueron de utilidad cuando se aplicaron a la población turca. Las tres subescalsa fueron: " ingesta de alimentos y hábitos dietéticos", "condiciones y dificultades que afectan a la ingestión de alimentos" y "cambios en el peso y restricción alimentaria". Al aplicar los valores de consistencia interna Cronbach alpha se evidenció que los ítems de cada subescala eran consistentes entre sí y constituían un todo.

Conclusión: los hallazgos han demostrado que SCREEN II es una escala confiable y válida para las personas mayores que viven en Turquía.

Palabras clave:

Nutrición de adultos mayores. Desnutrición. Evaluaciones nutricionales. Adultos mayores que viven en la comunidad. Herramientas de cribado nutricional.

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INTRODUCTION

Aging is an inevitable process that occurs in all living things and cannot be reversed. An adequate and balanced nutrition, medical care facilities, protection from diseases, and improvement of health are important for a quality and long-term life in the old age process (1,2).

Under the influence of aging, many changes occur in the body. Attrition is observed in organs and systems under the influence of aging and chronic diseases. Depending on the factors such as age, genetic structure, environmental factors, nutrition, socio-economic status and quality of life, this wear and the changes that occur may vary from person to person and lead to malnutrition (3-6).

With age, many inadequacies faced with individuals, gastrointestinal, endocrine, immune, genitourinary, urinary tract, central nervous, cardiovascular, skin, respiratory and changes occur in the skeletal system. Until the old age period, the nutritional status and nutrition in old age determine the quality of a person's life. (7,8). Many surveys and scales are used to determine the nutritional status and malnutrition (9). One of the scales used to determine nutritional status and evaluate nutritional risks is the SCREEN II questionnaire. It is a questionnaire that evaluates the risks of eating and nutrition of elderly people in society (10).

As a result, it is aimed to provide a questionnaire that can help determine the risks of nutritional deficiencies and malnutrition to the literature of methods used to determine nutritional status in the elderly together with this study. In this way, it will be a little easier to determine the nutritional risks and the studies conducted on this issue and the results that have been obtained will be more easily compared with studies conducted in other countries.

METHODS

SAMPLE

This study was conducted between January 2018 and September 2018. The sample of the study consisted of individuals aged 50 and over who applied to Ciftehavuzlar Family Health Center No. 4 in Bursa Osmangazi district. There were included 250 participants who did not have dementia, cognitive impairment, communication barrier (not severe hearing, blindness, etc.) and who could answer the questionnaire used in the study were included. However, after the Standardized Mini Mental Test was performed, some individuals were excluded from the study and the study was completed by including 207 participants. Are female 106 of the participants and 101 are male.

Prior to the research, copyright agreement was concluded with Heather Keller (Professor Heather Keller, RD, PhD, University of Guelph, Canada, 1999) and it was stated in the contract that Keller is the copyright and the translation tool will be used for research purposes.

Later, translation studies of the SCREEN II scale were carried out. At the stage of translation of the questionnaire into Turkish, standard translation-reversal method proposed by Brislin et al. (11) was applied. The English original of the questionnaire was translated into Turkish by a total of three specialists who speak English in the field of nutrition: one graduate of English Language Literature, one graduate of American Culture Literature and one graduate of English Translation and Interpreting. As a result of the translations, the articles in the three Turkish questionnaires were compared with each other and the articles with the same translation were determined. Articles with different translations were re-given to the specialist and translated back into English. The final form of the Turkish questionnaire was created by comparing the translated survey items with the original survey items and determining the differences and errors.

The validity and reliability of the Standardized Mini Mental Test (SMMT), consisting of eleven items, was performed for elderly individuals who volunteered for the Turkish society by a psychological consultant trained in scale development, implementation and evaluation. According to the result of the test, which was evaluated on a total of 30 points, the SCREEN II questionnaire was applied to individuals with a SMMT score of more than 20 points by looking at and evaluating whether the elderly had cognitive disabilities using the face-to-face interview technique.

The age of the elderly, gender, educational status, marital status, etc. and, at the same time, anthropometric measurements such as weight and height were recorded by taking sociodemographic information, and body mass index (BMI) values were calculated.

The height of the patient was measured with a height meter and their weight was measured with a weight meter. The height lengths of the individuals who were not dependent on the bed or chair were duly measured with a non-stretching tape measure. During the height measurement, attention was paid to the fact that the feet were adjacent, the knees were straight, the hips and shoulder blades were in contact with the vertical level, and the head was in the Frankfort plane. The body weights of the individuals were duly measured with a 0.1 kg precision digital scale. BMI was calculated by the formula body weight (kg)/length of stature (m^2). The BMI values of individuals were classified based on the BMI classification of the World Health Organization (WHO). Accordingly, BMI was evaluated as follows: < 18.49 kg/m^2 = lean (under weight); 18.50-24.99 kg/m^2 = normal; 25.00-29.99 kg/m^2 = over weight; 30 or higher obesity range. Obesity is frequently subdivided into categories: Grade 1: BMI of 30 to < 35, Grade 2: BMI of 35 to < 40, Grade 3: BMI of 40 or higher. Grade 3 obesity is sometimes categorized as "severe" obesity (12).

DATA COLLECTION TOOLS

The SCREEN II scale used in the study is a 17-item index with two additional weight questions (intention to change the weight in the last six months and perception of current weight). The question of food preparation is a two-stage question. It asks who is preparing the food, and then, the difficulty of preparing the food or the level of satisfaction of the dishes prepared by others. Item scores range from 0 to 4, and the total score is from 0 to 64. The three characteristics of nutritional risk are weight change (increase or decrease), nutrient intake, and risk factors. It is a questionnaire that can be administered by the researcher and does not require anthropometric measurements (13).

Nutritional risk indicators such as weight loss, poor food intake, and risk factors that may cause poor food intake (for example, difficulty in shopping) have been used together to determine whether an individual is at risk. Each item has a maximum of four points, and an increase in the score indicates a decrease in the risk, while a total score of less than 50 indicates a risk (14).

SCREEN II is valid and reliable and has been used to predict mortality and changes in quality of life over time (15).

The SMMT used in the study is used in epidemiological studies to screen for cognitive disorders of individuals living in the community and staying in nursing homes and to follow up on cognitive change in clinical trials. Güngen et al. (16) have confirmed its validity and reliability in the Turkish society. It has been determined that the SMMT is a valid and reliable test that can be applied in Turkish society in the diagnosis of mild dementia, and at the same time the threshold value is 23-24 (17).

ANALYSIS OF RESEARCH DATA

Before deciding on the analyses that should be performed on the collected data, it is necessary to examine how the data are distributed. For this reason, it is discussed how the SCREEN II satisfaction scale scores obtained from the participants are distributed. Table I shows the skewness value, kurtosis value, mode, median and arithmetic mean values of the total scores when examined.

ETHICS COMMITTEE

This research has been approved by the Ethics Committee of the Acibadem University with the decision number 2018-1/125.

SATATISTICAL ANALYSIS

The data obtained in the study were analyzed with the SPSS 24.0 (Statistical Package for Social Sciences) program. Parametric analyses were performed because the kurtosis value was between -1.5 and +1.5 and the skewness value was between -2 and +2. Question number 15 was not included in the analyses because no score of this question was available. In this study, factor analysis of the main components was used to determine the subscales in which the items were collected. In factor analysis, some variables and substances can be linked to more than one variable. In such a case, October operation called rotation is applied. The purpose of October rotation is to increase the load of a variable or substance on one factor, reduce its load on other factors, and find variables and substances that are close to each factor (18).

For the analysis of the data, t-test was used for unrelated samples for two-category groups and ANOVA analysis was used for groups with more than two categories to compare the averages of independent groups. In addition, exploratory factor analysis was performed to reveal the structure of the scale and to test its validity. Exploratory factor analysis is used to determine the characteristics of variables that are at the basis of a large number of measurements and have a smaller number and determine their number. Exploratory factor analysis is used as a method of extracting factor variables that are common to a large number of measurements. In order to test the reliability of the scale, the internal consistency coefficient Cronbach's alpha was calculated. The results of the analysis were reported at a significance level of 0.05.

RESULTS

FINDINGS ON THE VALIDITY OF THE SCREEN II SCALE

In order to test the construct validity, exploratory factor analysis was performed.

When table I is examined, the skewness, that is, the kurtosis value, is between -1.5 and +1.5, and the kurtosis, that is, the skewness value, is between -2 and +2, showing that the data are normally.

At the beginning of the factor analysis, the Kaiser-Mayer-Olkin (KMO) coefficient value of 0.66, Bartlett's value of 284.716, which was made to test the suitability of the data when starting the

Table I. Descriptive distribution of the data obtained from the participants

	I1	I2	I3	I4	I5	I6	I7	I8	I9	I10	I11	I12	I13	I14	I15	I16
Number of participants	207	207	207	207	207	207	207	207	207	207	207	207	207	207	207	207
Arithmetic mean	2.80	2.92	1.53	1.25	2.77	2.72	1.49	1.27	1.31	3.00	2.80	2.94	0.82	1.63	3.28	2.06
Median	4.00	4.00	.00	1.00	4.00	3.00	2.00	1.00	1.00	3.00	4.00	4.00	.00	2.00	4.00	2.00
Mode	4	4	0	1	4	3	2	1	1	4	4	4	0	2	4	2
Distortion	-0.76	-1.04	0.49	0.82	-0.77	-1.37	-0.73	0.72	-0.02	-0.98	-0.70	-1.05	1.37	0.05	-1.63	0.44
Skewness error kurtosis	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16
Kurtosis error	-0.97	-0.92	-1.77	0.98	-0.83	2.50	-0.70	-0.78	-0.06	0.25	-1.32	-0.29	.53	-1.06	1.09	-0.72
Arithmetic mean	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33

factor analysis ($p < .$the data presented as 000) indicate that it is in accordance with AFA. There is a widespread opinion in the literature of the field that the minimum magnitude of a substance for a factor load value should be 0.32, from which the cut-off point determined by the act is 0.32. In this study, Varimaks was used from vertical rotation analyses and it was decided that it should be in a three-factor structure with eigenvalues above 1 and the variance it describes is above 10 %.

The line graph used to decide the number of other dimensions is shown in figure 1. A structure explaining 45.35 % of the 12-item variance was obtained by subtracting four items with a factor load value below 0.32 and also boarding. Items 3, 6, 14 and 15 were excluded from the analysis.

In the nomenclature of the three sub-dimensions obtained as a result of the exploratory factor analysis, it was determined that the substances contained in the factor are more related to the food intake of individuals, and this factor was considered under the name of "Food intake and eating habits". The substances collected under this factor are actively assessing such features as the daily consumption of food groups in their dietary habits. Factor loads of six items collected between 23-24 under the factor of "Food intake and eating habits" vary (17).

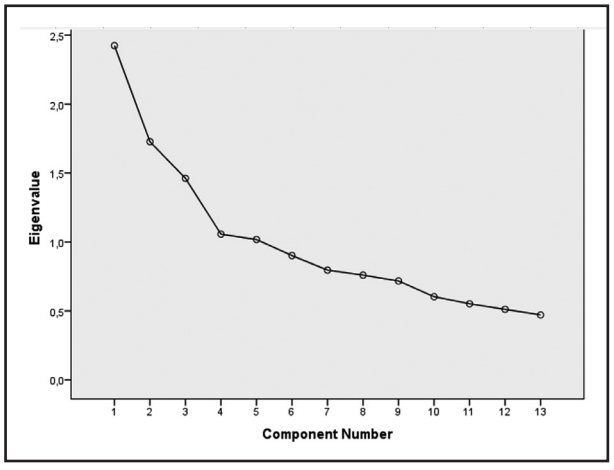

Figure 1.
Line graph of the SCREEN II satisfaction scale.

Findings on the reliability of the SCREEN II scale

Cronback's alpha values for the dimensions obtained as a result of exploratory factor analysis: were found to be 0.53 for the 1st dimension 0.61, for the 2nd dimension 0.57 for the 3rd dimension and 0.55 for the entire scale.

Multiple correlation coefficients in dimension 1 for all participants ranged from 0.30 (10. item) to 0.384 (4. item). The item subscale correlation coefficients are also the lowest at 0.08 (13. item); the highest is 0.17 (7. item) were found (Table II).

Multiple correlation coefficients in dimension 2 for all participants ranged from 0.31 (16. item) to 0.51 (12. item). Item sub-dimension correlation coefficients were found to be the lowest at 0.11 (16. item); the highest is 0.27 (12. item) were found (Table III).

For all participants, the multiple correlation coefficients in dimension 3 ranged from 0.27 (5. item) to 0.41 (1. item). The item subscale correlation coefficients were also found to be 0.08 (5. item); at the lowest and 0.22 (1. item) at the highest (Table IV). In subscales, nutritional intake and eating habits item's are 4, 7, 8, 9, 10, 13, conditions affecting nutritional intake and difficulties encountered item's are 11, 12, 16 and weight change and nutrient restriction item's are 1, 2, 5.

Of the individuals participating in the study, 106 (51.2 %) were female and 101 (48.8 %) were male. In addition, 47.8 % of the individuals are between 50-60; 34.8 % are between 61-70, and 17.4 % are between 71-80 years of age. Also, 10.1 % of individuals are illiterate, 73.4 % have an elementary school education status, and 16.4 % are high school or older. The marital status of the individuals is married, and 15 % are single (Table V).

Table II. Analysis of each item for all participants on the "Nutrition intake and eating habits" subscale of SCREEN II

	Arithmetic mean when item is deleted	Variance when item is deleted	Multiple correlation	Item sub-dimension total correlation	Alpha value when item is deleted
Item 4	7.89	9.727	0.385	0.088	0.483
Item 7	7.66	9.343	0.392	0.175	0.437
Item 8	7.87	8.547	0.331	0.120	0.456
Item 9	7.84	10.507	0.384	0.109	0.491
Item 10	6.14	9.888	0.301	0.066	0.522
Item 13	8.32	8.754	0.334	0.080	0.519

Table III. Analysis of each item for all participants regarding the "Conditions affecting nutritional intake and difficulties experienced" subscale of SCREEN II

	Arithmetic mean when item is deleted	Variance when item is deleted	Multiple correlation	Item sub-dimension total correlation	Alpha value when item is deleted
Item 11	5.00	4.704	0.442	0.228	0.482
Item 12	4.86	4.875	0.516	0.270	0.361
Item 16	5.74	6.803	0.319	0.112	0.638

Table IV. Analysis of each item for all participants on the "Weight change and nutritional restriction" subscale of SCREEN II

	Arithmetic mean when item is deleted	Variance when item is deleted	Multiple correlation	Item sub-dimension total correlation	Alpha value when item is deleted
Item 1	5.69	6.506	0.470	0.229	0.326
Item 2	5.57	5.906	0.396	0.195	0.440
Item 5	5.72	7.873	0.279	0.086	0.601

Table V. Sociodemographic and anthropometric characteristics of individuals

		n	%
Age	50-60	99	47.8
	61-70	72	34.8
	71-80	36	17.4
	Total	207	100.0
Gender	Female	106	51.2
	Male	101	48.8
	Total	207	100.0
Educational Status	Not literated	21	10.1
	Primary School	152	73.4
	High School and above	34	16.4
	Total	207	100.0
Marital Status	Married	176	85.0
	Single	31	15.0
	Total	207	100.0
BMI	Under weight	2	1.0
	Normal	31	15.0
	Over weight	71	34.3
	Grade 1 obese	56	27.1
	Grade 2 obese	32	15.5
	Grade 3 obese	15	7.2
	Total	207	100.0

In the t-test for unrelated samples, which was conducted to reveal whether the SCREEN II scale scores of individuals differ significantly according to the gender variable, no difference was observed ($t_{(205)}$ = -1,946, $p > 0.05$) between the mean score of women ($\bar{X}$ = 25.02) and the mean score of men ($\bar{X}$ = 25.88).

As a result of the ANOVA analysis performed to reveal whether the SCREEN II scale scores of individuals differ significantly according to their age levels, there was a significant difference ($F_{(2-204)} = 5.536$, $p < 0.05$) between the mean score of the participants aged 50-60 ($\bar{X}$ = 26.96), the mean score of the participants aged 61-70 ($\bar{X}$ = 24.18) and the mean score of the participants aged 71-80 ($\bar{X}$ = 23.77).

As a result of the Tukey multiple comparison analysis performed to reveal between which groups the significant difference was, the SCREEN II scale scores of the individuals aged 50-60 were higher than the individuals aged 61-70 and 71-80.

As a result of the ANOVA analysis performed to reveal whether the SCREEN II scale scores of the participants differed significantly according to their BMI status, there was no significant difference ($F_{(5-201)} = 1.006$, $p > 0.05$) between the mean score of the thin participants ($\bar{X}$ = 25.50), the mean score of the normal weight participants ($\bar{X}$ = 26.58), the mean score of the overweight participants ($\bar{X}$ = 26.069), and the mean score of the grade 1 obese participants ($\bar{X}$ = 25.41), and the mean score of the grade 2 obese participants ($\bar{X}$ = 23.96), and the mean score of the grade 3 obese participants ($\bar{X}$ = 23.26).

For unrelated samples conducted to determine whether the SCREEN II scale scores of individuals significantly according to the gender variable, there was no significant difference between the average score of women ($\bar{X}$ = 25.02) and the average score of men ($\bar{X}$ = 25.88) in the t test ($t_{(205)}$) = -1.946, ($p > 0.05$).

As a result of the ANOVA analysis performed to reveal whether the SCREEN II scale scores of individuals differ significantly according to their age levels, there was a significant difference between the mean score of the participants aged 50-60 ($\bar{X}$ = 26.96), the mean score of the participants aged 61-70 ($\bar{X}$ = 24.18), and the mean score of the participants aged 71-80 ($\bar{X}$ = 23.77). As a result of the Tukey multiple comparison analysis conducted to determine which groups had a significant difference, the SCREEN II scale scores of individuals the age range of 50-60 were higher than those in the age range of 61-70 and 71-80.

As a result of the ANOVA analysis conducted to determine whether the participants' SCREEN II scale scores differed significantly according to their BMI status, there was no significant difference between ($F_{(5-201)}$) = 1.006, $p > 0.05$) the average score of the under weight participants ($\bar{X}$ = 25.50), the average score of the normal weight participants ($\bar{X}$ = 26.58), the average score of the overweight participants ($\bar{X}$ = 26.069), the average score of grade 1 obese participants ($\bar{X}$ = 25.41), the average score of grade 2 obese participants ($\bar{X}$ = 23.96), nd the average of grade 3 obese participants ($\bar{X}$ = 23.26).

DISCUSSION

SCREEN-II was first developed to screen the general nutritional status of elderly living in the community, but later its validity was confirmed as a malnutrition screening tool. Validity has been proven to be good in elderly individuals living in the society of Canada and New Zealand (19), and SCREEN II adaptation studies are available in the Swedish society. In these studies, the sensitivity of the criterion validity ranged from 84 to 90 %, and the specificity from 62 % to 86 %. These are promising results for screening for malnutrition in older adults living in the community.

Living in society, nutritionally at risk older adults (55+ years) to identify a 14 point (+3 sub-questions) self-managed, which is a reliable and valid tool to SCREEN II; weight change, the intention of weight loss, body weight perception, risk factors that may adversely affect food intake and fluid intake and in addition includes questions about food. Use risk identification items that are not available in other screening tools (for example, difficulty shopping and preparing food, etc.) is taken into account. Questioning daily eating habits (daily amounts of milk and dairy product consumption, types and amounts of protein consumed, daily portions of vegetables and fruits eaten, etc.) it contains substances.

The concept of nutritional risk is complicated by the fact that the nutritional status is influenced by a wide range of psychosocial and biological factors, and screening for malnutrition in the elderly is considered to be difficult. The SCREEN II tool is mainly a risk assessment for eating and nutrition. It has been used to predict mortality and changes in quality of life over time.

Screening identifies those at nutritional risk from identified risk factors, such as living alone and lack of appetite, so that a detailed nutritional assessment can be done to measure food and nutrient intake. But the SCREEN II tool is not designed to study high-risk causes; for example, it is not designed to study why older adults do not consume enough fruits, vegetables, and dairy products (20).

This study is aimed to test the validity and reliability of the Turkish version of this scale for elderly people living in society. There are no studies in the Turkish literature regarding the scale. Adapting the scale to Turkish will be useful for other studies and researchers to identify elderly people at risk of nutrition.

It is stated that the item specified by Alpar (21) and Kayis (22) should be greater than 0.25, provided that the total correlation coefficient of the lower dimension is not minus sign. When evaluated in this context, the correlation coefficients obtained were found to be higher than the desired value of 0.25. In addition, if the total correlation value of the obtained item is on the original scale developed by Keller et al., it also shows similarities with the item-whole correlation coefficients (10).

One of the important results of our study is that the difference in BMI values does not constitute a significant difference in total score values. The presence of individuals in the weak, normal weight or obese class did not change the risk of nutritional deficiency. In other words, it can be concluded that obese or normal weight or thin individuals are not a criterion that indicates whether individuals are malnourished or not. A recent US study reported that there is a high prevalence of

nutritional deficiency in overweight and obese people compared to normal-weight individuals. The same study shows that these overweight and obese individuals may consume excessive amounts of dietary energy and do not meet their basic nutritional requirements (23).

CONCLUSION

When the analyses performed in this study were examined, statistically significant results were obtained. As a result, the questionnaire "Assessment of the risk of eating and nutrition of elderly people living in society" is a valid and reliable scale and is suitable for use in Turkish population. Nutritional risk assessments such as SCREEN II and also anthropometric measurements were used in this study.

The importance of this study is that it increases public awareness about malnutrition and provides the basis for changes in nutritional behavior in elderly people. This work also provides opportunities to improve the nutrition of the screened population and can be used to assess its effectiveness in free-living communities. Nutritional deficiencies are common in society, especially in the elderly population, and the first way to prevent this is to analyze correctly and to use the right assessment tools suitable for that society.

While this scale provides ease of application and analysis compared to other scales, it also provides a better assessment of the individual in terms of including specific questions that question the effect of social situations (living alone, etc.) or competencies (being able to do the shopping himself, etc.) on malnutrition.

In addition, this study can be further developed and supported with new studies in terms of reliability and community relevance by applying it to larger populations and making comparisons with other nutritional assessments and screening tools that ask and evaluate questions from different perspectives.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Nutrición en el anciano

Association of the triglyceride-glucose index with the occurrence of non-alcoholic fatty liver disease and mortality in elderly inpatients: a prospective observational study

Asociación entre el índice glucemia-triglicéridos con la presencia de hígado graso no alcohólico y mortalidad en pacientes hospitalizados de avanzada edad: estudio observacional prospectivo

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Abstract

Introduction: non-alcoholic fatty liver disease (NAFLD) is a disease in which there is excessive fat deposition in hepatocytes due to hepato-protective factors.

Objectives: to assess the association of the triglyceride-glucose index with the occurrence of non-alcoholic fatty liver disease and mortality in elderly inpatients. To identify the TyG index as a predictive factor of NAFLD.

Methods: this prospective observational study included elderly inpatients admitted to the Department of Endocrinology at the Linyi Geriatrics Hospital, Affiliated to Shandong Medical College, between August 2020 and April 2021. The TyG index was calculated according to an established formula: TyG = Ln [triglycerides (TG) (mg/dl) × Fasting plasma glucose (FPG) (mg/dl) / 2].

Result: a total of 264 patients were enrolled, with 52 (19.7 %) cases occurred NAFLD. Multivariate logistic regression analysis showed that TyG (OR = 3.889; 95 % CI: 1.134-11.420; p = 0.014) and ALT (OR = 1.064; 95 % CI: 1.012-1.118; p = 0.015) were independently associated with the occurrence of NAFLD. Furthermore, receiver operating characteristic (ROC) curve analysis showed that the area under the curve (AUC) of TyG was 0.727, with sensitivity = 80.4 % and specificity = 57.8 % at cut off = 8.71. A Cox proportional hazards regression model showed that, after adjusting for age, sex, smoking, drinking, hypertension, and type 2 diabetes TyG > 8.71 (HR = 3.191; 95 % CI: 1.347 to 7.560; p < 0.001) was an independent risk factor for mortality in the elderly.

Conclusions: the TyG index can predict non-alcoholic fatty liver disease and mortality in elderly Chinese inpatients.

Keywords:

Triglyceride-glucose index. Occurrence. Non-alcoholic fatty liver disease. Mortality. Prospective observational study.

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Conflicts of interest: the authors declare that they have no conflicts of interest.

Ethics statement: the study was approved by the Ethics Committee of the Affiliated Hospital of Shandong Medical College (Linyi Geriatric Hospital) [SDYZFSYY2020002] and was conducted in accordance with the Declaration of Helsinki. All patients signed an informed consent form to verify consent and compliance.

A data sharing statement: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Contributorship statement: author XGW conceived the paper. XGW and YX contributed to implementing the program and acquiring the data. WZ performed the statistical analysis. XGW and WZ wrote the paper. QQS finalized the paper. All authors contributed to the interpretation of data analysis, drafted or reviewed the paper, and approved this version for publication.

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Resumen

Introducción: la enfermedad del hígado graso no alcohólico (EHGNA) es una enfermedad en la que una cantidad excesiva de grasa se acumula en los hepatocitos debido a factores hepatoprotectores.

Objetivos: evaluar la asociación entre el índice glucemia-triglicéridos con la presencia de hígado graso no alcohólico (EHGNA) y mortalidad en pacientes hospitalizados de avanzada edad. Identificar el índice TyG como factor predictivo de la EHGNA.

Métodos: este estudio observacional y prospectivo incluyó a pacientes de avanzada edad hospitalizados en el Departamento de Endocrinología del Hospital de Geriatría de Linyi, Afiliado al Colegio Médico de Shandong, entre agosto de 2020 y abril de 2021. El índice TyG se calculó según una fórmula establecida: TyG = Ln [triglicéridos (TG) (mg/dl) × Glucosa en sangre en ayunas (FPG) (mg/dl) / 2].

Resultado: se incluyeron 264 pacientes, con 52 (19,7 %) casos de EHGNA. El análisis de regresión logística multivariante mostró que el TyG (razón de momios (OR) = 3,889; intervalo de confianza del 95 %: 1,134-11,420; p = 0,014) y ALT (razón de momios (OR) = 1,064; intervalo de confianza del 95 %: 1,012-1,118; p = 0,015) se asociaban de forma independiente con la aparición de EHGNA. Además, el análisis de la curva de características operativas del receptor (ROC) mostró que el área bajo la curva (AUC) de TyG era de 0,727, con una sensibilidad del 80,4 % y una especificidad del 57,8 % en el punto de corte de 8,71. El modelo de regresión de riesgos proporcionales de Cox mostró que, tras ajustar por edad, sexo, tabaquismo, consumo de alcohol, hipertensión y diabetes tipo 2, un TyG > 8,71 (HR = 3,191; intervalo de confianza del 95 %: 1,347 a 7,560; p < 0,001) era un factor de riesgo independiente de mortalidad para los paciente de edad avanzada.

Conclusiones: el índice TyG puede predecir la enfermedad del hígado graso no alcohólico y la mortalidad en pacientes chinos hospitalizados de avanzada edad.

Palabras clave:

Índice glucemia-triglicéridos. Presencia. Enfermedad del hígado graso no alcohólico. Mortalidad. Estudio observacional prospectivo.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a disease in which there is excessive fat deposition in hepatocytes due to hepatoprotective factors other than a history of significant alcohol consumption, drug use, hepatitis C virus infection, or other diseases such as starvation (1). Fatty liver can cause liver damage that leads to inflammation (non-alcoholic steatohepatitis [or NASH]) or liver scarring (cirrhosis) (2). NAFLD is a common worldwide disease with a 10-30 % prevalence in different countries. NAFLD is also increasingly recognized as the cause of elevated levels of liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), or γ-glutamyl transferase (GGT) (3). Several studies have shown that NAFLD is a significant risk factor for peripheral vascular disease, diabetes *mellitus,* cardiovascular disease, and renal disease, which have serious consequences (4-6).

Insulin resistance (IR) (7,8) is the inadequate response of adipocytes, muscle cells, and hepatocytes to normal insulin concentrations when the pancreas has no pathological abnormality. The liver is one of the main sites for the control of metabolic homeostasis. Metabolic diseases such as IR, type 2 diabetes (T2D), dyslipidemia, and NAFLD are linked through molecular biochemistry and complex immune mechanisms (9,10). Hyperinsulinemia is caused by β-cell efforts to overcome IR by enhancing insulin release. High caloric intake impairs insulin receptor signaling, resulting in defective inhibition of FFA release from adipocytes and defective nitric oxide (NO) release (11). Thus, IR and inflammation form a vicious circle in the presence of lipotoxicity, each contributing to the other and accelerating the development of NAFLD and other metabolic disorders (12). In obese and lean subjects, high IR was found to be the most critical predictor of NAFLD (13). Studies have shown that serum insulin levels are strongly associated with ballooning and hepatic lobular inflammation (14).

The aforementioned studies suggest that IR increases the risk of NAFLD and that IR may cause steatosis (15-17). In addition, the triglyceride glucose (TyG) index, an early marker of IR, is considered a cheap and reliable proxy for IR (18). An elevated TyG index has been reported to reflect more severe IR and is associated with all-cause and cardiovascular disease-induced mortality (19). In recent years, the relationship between TyG and NAFLD has been a hot research topic. However, the relationship between the TyG index and NAFLD risk remains limited. Most studied populations are adolescents and middle-aged adults (20-22). To the best of our knowledge, the relationship between the TyG index, NAFLD, and mortality in older Chinese adults has not been reported.

Therefore, this study aimed to explore the association between triglyceride glucose index and the occurrence and mortality of NAFLD in elderly inpatients.

MATERIALS AND METHODS

STUDY DESIGN AND POPULATION

This prospective observational study included elderly inpatients admitted to the Department of Endocrinology at the Linyi Geriatrics Hospital Affiliated to Shandong Medical College between August 2020 and April 2021.

Inclusion criteria were: 1) diagnosis of NAFLD according to the guidelines proposed by the APWG guidelines (23); 2) age above 65 years; and 3) availability of liver ultrasound. Exclusion criteria were: 1) having hepatic viral infection, autoimmune hepatic disease, other chronic hepatic diseases, carcinomatous cachexia (concerning the clinical history), severe infections, acute myocardial infarction, and acute cerebral infarction; and 2) long-term use of steatogenic medications and exceptionally high alcohol intake (more than 140 g per week in men and more than 70 g per week in women).

The study was approved by the Ethics Committee of the Affiliated Hospital of Shandong Medical College (Linyi Geriatric Hospital) [SDYZFSYY2020002] and was conducted by the Declaration of Helsinki. All patients signed an informed consent form to verify consent and compliance.

PROCEDURES

Using an ultrasound machine, trained sonographers performed liver ultrasound (Toshiba, Tokyo, Japan), and NAFLD was diagnosed by ultrasound imaging. The study objectives and experimental data were single-blinded to the sonographer. Images were acquired in a standard fashion, with the patient in the supine position with the right arm raised above the head.

Detailed medical history and lifestyle information, including age, sex, smoking, and drinking status, was confirmed by a trained physician from medical records. Current smoking status was defined as 'yes' if the patients had smoked at least one cigarette per day or seven cigarettes per week in the past six months. Current drinking status was defined as 'yes' if the subject had consumed alcohol at least once a week in the past six months. Blood pressure (BP) in the nondominant arm was measured in the seated position after 5 minutes of rest using an automated electronic instrument (OMRON HEM-752 FUZZY' Omron Corporation, Dalian, China). Three measurements were taken one minute apart, and the average of the three measurements was used for analysis. Measured BP above 140/90 mmHg or being treated with antihypertensive therapy was considered a criterion for hypertension. An experienced physician measured body height, weight, and waist circumference (WC) with an accuracy of 0.1 cm, 0.1 kg, and 0.1 cm, respectively, and participants wore light indoor clothing while standing without shoes. Body mass index (BMI) (kg/m^2) was calculated as weight (kg) divided by height (m^2). All patients fasted overnight before blood samples collection. Fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), hemoglobin A1c (HbA1c), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) measurements were analyzed and determined by an automated analyzer according to standard methods. TyG index was calculated according to the established formula: TyG = Ln [TG (mg/dl) × FPG (mg/dl) / 2].

Participants were followed up for six months, and survival was collected. Follow-up was conducted by telephone, and there were no missed visits.

STATISTICAL ANALYSIS

The SAS version 9.1 (SAS Institute, Cary, NC) was used for database management and statistical analysis. Data for continuous variables were expressed as mean ± standard deviation (SD), and data for categorical variables were expressed as numbers (percentages). The Kolmogorov-Smirnov test was used to test the normal distribution. Comparisons of means and proportions were performed using Student's t-test and the Chi-square test, respectively. In addition, logistic regression analysis was used to evaluate the association between the TyG index and NAFLD. Receiver operating characteristic (ROC) curves were used to determine the optimal TyG index cut off point for predicting NAFLD. Cox regression models with hazard ratios (HRs) and 95 % CIs were conducted to examine the association between TyG index and mortality. A two-sided $p < 0.05$ was considered statistically significant.

PATIENT AND PUBLIC INVOLVEMENT

Patients or the public WERE NOT involved in our research design, conduct, reporting, or dissemination plans.

RESULTS

A total of 264 patients were enrolled (mean age, 86.6 ± 6.4 years; male/female, 203/61), with 52 (19.7 %) of them having NAFLD. There were significant differences in TG, ALT, TyG index, BMI, and WC between NAFLD and non-NAFLD patients (all $p < 0.05$). However, age, sex, smoking status, alcohol consumption status, SBP, DBP, HbA1c, FPG, TC, LDL-c, HDL-c, AST, T2D, and hypertension between NAFLD and non-NAFLD patients were comparable (all $p > 0.05$). Moreover, mortality in NAFLD patients (20.8 %) was significantly higher than in non-NAFLD (8.8 %) patients ($p = 0.006$) (Table I). With the increase of the TyG index tertile**,** the occurrence of NAFLD increased significantly ($p_{trend} < 0.001$) (Fig. 1).

Table I. Characteristics of NAFLD and Non-NAFLD in older adults

Variables	NAFLD (n = 52)	Non-NAFLD (n = 212)	p-value
Age (years)	84.6 ± 5.1	85.9 ± 6.7	0.19
Male n (%)	41 (77.4)	162 (76.8)	0.93
Smoking status n (%)	8 (18.6)	39 (15.4)	0.59
Drinking status n (%)	2 (3.9)	7 (3.3)	0.86
SBP (mm Hg)	132.8 ± 14.3	133.2 ± 19.3	0.86
DBP (mm Hg)	72.6 ± 9.6	71.5 ± 11.0	0.51
HbA1c (%)	6.4 ± 1.2	6.1 ± 0.9	0.05
FPG (mmol/l)	6.1 ± 2.1	5.6 ± 1.6	0.07
TC (mmol/L)	4.2 ± 1.0	4.0 ± 0.9	0.12
TG (mmol/L)	1.6 ± 1.0	1.1 ± 0.7	< 0.001
LDL-c (mmol/L)	2.3 ± 0.7	2.2 ± 0.8	0.42
HDL-c (mmol/L)	1.1 ± 0.4	1.2 ± 0.3	0.09
ALT (U/L)	24.0 ± 13.5	15.5 ± 10.6	0.002
AST (U/L)	23.2 ± 8.8	15.5 ± 10.6	0.06
TyG	8.8 ± 0.6	8.3 ± 0.6	< 0.001
BMI (kg/m^2)	25.5 ± 2.9	23.3 ± 3.3	< 0.001
WC (cm)	95.2 ± 8.9	88.0 ± 10.0	< 0.001
T2D n (%)	21 (39.6)	87 (41.2)	0.83
Hypertension n (%)	46 (86.8)	189 (89.6)	0.57
Mortality n (%)	17 (20.8)	16 (8.8)	0.006

SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1c: hemoglobin A1c; FPG: fasting plasma glucose; TC: total cholesterol; TG: triglyceride; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TyG: triglyceride and glucose index; BMI: body mass index; WC: waist circumference; T2D: type 2 diabetes.

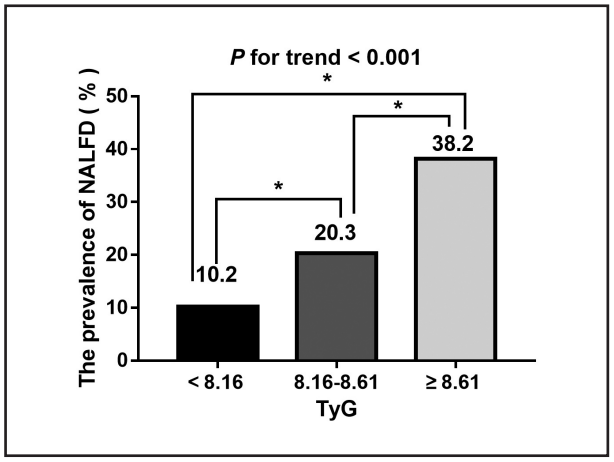

Figure 1.

The difference in the prevalence of NAFLD according to the TyG index tertile.

A multivariate logistic regression analysis showed that TyG (OR = 3.889; 95 % CI: 1.134-11.420; p = 0.014) and ALT (OR = 1.064; 95 % CI: 1.012-1.118; p = 0.015) were independent risk factors for NAFLD (Fig. 2 and Table II). ROC curve analysis of the TyG index for NAFLD showed an AUC of 0.727 [(p < 0.001); 95 % CI: 0.645 to 0.809], with sensitivity = 80.4 %, and specificity = 57.8 % at cut off = 8.71 (Fig. 3).

Furthermore, the Kaplan-Meier survival curve for TyG > 8.71 was significantly higher than that of the TyG < 8.71 group (p < 0.001) (Fig. 4). A Cox proportional hazard regression model showed that, after adjusting for age, sex, smoking, drinking, hypertension, and T2D, TyG > 8.71 (HR = 3.191; 95 % CI: 1.347 to 7.560; p < 0.001) was an independent risk factor for mortality (Fig. 5).

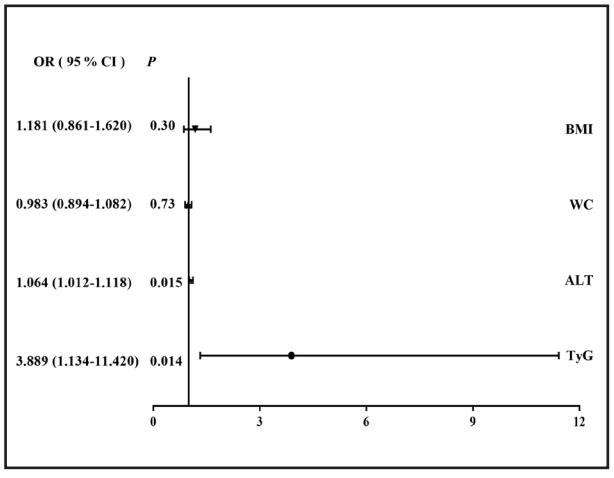

Figure 2.

Independent factors for NAFLD by multivariable logistic regression analysis. BMI: body mass index; WC: waist circumference; ALT: alanine aminotransferase; TyG: triglyceride and glucose index.

Table II. Risk factors associated with NAFLD

Variables	Multivariate analysis	
	OR (95 % CI)	p-value
BMI	1.181 (0.861, 1.620)	0.300
WC	0.983 (0.894, 1.082)	0.730
ALT	1.064 (1.012, 1.118)	0.015
TyG	3.889 (1.134, 11.420)	0.014

BMI: body mass index; WC: waist circumference; ALT: alanine aminotransferase; TyG: triglyceride and glucose index.

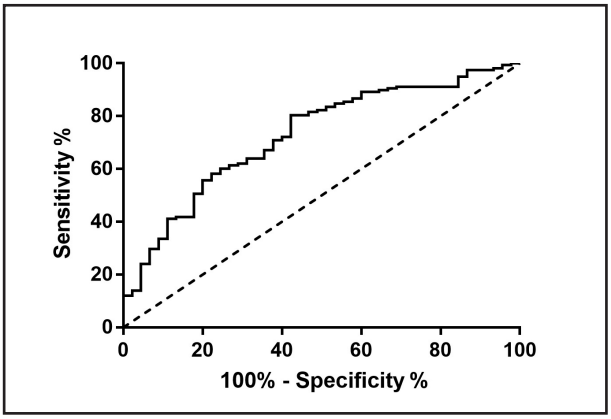

Figure 3.

ROC curve analysis of TyG for NAFLD. AUC = 0.727 (p < 0.001); 95 % CI: 0.645-0.809; TyG cut off point: 8.71; Youden index: 0.342; sensitivity: 80.4 %; specificity: 57.8 %.

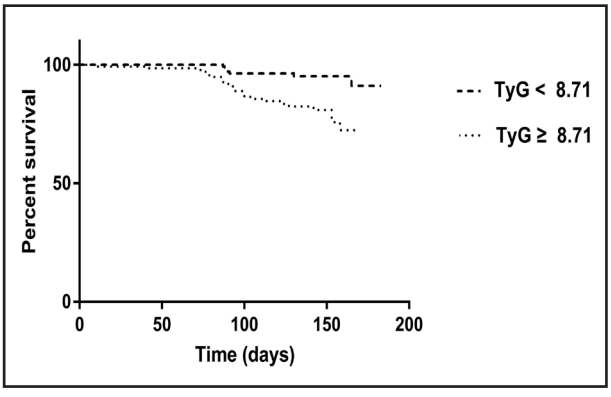

Figure 4.

Survival curves of the study population according to the TyG cut off point. Log-rank test (p < 0.001).

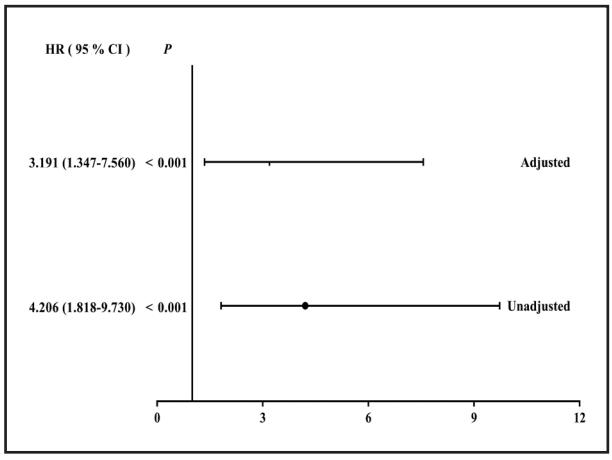

Figure 5.

Association between TyG and mortality (6-month follow-up) according to Cox regression models adjusted for potential confounders. Adjusted for age, sex, smoking, drinking, hypertension, and T2D.

DISCUSSION

This study suggested that the TyG index may be associated with the occurrence and mortality of NAFLD in elderly inpatients. Therefore, the TyG index may be a potential and non-invasive indicator to identify NAFLD.

Several studies have confirmed that IR is closely associated with the development and progression of NAFLD (24,25). Elevated IR can lead to changes from normal liver to NAFLD to non-alcoholic steatohepatitis (NASH) (20). The TyG index is associated with IR in muscle (26), and an increase in IR in muscle leads to glucose flow to the liver and a relatively low IR in the liver leading to fatty liver (27). Therefore, the TyG index is an inexpensive and reliable IR surrogate that plays a vital role in the development and progression of NAFLD (28). To our knowledge, our study is the first to focus on the effect of the TyG index on morbidity and mortality in NAFLD in Chinese elderly people, and elevated TyG remained an independent risk factor for death in the Chinese elderly patient population after adjusting for potential confounders. A retrospective cohort study showed that after adjusting for possible confounders (including sex, BMI, SBP, DBP, HbA1c, ALT, AST, and HDL-c), the prevalence of NAFLD in older adults aged 60 years or more senior was 12.1 % (29), which was lower than in our study (19.7 %). A higher TyG index has also been reported to be associated with a higher risk of NAFLD, which is consistent with our results (29). In this study, we identified an optimal TyG index threshold of 8.71 for predicting NAFLD morbidity in older Chinese adults, which is similar to other research (29), taking race, sex, age, and sample size into account.

This study also has some limitations. First, although ultrasonography showed high sensitivity and specificity in the diagnosis of moderate and severe fatty liver (29), it is still not accurate enough compared to liver biopsy-based diagnosis and may lead to the underdiagnosis of mild fatty liver. Therefore, we may only reveal a significant association between TyG index and moderate and severe fatty liver. Second, the sample size of this study was small, and the data were not analyzed according to gender. Finally, all participants in the study were Chinese, so the results may not apply to other ethnic groups.

In conclusion, the TyG index may be associated with the occurrence of NAFLD and mortality in elderly inpatients. TyG index may be a valuable indicator for NAFLD prediction and help prevent the development of NAFLD at an early stage.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Obesidad y síndrome metabólico

Relación del polimorfismo del gen de la resistina (rs7139228) con los niveles de resistina y el riesgo de síndrome metabólico en sujetos obesos

Relationship of resistin gene polymorphism (rs7139228) with resistin levels and metabolic syndrome risk in obese subjects

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Resumen

Antecedentes: a pesar de la relación de la resistina con el síndrome metabólico (SM), no se ha evaluado la relación del polimorfismo de nucleótido único (SNP) rs7139228 con variante C/T del intrón 5´UTR del gen *RETN* con la presencia de SM.

Objetivo: el objetivo del presente estudio es evaluar la influencia del SNP rs7139228 del gen *RETN* sobre las concentraciones de resistina circulante, así como sobre el SM en sujetos obesos**.**

Material y métodos: se reclutó una población caucásica de 1003 sujetos obesos. En todos los sujetos se realizó un análisis antropométrico (peso, perímetro de cintura, masa grasa), una evaluación de la ingesta nutricional, un estudio bioquímico (glucosa, insulina, proteína C-reactiva, perfil lipídico, insulina, HOMA-IR, resistina) y una evaluación del genotipo rs7139228.

Resultados: la distribución del genotipo fue la siguiente: 852 sujetos con GG (84,9 %), 147 sujetos con GA (14,7 %) y 4 sujetos con AA (0,4 %). La frecuencia alélica fue G (0,92) y C (0,08). Las concentraciones séricas de resistina (delta: 1,7 ± 0,2 ng/ml; p = 0,01), insulina (delta: 4,2 ± 0,4 UI/L; p = 0,01) y HOMA-IR (delta: 1,9 ± 0,2 unidades; p = 0,03) fueron mayores en los pacientes portadores del alelo A que en los no portadores. La prevalencia global del SM fue del 48,1 %. El análisis de regresión logística mostró un alto porcentaje de hiperglucemia (OR = 1,60, IC 95 % = 1,08-2,96; p = 0,02) y de síndrome metabólico (OR = 1,33, IC 95 % = 1,07-3,39; p = 0,02) en los portadores del alelo A después de ajustar las concentraciones de resistina, el sexo, el IMC y la edad.

Conclusiones: el alelo A de la variante genética rs7139228 se asocia con mayores niveles de resistina, insulina basal, resistencia a la insulina y prevalencia de síndrome metabólico en sujetos obesos.

Palabras clave:

Síndrome metabólico. Obesidad. Resistina. rs3138167.

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Declaración de ética: el Comité de Ética Local (HCUVA Clínico Universitario Valladolid-Comité-6/2018) aprobó el diseño experimental. Todos los voluntarios firmaron el consentimiento informado por escrito para participar en el estudio. Todos los procedimientos realizados en este estudio se realizaron de acuerdo con la Declaración de Helsinki.

Conflictos de intereses: los autores no tienen ningún conflicto de intereses que declarar.

Contribución de los autores: Daniel Antonio de Luis y Rocío Aller diseñaron el estudio y escribieron el artículo. Olatz Izaola y Rocío Aller realizaron la evaluación nutricional. D Primo y D de Luis realizaron la evaluación bioquímica.

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Abstract

Background: despite the relationship of resistin with metabolic syndrome (MS), the relationship of the 5'UTR intron C/T variant single nucleotide ploymorphism (SNP) rs7139228 of the *RETN* gene with the presence of MS has not been evaluated.

Objective: the objective of this study is to evaluate the influence of SNP rs7139228 of the *RETN* gene on circulating resistin levels, as well as on MS in obese subjects.

Material and methods: a Caucasian population of 1003 obese subjects was enrolled. An anthropometric evaluation (weight, waist circumference, fat mass), evaluation of nutritional intake, biochemical study (glucose, insulin, C-reactive protein, lipid profile, insulin, HOMA-IR, resistin) and rs7139228 genotype was carried out.

Results: genotype distribution was: 852 subjects with GG (84.9 %), 147 subjects with GA (14.7 %) and 4 subjects with AA (0.4 %). The allelic frequency was G (0.92) and A (0.08). Serum levels of resistin (delta: 1.7 ± 0.2 ng/ml; p = 0.01), insulin (delta: 4.2 ± 0.4 IU/L; p = 0.01) and HOMA-IR (delta: 1.9 ± 0.2 units; p = 0.03) were higher in patients carrying the A allele than in non-carriers. The overall prevalence of MS was 48.1 %. A logistic regression analysis showed a high percentage of hyperglycemia (OR = 1.60, 95 % CI = 1.08-2.96; p = 0.02) and metabolic syndrome (OR = 1.33, 95 % CI = 1.07-3.39, p = 0.02) in carriers of the A allele after adjusting for resistin levels, sex, BMI and age.

Conclusions: the A allele of the genetic variant rs7139228 is associated with higher levels of resistin, basal insulin, insulin resistance, and prevalence of metabolic syndrome in obese subjects.

Keywords:

Metabolic syndrome. Obesity. Resistin. rs3138167.

INTRODUCCIÓN

El tejido adiposo realiza, además de su bien conocido papel como deposito de energía, la producción de una serie de moléculas con múltiples acciones llamadas adipoquinas. Estas moléculas bioactivas tienen funciones importantes en el metabolismo, la sensibilidad a la insulina y los sistemas de control de la saciedad y el apetito (1). Estas adipoquinas podemos categorizarlas en dos subgrupos, antiinflamatorias y proinflamatorias, y ambos sistemas se encuentran en estado de equilibrio e involucrados en el metabolismo de la glucosa. Dentro del grupo de las adipoquinas proinflamatorias tenemos a la resistina. Esta molécula es secretada por los macrófagos infiltrados en el tejido adiposo y también a nivel del tejido hepático (2). En algunos trabajos de investigación, las concentraciones circulantes de resistina sérica se asocian con un aumento de la masa grasa total, la masa grasa visceral (3) y la presencia de diabetes *mellitus* de tipo 2 (4). Existe una relación entre los niveles elevados de resistina y la inhibición de la vía de señalización de la insulina. Esta inhibición está provocada por la acción del supresor de la señalización de citoquinas 3 (SOCS-3), que conduce a la inducción del sustrato del receptor de insulina 1/2 (IRS1/2) y a la degradación de la resistencia a la insulina (5).

Además, las concentraciones circulantes de resistina tienen un alto grado de heredabilidad (6), que puede alcanzar hasta el 80 %. El gen que codifica la resistina (*RETN*) se encuentra en el cromosoma 19p13.2, y en él se han descrito varios polimorfismos de un único nucleótido (SNP) con resultados contradictorios. Se ha demostrado que los polimorfismos de un solo nucleótido (SNP) de *RETN* aumentan la susceptibilidad a la diabetes *mellitus* al elevar las concentraciones de resistina (7-9). Sin embargo, otros SNP de este gen, como el rs7139228, apenas se han evaluado. Esta variante C/T del intrón 5'UTR (SNP rs7139228) es un polimorfismo asociado con concentraciones elevadas de resistina independientemente de la edad, el índice de masa corporal y el sexo (10). A pesar de estos datos, no existen estudios en la literatura que evalúen su relación con el riesgo de síndrome metabólico (SM) en pacientes obesos. Si tenemos en cuenta que la presencia de SM en el paciente obeso aumenta su riesgo cardiovascular (11), investigar el efecto de los polimorfismos de nucleótido único (SNP) del gen *RETN* es de alto interés para poder detectar a los pacientes predispuestos. Por tanto, el objetivo de nuestro estudio es evaluar la influencia del SNP rs7139228 del gen *RETN* sobre las concentraciones séricas de resistina, así como sobre la presencia de síndrome metabólico en pacientes obesos.

MATERIAL Y MÉTODOS

SUJETOS

Se reclutaron un total de 1003 sujetos obesos que acudieron a las consultas externas de nutrición en un muestreo no probabilístico consecutivo. El estudio se llevó a cabo en el Hospital Clinico Universitario de Valladolid de acuerdo con los principios de la Declaración de Helsinki, y fue aprobado por el Comité Ético Institucional para la Investigación en seres humanos (HCUVa 6/2018). Todos los participantes firmaron un consentimiento informado, con un anexo referente al estudio genético realizado, y se les explicó la importancia del estudio. Estos pacientes obesos fueron reclutados por el Servicio de Endocrinología y Nutrición tras ser derivados por los médicos de atención primaria del Área para evaluación de su obesidad. Los criterios de inclusión en el estudio fueron los siguientes: edad mayor de 18 años, índice de masa corporal (IMC) mayor de 30 kg/m^2 y ausencia de dieta durante los 6 meses previos al estudio. Los criterios de exclusión fueron los siguientes: antecedentes de enfermedad cardiovascular o accidente cerebrovascular durante los 12 meses anteriores, cáncer o cirugía mayor por cualquier causa en los 6 meses anteriores y uso actual de tratamientos farmacológicos para la diabetes, antiinflamatorios no esteroideos, fibratos o glucocorticoides.

PROCEDIMIENTOS

Se obtuvieron muestras de sangre venosa tras 12 h en ayunas de todos los sujetos mediante punción venosa. En estas muestras se determinaron los niveles de glucosa basal, el perfil

lipídico (colesterol total, colesterol-LDL, colesterol-HDL, concentración de triglicéridos plasmáticos), la proteína C-reactiva (PCR), la insulina, la resistencia a la insulina determinada por HOMA-IR y las concentraciones de resistina.

En todos los pacientes obesos se determinaron los siguientes parámetros antropométricos: masa grasa por bioimpedancia, peso, talla, índice de masa corporal (IMC) y circunferencia de la cintura, y finalmente se midió la presión arterial. Todas estas determinaciones antropométricas y la medida de la presión arterial se realizaron a la misma hora del día (por la mañana). También se registraron la ingesta dietética y el ejercicio físico que realizaba cada paciente.

Se utilizaron los criterios del *Adult Treatment Panel III* (ATPIII) para diagnosticar en los sujetos la presencia de síndrome metabólico (11). El diagnóstico de SM requirió al menos 3 de los siguientes datos: glucosa en ayunas elevada o tratamiento para la diabetes *mellitus,* triglicéridos elevados (> 150 mg/dl) o tratamiento para la hiperlipidemia, colesterol-HDL bajo < 40 mg/dl (hombres) o < 50 mg/dl (mujeres), presión arterial sistólica o diastólica elevadas (> 130/85 mmHg o tratamiento antihipertensivo) y perímetro de cintura aumentado (> 94 cm [hombres] o > 80 cm [mujeres]).

GENOTIPADO DEL POLIMORFISMO DEL GEN *RETN* RS7139228

El ADN genómico se extrajo de leucocitos de sangre periférica con el kit comercial Vineo Extract DNA (Biorad CA, LA, EE. UU.). La cantidad de ADN extraído se analizó con un espectrofotómetro (Fischer, Madrid, España). La reacción en cadena de la polimerasa (RCP) en tiempo real se realizó con un termociclador (Biorad CA, LA, EE. UU.). En primer lugar se marcó el ADN amplificado (fluorescente; 5'6-carboxiffluoresceína (FAM) y 6-hexaclorofluoresceína [HEX]), y posteriormente se midió la cantidad de fluorescencia liberada durante la amplificación, la cual es directamente proporcional a la cantidad de ADN amplificado. Los cebadores y sondas de oligonucleótidos se diseñaron con el programa informático Beacon Designer 5.0 (Premier Biosoft International®, LA, CA, EE. UU.). Se realizó una PCR con 50 ng de ADN genómico y 0,5 µL de cada oligonucleótido cebador (cebador directo: 5'- ACGTTGGATGGCAAAGATTCTGATCTCGGG -3' y reverso 5'- ACGTTGGATGCCATCATTTTCAGCATGTATG -3'). El ADN se desnaturalizó a 95 °C durante 3 minutos; se realizaron 45 ciclos de desnaturalización a 95 °C durante 15 segundos y, posteriormente, a 59,3 °C durante 45 segundos. La PCR se realizó en un volumen final de 25 µl que contenía 12,5 µl de IQTM Supermix (Bio-Rad®, Hercules, CA, EE. UU.) con ADN-polimerasa TAq. Si ambas cadenas crecían en una muestra de paciente, este paciente se clasificó como heterocigoto. Si solo crecía una hebra en una muestra de paciente, este paciente se clasificó como homocigoto. El software del termociclador clasifica a cada paciente como homocigoto de tipo salvaje (GG), heterocigoto (GA) y homocigoto mutante (AA). Además, en cada reacción se incluyeron un control negativo y muestras de control que representaban todos los genotipos. El equilibrio de Hardy-Weinberg se determinó con una prueba estadística (chi cuadrado). La variante del gen *RETN* estaba en equilibrio de Hardy-Weinberg (p = 0,26).

DETERMINACIONES DE LABORATORIO

El análisis bioquímico sérico de glucosa, insulina, proteína C-reactiva (PCR), colesterol total, colesterol-HDL y triglicéridos se llevó a cabo utilizando el analizador COBAS INTEGRA 400 (Roche Diagnostic, Basilea, Suiza). El colesterol-LDL se calculó mediante la fórmula de Friedewald (colesterol-LDL = colesterol total – colesterol-HDL – triglicéridos / 5) (12). La resistencia a la insulina se calculó mediante el método modelo de homeostasis para la resistencia a la insulina (HOMA-IR) con la siguiente fórmula: glucosa x insulina / 22,5 (13). Las concentraciones de resistina se determinaron por ELISA (Biovendor Laboratory, Inc., Brno, República Checa) con una sensibilidad de 0,2 ng/ml y con un rango de normalidad de 4-12 ng/ml (14).

TENSIÓN ARTERIAL, MEDIDAS ANTROPOMÉTRICAS Y ENCUESTA NUTRICIONAL

La tensión arterial se midió en tres ocasiones después de un tiempo de reposo de 10 minutos con un esfigmomanómetro de mercurio (Omrom, LA, CA, EE. UU.), y se promediaron los resultados. El peso corporal se midió con una balanza con precisión de 100 g (Omrom, LA, CA, EE. UU.) y el índice de masa corporal se calculó como peso (kg) / talla (m^2), clasificando como obesos a los pacientes con un índice de masa corporal superior a 30 kg/m^2 (15). También se determinó la circunferencia de la cintura con una cinta métrica (tipo SECA, SECA. Birmingham, UK) (diámetro más estrecho entre la xifoides y la cresta ilíaca). La masa grasa total se calculó mediante impedanciometría con una precisión de 5 g (16) (EFG BIA 101 Aniversario, Akern, It). Se utilizó la siguiente fórmula (0,756 x Altura^2 / Resistencia) + (0,110 x Masa corporal) + (0,107 x Reactancia) – 5,463. Todos los sujetos recibieron instrucciones para registrar su ingesta dietética diaria durante tres días no consecutivos, incluido un día de fin de semana. Los registros fueron analizados con un sistema de evaluación de datos basado en el software (Dietosource®, Ge, Swi) (17). Todos los sujetos registraron el ejercicio físico diario en minutos por semana con un cuestionario autoadministrado, que consistía en la recogida diaria de la actividad en una agenda.

ANÁLISIS ESTADÍSTICO

El tamaño de la muestra del estudio se calculó para detectar diferencias en la prevalencia del síndrome metabólico del 5 % con una potencia del 90 % y una significación del 5 % (n = 1000). Se utilizó la prueba de Kolmogorov-Smirnov para determinar la distribución de las variables. Los resultados se expresa-

ron como media +/- desviación estándar. Las variables numéricas cuantitativas con distribución normal se analizaron con una prueba t de Student. Las variables no paramétricas se analizaron con la prueba U de Mann-Whitney. Las variables categóricas se analizaron con la prueba del chi cuadrado, con la corrección de Yates y la prueba de Fisher. Se determinó la *odds ratio* (OR) con un intervalo de confianza del 95 % para evaluar la influencia de este SNP en la presencia de síndrome metabólico y sus criterios; posteriormente se realizó un análisis de regresión logística (método *forward*) con la variable dependiente dicotómica. El análisis estadístico se realizó para los genotipos GA y AA combinados como un grupo (grupo mutante, alelo menor) y GG como un genotipo de tipo salvaje, con un modelo dominante. Se consideró estadísticamente significativo un valor de $p < 0,05$ (SPSS 23.0, IL, EE. UU.).

RESULTADOS

Un total de 733 (73,1 %) eran mujeres y 270 (26,9 %) eran hombres (n = 1003). La edad media del grupo era de 48,3 ± 6,2 años, sin diferencias significativas de edad entre varones y mujeres (48,1 ± 5,2 años *vs.* 48,9 ± 6,1 años: ns).

Tras el genotipado de los 1003 sujetos obesos en función del polimorfismo rs7139228, la distribución del genotipo fue la siguiente: 852 sujetos con GG (84,9 %), 147 sujetos con GA (14,7 %) y 4 sujetos con AA (0,4 %). La frecuencia alélica fue G (0,92) y A (0,08). Al agrupar a los sujetos para realizar un análisis dominante, se obtuvieron las siguientes frecuencias: 852 sujetos con genotipo salvaje GG (84,9 %), con un total de 614 mujeres (72,1 %) y 238 hombres (27,9 %), y un total de 151 (15,1 %) sujetos con genotipo mutante (GA+AA), siendo 119 (78,9 %) mujeres y 32 (21,1 %) hombres.

En la tabla I se muestran los valores medios de los diferentes parámetros antropométricos y la presión arterial en relación con el polimorfismo rs7139228, sin diferencias significativas entre ambos grupos de genotipos (análisis dominante).

Tabla I. Parámetros antropométricos y presión arterial

Parámetros	GG n = 852	GA+AA n = 151	p
IMC	36,1 ± 0,2	36,2 ± 0,5	0,43
Peso (kg)	95,9 ± 2,2	94,8 ± 1,3	0,49
Masa grasa (kg)	39,5 ± 1,1	39,0 ± 1,0	0,50
CC (cm)	112,1 ± 3,0	111,9 ± 2,9	0,31
TAS (mmHg)	130,1 ± 2,2	129,2 ± 3,1	0,32
TAD (mmHg)	81,2 ± 3,1	81,7 ± 4,2	0,42

IMC: índice de masa corporal; TAD: tensión arterial diastólica; TAS: tensión arterial sistólica; CC: circunferencia de la cintura. Sin diferencias estadísticamente significativas entre los genotipos, análisis dominante (GG vs. GA+AA).

En la tabla II se muestran los valores bioquímicos en relación al polimorfismo rs7139228, sin diferencias significativas entre ambos grupos de genotipos en el perfil lipídico, la glucosa basal y los niveles de proteína C-reactiva. Sin embargo, las concentraciones séricas de resistina (delta: 1,7 ± 0,2 ng/ml; p = 0,01), insulina (delta: 4,2 ± 0,4 UI/L; p = 0,01) y HOMA-IR (delta: 1,9 ± 0,2 unidades; p = 0,03) fueron mayores en los pacientes portadores del alelo A que en los no portadores.

Tabla II. Parámetros bioquímicos y niveles circulantes de resistina (media ± DE)

Parámetros	GG n = 852	GA+AA n = 151	p
Glucosa (mg/dl)	99,1 ± 5,1	99,9 ± 3,0	0,43
Colesterol total (mg/dl)	205,1 ± 12,8	204,9 ± 13,2	0,61
Colesterol-LDL (mg/dl)	125,9 ± 4,9	124,8 ± 3,9	0,32
Colesterol-HDL (mg/dl)	51,9 ± 2,8	50,8 ± 2,7	0,39
Triglicéridos (mg/dl)	129,2 ± 7,1	126,1 ± 8,1	0,41
Insulina (mUI/L)	13,1 ± 1,0	17,2 ± 0,8*	0,01
HOMA-IR	3,2 ± 0,3	5,0 ± 0,5*	0,03
PCR (mg/dl)	3,9 ± 0,3	3,8 ± 0,4	0,41
Resistina (ng/ml)	5,2 ± 0,5	7,0 ± 0,7	0,02

HOMA-IR: homeostasis model assessment of insulin resistance; PCR: proteína C-reactiva. Diferencias estadísticamente significativas entre los genotipos (insulina-HOMA-IR), análisis dominante (GG vs. *GA+AA).*

Para evaluar la relación de la ingesta dietética y de la actividad física, se compararon estos parámetros en ambos grupos de sujetos obesos, sin encontrar diferencias estadísticamente significativas ni en la ingesta calórica, ni en la distribución de macronutrientes (análisis dominante) (Tabla III).

Para analizar la relación entre las concentraciones de resistina, los genotipos SNP rs7139228 y la presencia de síndrome metabólico (SM), se compararon los valores de resistina en ambos genotipos. Las concentraciones séricas de resistina fueron mayores en los portadores del alelo A con síndrome metabólico (SM 7,9 ± 0,4 ng/ml *vs.* sin SM 4,7 ± 0,3 ng/ml; p = 0,03); sin embargo, no existieron diferencias en las concentraciones séricas de resistina en los pacientes no portadores del alelo A (SM 5,3 ± 0,5 ng/ml *vs.* sin MS 5,1 ± 0,8 ng/ml; p = 0,43).

La prevalencia global de síndrome metabólico en la muestra fue del 48,1 %. El porcentaje de pacientes con síndrome metabólico y sus diferentes componentes (obesidad central, niveles bajos de colesterol HDL, hipertrigliceridemia, hipertensión o hiperglucemia) se muestran en la tabla IV. El porcentaje

de sujetos con obesidad que presentaban hiperglucemia (OR = 1,63, IC 95 % = 1,12-2,37; p = 0,02) y síndrome metabólico (OR = 1,44, IC 95 % = 1,02-2,04; p = 0,02) fueron mayores en los portadores del alelo A que en los no portadores de este alelo de riesgo.

Por último, el análisis de regresión logística mostró un mayor porcentaje de hiperglucemia (OR = 1,60, IC 95 % = 1,08-2,96; p = 0,02) y de síndrome metabólico (OR = 1,33, IC 95 % = 1,07-3,39; p = 0,02) en los portadores del alelo A después de ajustar los niveles de resistina, el sexo, el IMC y la edad.

Tabla III. Ingesta dietética y actividad física (media ± DE)

Parámetros	GG n = 852	GA+AA n = 151	p
Calorías (cal/día)	1911,5 ± 110,9	1908,2 ± 108,9	0,31
Carbohidratos (g/día)	260,2 ± 7,1	259,7 ± 8,3	0,32
Proteínas (g/día)	81,1 ± 5,3	83,9 ± 3,2	0,43
Lípidos (g/día)	62,9 ± 4,9	62,1 ± 4,0	0,33
Fibra (g/día)	14,0 ± 2,1	14,9 ± 1,1	0,32
Colesterol (mg/día)	260,1 ± 23,1	259,3 ± 21,1	0,39
Ácidos grasos saturados (g/día)	17,9 ± 2,1	18,1 ± 2,2	0,38
Ácidos grasos monoinsaturados (g/día)	29,5 ± 4,1	29,4 ± 5,1	0,51
Ácidos grasos polinsaturados (g/día)	6,8 ± 3,0	6,9 ± 3,1	0,41
Actividad fisica (minutos/semana)	153,2 ± 21,2	154,1 ± 22,1	0,49

Sin diferencias estadísticamente significativas entre los genotipos; análisis dominante (GG vs. *GA+AA).*

Tabla IV. Síndrome metabólico y componentes del síndrome metabólico

Parámetros	GG n = 852	GA+AA n = 151	p
Porcentaje de SM	47,2 %	52,1 %*	0,02
Porcentaje de obesidad central	50,1 %	50,8 %	0,43
Porcentaje de hipertrigliceridemia	11,9 %	9,5 %	0,51
Porcentaje de niveles bajos de colesterol-HDL	32,5 %	30,7 %	0,49
Porcentaje de hipertensión	44,5 %	40,0 %	0,35
Porcentaje de hiperglicemia	23,9 %	33,7 %*	0,02

*Los puntos de corte para los criterios son: obesidad central (perímetro de cintura > 88 cm en mujeres y > 102 en hombres), hipertensión (TA sistólica > 130 mmHg o TA diastólica > 85 mmHg o tratamiento específico), hipertrigliceridemia (triglicéridos > 150 mg/dl o tratamiento específico) o hiperglucemia (glucosa plasmática en ayunas > 110 mg/dl o tratamiento farmacológico para la glucemia elevada). *p < 0,05 entre genotipos en un modelo dominante (GG vs. GA+AA).*

DISCUSIÓN

La relación entre la variante rs7139228 del gen RETN y la presencia de síndrome metabólico aún no se ha evaluado a pesar de la consistente relación detectada en la literatura entre las concentraciones sanguíneas de resistina y las alteraciones metabólicas (18,19). En nuestro estudio transversal que analiza esta variante del gen *RETN* en pacientes adultos caucásicos obesos, mostramos una asociación significativa entre el alelo A del SNP rs7139228, con la variante C/T del intrón 5´UTR, y las concentraciones de resistina, insulina y resistencia a la insulina (HOMA-IR). Además, de manera independiente, se detectó una relación con una mayor prevalencia de hiperglucemia y síndrome metabólico y con la presencia del alelo A.

Estas asociaciones metabólicas encontradas tienen una base fisiopatológica y se ha demostrado que la resistina incrementa la síntesis de citocinas inflamatorias en los macrófagos del tejido adiposo y que este estado inflamatorio induce a su vez la

expresión del gen de la resistina (20). A su vez, esta situación proinflamatoria mantenida en el tiempo se involucra en la patogenia de la resistencia a la insulina y, por tanto, la resistina podría ser el nexo de unión entre la situación inflamatoria del obeso y la resistencia a la insulina que este presenta. Además, se ha demostrado que la resistina incrementa las concentraciones plasmáticas de TNF-alfa (21), estando las concentraciones elevadas en los pacientes obesos junto con los ácidos grasos libres circulantes. Además, la resistina disminuye la secreción y expresión de otras adipocinas antiinflamatorias como la adiponectina (22). Todas estas alteraciones metabólicas previamente comentadas producen un aumento de la resistencia a la insulina. Aunque nuestro trabajo es el primero en la literatura que evalúa el papel del polimorfismo rs7139228 sobre todas estas alteraciones metabólicas, otros trabajos con diferentes polimorfismos de este gen (23) han demostrado que la variante 3745367 está directamente relacionada con la HOMA-IR en sujetos diabéticos, y esta asociación se ha observado en diferentes etnias (24-26).

Por otra parte, la resistina suprime la diferenciación de los adipocitos, lo que conduce a una sobrecarga de ácidos grasos y una alta lipotoxicidad al aumentar la producción de colesterol-LDL y la degradación de los receptores de LDL en los músculos y el tejido hepático, lo que conlleva un aumento de la presencia de síndrome metabólico (27). Y, en segundo lugar, la resistina circulante induce la resistencia a la insulina al disminuir la supresión de la gluconeogénesis hepática inducida por la insulina, así como los niveles altos de glucosa, al disminuir el transporte de glucosa en los músculos (28).

El aumento de las concentraciones de resistina en nuestro estudio debido al polimorfismo rs7139228 de *RETN* puede explicarse mediante varias hipótesis. La primera hipótesis es relacionar estas concentraciones elevadas de resistina circulante con la unión específica de los factores de transcripción Sp1 y Sp3 a un elemento promotor que genera un incremento de la actividad promotora, como se muestra con otros SNP (8). En segundo lugar, la metilación del ADN, una modificación por tanto epigenética, también puede desempeñar un papel importante en la regulación de la expresión génica (29), mostrando una relación inversa de los niveles de resistina circulantes con el nivel de metilación. En tercer lugar, este SNP puede estar en desequilibrio de ligamiento con otro SNP desconocido que module a su vez el nivel de expresión génica de la resistina (8). Otra teoría podría ser que esta variante genética formara parte de una secuencia del elemento regulador que media la unión de proteína correguladora implicada en la regulación de la expresión del gen RETN (30). Finalmente, este SNP podría formar parte de una transcripción de micro-ARN que regularía la estabilidad de la transcripción de un gen involucrado en la fisiopatología del síndrome metabólico (31).

Hasta la fecha, en la literatura no existen estudios de intervención con este SNP y solo hemos encontrado un estudio de diseño transversal (10). Sin embargo, podríamos suponer que, al igual que ha ocurrido con otros SNP del gen *RETN*, este SNP rs7139228 también podría modificar la respuesta a las intervenciones dietéticas (32) y las intervenciones de cirugía bariátrica (33). También es necesario tener en cuenta que la actividad física genera una regulación del eje de la resistina (34) y, por tanto, es otro elemento a tener en cuenta en los estudios de intervención. Por tanto, nuestro estudio puede generar las bases para futuros estudios de intervención y nutrición personalizada del paciente obeso.

Nuestro trabajo presenta algunas limitaciones. En primer lugar, solo hemos evaluado un SNP del gen *RETN* y otros SNP de este gen podrían estar involucrados en los parámetros metabólicos e interactuar con otros haplotipos. En segundo lugar, un diseño transversal no genera causalidad y son necesarios estudios prospectivos para demostrar esta causalidad. En tercer lugar, son necesarios nuevos estudios para validar estos hallazgos en pacientes con sobrepeso, así como en pacientes obesos diabéticos. Finalmente, nuestros datos solo pueden generalizarse en pacientes obesos, no siendo extrapolables a la población general ni a la población con normopeso. Como fortalezas del trabajo, tenemos un estudio con un tamaño muestral importante y la muestra representa a los pacientes obesos que acuden en la práctica clínica real a nuestras consultas.

En conclusión, el alelo A de la variante genética rs7139228 se asocia con mayores concentraciones de resistina, insulina basal, resistencia a la insulina y prevalencia de síndrome metabólico en sujetos obesos.

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ARÁN

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Trabajo Original

Obesidad y síndrome metabólico

Associations among single nucleotide ploymorphisms in two addictive genes, food addiction, and antioxidant markers in recreationally active young women

Asociaciones entre polimorfismo de nucleótido único en dos genes adictivos, adicción a la comida y marcadores antioxidantes en mujeres jóvenes recreativamente activas

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Resumen

Introduction: food addiction is associated with genetic polymorphisms and decreased antioxidant intake.

Objectives: this study determined the associations among food addiction, dopamine receptor 2 (DRD2) and toll-interleukin 1 receptor (TIR) domain-containing adaptor protein (TIRAP rs625413) gene polymorphisms, antioxidant capacities, and zinc levels among recreationally active Turkish women.

Methods: the Yale Food Addiction Scale was used to evaluate the food addiction status. Serum antioxidant capacities and zinc levels were evaluated by blood analyses. Deoxyribonucleic acid (DNA) extraction was performed using peripheral blood leukocytes, and the polymorphism status of the *DRD2* Taq 1A and *TIRAP* genes was investigated using a commercial kit.

Results: the frequencies of the heterozygous genotypes of *DRD2* Taq 1A and *TIRAP* were 23.1 % and 31.4 %, respectively, and the frequency of risk allele homozygous genotypes was 3.2 %. Most participants (94.4 %) had a nonpolymorphic/wild (CC) genotype in both genes; however, 11.5 % of the participants had a food addiction. The differences between serum antioxidant capacities, zinc levels, and body mass indices of those with and without food addiction were statistically significant. However, there were no differences in the serum zinc and antioxidant levels among the different genotypes.

Conclusion: food addiction in young Turkish women was not associated with *DRD2* Taq 1A or *TIRAP* polymorphisms but was associated with serum antioxidant capacities and zinc levels. Further studies on different loci of the same genes or genotypes of different genes with larger sample sizes are warranted.

Keywords:

Food addiction. Women. Gene polymorphism. Allele. Genotypes.

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Resumen

Introducción: la adicción a la comida está asociada con polimorfismos genéticos y disminución de la ingesta de antioxidantes.

Objetivos: este estudio determinó las asociaciones entre la adicción a la comida, los polimorfismos del gen de la proteína adaptadora que contiene el dominio del receptor de dopamina 2 (DRD2) y del receptor de interleucina 1 (TIR) (TIRAP rs625413), las capacidades antioxidantes y los niveles de zinc entre mujeres turcas recreativamente activas.

Métodos: se utilizó la escala de adicción a la comida de Yale para evaluar el estado de adicción a la comida. Las capacidades antioxidantes séricas y los niveles de zinc se evaluaron mediante análisis de sangre. La extracción de ácido desoxirribonucleico (ADN) se realizó a partir de leucocitos de sangre periférica y el estado de polimorfismo de los genes DRD2 Taq 1A y TIRAP se investigó con un kit comercial.

Resultados: las frecuencias de los genotipos heterocigotos de DRD2 Taq 1A y TIRAP fueron 23,1 % y 31,4 %, respectivamente, y la frecuencia de genotipos homocigotos de alelos de riesgo fue de 3,2 %. La mayoría de las participantes (94,4 %) tenían un genotipo no polimórfico/salvaje (CC) en ambos genes; sin embargo, el 11,5 % de las participantes tenía adicción a la comida. Las diferencias entre las capacidades antioxidantes séricas, los niveles de zinc y los índices de masa corporal de aquellas con y sin adicción a la comida fueron estadísticamente significativas. Sin embargo, no hubo diferencias en los niveles séricos de zinc y antioxidantes entre los diferentes genotipos.

Conclusión: la adicción a la comida en mujeres jóvenes turcas no se asoció con los polimorfismos DRD2 Taq 1A o TIRAP, pero se asoció con las capacidades séricas antioxidantes y los niveles de zinc. Se justifican más estudios sobre diferentes loci de los mismos genes o genotipos de diferentes genes con tamaños de muestra más grandes.

Palabras clave:

Adicción a la comida. Mujer. Polimorfismo genético. Alelo. Genotipos.

INTRODUCTION

Food addiction is defined as an uncontrolled craving for food and anxiety about food. It has been shown that dopamine release is stimulated in the brain, especially following carbohydrate intake, which is similar to the effects of substances such as nicotine and alcohol (1). The symptoms of food addiction that predispose individuals to develop obesity are prevented by a diet rich in antioxidants, and the feeling of hunger and food intakes are reduced (2); such diets are also protective against high oxidative stress as caused by diets with high fat and sugar contents (3).

Oxidative stress is a risk factor for obesity, both in itself and as a mediator in metabolic processes. It also plays a role in adipogenesis and is associated with leptin resistance, chronic inflammation, sleep disturbance, dysbiosis, insulin resistance, adipocytokines, and obesity genes (4). It also plays a role in the food addiction behaviors of obese and overweight individuals by acting on brain signals and neurotransmitters (5).

In studies, it was shown that zinc (Zn) is an effective antioxidant to decrease oxidative stress, and there was a relationship between high oxidative stress and Zn redistributions in plasma, urine, erythrocytes and saliva (6). Low Zn levels were detected in obese individuals in many studies (7). On the other hand, studies show a correlation between appetite and serum zinc levels that leads to obesity (8).

Food addiction develops in a neurobiological, behavioral, and clinical framework that is parallel to substance addiction, and the genetic background plays an important role in addition to environmental factors (9). Dopamine, which is associated with addiction, is the main neurotransmitter involved in the reward system in the brain (10). With food intake, dopamine release from the dorsal striatum begins, and it has been reported that the degree of pleasure derived from eating is proportional to the amount of dopamine released (11). It has also been suggested that the numbers of dopamine receptor 2 (DRD2) in the central nervous system are lower in obese individuals than in nonobese individuals, and they have a greater desire to eat to compensate for this situation (12). In studies, it has been determined that the *DRD2 receptor gene Taq1A (rs 1800497) and toll-interleukin 1 receptor (TIR) domain-containing adaptor protein (TIRAP rs625413)* gene polymorphisms are responsible for increases in food addiction, especially for carbohydrate foods (1,10).

Physical activity prevents the risk of obesity development by helping maintain energy balance (13). Additionally, it was noted that energy intake, physical activity and *DRD2* Taq1A gene polymorphisms prevent overweight and obesity (14).

Although there is a study evaluate the relationships among oxidative stress, food addiction, physical activity and obesity (15), no study exists that has evaluated the relationship between food addiction and gene polymorphisms in recreationally active individuals.

In this study, we hypothesized that food addiction is associated with genetic polymorphisms, decreased serum total antioxidant capacities and Zn levels. We aimed to question the possible effect of Zn on appetite in food addiction separately from its antioxidant properties. Recreationally active women were selected, and the relationships among *DRD2/TIRAP* gene polymorphisms, food addiction, antioxidant capacities, and zinc were evaluated among those who were engaged in regular activities at least 3 days per week. There is only one study in the literature that evaluates the relationship between gene polymorphisms and antioxidant levels (16); therefore, our study will also contribute to this subject.

MATERIALS AND METHODS

PARTICIPANTS

This cross-sectional-analytical study was conducted among women who were engaged in recreational activities. To conduct this study, approval by the ethics committee (decision number 2019/17-42 and dated 02/07/2019) was obtained from the Hacettepe University Non-Interventional Clinical Research Ethics Committee. The aims and methods of the study were explained to the participants, and those who agreed to participate in the study were asked to sign a voluntary consent form that followed the Declaration of Helsinki (World Medical Association).

In this context, 210 young adult women (18-31 years old) were enrolled between December 2020 and April 2021 at a university in Ankara (95 % power), and the analysis process included 156 women who fully complied with the study and did not have any deficiencies/misrepresentations in their data. The inclusion criteria included the following: age greater than 18 years, engaging in recreational activities (at least 3 days of regular exercise per week), not diagnosed with depression by a doctor, not using antidepressants or oral contraceptives, not diagnosed with cancer, liver or kidney failure, without overt diabetes, consenting to participate in the study, and researchers' decisions.

DETERMINATION OF GENERAL CHARACTERISTICS

Within the scope of the study, a questionnaire form to evaluate the general information and health histories of the participants was used by the researchers by using a face-to-face interview technique.

EVALUATION OF FOOD ADDICTION

The food addiction status of participants was evaluated using the "Yale Food Addiction Scale." The Yale Food Addiction Scale was developed by " et al. (2009) (17) to obtain the eating habits of the participants during the previous year based on the seven symptoms and eating disorders specified in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV (18).

A Turkish validity and reliability study of this scale was carried out by Bayraktar et al. in 2012 (19). The scale consists of 26 items, and the answers provided to the questions are scored 0 or 1 point. The score for each diagnostic criterion was calculated separately. The total score varied between 0 and 7. To determine food addiction, the 15th or 16th question is important, and 1 point should be taken. When the number of symptoms is more than 3, a diagnosis of food addiction is made.

ANTHROPOMETRIC MEASUREMENTS

Body weights (kg) were measured by bioelectrical impedance analysis (BIA) using a TANITA BC418-MA Segmental Body Composition Analyzer (Tokyo, Japan) when the participants were hungry in the morning and wearing light clothes. Height measurement (cm) were conducted using a stadiometer with standard protocols. BMIs were calculated as "body weight/height^2" (kg/m^2), and the classification of the World Health Organization (WHO) according to BMI in adults was used (20).

BIOCHEMICAL ANALYSIS

Venous blood samples were obtained from participants in the morning after 8 h of fasting. Serum samples were stored in a deep freezer at −80 °C until analysis. Total antioxidant capacity analysis was performed with an enzyme-linked immunosorbent assay using a commercial kit (Relassay, Turkey). In this method, the antioxidants in the samples convert the dark blue-green ABTS (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) radical solution into a colorless ABTS form. Absorbance changes at a wavelength of 660 nm are related to the total amounts of antioxidants. The results are expressed in vitamin E-like Trolox equivalents (mmol Trolox equivalent/L) (21).

Zinc present in the samples changes the red-orange color of 5-Br-PAPS to light pink under alkaline conditions. The absorbance changes at 548 nm are proportional to the total zinc levels (µg/dL) in samples. The test can be calibrated with zinc sulfate dissolved in deionized water (Relassay, Turkey).

GENETIC ANALYSIS

DNA extraction was performed with the isolation kit, GF-1 Blood DNA Extraction Kit (Vivantis, Malaysia), for whole blood samples collected in EDTA tubes.

The nucleic acid loads (ng values) of the samples obtained from the total DNA extraction process were measured using a Colibri Microvolume Spectrometer (Titertek-Berthold, Germany) device for use in the next steps of the study.

Within the scope of this study, the oligonucleotide designs of single-nucleotide polymorphisms with known nucleotide database codes for gene regions were studied with a real-time polymerase chain reaction (PCR) device (Table I).

The lyophilized primers synthesized in the study were dissolved with nuclease-free dH_2O to a 100 mM concentration. For real-time PCR, a SensiFAST Probe No-ROX Kit (Bioline, US) was used. For a 20-µl reaction mix, 10 µL of SensiFAST Probe Mix (1X), 2.5 µL of Primer/Probe mix (0.3 mM forward primer 10 mM) and 0.3 mM reverse primer (10 mM), 0.1 mM probe (P1-P2, 10 mM), 2.5 µl of DNA, and 5 µl of nuclease-free dH_2O were used. The reaction was performed using LightCycler 480 (Roche, Switzerland) 8-strip tubes with the following program: initial denaturation at 95 °C for 5 min, 40 repetitions at 95 °C for 10 sec, 66 °C (rs625413), 68 °C (rs1800497) for 30 sec (read), and fragment duplication. Real-time PCR was based on the allele-specific probe data obtained (Table II).

To detect polymorphisms in the *DRD2* gene region (rs1800497 T > C), fluorescent dye-labeled probes for the C (FAM) and T (HEX) alleles were used. Using real-time PCR, the genotypes were determined as CC (wild-type genotype), TT (homozygous genotype for the risk allele), and CT (heterozygous genotype for the risk allele) according to the fluorescence levels.

Fluorescent dye-labeled probes for the T (FAM) and C (HEX) alleles were used to detect polymorphisms in the *TIRAP* gene region (rs625413 T > C). By using real-time PCR, the genotypes were determined as TT (homozygous genotype for the risk allele), CC (wild type genotype), and TC (heterozygous genotype for the risk allele) according to the fluorescence levels.

The frequencies of the alleles detected as a result of genetic analysis were evaluated according to the Hardy-Weinberg bal-

ance ($p + q = 1$), and genotype frequencies were compared with expected frequencies according to Hardy-Weinberg (22).

Hardy-Weinberg equation = $p^2 + 2pq + q^2 = 1$.

For *DRD2* Taq 1A genotype frequencies:

– p^2 = Dominant homozygous genotype frequency (CC).
– q^2 = Homozygous genotype frequency (TT).
– 2pq = Heterozygous genotype frequency (CT).

STATISTICAL ANALYSES

Data obtained in the study were evaluated with Statistical Package for the Social Sciences (SPSS) 22.0 software. The normality of the data distribution was examined using visual (e.g., histogram and probability graphs) and analytical methods (e.g., Kolmogorov-Smirnov/Shapiro-Wilk tests). The χ^2 test was used to compare general characteristics according to food addiction status and gene variants. For comparing serum total antioxidant capacities and zinc levels of the participants in this study in terms of food addiction status (presence/absent), independent sample tests (t or z tests) or Mann-Whitney U-tests were used. In the comparisons of serum antioxidant capacities and zinc levels of individuals according to gene variants, a one-way analysis of variance or the Kruskal-Wallis test was used. Spearman's and Pearson's correlation tests were used to evaluate the relationships among different parameters. In all analyses, a value of $\alpha = 0.05$ was chosen as the error level, and it was interpreted that "the difference is statistically meaningful/significant" for p-values equal to or less than this value.

RESULTS

A total of 156 volunteer women with a mean age of 20.47 ± 2.00 years and BMI of 24.55 ± 3.05 kg/m^2 were included in this study, and 12.3 % of them were underweight, 41.4 % were of normal weight, 36.7 % were overweight, and 9.6 % were obese.

The distributions in the frequencies of the *DRD2* Taq 1A (rs1800497 T > C) and *TIRAP* gene (rs625413) polymorphisms of participants are shown in table III. The frequencies of participants with *DRD2* Taq 1A and *TIRAP* homozygous genotypes (homozygous for the risk allele) were determined to be 3.2 %, and those with heterozygous genotypes were 23.1 % and 31.4 %, respectively (Table III).

Table I. Presentation of oligonucleotide regions on toll-interleukin 1 receptor (TIR) domain- containing adaptor protein (TIRAP rs625413) and dopamine receptor 2 (DRD2) genes

Single nucleotide ploymorphisms	Primer	5' Sign	Sequence (5′-3′)	3' Sign	Allel
TIRAP region on gene (rs625413)	rs625413-hsa-F		GAGGGAGCAAGTGAAGAGATG		
	rs625413-hsa-R		GGTGAAGATGGTGACTGTGAA		
	rs625413-hsa-P1	FAM	TCAGGGTTCAA**T**GCCTTCACCT	BHQ1	T
	rs625413-hsa-P2	HEX	TCAGGGTTCAA**C**GCCTTCACCT	BHQ1	C
DRD2 region on genes (rs1800497)	rs1800497-hsa-F		GTGTCATCAACCTCCTAGAACATC		
	rs1800497-hsa-R		GTGCAGCTCACTCCATCC		
	rs1800497-hsa-P1	FAM	CGCCTGCCT**C**GACCAGCACT	BHQ1	T
	rs1800497-hsa-P2	HEX	CGCCTGCCTTGACCAGCACT	BHQ1	C

Table II. List of primer-probe sets used for toll-interleukin 1 receptor (TIR) domain-containing adaptor protein *(TIRAP rs625413)* and dopamine receptor 2 *(DRD2)* genes region detection

Gene region	Primer set	Primer concentration	Annealing Tm °C
TIRAP gene region	rs625413 F/R/P	F: 0,3 µM R: 0,3 µM P1: 0,1 µM P2: 0,1 µM	66 °C
DRD2 gene region	rs1800497 F/R/P		68 °C

F: forward primer; R: reverse primer; P: probe.

DRD2 Taq 1A (rs1800497 T > C) (CC: 72.6 %; CT: 25.1 %; TT: 2.1 %) and *TIRAP* (CC: 65.7 %; TC: 30.6 %; TT: 3.5 %) genotype frequencies were not different from those expected from Hardy-Weinberg equilibrium ($p > 0.05$).

In addition, it was determined that most participants had nonpolymorphic/wild genotypes (CC genotype) in the *DRD2* and *TIRAP* genes (Table III).

It was determined that 11.5 % of the participants had food addiction. The distributions of the *DRD2* Taq 1A (rs1800497) and *TIRAP* (rs625413) genotype frequencies according to the food addiction status of the participants are shown in table IV. Accordingly, 94.4 % of participants with and without food addiction had the *DRD2* Taq 1A CC genotype and *TIRAP* gene CC genotype (nonpolymorphic/wild genotype). Homozygous/at-risk genotypes in terms of risk alleles were not detected in the *DRD2* Taq 1A and *TIRAP* genes of participants with food addiction (Table IV).

The serum antioxidant capacities and Zn levels of the participants with different genotypes and food addiction statuses are compared in table V. There were no statistically significant differences between the serum antioxidant capacities and zinc levels of participants with and without food addiction who had different *DRD2* Taq 1A genotypes ($p > 0.05$). Similarly, there were no differences between the serum antioxidant and zinc levels of women with and without food addiction with different *TIRAP* (rs625413) genotypes ($p > 0.05$) (Table V).

Serum antioxidant capacities, zinc levels and BMI of the recreationally active Turkish women according to their food addiction status are shown in table VI. There were statistically significant differences between the serum antioxidant capacities, serum zinc levels and BMI of participants with and without food addiction ($p < 0.05$) (Table VI).

DISCUSSION

The food addiction hypothesis suggests that exposure to palatable foods alters the brain's reward circuit and drives the behavioral phenotype to compulsive overeating (23). Food addiction is related to overeating outcomes of obesity and micronutrient deficiencies (24). Recently, some data have shown that genetic polymorphisms may be associated with food addiction (14). In this study, our hypothesis was rejected; the *DRD2/TIRAP* genotype was not found to be related to food addiction, serum total antioxidant capacities, or antioxidant and appetite stimulant agent Zn levels among recreationally active Turkish women.

Table III. The frequencies of dopamine receptor 2 *(DRD2)* Taq 1A (rs1800497) and *TIRAP* (rs625413) genotypes of recreationally active Turkish women

Genotypes	Total (n: 156)	
	n	%
DRD2 gene Taq 1A (rs1800497)		
CC genotype	115	73.7
CT genotype	36	23.1
TT genotype	5	3.2
TIRAP gene (rs625413)		
CC genotype	102	65.4
TC genotype	49	31.4
TT genotype	5	3.2

Table IV. The frequencies of dopamine receptor 2 *(DRD2)* Taq 1A (rs1800497) and *TIRAP* (rs625413) genotypes according to the food addiction status of recreationally active Turkish women

Food addiction	DRD2 Taq 1A			TIRAP (rs625413)		
	CC n (%)	CT n (%)	TT n (%)	CC n (%)	TC n (%)	TT n (%)
Addicted (n: 18)	17 (94.4)	-	1 (5.6)	17 (94.4)	1 (5.6)	-
Non-addicted (n: 138)	98 (71.0)	36 (26.1)	4 (8.9)	85 (61.6)	48 (34.8)	5 (3.6)

Table V. Serum antioxidant capacities (mmol Trolox equivalent/L) and zinc levels (µg/dL) of the recreationally active Turkish women according to their food addiction status and *DRD2* Taq 1A (rs1800497) and TIRAP (rs625413) genotypes

	Food addiction	DRD2 Taq 1A						p value	TIRAP (rs625413)						p value > 0.05
		CC		CT		TT			CC		TC		TT		
		$\bar{x}$ ± SD	CV	$\bar{x}$ ± SD	CV	$\bar{x}$ ± SD	CV		$\bar{x}$ ± SD	CV	$\bar{x}$ ± SD	CV	$\bar{x}$ ± SD	CV	
Serum Antioxidant Capacities	Addicted	1.4 ± 0.17	12.14	-	-	1.5 ± 0.00	0.00	> 0.05	1.4 ± 0.17	12.14	1.5 ± 0.00	0.00	-	-	
	Non-addicted	1.6 ± 0.34	21.25	1.5 ± 0.42	28.00	1.5 ± 0.14	9.33		1.5 ± 0.29	19.33	1.6 ± 0.46	28.75	1.6 ± 0.16	10.00	
		DRD2 Taq 1A							TIRAP (rs625413)						
	Food addiction	CC		CT		TT		p value	CC		TC		TT		p value > 0.05
		$\bar{x}$ ± SD	CV	$\bar{x}$ ± SD	CV	$\bar{x}$ ± SD	CV		$\bar{x}$ ± SD	CV	$\bar{x}$ ± SD	CV	$\bar{x}$ ± SD	CV	
Serum Zinc Levels	Addicted	28.0 ± 23.02	82.21	-	-	10.4 ± 0.00	0.00		28.3 ± 22.72	80.28	25.0 ± 0.00	0.00	-	-	
	Non-addicted	21.4 ± 28.11	131.35	23.3 ± 20.24	86.86	38.7 ± 25.43	65.71	> 0.05	21.8 ± 27.53	126.28	24.1 ± 25.51	105.85	17.4 ± 8.25	47.41	

$\bar{x}$: mean; SD: standard deviation; CV: coefficient variation.

In a study, the relationship between food addiction and physical activity was evaluated in university students, and more food addiction symptoms were detected in association with high physical activity levels (25). In another study that evaluated 1344 adults, lower physical activity levels (less than 1.8 hours of walking per week, less than 32 minutes of walking per week, or less than 58 minutes of normal or vigorous exercise per week) in individuals with food addiction were determined to be inversely related. It has been shown that the frequency and duration of physical activity may be inversely related to food addiction (26). In this study, it was ensured that all the participants were recreationally active, which made it possible to exclude the effect of different physical activity levels on food addiction and observe the effect of only genetic polymorphisms on food addiction.

Food addiction levels were determined to be 11.5 % in our study. In another study conducted in university students in Turkey, it was found to be 9.0 % (27). The difference in our findings can be explained by the fact that all of our samples consisted of women, and food addiction is higher in women than in men. In a study that evaluated food addiction in 967 university students in the US, the incidence of food addiction was found to be higher in women than men (12.3 % vs. 4.6 %) (28). In other study in which food addiction was evaluated in university students in Spain, it was shown that the rate of food addiction was 6.4 % (26).

DRD2 Taq 1A was the first genetic polymorphism identified as responsible for food addiction (15). In this study, it was determined that the food addiction frequency in the participants with *DRD2* Taq 1A homozygous genotypes (homozygous for the risk allele) was 3.2 %, and the frequencies of those with heterozygous genotypes were 23.1 % and 31.4 %. In Asian students, CT variants were found to be higher than TT and CC of the *DRD2* Taq1A gene polymorphism (29). It has been reported that the frequency of the *DRD2* Taq 1A genetic polymorphism is 2.95 % (30) in Caucasians, 37.9 % and 29 % (31) in China and India. Our findings are compatible with those of the Caucasian population. The fact that the origin of Caucasian cuisine comes from Circassian cuisine and that the characteristics of this culture are seen in the Aegean Region in our country explain the similarity. Ethnicity and diet can influence differences between genotypes and alleles.

In a Mexican study, the *DRD2* TaqIA polymorphism was shown to be associated with an increased frequency of unhealthy food consumption (32). In our study, no risky genotype was found in terms of the risk alleles in the *DRD2* Taq 1A gene of participants with food addiction. Additionally, in our country, similar evidence was found to evaluate the association among *DRD2* Taq 1A and 1B polymorphisms and other addiction conditions, namely, heroin, which did not show any difference in terms of this genetic polymorphism between individuals (33). It has been stated that this relationship may vary among populations due to differences in the frequency of the TaqIA allele (32).

The second gene evaluated concerning food addiction status is *TIRAP*. It is involved in cytokine release, the inflammatory response, and the regulation of TNF-α production (33). In a study evaluating food addiction in overweight/obese individuals, lower

Table VI. Serum antioxidant capacity (mmol Trolox equivalent/L), zinc levels (µg/dL), and BMI (kg/m^2) of the recreationally active Turkish women according to their food addiction status

Variables	Food addiction				
	Addicted (n: 18)		Non-addicted (n: 112)		p value
	$\bar{x}$ ± SD	CV	$\bar{x}$ ± SD	CV	
Serum antioxidant capacity (mmol Trolox equivalent/L)	1.39 ± 0.10	7.19	1.59 ± 0.36	22.64	0.024*
Serum zinc level (µg/dL)	27.02 ± 22.71	84.04	22.53 ± 26.27	116.60	0.039*
BMI (kg/m^2)	23.26 ± 3.39	14.51	21.00 ± 2.72	12.95	0.002*

*$\bar{x}$: mean; SD: standard deviation; CV: coefficient variation; BMI: body mass index. *p < 0.05.*

TNF-α levels were found in the obese group, and it has been stated that low levels of TNF-α, an anorexigenic cytokine, may be related to *TIRAP* gene polymorphisms (34).

Of these data, *TIRAP* is a newly discovered single nucleotide ploymorphisms (SNP) region associated with addiction, and there are not enough relevant studies in the literature. We did not find any association between *TIRAP* and food addiction in our study.

Food addiction occurs during the consumption of frequently processed foods, and these foods have no or extremely low micronutrient and antioxidant contents (24). Therefore, we investigated the relationships among serum total antioxidant capacities, Zn levels, and food addiction in our study. Since the definition of total antioxidant capacity covers the cumulative effect of all antioxidants and provides more accurate results than separate evaluations (35), we preferred to evaluate the total serum antioxidant capacity.

In the present study, although no differences were found in the serum total antioxidant capacities and zinc levels based on genotypes, the serum antioxidant capacities were lower and Zn levels were higher in the group with food addiction.

For the serum Zn levels in individuals with food addiction, in a study evaluating the effect of food addiction on food consumption in our country, similar to our findings, the addiction status incidence was found to be 11.4 %, and zinc consumption was found to be higher in the addiction group (36). Considering the function of zinc in the sense of taste (37), it can be related to elevated serum levels in the food addiction group, which are known to be associated with high taste intensities, fat, sugar, and salt contents and excessive consumption of foods. Moreover, it is a micronutrient that can affect many neurotransmitters in the serotonergic, glutamatergic, and dopaminergic systems (38); therefore, in this study, we thought it would be related to the development of addiction-like behavior.

The tendency to consume prooxidant foods in individuals with food addiction promotes the production of antioxidant enzymes and reactive oxygen species that reveal the activation of heat (39). To protect health and prevent the oxidative stress imbalance detected in obesity and food addiction, it is recommended to consume prooxidant and antioxidant foods at a ratio of 2:3 per meal (40). In this study, the serum total antioxidant capacity of individuals with food addiction was found to be lower. It is necessary to develop recommendations to support antioxidant consumption by evaluating the daily food consumption of individuals with food addiction.

To the best of our knowledge, the present study is the first to evaluate the relationship among genetic polymorphisms, serum total antioxidant capacities and Zn levels. Despite the accumulated literature on *DRD2*, we investigated the novel candidate gene, *TIRAP*, which is another strength of this study.

Despite these strengths, there are also some limitations. First, the food consumption of individuals has not been evaluated, and evaluating only one gender is one of the other limitations. Comparing nutritional patterns with biochemical findings in the larger sample with both sexes will strengthen the findings.

In conclusion, in our study, it was shown that *DRD2* and *TIRAP* gene polymorphisms are not associated with food addiction, serum antioxidant capacities, or Zn levels, whereas individuals with food addiction have low serum antioxidant capacities and high serum Zn levels. Despite the antioxidant properties of Zn, Zn levels were found to be high regardless of the low antioxidant capacity levels.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Comparación de distintas herramientas para la evaluación de la malnutrición y la sarcopenia en pacientes con cirrosis hepática

Comparison of different tools for the evaluation of malnutrition and sarcopenia in patients with liver cirrhosis

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Resumen

Introducción: la malnutrición y la sarcopenia son frecuentes en la población con cirrosis hepática y generan un impacto negativo en el estado funcional y la esperanza de vida de estos pacientes. Existen múltiples herramientas para la valoración de la malnutrición y la sarcopenia en los pacientes con cirrosis hepática. Algunas de estas herramientas son de fácil aplicación y reproducibilidad, lo que facilita su aplicación global.

Objetivo: valorar la malnutrición y la sarcopenia en la cirrosis hepática y comparar distintas herramientas diagnósticas aplicables en esta población.

Método: se realizó un estudio analítico de corte transversal con muestreo a conveniencia mediante inclusión continua de pacientes con cirrosis hepática en un hospital de tercer nivel durante diciembre de 2018 a mayo de 2019. Se realizó la valoración nutricional con la antropometría del brazo, el índice de masa corporal (IMC) y el algoritmo del *Royal Free Hospital Subjetive Global Assessment* (RFH-SGA). Para la valoración de la sarcopenia se aplicó la fuerza de agarre de la mano con un dinamómetro. Los resultados se reportaron en medidas de tendencia central expresadas en frecuencia y porcentaje. Se realizó un coeficiente de correlación con Tau-b de Kendall en las variables no paramétricas, considerándose como valor estadísticamente significativo una $p < 0,05$.

Resultados: se incluyeron un total de 103 pacientes, predominando el género masculino (79,6 %), con una edad media de 51 años. La etiología más frecuente de la cirrosis hepática fue el consumo de alcohol (68 %), predominando la clase Child-Pugh C (57,3 %) con una media de MELD de 21,9 (± 8,9). Se reportó una media de IMC con peso seco de 25,2 kg/m^2 y, respecto a la clasificación de la OMS, un 7,8 % se encontraban en bajo peso y un 59,2 % en malnutrición según la RFH-SGA. Un 88,3 % presentó sarcopenia al utilizar la fuerza de agarre de la mano, cuyo valor medio fue de 18,99 kg. Se realizó una correlación con Tau b de Kendall entre IMC y RFH-SGA sin evidenciarse ninguna asociación significativa, al igual que entre los percentiles de la circunferencia muscular media de brazo (MAMC) y la fuerza de agarre de la mano.

Conclusiones: la valoración integral de la cirrosis hepática debe incluir el escrutinio de la malnutrición y la sarcopenia, existiendo herramientas de fácil acceso y aplicación segura validadas en esta población, como la valoración antropométrica, el RFH-SGA y la fuerza de agarre de la mano.

Palabras clave:

Cirrosis hepática.
Disfunción muscular.
Malnutrición. Sarcopenia.

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Abstract

Introduction: malnutrition and sarcopenia are frequent in the population with liver cirrhosis and have a negative impact on the performance status and life expectancy of these patients. There are multiple assessment tools for malnutrition and sarcopenia in cirrhosis. Some of these tools are reproducible and easy to apply, which facilitates their global application for screening malnutrition and sarcopenia.

Objective: to assess malnutrition and sarcopenia in liver cirrhosis and to compare the accuracy of diagnostic tools in this population.

Method: a cross-sectional analytical study was conducted with convenience sampling by using continuous inclusion of patients with liver cirrhosis in a tertiary care center during December 2018 to May 2019. The nutritional assessment was carried out with arm anthropometry, body mass index (BMI), and the algorithm of the Royal Free Hospital Subjective Global Assessment (RFH-SGA). For the evaluation of sarcopenia, the hand grip strength test with a hand dynamometer was applied. The results were reported in measures of central tendency expressed in frequency and percentage. A Kendall's Tau-b rank correlation coefficient was performed with non-parametric variables, considering a $p < 0.05$ as a statistically significant value.

Results: a total of 103 patients were included with a predominance of the male gender (79.6 %) and a mean age of 51 years (± 10). The etiology of liver cirrhosis corresponded more frequently to alcohol consumption (68 %) and most of the patients were Child-Pugh C (57.3 %) with a mean MELD of 21.9 (± 8.9). A mean BMI with dry weight of 25.2 kg/m^2 was reported, and with respect to the WHO classification by BMI, 7.8 % were underweight and 59.2 % were malnourished by RFH-SGA. Sarcopenia was present in 88.3 % using the hand grip strength test, for which a mean of 18.99 kg was found. A Kendall's Tau-b rank correlation coefficient was performed between BMI and RFH-SGA, which showed no statistically significant association, as well as between mean arm muscle circumference percentiles and hand grip strength.

Conclusions: global assessment in liver cirrhosis should include screening for malnutrition and sarcopenia, for which validated, accessible and safe application tools should be used, such as anthropometric assessment, RFH-SGA, and hand grip strength.

Keywords:

Liver cirrhosis. Muscle dysfuntion. Malnutrition. Sarcopenia.

INTRODUCCIÓN

La malnutrición es un síndrome secundario al desequilibrio de nutrientes y genera efectos adversos que se manifiestan fenotípicamente a manera de fragilidad o sarcopenia (3). Esta entidad patológica es una complicación frecuente en los pacientes con hepatopatía crónica, reportándose una prevalencia del 20 % en los pacientes con cirrosis compensada y de más del 60 % en aquellos que se encuentran en fase de descompensación (4,6,9,10). El mecanismo fisiopatológico de la malnutrición en estos pacientes es de etiología multifactorial, con factores no modificables propios de la cirrosis hepática, como la alteración de la función de síntesis hepática con disfunción catabólica, la disfunción metabólica con resistencia a la insulina asociada a la hepatopatía crónica y la falla intestinal asociada a los estados críticos de descompensación (5). De igual manera existen factores modificables implicados en el desarrollo de malnutrición del paciente con cirrosis hepática, dentro de los que destacan la ingesta inadecuada de micronutrientes y macronutrientes, así como un factor social con implicaciones en la dependencia funcional y la responsabilidad del cuidador en el cuidado global de estos pacientes (5). La malnutrición genera un impacto negativo en la calidad de vida y el pronóstico de la enfermedad, asociándose al desarrollo de descompensación inestable por encefalopatía hepática, ascitis y lesión renal, así como a una menor esperanza de vida libre de trasplante hepático. De igual manera, la malnutrición se considera un factor de mal pronóstico en los pacientes que se someten a trasplante hepático, siendo ya este un factor de riesgo independiente de sarcopenia, presentándose como nueva manifestación en un 26 % de los casos (27). La presentación de malnutrición en el paciente con cirrosis hepática es a manera de disfunción muscular con dos fenotipos de presentación, el síndrome de fragilidad y la sarcopenia, esta última entidad presentándose en un 40-60 % de los casos y definiéndose como un trastorno degenerativo y progresivo de la función del músculo esquelético que se asocia a un aumento de eventos adversos como caídas, fracturas, dependencia funcional y mortalidad (11,12,28). Por lo mencionado previamente, es de gran importancia implementar medidas de cribado de la malnutrición y la sarcopenia en estos pacientes, existiendo múltiples herramientas para el mismo, como las escalas para valorar la malnutrición de *The Royal Free Hospital–Nutritional Priotizing Tool* (RFH-NPT) y *The Royal Free Hospital–Subjetive Global Assesment* (RFH-SGA), que presentan una adecuada correlación con el impacto de la malnutrición en la morbilidad y mortalidad del paciente con cirrosis hepática (6-8). En relación con la valoración de la sarcopenia se han propuesto múltiples estrategias de cribado, refiriéndose al índice tomográfico musculoesquelético en L3 como el método ideal; sin embargo, existen otras estrategias de fácil acceso, aplicación y reproducibilidad como la valoración antropométrica y la fuerza de apretón de la mano, considerándose incluso esta última como una herramienta para el diagnóstico del síndrome de fragilidad en el paciente con cirrosis hepática (4,5).

Por todo lo anterior, además de existir pocas referencias sobre la evaluación de pacientes con hepatopatía crónica hospitalizados, se determinó como objetivo evaluar el estado nutricional con el RFH-SGA y el IMC, así como con la fuerza de agarre de la mano, en pacientes con cirrosis hepática hospitalizados en la Clínica de Hígado del Servicio de Gastroenterología de un hospital de tercer nivel de atención.

MATERIAL Y MÉTODOS

Se realizó un estudio analítico de corte transversal con selección de muestreo a conveniencia mediante inclusión continua, seleccionándose a la población que ingresaba a hospitalización al servicio de gastroenterología de un hospital de tercer nivel con diagnóstico de cirrosis hepática durante el periodo de diciembre de 2018 a mayo de 2019. Como criterios de inclusión se consi-

deró a aquellos pacientes con diagnóstico de cirrosis hepática, con edad entre 18 y 70 años. Se excluyó a la población con diagnóstico de patología oncológica o encefalopatía hepática manifiesta, a los pacientes que se encontraban bajo ventilación mecánica invasiva y a aquellos en que durante su estancia hospitalaria resultó imposible la evaluación nutricional. Se realizó la valoración nutricional con cuantificación del peso en kg con una báscula análoga Taylor, mientras que la talla se estimó mediante la fórmula de Chumlea (17) en caso de que el paciente no recordara su talla. El peso seco se estimó de acuerdo con el grado de ascitis de los pacientes de acuerdo a lo establecido en las guías de la EASL (por sus siglas en inglés, Asociación Europea para el Estudio del Hígado) (3). Para el cálculo del índice de masa corporal se utilizó el peso seco y se estratifico a los pacientes en: bajo peso (< 18,5 kg/m^2), normopeso (18,5-24,99 kg/m^2), sobrepeso (25-29,99 kg/m^2) y obesidad (> 30 kg/m^2). La antropometría del brazo se realizó en el brazo no dominante; sin embargo, en caso de anormalidades o impedimento por acceso venoso, se utilizó el brazo dominante. La medición de la circunferencia media del brazo (MAC) se realizó en el punto medio entre el acromion subescapular y el olécranon del codo, utilizando una cinta metálica antropométrica de Lufking; el pliegue cutáneo tricipital (PCT) se midió con un plicómetro "Slim guide" (1 mm). A partir de la antropometría del brazo se calcularon el área total del brazo (ATB), el área muscular del brazo (MAMA), el área grasa del brazo (MAFA) y la circunferencia muscular del brazo (MAMC). El resultado de MAMA, MAFA y MAMC se comparó con los percentiles de acuerdo con la edad y el sexo del paciente (18,19), considerándose muy bajo el percentil < 5. La medición de la fuerza de agarre de la mano se realizó con un dinamómetro CAMRY EH 101, tomándose como punto de corte para la sarcopenia una fuerza de agarre < 30 kg en los hombres y < 20 kg en las mujeres (13). Para la evaluación del estado nutricional se utilizó el RFH-SGA (8), clasificándose a los pacientes como adecuadamente nutridos (AD), moderadamente malnutridos (MM) y severamente malnutridos (SM).

Se realizó un análisis estadístico con el SPSS versión 23, reportándose medidas de tendencia central expresadas en frecuencia y porcentaje, además del coeficiente de correlación con Tau-b de Kendall en las variables no paramétricas, considerándose como valor estadísticamente significativo una $p < 0,05$.

RESULTADOS

Se incluyeron en total 103 pacientes, de los cuales el 79,6 % (n = 82) correspondían al sexo masculino, con una edad media de 51,5 años (DE: ± 10). La etiología de la cirrosis hepática fue secundaria al consumo de alcohol en el 68 % (n = 70) de los casos, seguida por la infección crónica por el virus de la hepatitis C (VHC) en un 8,7 % (n = 9), el VHC asociado al consumo de alcohol en un 7,8 % (n = 8), la enfermedad hepática grasa no alcohólica (EGHNA) en el 3,9 % (n = 4) y otras entidades patológicas como la hepatitis autoinmune (HAI) y la infección crónica por el virus de la hepatitis B (VHB) en un 1 % (1) de los casos, mientras que en un 9,7 % (10) la etiología continuaba en estudio.

En cuanto al grado de insuficiencia hepática, presentaron un puntaje Child-Pugh medio de 9,7 (DE: ± 2,1), predominando el Child-Pugh C con un 57,3 % (n = 59), seguido de un 37,9 % (n = 39) de Child-Pugh B y un 4,9 % (n = 5) de Child-Pugh A. El puntaje MELD medio fue de 21,9 (± 8,9).

Del total de la población, el 57,28 % (n = 59) reportaron otras comorbilidades, como diabetes *mellitus* de tipo 2 (DM2) el 55,93 % (n = 33), hipertensión arterial sistémica (HAS) el 32,3 % (n = 19), enfermedad renal crónica (ERC) el 5,09 % (n = 3) e hipotiroidismo o patología neuropsiquiátrica el 3,39 % (n = 2).

Dentro de las variables antropométricas se encontró una media de talla de 1,66 m, de peso seco de 70 kg y de IMC seco de 25,2 kg/m^2; respecto a la clasificación del estado nutricional por IMC, el 45,6 % (n = 47) tenían normopeso, el 30,1 % (n = 31) sobrepeso, el 16,5 % (n = 17) obesidad y el 7,8 % (n = 8) bajo peso (Fig. 1).

En la antropometría del brazo se encontró una media de MAC de 27,5 cm, de MAMA de 46,7 cm², de MAFA de 15,94 cm² y de MAMC de 24 cm, con un PCT de 1,2 cm. Respecto a la ubicación del percentil < 5, en él se encuentran el 23 % de los valores de MAMA, el 25,5 % de los de MAFA y el 37,9 % de los de MAMC (Tabla I). En la evaluación del estado nutricional con RFH-SGA se encontró que un 59,2 % (n = 61) tenían malnutrición, un 41,7 % (n = 43) estaban moderadamente malnutridos, un 17,5 % (n = 18) estaban severamente malnutridos y un 40,8 % (n = 42) estaban adecuadamente nutridos (Fig. 2).

Respecto a la fuerza de agarre de la mano, se obtuvo una media de 18,99 kg; al analizarla por sexos, se obtuvo en hombres una media de fuerza de agarre de la mano de 20,9 kg (± 8,94) y en mujeres una de 11,5 (± 6,04). Además, el 88,3 % (n = 91) presentaban sarcopenia por fuerza de agarre de la mano y, de ellos, el 58,25 % (n = 60) se encontraban en algún grado de malnutrición y el 30,1 % (n = 31) estaban adecuadamente nutridos (Tabla II). En relación con la sarcopenia en los diversos grupos de estratificación por IMC, se encontró que solo un 7,8 % (n = 8) de los pacientes con bajo peso presentaban sarcopenia y que la gran mayoría de los casos de sarcopenia se concentraban en los pacientes con normopeso y sobrepeso, con un 41,7 % (n = 43) y un 23 % (n = 24), respectivamente (Tabla III). No se encontraron diferencias significativas entre la etiología de la cirrosis hepática y la presencia de sarcopenia. En la correlación con Tau b de Kendall entre IMC y RFH-SGA se encontraron resultados negativos sin evidenciarse ninguna asociación estadísticamente significativa, al igual que entre los percentiles de MAMC y la fuerza de agarre de la mano. En cuanto al grado de insuficiencia hepática y el estado nutricional por IMC, se encontró una mayor frecuencia de obesidad en aquellos con Child-Pugh A, de normopeso en los Child-Pugh B y de sobrepeso en los Child-Pugh C (Fig. 3), mientras que por RFH-SGA se encontró mayor frecuencia de adecuadamente nutridos entre los pacientes con Child-Pugh A y Child-Pugh B. Los pacientes con Child-Pugh C se encontraban moderadamente malnutridos (Fig. 4).

Se observó que aquellos con bajo peso presentaban algún grado de malnutrición, mientras que los que se tenían normopeso se reportaron como moderadamente malnutridos y aque-

llos con sobrepeso u obesidad como adecuadamente nutridos o moderadamente malnutridos. En la asociación de la valoración antropométrica con MAMA, MAFA, MAMC y la clasificación del estado nutricional por RFH-SGA, se encontró que los pacientes en el percentil < 5 se encontraban con mayor frecuencia severamente malnutridos y moderadamente malnutridos.

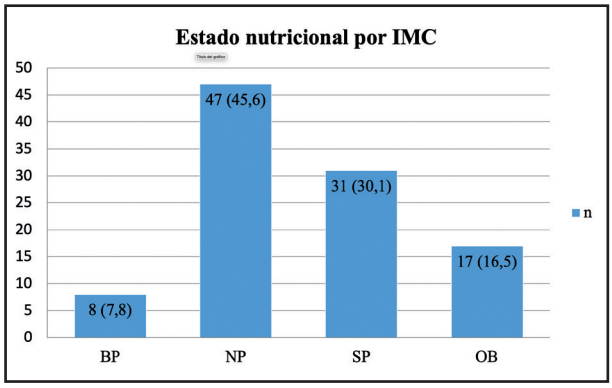

Figura 1.

Estado nutricional por IMC. En esta gráfica se representa en color azul la frecuencia de cada clasificación del estado nutricional (BP: bajo peso; NP: normopeso; SP: sobrepeso; OB: obesidad).

Tabla I. Antropometría del brazo: área muscular media del brazo (MAMA), área grasa del brazo (MAFA) y circunferencia muscular media del brazo (MAMC)

Antropometría del brazo	
MAMA* 46,73 ± 14,69 cm²	
	n (%)
Percentil < 5	23 (22,3)
Percentil 5-15	14 (13,6)
Percentil 15-85	44 (42,7)
Percentil > 85	22 (21,4)
MAFA* 15,94 ± 10,62 cm²	
	n (%)
Percentil < 5	26 (25,2)
Percentil 5-15	14 (13,6)
Percentil 15-85	57 (55,3)
Percentil > 85	6 (5,8)
MAMC* 24,02 ± 4,15 cm	
	n (%)
Percentil < 5	39 (37,9)
Percentil 5-10	6 (5,8)
Percentil 10-90	49 (47,6)
Percentil > 90	9 (8,7)

**Datos expresados en promedio y desviación estándar.*

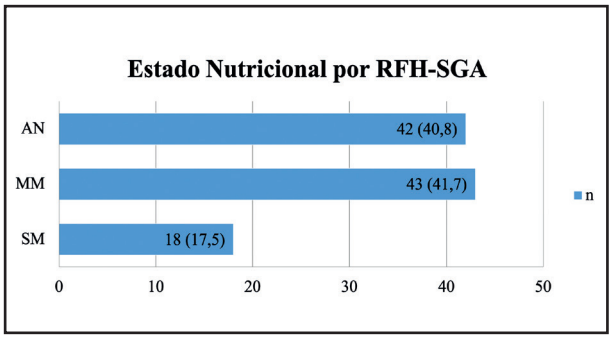

Figura 2.

Estado nutricional por RFH-SGA. En esta gráfica se representa en color azul la frecuencia de cada clasificación del estado nutricional (AN: adecuadamente nutrido; MM: moderadamente malnutrido; SM: severamente malnutrido).

Tabla II. Clasificación de estado nutricional por RFH-SGA y presencia de sarcopenia

Clasificación por RFH-SGA		
	Con sarcopenia: n (%)	**Sin sarcopenia: n (%)**
AN	31 (30,1 %)	11 (10,7 %)
MM	42 (40,8 %)	1 (1 %)
SM	18 (17,5 %)	0 (0 %)
Total	91 (88,3 %)	12 (11,7 %)

AN: adecuadamente nutrido; MM: moderadamente malnutrido; SM: severamente malnutrido.

Tabla III. Cruce de clasificación por RFH-SGA y ubicación del percentil de MAMA, MAFA y MAMC

RFH-SGA y percentiles de MAMA, MAFA, MAMC			
	AN 42 (40,8)	**MM 43 (41,7)**	**SM 18 (17,5)**
MAMA			
Percentil < 5	0 (0)	12 (11,7)	11 (10,7)
Percentil 5-15	2 (1,9)	7 (6,8)	5 (4,9)
Percentil 15-85	25 (24,3)	18 (17,5)	1 (1)
Percentil > 85	15 (14,6)	6 (5,8)	1 (1)
MAFA			
Percentil < 5	1 (1)	13 (12,6)	12 (11,7)
Percentil 5-15	6 (5,8)	5 (4,9)	3 (2,9)
Percentil 15-85	29 (28,2)	25 (24,3)	3 (2,9)
Percentil > 85	6 (5,8)	0 (0)	0 (0)

(Continúa en página siguiente)

Tabla III (Cont.). Cruce de clasificación por RFH-SGA y ubicación del percentil de MAMA, MAFA y MAMC

RFH-SGA y percentiles de MAMA, MAFA, MAMC			
	AN 42 (40,8)	MM 43 (41,7)	SM 18 (17,5)
MAMC			
Percentil < 5	0 (0)	23 (22,3)	16 (15,5)
Percentil 5-10	4 (3,9)	2 (1,9)	0 (0)
Percentil 10-90	31 (30,1)	16 (15,5)	2 (1,9)
Percentil > 90	7 (6,8)	2 (1,9)	0 (0)

AN: adecuadamente nutrido; MM: moderadamente malnutrido; SM: severamente malnutrido; MAMA: área muscular media del brazo; MAFA: área grasa media del brazo; MAMC: circunferencia muscular media del brazo.

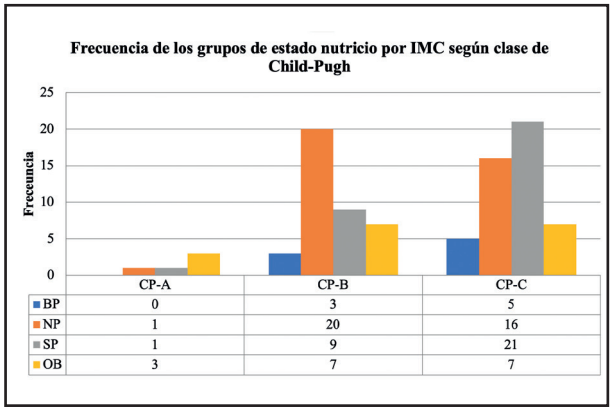

Figura 3.

Child-Pugh y estado nutricional por IMC. En esta gráfica se representa la frecuencia de cada clasificación del estado nutricional por IMC, correspondiendo el color azul al bajo peso (BP), el rojo al normopeso (NP), el verde al sobrepeso (SP) y el morado a la obesidad (OB).

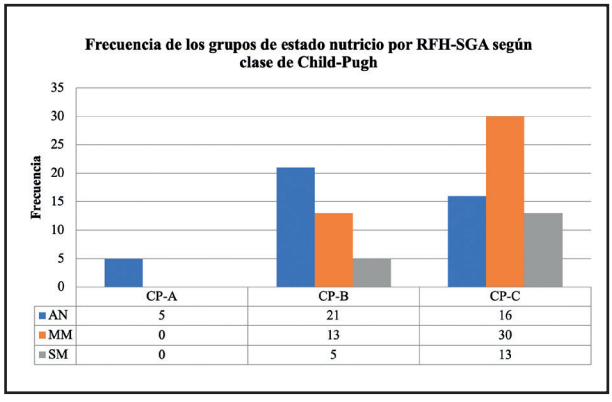

Figura 4.

Child-Pugh y estado nutricional por RFH-SGA. En esta gráfica se representa la frecuencia de cada clasificación del estado nutricional por RFH-SGA, correspondiendo el color azul a adecuadamente nutrido (AN), el rojo a moderadamente malnutrido (MM) y el verde a severamente malnutrido (SM).

DISCUSIÓN

En el presente estudio se determinó la frecuencia de la asociación de la sarcopenia y la malnutrición en una población mexicana con cirrosis hepática y se corroboró que la aplicación del IMC como herramienta para la valoración del estado nutricional de estos pacientes carece de utilidad clínica. En el caso del estado nutricional, se ha descrito la RFH-SGA como una herramienta útil en el paciente con cirrosis hepática, pero no se ha descrito una herramienta ideal para el cribado de la sarcopenia, la cual es un punto clave en el pronóstico del paciente con cirrosis. Dentro de los métodos descritos para el diagnóstico de sarcopenia en pacientes con cirrosis hepática se encuentran el índice tomográfico de músculo esquelético en L3 y la absorciometría dual de rayos X (DEXA), siendo estos estudios de alto costo y poca accesibilidad global. También se ha descrito la BIA para el diagnóstico de la sarcopenia pero, en el caso de la cirrosis hepática, los resultados de dicho estudio pueden verse alterados por la presencia de sobrecarga hídrica y ascitis (6,15). Existe evidencia creciente de fragilidad, sarcopenia y desnutrición en el paciente con cirrosis hepática, pero es poca la información en relación con la variabilidad racial, existiendo muy pocos estudios en la población mexicana. La importancia de conocer el papel de dichas entidades patológicas en la población mexicana con cirrosis hepática radica en las diferencias sociodemográficas que presentan con respecto a la población de otros países, como la etiología, el nivel socioeconómico y la infraestructura hospitalaria, incluyendo la accesibilidad a centros de trasplante hepático (20,27).

La frecuencia de la malnutrición y la sarcopenia fue similar a la prevalencia reportada en la literatura internacional, que va de un 20 a un 60 % y de un 40 a un 60 % para la malnutrición y la sarcopenia, respectivamente (4,6,13,21-23). En comparación con algunos estudios, el diagnóstico de sarcopenia se realizó por medio de medidas antropométricas y de la fuerza de agarre de la mano, sin valorar el índice tomográfico de músculo esquelético en L3, debido a la nula factibilidad de realizarlo, mientras que la BIA resultaba errónea por la presencia de ascitis.

En cuanto a la valoración por medio de antropometría, la tasa de pacientes que se encontraban en un percentil < 5 de MAMC fue similar a los resultados descritos en otros estudios, con un 25 % y un 25,8 % (24,9). También se valoró la asociación de la sarcopenia con el estado nutricional por IMC y RFH-SGA, encontrándose que los cirróticos con bajo peso y severamente malnutridos presentaban sarcopenia con mayor frecuencia. Así mismo, se reportó obesidad sarcopénica en un 15,5 % de la población estudiada, cifra inferior a la descrita globalmente con una prevalencia del 20-35 % (28). A pesar de describirse una alta frecuencia de malnutrición y sarcopenia, en los pacientes con cirrosis hepática no se encontró una correlación significativa entre bajo peso, sobrepeso y obesidad, estratificados por el IMC, y la estratificación de adecuadamente nutridos, moderadamente malnutridos y severamente malnutridos según la RFH-SGA. De igual manera, se realizó el mismo análisis estadístico para correlacionar la MAMC y la fuerza de agarre de la mano, sin encontrarse una relación estadísticamente significativa.

En cuanto a la fuerza de agarre de la mano, nuestro estudió evidenció sarcopenia en el 88 % de nuestros pacientes, reportando como media de la fuerza de agarre 20,9 kg en los hombres y 11,5 kg en las mujeres. En el consenso asiático de sarcopenia se define la sarcopenia por fuerza de agarre de la mano como < 28 kg en hombres y < 18 kg en mujeres (29). Por otro lado, en el consenso europeo de 2010 sobre la sarcopenia del paciente mayor, se define la sarcopenia por fuerza de agarre de la mano como < 30 kg en los hombres y < 20 kg en las mujeres (28), mientras que en el consorcio de diagnóstico y consecuencias de la sarcopenia se define la sarcopenia como una fuerza de agarre de la mano < 35,5 kg en los hombres y < 20 kg en las mujeres (30). Como observamos, existen diferentes puntos de corte para definir la sarcopenia por la fuerza de agarre de la mano y estos dependen de la raza y la población; sin embargo, todos la consideran por debajo de 25 kg en los hombres y por debajo de 18 kg en las mujeres, lo que nos invita a realizar estudios posteriores para definir el punto de corte de nuestra población. La fuerza de agarre de la mano, además de haber demostrado su papel determinante en el diagnóstico de la sarcopenia, ha demostrado también su asociación con incidentes tales como caídas, limitaciones de la movilidad, fracturas de cadera y mortalidad tanto en hombres como en mujeres (30).

Así mismo, se han reportado puntajes clínicos de síntomas para el diagnóstico del riesgo de sarcopenia, como el "SARC-F" (puntaje de síntomas simples para el escrutinio de la sarcopenia), el cual ha demostrado efectividad en la población adulta (31).

En pacientes con cirrosis existen 2 estudios asiáticos donde se evaluó el rendimiento del puntaje "SARC-F", observándose un adecuado rendimiento pero en combinación con la fuerza de agarre de la mano y las medidas antropométricas. El mejor rendimiento se obtuvo para descartar la sarcopenia: en aquellos con 1 punto se reportó un área bajo la curva ROC de 0,68, con sensibilidad del 65 % y especificidad del 68 %, con VPP del 27 % y VPN del 92 % para la sarcopenia. Los ítems con mayor riesgo de asociación con la sarcopenia fueron "Fuerza", con OR = 1,98 (IC 95 %: 1,03-3,80), y "Caídas", con OR = 2,44 (IC 95 %: 1,48-4,03). Por lo anterior, esta escala podría ser de gran valor y aplicabilidad en nuestra población; sin embargo, hay que tomar en cuenta que, al final, las medidas antropométricas y la fuerza de agarre de la mano podrían ser suficientes para detectar a los pacientes cirróticos con sarcopenia (32,33).

Por último, es importante señalar que la valoración de la sarcopenia y la desnutrición se debe realizar anualmente en los pacientes cirróticos en estado de compensación y tan frecuente como cada 8 a 12 semanas según las recomendaciones emitidas por las guías de práctica clínica de la AASLD (*American Association for the Study of Liver Diseases*); a pesar de que estas guías dicen que no existe un nivel de evidencia suficiente como para apoyar alguna prueba clínica en la cama del paciente con cirrosis, la fuerza de agarre de la mano y las medidas antropométricas se posicionan como una buena opción (34).

LIMITACIONES

Al realizar la prueba de la fuerza de agarre de la mano, los pacientes no tenían signos de encefalopatía hepática manifiesta; sin embargo, no se descartó la presencia de encefalopatía hepática no manifiesta. No se comparó la fuerza de agarre de la mano con el estándar de oro que es al índice tomográfico musculoesquelético en L3 por indisponibilidad de dicho estudio en nuestro medio.

CONCLUSIÓN

La presencia de sarcopenia y malnutrición es frecuente en los pacientes con cirrosis hepática (> 50 %). Se debe realizar un tamizaje de la malnutrición y la sarcopenia en todo paciente con cirrosis hepática; no se recomienda la utilización de la clasificación de la OMS según el IMC y, en cambio, se pueden utilizar herramientas de fácil acceso y aplicación segura como la valoración antropométrica, la fuerza de agarre de la mano y el RFH-SGA.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Estado de nutrición y frecuencia de consumo de alimentos de niños con trastorno del espectro autista

Nutritional status and food intake frequency in children with autism spectrum disorder

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Resumen

Introducción: comúnmente, los niños con trastorno del espectro autista (TEA) presentan hiperselectividad, que podría llevarlos a desnutrición; sin embargo, suelen observarse con desarrollo eutrófico y tendencia al sobrepeso o la obesidad, probablemente por la preferencia de determinados alimentos.

Objetivos: evaluar el estado de nutrición basándose en mediciones antropométricas, y determinar la frecuencia de consumo de alimentos de los niños mexicanos con TEA.

Métodos: estudio transversal que incluyó a 31 niños de ambos sexos, de 5 a 10 años de edad, con TEA, reclutados por conveniencia en el Hospital del Niño DIF Hidalgo, México. Las variables consideradas fueron: peso, talla, índice de masa corporal, masa muscular, masa grasa y frecuencia de consumo de alimentos.

Resultados: el estado de nutrición eutrófico tuvo una prevalencia del 70,9 %, el sobrepeso del 12,9 % y la obesidad del 12,9 %. De acuerdo al sexo, las mujeres presentaron significativamente menor IMC y masa grasa pero mayor masa muscular que los varones. Al comparar por diagnóstico, no existieron diferencias estadísticas. Los alimentos más consumidos fueron: jitomate, zanahoria, plátano, manzana, tortilla, pan de harina de trigo, arroz, frijol, pollo, huevo, leche entera, aceite vegetal, gelatina y bebidas endulzadas. En su mayoría consumían agua natural todos los días.

Conclusiones: los niños con TEA presentan un estado nutricional eutrófico; sin embargo, existe una importante tendencia al sobrepeso y la obesidad, probablemente relacionada con un elevado consumo de bebidas endulzadas y gelatina, así como una escasa ingesta de verdura. Lo anterior indica la necesidad de vigilancia nutricional, para prevenir el desarrollo de enfermedades crónico degenerativas.

Palabras clave:

Estado de nutrición. Trastorno del espectro autista. Frecuencia de consumo de alimentos.

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Abstract

Introduction: children with autism spectrum disorder (ASD) commonly present food hyperselectivity, which could lead to malnutrition. Furthermore, they are usually observed with eutrophic development, and a tendency to overweight or obesity, which might occur because of food preferences.

Objectives: to evaluate nutritional status based on anthropometric measurements, and to determine the food intake frequency of Mexican children with ASD.

Methods: a cross-sectional study that included 31 children of both sexes, from 5 to 10 years of age, with ASD, recruited for convenience at the Hospital del Niño DIF Hidalgo, Mexico. The variables considered were: weight, height, body mass index, muscle mass, fat mass, and frequency of food consumption.

Results: the eutrophic nutritional status had a prevalence of 70.9 %, overweight of 12.9 % and obesity of 12.9 %. According to sex, women had significantly lower BMI and fat mass, but higher muscle mass than men. When comparing by diagnosis, there were no statistical differences. The most commonly consumed foods were tomato, carrot, banana, apple, corn tortilla, wheat flour bread, rice, beans, chicken, egg, whole milk, vegetable oil, gelatin and sweetened beverages. They mostly consumed plain water every day.

Conclusions: children with ASD have a eutrophic nutritional status in addition to a significant tendency to overweight and obesity, probably related to a high consumption of sweetened beverages and jelly, as well as a low intake of vegetables. This indicates the need for nutritional surveillance to prevent the development of chronic degenerative diseases.

Keywords:

Nutritional status. Autism spectrum disorder. Food frequency.

INTRODUCCIÓN

Los trastornos del espectro autista (TEA) son un conjunto de desórdenes del neurodesarrollo con características en común, entre las que destacan: la dificultad en la interacción social, alteración de la comunicación verbal y no verbal, comportamientos estereotipados y repetitivos (1). El término "espectro" se utiliza para hacer alusión a la variabilidad de los síntomas que se presentan, dependiendo de la severidad o el alto funcionamiento, así serán la especialización y el tiempo en que se requerirá el apoyo (2). De acuerdo a la Clasificación Internacional de Enfermedades (CIE-10, 2019), los TEA se encuentran como parte de los trastornos del comportamiento y neurodesarrollo, específicamente dentro de los síndromes psiquiátricos clínicos, y se subclasifican como: Autismo infantil (F84.0), Autismo atípico (F84.1), Síndrome de Rett (F84.2), Otro trastorno desintegrativo de la infancia (F84.3), Trastorno hipercinético con retraso mental y movimientos estereotipados (F84.4) y Síndrome de Asperger (F84.05) (3).

Los pacientes con autismo infantil y síndrome de Asperger presentan hiperselectividad alimentaria, que hace referencia al rechazo de determinada comida y la escasa variedad en la dieta, relacionado con la composición nutricional (proteínas, hidratos de carbono, etc.) y/o sensorial (textura, olor, sabor, aspecto visual, temperatura) (4-7). Esto es importante porque la alimentación y la nutrición son procesos en los que influyen factores biológicos, ambientales y socioculturales que durante la infancia contribuyen al crecimiento, desarrollo y maduración biopsicosocial (8). En teoría, las conductas alimentarias en los niños con TEA podrían llevarlos a la desnutrición calórico-proteica o bien a padecer deficiencias de micronutrimentos (9).

Los estudios que se han centrado en la evaluación del estado de nutrición de estos niños sugieren que, a pesar de la hiperselectividad alimentaria que presentan, no suelen encontrarse en desnutrición sino que es más común que tengan un desarrollo adecuado respecto al peso, la talla y el índice de masa corporal para la edad (9-13); incluso se ha reportado una importante tendencia al sobrepeso y la obesidad (10-17), probablemente por la elevada preferencia hacia alimentos de alta densidad energética y el bajo consumo de verduras y frutas (6,10,16).

Esto indica que conocer las preferencias alimentarias de los niños con TEA permitiría abordar los factores subyacentes asociados con la selectividad alimentaria y mitigar las comorbilidades asociadas con la ingesta nutricional inadecuada a largo plazo en esta población. Una manera de conocer los hábitos de alimentación es mediante encuestas alimentarias, incluido el cuestionario de frecuencia de consumo de alimentos, que es ampliamente utilizado en la epidemiología nutricional (18), permite conocer el consumo de grupos de alimentos, clasificar a los individuos por su patrón dietético de una forma rápida, con un bajo costo, e incluso estimar medidas de asociación del patrón dietético con el desarrollo de enfermedades (19).

En México no existe información respecto al estado de nutrición y los patrones de alimentación de los niños con TEA; en países como Estados Unidos, India y Paraguay (9,10,15), los datos encontrados son diversos y difieren unos de otros, probablemente por la amplia variabilidad de factores que influyen en la alimentación de cada población; por lo tanto, el presente estudio tuvo como objetivo evaluar el estado de nutrición y la frecuencia de consumo de alimentos en niños mexicanos con TEA.

MATERIALES Y MÉTODOS

El presente estudio transversal evaluó el estado de nutrición y la frecuencia de consumo de alimentos de niños con TEA. La muestra fue reclutada por conveniencia en el Hospital del Niño DIF Hidalgo. Los pacientes incluidos tenían diagnóstico de TEA (F84.0 y F84.5), una edad de 5 a 10 años, con sexo indistinto; se excluyeron aquellos que contaban con enfermedades neurológicas capaces de alterar el funcionamiento cognitivo. Los datos se recopilaron entre agosto y noviembre del año 2021.

Para la evaluación antropométrica se utilizó un estadímetro (SECA 206, Alemania), siguiendo la metodología antropométrica recomendada por la OMS (Lohman y cols., 1988) (20). Para estimar el peso, la masa grasa (MG) y lamasa muscular (MM) se empleó la bioimpedancia eléctrica (InBody270, E.U.A.). Se usaron las mediciones de peso y talla para calcular el IMC (peso dividido por el cuadrado de la altura), que se expresó en kg/m^2.

Se empleó el *software* Anthro Plus de la OMS, v.1.0.4, para determinar el puntaje Z de la talla para la edad (T/E), el peso para la edad (P/E) y el índice de masa corporal para la edad (IMC/E). Los diagnósticos nutricionales se evaluaron de acuerdo con los patrones de la OMS (2007), que consideran: T/E < -3 DE, baja talla severa; < -2 DE, baja talla; +3 a -1 DE, talla normal; P/E < -3 DE, bajo peso severo; < -2 DE, bajo peso; IMC/E < -3 DE, severamente emaciado; < -2 DE, emaciado; -1 a +1 DE, normal/eutrófico; > 2 DE, sobrepeso; > 3 DE, obesidad (21).

Se aplicó un cuestionario de frecuencia de consumo de alimentos de tipo cualitativo, que estaba adaptado a la población y la región, y se evaluó el consumo de 49 alimentos, de diferentes grupos: verduras, frutas, cereales y tubérculos, leguminosas, alimentos de origen animal, leche y lechadas vegetales, aceites y grasas, azúcares, otros productos.

Para el análisis estadístico se determinaron las frecuencias absolutas y los porcentajes para las variables cualitativas, mientras que a las variables cuantitativas (T/E, P/E, IMC/E, MM, MG) se les aplicó la prueba de Kolmogorov-Smirnov para verificar la normalidad; posteriormente se realizó la prueba del chi cuadrado, considerando un valor de $p < 0,05$ como estadísticamente significativo, y se expresaron como medias y desviaciones estándar. Se utilizó el paquete de análisis estadístico SPSS, versión 28.0.0.0.

El presente estudio forma parte del protocolo de investigación CICEICB-PEx-2021-0, que fue aprobado por el Comité de Investigación, el Comité de Ética en Investigación y el Comité de Bioseguridad del Hospital del Niño DIF Hidalgo. Todos los procedimientos se realizaron conforme a lo que establece la Ley General de Salud en Materia de Investigación para la Salud (México, 2014) (22).

RESULTADOS

En la tabla I se muestran las características generales del grupo de estudio (edad, sexo, y diagnóstico de acuerdo al trastorno del espectro autista y al estado de nutrición). De los 31 participantes, la edad media fue de 7,5 ± 1,16 años. En su mayoría fueron del sexo masculino (24 sujetos). Además, 19 de los evaluados tenían un diagnóstico de síndrome de Asperger y 12 de autismo. De acuerdo con el IMC para la edad, la mayoría de los individuos estaban en un estado de nutrición normal, seguido del sobrepeso y la obesidad, lo que es acorde con los resultados obtenidos al evaluar la talla para la edad y el peso para la edad, en donde predominó el diagnóstico "eutrófico".

Se clasificaron los resultados de P/E, T/E, IMC/E, % de grasa corporal y masa muscular de acuerdo a la muestra en general, así como por sexo y diagnóstico (F84.0 y F84.5), lo que se puede observar en la tabla II. El peso, la talla y el IMC para la edad fueron en el sexo masculino mayores que en el femenino, aunque solo el P/E mostró una diferencia estadísticamente significativa ($p = 0,021$). En cuanto a la composición corporal, las mujeres presentaron significativamente un menor porcentaje de grasa corporal ($p < 0,001$) que los hombres, pero mayor masa muscular. A pesar de no mostrar una diferencia significativa, los sujetos con síndrome de Asperger (F84.5) tuvieron mayor puntuación en el peso, la talla y el IMC para la edad, pero menor porcentaje de grasa corporal y masa muscular, en comparación con aquellos que tenían autismo (F84.0).

En la frecuencia de consumo de alimentos (Tabla III) se aprecia que las verduras que más se consumían eran el jitomate y la zanahoria; sin embargo, el jitomate se ingería un mayor número de veces a la semana. La verdura menos consumida por los niños fue el nopal. Respecto al consumo de frutas, la pera fue la menos consumida, seguida de la fresa, que los padres destacaron que era por su elevado costo en determinadas temporadas, lo que no sucede con las frutas más consumidas: plátano, manzana y naranja. En cuanto al grupo de los cereales y tubérculos, el pan de harina de trigo y el arroz los consumían el 86 % de los niños, aunque la tortilla era el alimento más popular, consumiéndola

Tabla I. Características generales de la muestra de niños con trastorno del espectro autista (n = 31)

Características	Media ± DE n and %
Edad (años)	7,5 ± 1,16
Sexo	
Masculino	(24) 74,2
Femenino	(8) 25,8
Trastorno del espectro autista	
F84.5	(19) 61,3
F84.0	(12) 38,7
Estado de nutrición (IMC/E)	
Severamente emaciado	(1) 3,2
Emaciado	0) 0,0
Eutrófico	(22) 70,9
Riesgo de sobrepeso	(0) 0,0
Sobrepeso	(4) 12,9
Obesidad	(4) 12,9
Talla para la edad (puntaje Z)	
Talla baja	(2) 6,5
Eutrófico	(29) 93,5
Talla alta	(0) 0,0
Peso para la edad (puntaje Z)	
Bajo peso severo	(1) 3,2
Bajo peso	(0) 0,0
Eutrófico	(21) 67,7
Elevado	(4) 12,9
Muy elevado	(3) 9,7
N/A	(2) 6,5

Valores expresados como media, desviación estándar y porcentaje. El puntaje Z se calculó con el sofware *AntroPlus v1.0.4 según los valores de referencia para el sexo y la edad (OMS, 2007). F84.5: síndrome de Asperger; F84.0: autismo (de acuerdo con la CIE-10); IMC/E: índice de masa corporal/edad).*

30 de los 31 sujetos encuestados; en su mayoría, la consumían todos los días de la semana. Entre los grupos de alimentos que proporcionan una mayor cantidad de proteína se encuentra el de las leguminosas; de estas, el frijol era el más aceptado, consumido por la mayoría de los sujetos entre 1 y 2 días a la semana, en contraste con las habas, que solo las consumía uno de los encuestados. El pollo y el huevo fueron los alimentos de origen animal más consumidos (93 y 90 %, respectivamente), mientras que el pescado y el atún, junto con la carne de cerdo, solo los ingerían el 58 %, principalmente 1 vez a la semana. El 70 % de los encuestados consumían leche entera y solo 5 bebían leche deslactosada, reportando que la razón por la cual no consumían leche entera era porque les causaba algún malestar o habían presentado alergia a la proteína de la leche. De las grasas y aceites, el aceite vegetal (soya, canola, maíz) lo consumían todos los días la mayoría de los sujetos. El aguacate, la crema y la mantequilla los consumían con mayor frecuencia los niños con autismo. La gelatina era el alimento más aceptado del grupo de las azúcares; sin embargo, 11 sujetos reportaron consumir azúcar todos los días, 12 de ellos entre 1 y 6 veces a la semana y solo 8 no la consumían. Finalmente, solo 1 individuo no bebía agua natural todos los días y el 74 % de los sujetos del estudio alternaban su consumo con el de agua de frutas endulzada en al menos un tiempo de comida. En cuanto a los condimentos alimenticios, el 100 % reportaron consumir sal añadida en la preparación de alimentos y el 78 % comían alimentos preparados con especias como la pimienta, los cominos, la canela y las hierbas de olor.

Tabla II. Composición corporal por medio de BIA e indicadores antropométricos de los niños con TEA

Variable	Muestra total Media ± DE n = 31	Mujeres Media ± DE n = 8	Hombres Media ± DE n = 23	Valor p	F84.5 Media ± DE n = 19	F84.0 Media ± DE n = 12	Valor p
Puntaje Z P/E	0,54 ± 1,88	-0,85 ± 1,40	0,98 ± 1,81	0,021*	0,82 ± 1,90	0,07 ± 1,82	0,136
Puntaje Z T/E	0,24 ± 1,32	-0,36 ± 1,51	0,45 ± 1,21	0,066	0,43 ± 1,24	0,05 ± 1,43	0,159
Puntaje Z IMC/E	0,70 ± 1,72	-0,30 ± 1,69	1,05 ± 1,62	0,054	0,87 ± 1,63	0,42 ± 1,90	0,248
% GC	29,39 ± 0,14	25,70 ± 0,10	29,81 ± 0,15	< 0,001	28,03 ± 0,16	32,66 ± 0,10	0,403
MM (kg)	14,50 ± 4,16	12,40 ± 5,32	11,35 ± 4,09	< 0,001	10,47 ± 3,99	14,10 ± 3,72	0,129

Valores expresados como media ± desviación estándar; el puntaje Z se calculó con el sofware *AntroPlus v1.0.4 según los valores de referencia para el sexo y la edad (OMS, 2007). P/E: peso/edad; T/E: talla/edad; IMC/E: índice de masa corporal/edad; %GCT: porcentaje de grasa corporal; MM (kg): masa muscular.*

Tabla III. Frecuencia de consumo de alimentos de los niños con TEA

Grupo de alimentos	Variedades	Porcentaje de niños que lo consumen (%) n = 31	Nunca o casi nunca	1-2 días/ semana	3-4 días/ semana	5-6 día/ semana	Todos los días
Verduras	Jitomate	86	3	1	9	4	14
	Lechuga	71	8	15	5	1	2
	Zanahoria	86	3	10	15	1	2
	Chayote	74	7	19	4	0	1
	Jícama	55	13	11	4	2	1
	Nopal	52	14	13	3	0	1
Frutas	Manzana	86	3	8	11	1	8
	Plátano	96	1	3	11	1	15
	Fresas	52	14	13	3	0	1
	Sandía	71	8	15	2	2	4
	Pera	46	16	13	1	0	1
	Naranja	77	6	10	7	3	5

(Continúa en página siguiente)

Tabla III (Cont.). Frecuencia de consumo de alimentos de los niños con TEA

Grupo de alimentos	Variedades	Porcentaje de niños que lo consumen (%) n = 31	Nunca o casi nunca	1-2 días/ semana	3-4 días/ semana	5-6 día/ semana	Todos los días
Cereales y tubérculos	Pan de harina de trigo	86	3	12	10	2	4
	Pan dulce	80	5	12	7	1	6
	Arroz	86	3	14	12	2	0
	Sopa de pasta	90	2	14	9	3	3
	Tortilla	93	1	1	2	2	25
	Palomitas de maíz	68	9	21	0	1	0
	Papa	83	4	11	12	0	4
Leguminosas	Frijol	90	2	20	6	0	3
	Lenteja	52	14	13	4	0	0
	Garbanzo	27	22	9	0	0	0
	Haba	7	30	1	0	0	0
Alimentos de origen animal	Pollo	93	1	19	10	1	0
	Pescado/atún	58	12	18	1	0	0
	Res	68	9	19	2	1	0
	Cerdo	58	13	15	3	0	0
	Jamón	80	5	17	6	0	3
	Huevo	90	2	6	19	0	4
	Queso	74	7	11	8	0	5
Leche y lechadas vegetales	Leche entera	70	9	1	1	1	19
	Leche deslactosada	16	26	0	1	0	4
	Yogurt	62	11	10	5	1	4
	Lechadas de soya, almendra, coco, arroz	7	30	0	0	1	0
Aceites	Aceite de canola/soya	93	1	0	1	2	27
	Aceite de oliva	37	19	8	2	0	2
	Nuez, almendras, cacahuates	68	9	16	3	0	3
	Crema	65	10	14	7	0	0
	Aguacate	59	12	8	8	2	1
	Mantequilla	59	12	12	7	0	0
Azúcares	Azúcar	71	8	3	7	2	11
	Miel	25	23	7	1	0	0
	Jugos industrializados	55	13	13	5	0	0
	Refrescos	65	10	17	4	0	0
	Gelatina	84	4	15	9	0	3
Otros productos	Agua natural	93	1	1	1	0	28
	Agua de frutas	74	7	12	4	2	6
	Sal	100	0	1	0	1	29
	Pimienta, hierbas de olor, cominos, canela	78	6	6	2	4	13

Valores expresados como porcentaje (%) y frecuencias absolutas.

DISCUSIÓN

El peso y la talla para la edad son los indicadores más utilizados para monitorizar que el crecimiento de los niños sea adecuado (23), aunque se considera que el IMC en este grupo de edad es un instrumento para detectar el sobrepeso y la obesidad (24). Ya que el grupo de estudio estuvo conformado por 24 hombres y 7 mujeres de entre 5 y 10 años de edad, los sujetos se evaluaron según los actuales valores de referencia de crecimiento de la OMS para sexo y edad (OMS, 2007) (21).

En la presente investigación se encontraron niños con diagnóstico "eutrófico" respecto a la talla para la edad al 87 %, en peso para la edad al 64,5 %, y de acuerdo con el indicador IMC al 70,9 %; sin embargo, el 25,8 % se situaban en rangos de sobrepeso y obesidad. Los resultados fueron similares a lo reportado en un estudio realizado en Paraguay por Ojeda y cols. (2013) (9), en donde el 80 % tenían talla para la edad eutrófica, el 60 % peso para la edad normal, el 60 % un IMC entre -1 y +1 DE y el 30 % sobrepeso y obesidad. Esto es diferente a lo reportado en un metaanálisis de Estados Unidos y Canadá en el cual solo el 31,9 % de los escolares y el 8,2 % de este mismo grupo de edad pero de origen hispano o latinoamericano tenían un IMC eutrófico (15). En España también se describieron altas cifras de sobrepeso y obesidad, pues el 63,4 % de los evaluados contaban con un IMC por encima de las 2 DE (16). A pesar de que los estudios mencionados sugieren que los niños con TEA están en riesgo de sobrepeso y obesidad, y han planteado que pueden existir factores de riesgo en esta población distintos de los del resto de los niños, en un proyecto estadounidense muestran que no existió diferencia estadísticamente significativa en el IMC al comparar niños con TEA con otros de desarrollo neurotípico (6). De acuerdo con los porcentajes de masa grasa se obtuvo una media del 29,39 ± 0,14 %, mientras que un estudio realizado en Polonia mostró un 18,46 ± 5,38 % (3,0-28,9 %) (12) y otro en Brasil un 23,2 % (13,8-35,6 %) (25).

Respecto al consumo de alimentos, los resultados de este estudio muestran con qué frecuencia se consumen algunos alimentos en una semana. El 86 % de los encuestados consumían verdura entre 1 y 7 días a la semana y al menos el 45 % un tipo de verdura todos los días. En su mayoría consumían fruta diariamente. El 90 % comían huevo y el 93 % pollo entre 1 y 4 veces a la semana. Del grupo de los cereales y tubérculos, el más consumido fue la tortilla de maíz (93 %), seguido de los panes de harina de trigo y el arroz (86 %). En las leguminosas, el 90 % refirió comer frijoles al menos 2 veces a la semana y el 45 %, lentejas. Respecto al consumo de aceites y grasas, se encontró que el 97 % de las personas que preparaban los alimentos de estos niños utilizaban aceite vegetal todos los días. En cuanto al consumo de bebidas, el 93 % bebían agua natural todos los días y el 83 % algún tipo de leche de origen vacuno. Referente a las bebidas no lácteas endulzadas, el 74 % consumían agua de frutas endulzada, el 65 % refrescos y el 55 % jugos industrializados.

Respecto al consumo de frutas y verduras, los resultados del presente trabajo difieren de lo reportado en México por la Encuesta Nacional de Salud y Nutrición (ENSANUT), Hidalgo (2018), pues menciona que solo el 14,1 % de los niños de esta región y grupo de edad las consume todos los días (26). De la misma manera, estudios realizados en EUA y Australia mencionan que los patrones de alimentación delos niños con TEA no muestran apego a las respectivas recomendaciones nacionales para este mismo grupo de alimentos (6,7).

En México no se han reportado resultados del consumo de alimento en niños con TEA: sin embargo, en un estudio en Paraguay se refirió que el 100 % de la muestra consumían alimentos de origen animal, siendo la carne de res y pollo las principales, en tanto que en el grupo de cereales y tubérculos, los panes de harina de trigo eran los más frecuentes (86 %), seguidos por los de harina de arroz (36 %); del grupo de las leguminosas, el 77 % consumían algún tipo de estas de 1 a 2 veces a la semana, similar en frecuencia a los resultados del presente estudio. Finalmente, al igual que en el presente, se reportó que los aceites vegetales y las grasas saturadas se ingerían todos los días por el total de los participantes (9). Se observó un elevado consumo de jugos industrializados y refrescos, con lo reportado en la ENSANUT, en la cual el 77,3 % de los escolares consumían bebidas endulzadas y el 88,7 % agua natural. En la actual investigación se observó una alta preferencia por el consumo de leche de vaca, difiriendo de lo mencionado por la Encuesta Nacional de Nutrición (58,3 %) (26).

Dentro de los factores que influyen en el estado de nutrición de una población se encuentran los patrones de alimentación (27). Tras una revisión sistemática de estudios observacionales, Siles y cols. (2015) (4) reportaron que la mayoría de los niños y adolescentes con TEA presentan mayor selectividad alimentaria que aquellos con desarrollo neurotípico y una elevada ingestión de alimentos de alta densidad energética y poco valor nutricional, suponiendo que esto se relaciona con las altas prevalencias del sobrepeso y la obesidad en los niños con esta condición. Sin embargo, en un estudio de Whitney y cols. (2012) (6), los autores buscaron asociar estos patrones de alimentación con un mayor IMC, aunque no lo lograron y consideraron que la frecuencia y la cantidad en que se ingieren productos como las bebidas industrializadas, en conjunto con otros factores como el bajo consumo de verduras y frutas, sí puede contribuir al desarrollo de obesidad en las personas con TEA.

Se considera que el contraste entre las prevalencias del sobrepeso y la obesidad de otros estudios y las encontradas en el presente trabajo podrían estar relacionadas con la amplia variabilidad de los patrones de alimentación entre estos países, incluso entre entidades federativas y/o regiones, ya que los resultados obtenidos respecto al estado de nutrición son similares a las prevalencias regionales y diferentes a las nacionales (29,4 % y 35,6 %, respectivamente) (26,28).

Se ha descrito que la alimentación mexicana variada y suficiente (con consumo de cereales, leguminosas, frutas, verduras y porciones modestas de alimentos de origen animal) puede ser más recomendable que las dietas de alta densidad energética (basadas principalmente en alimentos de origen animal, cereales refinados, azúcares simples y grasas saturadas) que habitual-

mente se consumen en los países de gran desarrollo industrial (27). Los patrones de alimentación de los participantes del presente estudio podrían explicar su estado de nutrición.

El presente estudio tuvo algunas limitaciones, dentro de las cuales se encuentra el reducido tamaño muestral, que estuvo sujeto a la falta de afluencia regular de los pacientes al centro de investigación en relación con la actual pandemia por COVID-19. Sin embargo, ante la ausencia de estudios similares dentro de México, esta investigación podría representar un punto de referencia para investigaciones futuras, considerando aplicar una frecuencia de consumo de alimentos cuali-cuantitativa para poder realizar pruebas de asociación entre los patrones de consumo de alimentos y el estado de nutrición.

CONCLUSIONES

Los participantes del presente estudio presentaron en su mayoría un estado nutricional eutrófico; no obstante, existe una importante tendencia al sobrepeso y la obesidad. Los resultados sugieren una probable relación entre el estado de nutrición y el bajo consumo de verdura (solo el 45 % consumían alguna verdura todos los días). Además, había una elevada ingesta de agua de fruta endulzada, refrescos, gelatina y jugos industrializados. Lo anterior indica la necesidad de vigilancia nutricional y orientación alimentaria en los niños con TEA, con un enfoque especial en la distribución adecuada de macronutrimentos para prevenir el desarrollo de enfermedades crónico-degenerativas.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Adaptación en español y validación en México de la herramienta de tamizaje nutricional STAMP *(Screening Tool for the Assessment of Malnutrition in Paediatrics)*

Adaptation in Spanish and validation in Mexico of the Screening Tool for the Assessment of Malnutrition in Paediatrics (STAMP)

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Resumen

Antecedentes: la desnutrición pediátrica es una de las principales causas de complicaciones en niños hospitalizados, por ello, el tamizaje nutricional al ingreso es indispensable. La Screening Tool for the Assessment of Malnutrition in Paediatrics (STAMP) es una herramienta sencilla, reproducible y fácil de interpretar, sin embargo, en México no se encuentra validada. El objetivo del estudio fue validar y adaptar a la población mexicana la herramienta de tamizaje nutricional STAMP.

Metodología: la validación se realizó en dos fases: en primer lugar, se realizó la traducción y adaptación cultural; y en segundo lugar, se llevó a cabo un estudio transversal comparando la herramienta STAMP con una evaluación nutricional completa (ENC). Un médico pediatra especialista en nutrición realizó la ENC con la evaluación de parámetros antropométricos, clínicos y dietéticos y, posteriormente, dos nutriólogas realizaron la misma evaluación con la herramienta STAMP. Finalmente, se tamizaron todos los pacientes en leve y moderado o grave riesgo de desnutrición.

Resultados: de los 300 pacientes incluidos en el estudio, 160 fueron niños (53,3 %) y 140, niñas (46,7 %), con una media de edad de 9,44 ± 5,73 años. Las valoraciones realizadas con la herramienta STAMP tuvieron una concordancia del 100 %. Comparado con la ENC, se obtuvo un índice kappa de 0,480 ($p < 0,01$). La prueba STAMP mostró una sensibilidad del 92 %, una especificidad del 75 %, valor predictivo positivo (VPP) del 45 %, valor predictivo negativo (VPN) del 97 %, LR- de 3,68 y LR- de 0,10.

Conclusiones: la herramienta de tamizaje STAMP cuenta con los elementos necesarios para evaluar de forma objetiva el riesgo de desnutrición en niños mexicanos y es una prueba altamente sensible y específica.

Palabras clave:

Tamizaje. Desnutrición. Riesgo nutricional. Evaluación nutricia.

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Abstract

Background: pediatric malnutrition is one of the main causes of complications in hospitalized children. Nutritional screening at admission is essential. The Screening Tool for the Assessment of Malnutrition in Paediatrics (STAMP) is a simple, reproducible and easy-to-interpret tool, but it is not validated in Mexico. The objective of the study was to validate and adapt the STAMP nutritional screening tool to the Mexican population.

Methods: the validation was carried out in two phases: firstly, the translation and cultural adaptation was carried out; and secondly, a cross-sectional study was performed comparing the STAMP tool with a complete nutritional assessment (CNA). A pediatrician specialized in nutrition performed the CNA with the evaluation of anthropometric, clinical and dietary parameters; later, two nutritionists carried out the same evaluation with the STAMP tool. Finally, the patients were graded as low risk and moderate or severe malnutrition risk.

Results: of the 300 patients included in the study, 160 were boys (53.3 %) and 140 were girls (46.7 %), with a mean age of 9.44 ± 5.73 years. The assessments made by with the STAMP tool had a 100 % concordance. Compared with CNA, a kappa index of 0.480 ($p < 0.01$) was obtained. The STAMP test showed a sensitivity of 92 %, a specificity of 75 %, positive predictive value (PPV) of 45 %, negative predictive value (NPV) of 97 %, RVN of 3,68, and RVN of 0,10.

Conclusions: the STAMP screening tool has the necessary elements to objectively assess the risk of malnutrition in Mexican children and is a highly sensitive and specific test.

Keywords:

Screening. Malnutrition. Nutritional risk. Nutritional evaluation.

INTRODUCCIÓN

En la actualidad, la desnutrición pediátrica hospitalaria es una de las principales causas de complicaciones en niños. En consecuencia, un tamizaje nutricional correcto que permita determinar la prevalencia y el riesgo de desnutrición es indispensable para prevenir retraso en el crecimiento, morbimortalidad, emaciación, insuficiencia ponderal, carencia o insuficiencia de micronutrientes, mayor tiempo de estancia hospitalaria, costos elevados y tasas de readmisión (1). Por el alto número de pacientes y los estrechos tiempos de consulta, contar con un instrumento fácil y sencillo sería la mejor estrategia (2-4).

Las guías de la Sociedad Americana de Nutrición Parenteral y Enteral (ASPEN) y la Sociedad Europea de Nutrición Parenteral y Enteral (ESPEN) recomiendan el tamizaje nutricional al ingreso hospitalario durante las primeras 48 horas para prevenir y abordar al paciente con el mejor tratamiento médico-nutricional (5). La herramienta de tamizaje STAMP (por sus siglas en inglés, Screening Tool for the Assessment of Malnutrition in Paediatrics), es un cuestionario validado en diferentes poblaciones que evalúa el riesgo de desnutrición en función del diagnóstico, la ingesta nutrimental y la antropometría del paciente de forma semicuantitativa, generando una clasificación y un plan de acción. Esta herramienta ha mostrado una buena sensibilidad (70 %), especificidad (91 %), valor predictivo positivo (VPP) (54,8 %), valor predictivo negativo (VPN) (94,9 %) y concordancia interevaluador ($\kappa = 0{,}882$) para detectar el riesgo nutricional en niños, comparado con otras pruebas de tamizaje (6). Sin embargo, no se encuentra validada y adaptada culturalmente para su uso en población mexicana. Por lo anterior, el objetivo de este estudio fue validar y adaptar a la población mexicana la herramienta de tamizaje nutricional STAMP.

MÉTODOS

El presente estudio de validez se realizó a través de un estudio transversal en la Unidad de Pediatría del Hospital General de México Dr. Eduardo Liceaga (HGMEL), durante febrero de 2019 y marzo de 2020.

RESPONSABILIDADES ÉTICAS

El estudio se llevó a cabo bajo los estatutos de la ley general de salud en materia de investigación en México y la Declaración de Helsinki. El protocolo fue aprobado por el Comité de Ética en Investigación del HGMEL (n.º DI/19/301/014). Todos los padres o tutores de los menores firmaron la carta de consentimiento informado y aprobaron el asentimiento informado que se entregó a los niños. A los niños mayores de seis años se les entregó un asentimiento donde se les explicaban los procedimientos y las mediciones durante el estudio de forma didáctica y los niños consintieron su participación a través de imágenes de aprobación o rechazo.

VALIDACIÓN

La traducción, adaptación cultural y validación del STAMP se realizó en dos fases (Fig. 1).

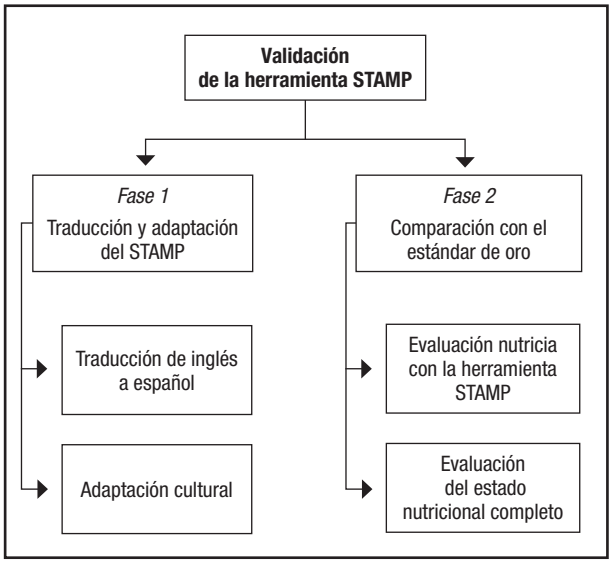

Figura 1.

Diagrama de flujo de las fases en las que se realizó el estudio de validación de la herramienta de tamizaje nutricional STAMP *(Screening Tool for the Assessment of Malnutrition in Paediatrics).*

Fase 1

Se realizó la traducción, adaptación cultural y validez de contenido de la herramienta STAMP. El cuestionario en inglés fue traducido al español por un traductor bilingüe certificado cuyo idioma nativo es el español y la adaptación cultural la realizó una traductora especialista en ciencias de la salud; en ella se modificaron palabras y frases para adaptarla al contexto en México. La validez de contenido del cuestionario se realizó con una prueba piloto con profesionales de la salud, donde se analizó que la prueba fuera fácil de entender, interpretar y aplicar a los pacientes y que tuviera la capacidad de discriminar entre pacientes con riesgo de desnutrición y sin riesgo (Fig. 2).

STAMP (Screening Tool for the Assessment of Malnutrition in Pediatrics): español

Folio: _____ **Nombre:** _____ **Género:** Masculino/Femenino

Talla (> 2ª) o longitud (< 2ª): _____ cm **Edad:** _____ meses **Peso:** _____ kg

P/T: _____ cm **P/E:** _____ cm **T/E:** _____ cm **Diagnósticos:** _____

Fecha de ingreso: ____ / ____ / ____ **Fecha de valoración:** ____ / ____ / ____ **Fecha de egreso:** ____ / ____ / ____

PASO 1: DIAGNÓSTICO

1. ¿El diagnóstico médico conlleva una implicación nutricional al paciente?	***Puntuación***
Definitivamente (p. ej., falla intestinal, malabsorción intestinal, disfagia, cirugía mayor, tratamiento activo oncológico, errores innatos del metabolismo)	**3**
Probablemente (p. ej., trastornos de conducta alimentaria, cardiopatías, labio y paladar hendido, enfermedad neurológica o psiquiátrica, diabetes, enfermedad por reflujo gastroesofágico, cirugía menor, alergia o intolerancia alimentaria, dificultad respiratoria)	**2**
No (p. ej., estancia corta)	**0**

PASO 2: INGESTA NUTRIMENTAL

2. ¿Cómo es la ingesta nutricional actual?	***Puntuación***
Ayuno	**3**
Cambios en la alimentación o disminución de ingesta en las últimas semanas	**2**
Sin cambios en la alimentación o alimentación adecuada	**0**

PASO 3: PESO Y TALLA PARA LA EDAD (dos o más parámetros son válidos para tamizar)

3. Con base en las tablas de crecimiento (OMS < 2 años, CDC NHANES > 2 años), clasificar los parámetros antropométricos*	***Puntuación***
Diferencias de > 3 percentiles o ≥ 3 columnas de diferencia (o peso < 2 percentiles)	**3**
Diferencias de > 2 percentiles o 2 columnas de diferencia	**1**
Diferencias de 0-1 percentil o 0-1 columna	**0**

PASOS 4 Y 5: CLASIFICACIÓN DE RIESGO Y PLAN DE ACCIÓN

CLASIFICACIÓN	PUNTUACIÓN	PLAN
Alto	≥ 4 puntos	– Adopción de medidas – Intervención de nutrición clínica – Monitoreo diario del paciente
Medio	2-3 puntos	– Monitorear ingesta durante 3 días – Repetir tamizaje al tercer día – Realizar modificaciones necesarias
Bajo	0-1 puntos	– Continuar tratamiento nutricional actual – Repetir tamizaje a los 7 días – Modificar indicaciones si es necesario

Puntuación: _____ Total: _____

Clasificación: _____

2.º TAMIZAJE	3.er TAMIZAJE	4.º TAMIZAJE

Nombre de quien realiza tamizaje: _____

**Consultar: Norma Oficial Mexicana 008-SSA2-1993. Control de la nutrición, crecimiento y desarrollo del niño y adolescente. Criterios y prestación del servicio. Diario Oficial de la Federación.*

Figura 2.

Herramienta de tamizaje nutricional STAMP *(Screening Tool for the Assessment of Malnutrition in Paediatrics)* validada, traducida y adaptada culturalmente al personal de salud en México.

Fase 2

En esta fase se realizó la validez de criterio del STAMP, en la cual se correlacionaron los datos del STAMP con el estándar de oro, que fue la evaluación nutricional completa (ENC) por parte del pediatra.

Participantes

Se incluyeron menores de edad que ingresaron al hospital a los servicios de Pediatría, Cirugía, Infectología y Hematooncología, que tuvieran de un día de nacidos hasta 17 años con once meses. Se consideró recién nacido a los bebes menores de 28 días; lactante menor o infante, a niños menores de 12 meses; lactante mayor, a niños de entre un año y un año con once meses; preescolares, de dos a cuatro años; escolares, de cinco a nueve años; y adolescentes, de diez a 17 años con once meses. La clasificación de los participantes se realizó con base a lo establecido en la Norma Oficial Mexicana 008 (NOM-008-SSA3-2017) (7), las gráficas de la Organización Mundial de la Salud (OMS) para menores de dos años, las del centro para el control y la prevención de enfermedades (CDC) y la encuesta nacional de examen de salud y nutrición (NHANES) para mayores de dos años. En pacientes con síndrome de Down o parálisis, se utilizaron las gráficas correspondientes para dicha población (8). Se excluyeron pacientes en terapia intensiva o aquellos en los que, por su enfermedad, no se pudieran realizar la ENC y el STAMP.

Todas las valoraciones se realizaron por duplicado, en las primeras 24 horas de ingreso y bajo los procedimientos establecidos por la OMS (9), con el paciente en ayuno y con la mínima cantidad de ropa. La talla (preescolares, escolares y adolescentes) o longitud (lactantes) se midió con la espalda recta y plano de Frankfurt. Los pacientes también se clasificaron de acuerdo a los diferentes grados de estrés hospitalario: a) leve, estancia corta; b) moderado, cardiopatía, paciente con alteraciones neurológicas o psiquiátricas, diabetes, cirugía menor, alergia o intolerancia alimentaria y dificultad para respirar; y c) alto, falla intestinal, malabsorción, disfagia, cirugía mayor, tratamiento oncológico activo o errores innatos del metabolismo.

Evaluación nutricional completa

La ENC fue realizada por un médico pediatra especialista en nutrición clínica, quien condujo toda la evaluación de acuerdo a la NOM-008-SSA3-2017, las guías de la OMS y siguiendo el protocolo establecido por Lara-Pompa y cols. (10). La evaluación consistió en la medición de tres parámetros:

1. Antropometría, que consideró la medición de peso (báscula SECA® 813 o pesabebés SECA® 354), talla o longitud (estadímetro SECA® 213l o infantómetro 417), perímetro cefálico (PC) (cinta SECA® 201), circunferencia de brazo (CB), peso para la edad (P/E), peso para la talla (P/T), talla para la edad (T/E), índice de masa corporal (IMC), índice de masa corporal para la edad (IMC/E), pliegue cutáneo tricipital (PCT) y pliegue cutáneo bicipital (PCB) (plicómetro Lange). Específicamente en los lactantes se realizó: PC, PC/E, P/E gestacional, T/E gestacional y velocidad de ganancia de peso (g/kg/día) para la evaluación clínica.
2. Datos clínicos, que consistía en la evaluación de edema, caquexia, signos y síntomas asociados a la enfermedad, cambios gastrointestinales y pérdida de peso.
3. Composición corporal a través de impedancia bioeléctrica, considerando masa grasa, masa libre de grasa, porcentaje de masa grasa, porcentaje de masa libre de grasa, agua corporal total y agua intracelular y extracelular (RJL IV systems). Se utilizaron los parámetros de *Z score* con la fórmula de conversión del percentil correspondiente a la edad. Los datos de composición corporal fueron valorados utilizando los estándares publicados por Wells y cols. utilizando las gráficas con valores Z de edad y género (11).

Tamizaje nutricional con STAMP

La aplicación de la prueba STAMP se realizó por dos nutriólogas cegadas al diagnóstico de la ENC y se llevó a cabo inmediatamente después de la ENC. Se consideraron tres parámetros de evaluación: a) diagnóstico, en el cual se clasificó si este conlleva un riesgo nutricional definitivo, probable o sin riesgo; b) ingesta nutrimental, si el paciente se encontraba en ayuno, con disminución en la ingesta en las últimas semanas o con alimentación adecuada; y c) medición del peso y la talla o longitud, con base en las tablas de crecimiento de la OMS para menores de dos años y la CDC-NHANES en mayores de dos años (Fig. 2).

TAMAÑO DE LA MUESTRA

Se utilizó el *software* R de la librería IRR con la siguiente función: N.cohen.kappa: rate1, rate2, k1, k0, alpha=0,05, power=0,8, twosided=Verdadero. Esto nos dio un valor de 270 pacientes, más el 10 % de pérdidas. Nos quedamos con 300 pacientes estudiados.

ANÁLISIS ESTADÍSTICO

Todos los datos por ambas evaluaciones (STAMP y ENC) se clasificaron en bajo riesgo de malnutrición, moderado riesgo de malnutrición y severo riesgo de malnutrición. Se evaluó la distribución de los datos con la prueba de Kolmogorov-Smirnov y se realizó una prueba t de Student para variables con distribución normal y U de Mann-Whitney para las variables no paramétricas. La concordancia de los datos entre pruebas se evaluó con el coeficiente kappa y correlación de Pearson. Se realizaron medidas de exactitud como sensibilidad, especificidad, VPP, VPN, razón de verosimilitud positiva (RVP) y razón de verosimilitud negativa (RVN). Se utilizó el paquete estadístico SPSSv22 y se consideró un valor de $p < 0,05$ como significativo.

RESULTADOS

La traducción y adaptación del cuestionario STAMP fue aprobada por el 100 % de los clínicos, que la consideraron adecuada al lenguaje utilizado por el personal de salud en México. Asimismo, se consideraron pertinentes y útiles las preguntas del cuestionario.

CARACTERÍSTICAS DE LA MUESTRA

Se incluyeron 300 pacientes, de los cuales 160 fueron niños (53 %) y 140 fueron niñas (47 %), con una edad promedio de 9,4 ± 5,73 años; 36 (12 %) fueron lactantes; 66 (22 %), preescolares; 89 (30 %), escolares; y 109 (36 %), adolescentes (Tabla I). La media de días de hospitalización fue de 6,5 ± 4 en niños y 7,5 ± 10,7 en niñas; de estos, 103 (34 %) se encontraban sometidos a estrés leve; 147 (48 %), a estrés moderado; y 54 (18 %), a estrés alto.

EVALUACIÓN NUTRICIA COMPLETA

En la ENC se encontraron 111 (33 %) niños con riesgo de malnutrición leve, 144 (48 %) con desnutrición moderada y 45 (15 %) con desnutrición grave. Se encontraron diferencias significativas entre los pacientes con riesgo de malnutrición leve y moderada-grave en los *Z score* de los valores antropométricos y de composición corporal (Tabla II).

EVALUACIÓN NUTRICIA POR STAMP

En la evaluación del estado nutricional por la herramienta STAMP, se encontraron 54 (18 %) pacientes en bajo riesgo de malnutrición, 115 (38 %) en riesgo moderado y 131 (44 %) en riesgo de malnutrición grave (Tabla II). Entre los grupos con riesgo de malnutrición leve y moderada o grave, se encontraron diferencias significativas en el *Z score* de P/E (-0,1 ± 0,8 *vs.* -0,4 ± 1,2; p = 0,04) e IMC/E (0,2 ± 0,9 *vs.* -0,02 ± 1,2; p = 0,01) y PCT/E (0,5 ± 0,7 *vs.* 0,3 ± 0,9; p = 0,07).

VALIDACIÓN DEL STAMP CON LA EVALUACIÓN NUTRICIONAL COMPLETA

En el estudio de validez interna llevada a cabo por los dos especialistas en nutrición se encontró una concordancia en el 100 % de los diagnósticos, con un índice kappa por evaluación de 0,480 e IC 95 %: 0,381-0,579; p < 0,01.

La prueba STAMP correlacionó significativamente con la ENC (r = 0,634; p < 0,01) (Tabla III). En la evaluación por ambas pruebas y clasificación de los pacientes por grupos de riesgo, se encontraron 50 (17 %) pacientes con riesgo de malnutrición leve y 185 (62 %) con riesgo de malnutrición moderada-grave, lo cual mostró una concordancia del 78 %; la prevalencia de desnutrición por la prueba STAMP fue del 82 % de los pacientes, mientras que con la ENC fue del 63 %. Además, la prueba STAMP mostró una sensibilidad del 92 %, una especificidad del 75 %, VPP del 45 %, VPN del 97 %, RVN del 3,68 y RVN del 0,10.

PREVALENCIA DE DESNUTRICIÓN

La prevalencia de desnutrición es alta en la mayoría de los servicios que presentan alteraciones del tubo digestivo o mayor gasto metabólico, como apendicetomía (30 %), enfermedad oncológica (14 %), enfermedad pulmonar (12 %), neumonía (12 %) y leucemia linfoblástica (11 %) (Tabla IV).

Tabla I. Características demográficas y *Z score* de los valores de antropometría de la muestra estudiada de acuerdo al grupo de edad correspondiente

Parámetro	Lactantes (n = 36)	Preescolares (n = 66)	Escolares (n = 89)	Adolescentes (n = 109)
Edad (meses)	0,5 ± ,6	4 ± 1,5	9,3 ± 2,2	15,7 ± 1,3
Sexo (M/F)	20/16	35/31	48/41	57/52
Peso (kg)	6,9 ± 1,7	16,4 ± 5,4	33,2 ± 13,2	58,2 ± 13,1
Altura o longitud (cm)	69,8 ± 8,2	103,3 ± 11,3	133,5 ± 15,4	161,8 ± 7,3
P/E	-0,9 ± 1,6	-0,6 ± 0,9	-0,1 ± 1,1	-0,2 ± 1,1
T/E	-0,7 ± 1,3	-0,3 ± 0,9	-0,3 ± 1	-0,8 ± 0,8
P/T	-0,5 ± 1,4	-0,4 ± 1	-0,3 ± 1,2	
IMC/E	-0,51 ± 1,5	-0,3 ± 1,1	-0,05 ± 1,2	0,02 ± 1,1
PCT/E	0,07 ± 1,3	0,2 ± 0,9	0,4 ± 0,8	0,4 ± 0,7
CB/E	-0,9 ± 1,4	-0,8 ± 1	-0,7 ± 0,9	-0,5 ± 0,9

Los datos se representan como media ± desviación estándar. M: masculino; F: femenino; P/E: peso para la edad; T/E: talla para la edad; P/T: peso para la talla; PC: perímetro cefálico; PC/E: perímetro cefálico para la edad; IMC: índice de masa corporal; IMC/E: índice de masa corporal para la edad; PCT: pliegue cutáneo tricipital; PCT/E: pliegue cutáneo tricipital para la edad; PCB: pliegue cutáneo bicipital; CB: circunferencia de brazo; CB/E: circunferencia de brazo para la edad.

Tabla II. Comparación de los *Z score* de los datos antropométricos y de composición corporal entre los riesgos de desnutrición por medio de la evaluación nutricia completa

Variable	ENC (n = 300)		p	STAMP (n = 300)		p
	Leve (n = 111)	Moderado/grave (n = 189)		Leve (n = 54)	Moderado/grave (n = 246)	
P/E	-0,03 ± ,7	-0,5 ± 1,3	< 0,01*	-0,1 ± ,8	-0,4 ± 1,2	*0,04**
T/E	-0,2 ± ,8	-0,7 ± 1	< 0,01*	-0,4 ± 0,9	-0,6 ± 1	0,20
P/T	-0,1 ± ,9	-0,6 ± 1,3	< 0,01*	-0,1 ± 1	-0,5 ± 1,2	0,17
IMC/E	0,1 ± ,9	-0,3 ± 1,3	< 0,01*	0,2 ± 0,9	-0,02 ± 1,2	*0,01**
PCT/E	0,5 ± ,7	0,2 ± 0,9	< 0,01*	0,5 ± 0,7	0,3 ± 0,9	*0,07*
CB/E	-0,5 ± ,8	-0,7 ± 1,1	0,01*	-0,6 ± 0,8	-0,7 ± 1	0,40

*Los datos se representan como media ± desviación estándar. La comparación entre grupos se realizó mediante la prueba t de Student o la prueba U de Mann-Whitney. *p < 0,05. ENC: evaluación nutricia completa; STAMP; Screening Tool for the Assessment of Malnutrition in Pediatrics; P/E: peso para la edad; T/E: talla para la edad; P/T: peso para la talla; PC: perímetro cefálico; PC/E: perímetro cefálico para la edad; IMC: índice de masa corporal; IMC/E: índice de masa corporal para la edad; PCT: pliegue cutáneo tricipital; PCT/E: pliegue cutáneo tricipital para la edad; PCB: pliegue cutáneo bicipital; CB: circunferencia de brazo; CB/E: circunferencia de brazo para la edad.*

Tabla III. Correlaciones en ambas pruebas de tamizaje STAMP y ENC

	ENC	P/E	T/E	IMC/E	PCT	CB
ENC	1	0,4 (< 0,01)	0,25 (< 0,01)	0,08 (< 0,16)	-0,13 (< 0,05)	0,36 (< 0,01)
STAMP	0,63 (< 0,01)	0,16 (< 0,01)	0,12 (< 0,05)	0,01 (0,95)	-0,17 (< 0,01)	0,22 (< 0,01)

ENC: evaluación nutricia completa; STAMP: Screening Tool for the Assessment of Malnutrition in Pediatrics; P/E: peso para la edad; T/E: talla para la edad; IMC/E: índice de masa corporal para la edad; PCT: pliegue cutáneo tricipital; CB: circunferencia de brazo.

Tabla IV. Riesgo de desnutrición por patología, evaluado por la herramienta STAMP

	Leve (n = 20)	Moderado a grave (n = 194)	p
Neumonía, n (%)	0 (0)	23 (12)	*0,009*
Infección de vías urinarias, n (%)	1 (5)	6 (3)	0,632
Leucemia linfoblástica aguda, n (%)	1 (5)	21 (11)	0,067
Enfermedad oncológica, n (%)	0 (0)	27 (14)	*0,004*
Apendicectomía, n (%)	0 (0)	58 (30)	*> 0,005*
Traumatismo craneoencefálico, n (%)	1 (5)	3 (2)	0,55
Crisis asmática, n (%)	0 (0)	12 (6)	0,088
Trombocitopenia, n (%)	2 (10)	1 (1)	0,085
Hipospadia, n (%)	3 (15)	0 (0)	*0,006*
Cirugía de extremidades, n (%)	4 (20)	4 (2)	0,083
Ileostomía, n (%)	0 (0)	4 (2)	0,450
Colestasis, n (%)	0 (0)	3 (2)	0,550
Heridas superficiales, n (%)	8 (40)	0 (0)	*> 0,005*
Oclusión intestinal, n (%)	0 (0)	4 (2)	0,450
Enfermedad pulmonar, n (%)	0 (0)	24 (12)	*0,007*
Hidrocefalia, n (%)	0 (0)	4 (4)	0,450

DISCUSIÓN

La evaluación del estado nutricio y tamizaje de los pacientes pediátricos es siempre un reto durante la práctica clínica debido a la complejidad de las mediciones y la enfermedad de base. El tamizaje nutricional en niños debe incluir los efectos de la desnutrición en la composición corporal y características de los pacientes que pudieran condicionar el bajo peso, tales como cromosomopatías, endocrinopatías y patologías que conlleven a retraso en el crecimiento, por lo cual la ENC podría ser la mejor estrategia por todas las mediciones que realiza (12). Sin embargo, una clínica u hospital debe invertir mucho tiempo (1-2 horas), recursos y personal altamente especializado en nutrición pediátrica para su realización. Es por ello que el uso de la prueba STAMP para la evaluación del estado nutricio y tamizaje es una mejor estrategia, ya que toma menos tiempo (15-20 minutos) y se lleva a cabo únicamente por personal capacitado (13).

ESPEN y ASPEN sugieren la estratificación de niños hospitalizados con herramientas de tamizaje nutricional fáciles y que puedan ser administradas por cualquier integrante del servicio salud (14). La ESPEN establece que una correcta herramienta de tamizaje nutricional debe incluir cuatro principios básicos: a) historial reciente del estado nutricio que incluya IMC ajustado por la edad o peso para la talla en menores de dos años; b) IMC e historial de pérdida de peso no intencional en menos de seis meses; c) alteración de la ingesta de alimentos; y d) efecto de la enfermedad de base sobre el estado de desnutrición. La herramienta de tamizaje STAMP cumple con todos estos criterios establecidos (Fig. 2), lo que la hace una excelente opción en México.

Otras pruebas de tamizaje, como la herramienta de detección del riesgo de deterioro del estado nutricional y crecimiento (STRONG kids), la puntuación pediátrica de malnutrición de Yorkhill (PYMS) y la valoración global subjetiva (VGS), presentan una falta de concordancia entre los observadores y la clasificación real de los pacientes debido a que este tipo de herramientas consideran la evaluación de la historia clínica realizada por el médico tratante y el examen físico realizado por el evaluador, lo cual hace complejo el proceso y se enfoca menos al propósito de detección rápida (15). Pars y cols. realizaron un estudio de validación de las tres pruebas STAMP, STRONG kids y PYMS, y concluyeron que el idioma de la prueba afecta significativamente la estratificación del riesgo nutricional, lo que desencadena posibles sesgos en la interpretación de los resultados, especialmente en las pruebas cualitativas. Asimismo, la herramienta STAMP presenta la mejor concordancia entre enfermeras y dietistas (kappa = 0,98; IC 95 %: 0,953-1,00) (16).

Estudios de validación y adaptación cultural de la herramienta STAMP muestran que es una herramienta confiable, con la mejor sensibilidad (70 %) y especificidad (90 %) (6,17). Lama y cols., durante la validación en español castellano, encontraron una sensibilidad (75 %) y una especificidad significativas (60,8 %), sin embargo, en México esta herramienta no se podía utilizar debido a que los valores podrían verse afectados por la influencia cultural, la interpretación del idioma y la traducción al momento de ser aplicada (18). Actualmente, la herramienta STAMP concuerda con lo encontrado internacionalmente, con terminología propia de los pacientes y del personal de salud que lo aplicó. En nuestro estudio se hallaron una sensibilidad del 92 % y una especificidad del 75 %, lo que nos permite hacer un tamizaje de los niños sin riesgo de desnutrición de forma más objetiva, con menos inversión de tiempo, sin necesidad de personal altamente especializado y con menos recursos hospitalarios. El tamizaje nutricional con la herramienta STAMP es válido en población pediátrica mexicana. Además, es útil para detectar y estratificar el riesgo en el que se encuentran los pacientes en un hospital.

Por otra parte, durante el estudio, el riesgo de desnutrición encontrado en los niños fue mayor en pacientes con apendicectomía, enfermedad oncológica, enfermedad pulmonar, neumonía y leucemia linfoblástica. Poder tamizar este grupo de pacientes con mayor necesidad calórica y riesgo de complicaciones por desnutrición a través de la herramienta STAMP permitió tener un abordaje nutricional oportuno, con menos riesgo de complicaciones por la enfermedad de base y tratamiento nutricional especializado previo a un procedimiento quirúrgico.

Como en cualquier herramienta de tamizaje, se deben considerar la necesidad nutricia y las características de la población de estudio, además de las limitantes propias de una herramienta de tamizaje, como la posibilidad de encontrar bajo peso por deshidratación o complexión del paciente. Por todo ello, es importante complementar, en caso de ser necesario, cualquier tipo de tamizaje con análisis clínicos, bioquímicos o de gabinete para el correcto abordaje de un paciente en riesgo. No obstante, mediante la validación de esta herramienta se espera tener más opciones de tamizajes pediátricos en población mexicana y, en un futuro, poder obtener una comparación entre esta y otras herramientas para lograr disminuir el riesgo de desnutrición en todo tipo de población pediátrica.

CONCLUSIONES

La herramienta de tamizaje STAMP cuenta con los elementos necesarios para evaluar de forma objetiva el riesgo de desnutrición en niños mexicanos de acuerdo a lo recomendado por guías internacionales, tales como diagnóstico, ingesta nutrimental y evaluación antropométrica. Además, la prueba STAMP es altamente sensible (92 %) y específica (75 %) para la evaluación del riesgo de desnutrición en niños mexicanos.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Accuracy in body composition scanning by adult half-body DXA scanning

Precisión en la exploración de la composición corporal mediante DXA de medio cuerpo en adultos

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Abstract

Introduction: dual-energy X-ray absorptiometry (DXA) is the gold standard method, although one limitation is the size of the scan area.

Objective: the objective was to verify the accuracy of body composition (BC) scanning through half-body DXA scanning compared to standard total body scanning.

Methods: a study was conducted on 145 volunteers. Weight and height were assessed. Body mass index (BMI) was calculated. DXA was used for whole-body scan (WBS) and half-body scan (HBS). WBS was used as the reference method and the following indicators were extracted: bone mineral content (BMC), fat mass (FM), lean soft tissue (LST) and percentage fat mass (%FM).

Results: no differences were observed in the body composition indicators (BMC, FM, LST and %FM) when compared between the reference WBS scanner and the HBS scanner. The predictive power between both scans ranged in both sexes between R2 = 0.94 and 0.98. The DRI desirable reproducibility index values defining the degree of agreement between both scans ranged from 0.97 to 0.99, and the values for precision (0.97 to 0.99) and accuracy (0.99) were high.

Keywords:

DXA. Body composition. Accuracy. Adult.

Conclusion: HBS scanning by DXA evidenced agreement, and high values of accuracy and precision to assess body composition indicators (BMC, FM, LST and %FM).

Resumen

Introducción: la absorciometría de rayos X de doble energía (DXA) es el método de referencia, aunque una limitación es el tamaño del área de exploración.

Objetivo: el objetivo fue verificar la precisión de la exploración de la CB mediante la exploración DXA de medio cuerpo en comparación con la exploración estándar de todo el cuerpo.

Métodos: se realizó un estudio con 145 voluntarios. Se evaluaron el peso y la altura. Se calculó el índice de masa corporal (IMC). Se utilizó la DXA para la exploración de cuerpo entero (WBS) y la exploración de medio cuerpo (HBS). Se utilizó la PEP como método de referencia y se extrajeron los siguientes indicadores: contenido mineral óseo (CMO), masa grasa (MG), tejido blando magro (TBL) y porcentaje de masa grasa (%MG).

Resultados: no se observaron diferencias en los indicadores de composición corporal (BMC, FM, LST y %FM) cuando se compararon entre el escáner WBS de referencia y el escáner HBS. El poder predictivo entre ambos escáneres osciló en ambos sexos entre R2 = 0,94 y 0,98. Los valores del índice de reproducibilidad deseable DRI que definen el grado de acuerdo entre ambas exploraciones oscilaron entre 0,97 y 0,99, y los valores de precisión (0,97 a 0,99) y exactitud (0,99) fueron altos.

Palabras clave:

DXA. Composición corporal. Precisión. Adulto.

Conclusión: la exploración de HBS mediante DXA evidenció concordancia y altos valores de exactitud y precisión para evaluar los indicadores de composición corporal (BMC, FM, LST y %FM).

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INTRODUCTION

Dual-energy X-ray absorptiometry (DXA) is an accurate method for measuring total body and subregional bone mineral density (BMD), bone mineral content (BMC), fat mass (FM), and lean soft tissue (LST) (1-3). This method has the advantage of a short scan time (5-20 min) (4) and a low radiation dosage (± 10 µSv) (5). Moreover, it can be used with children and adolescents (6,7).

The three major commercial manufacturers of DXA are GE Medical Systems Inc. (formerly Lunar), Madison, WI, USA; Hologic Inc., Waltham, MA, USA; and Cooper-Surgical (formerly Norland Medical Systems, Inc.), Trumbull, CT, USA (8,9). One of the limitations of DXA is the size of the active scanning area. DXA machines have dimensions of approximately 60-67 cm in width and 193-198 cm in length (8,9).

The width of the scanning area can compromise the accuracy of the measurement when body dimensions exceed these limits. This is also true for people with a large trunk and skeletal muscle mass favorable for particular sports, such as bodybuilding, rowing, and rugby or obese patients (9), although currently new equipment can assess an area of 228 cm in length, 137 cm in width and a weight of 280 kg (7). However, these devices are not always available in laboratories, so in order to solve this methodological limitation, some researchers have studied the accuracy of half-body scans using DXA (HBS) for estimating the whole-body composition (10,11).

Indeed, some studies measured body composition by DXA in obese adults (4,12), obese children (7,13) and physically active young adults (11). Thus, analysis of the accuracy and homogeneity of half-body scans can improve the applicability of the technique in a clinical context (7), mainly when a person's body dimensions exceed these limits and even in patients with metallic implants in their extremities (14).

In general, to our knowledge, a study of this nature was not performed in the Chilean population, so this information could be relevant when evaluating heterogeneous adult populations.

Therefore, the aim of the study was, to verify the accuracy in body composition scanning through the half-body DXA scan compared to the standard total body scan, using GE Lunar Prodigy DXA

MATERIALS AND METHODS

SUBJECTS

A cross-sectional study was carried out on 145 volunteers (62 males and 83 females) between 18 and 70 years of age to compose the sample. Subjects fitting into the scanning area (197.5 x 66) of GE Lunar Prodigy were eligible to participate in the study. Those who did not complete the evaluations and those who presented some type of physical disability that prevented them from moving on their own were excluded. All volunteers were informed of the objective of the study and subsequently signed and authorized the informed consent form.

The data collection process was carried out in a laboratory of the Autonomous University between April and July 2019 from Monday to Friday from 8:30 am to 12:30 pm. The study was approved by the Research Ethics Committee of the local university.

INSTRUMENTATION

The anthropometric variables of weight and height were evaluated following the recommendations of Ross, Marfell-Jones (15). Body weight (kg) was assessed with a scale (SECA, Hamburg, Germany) accurate to 0.1 kg. Standing height was measured with a stadiometer (SECA, Hamburg, Germany) to the nearest 0.1 cm. BMI was calculated by means of the formula [BMI = weight (kg) / height $(m)^2$].

Two DXA scans were performed the same day for analysis. First, WBS was performed and used as a reference. Second, HBS was performed to estimate the whole-body composition to compare it with the reference method. The same technician positioned the subjects, performed the three scans, and executed the analysis according to the operator's manual using the standard analysis protocol. Standardized positioning was maintained during HBS with volunteers in a supine position with the left sagittal line of scan window under the left upper limb. Right half-body composition was used to estimate the whole-body composition. Subjects were warned not to wear jewelry and to avoid and the presence of any type of metal on the body that could impede scanning.

DUAL ENERGY X-RAY ABSORPTIOMETRY (DXA)

DXA measurements were taken using a total-body scanner (Lunar Prodigy; GE Healthcare, Madison, WI, USA). The Lunar Prodigy DXA is an instrument with a weight limit of 160 kg and a relatively large space exploration of 197.5 x 66 cm. Scan analysis was performed using GE Encore 11.10 software (GE, Madison, WI, USA). The following variables were extracted from the DXA software: bone mineral content (BMC), fat mass (FM), Lean sof tissue (LST) and fat mass percentage %FM. The DXA was calibrated each day before measurement according to the manufacturer's guidelines. The coefficients of variation (CV) in our laboratory were 1.4 %, 1.6 %, and 1.0 % for BMC, FM, and LST, respectively.

STATISTICAL ANALYSIS

A descriptive analysis (mean ± standard deviation [SD], minimum and maximum), and the Kolmogorov-Smirnov test for normality were performed. We used Student's paired t-test to compare Pearson's correlation coefficient (r) to verify the relationship between the variables and linear regression analysis (adjusted coefficient of determination [R^2]. Additionally, the standard error of estimate [SEE]) was used to verify explanation power of HBS in estimating the whole-body composition with WBC. The concor-

dance correlation coefficient (CCC) proposed by Lawrence, Lin (16) was also calculated to verify precision and accuracy. The significance level was set at $\alpha \leq 0.05$. The SPSS version 16.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis, as wellas MedCalc 11.1.0.

RESULTS

The anthropometric variables characterizing the sample studied can be seen in table I. There were no significant differences in age (p = 0.23) and BMI (p = 0.74) between both sexes. However, as expected, men presented higher weight and height in relation to women p < 0.000).

Comparisons of BMC, FM, LST and %FM values between total body and half body by sex are shown in table II. There were no significant differences between both scans (p = 0.81 to 0.99) in both men and women.

The correlations between both scans according to body composition indicators are shown in figure 1. In men and in the four indicators (BMC, FM, LST and %FM) the predictive power ranged from R2 = 0.94 to 0.98. For women the values explained from R2= 0.96 to 0.98, respectively.

The DRI values that define the degree of agreement between both scans are shown in table III. In general, it is observed that the half-body scan shows a CCC with the reference method (total body) from 0.97 to 0.99. In addition, the values of precision (0.97 to 0.99) and accuracy (0.99) in both sexes are high.

Table I. Characteristics of the sample studied

Variables	Males (n = 62)		Females (n = 83)		t	p
	X	SD	X	SD		
Age (years)	51.9	21.9	55.8	17.4	-1.230	0.223
Weight (kg)	77.8	14.4	67.0	14.0	4.540	0.000
Height (cm)	169.2	7.4	154.3	11.5	8.930	0.000
BMI (kg/m^2)	27.2	4.5	27.4	4.2	-0.330	0.746

X: mean; SD: standard deviation; BMI: body mass index.

Table II. Comparison of total-body and half-body composition indicators in both sexes

Indicators	Whole-body scan		Half-body scan		p
	X	SD	X	SD	
Males					
BMC (kg)	2.87	0.41	2.87	0.39	0.999
FM (kg)	21.01	8.62	21.09	8.66	0.959
LST (kg)	56.67	8.39	56.4	8.35	0.849
%FM	26.36	7.32	26.54	7.26	0.891
Females					
BMC (kg)	2.07	0.33	2.09	0.7	0.814
FM (kg)	25.93	7.3	26.03	7.53	0.931
LST (kg)	40.15	5.07	40.06	5.23	0.911
%FM	38.68	6.59	38.79	6.74	0.916

X: mean; SD: standard deviation; BMC: bone mineral content; FM: fat mass; LST: lean soft tissue; %FM: percentage of fat mass.

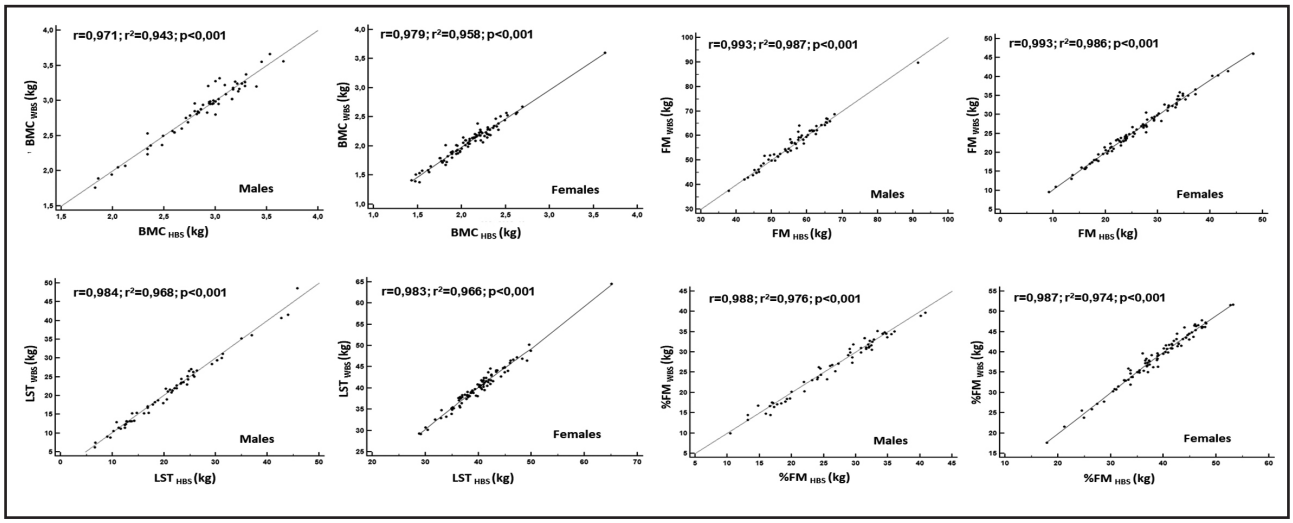

Figure 1.

Relationship between both scans (total body and half body) according to body composition indicators in both sexes.

Table III. Desirable reproducibility index (DRI) values to define the agreement between total body and half body DXA scans

Indicators	X	SD	CCC	Precision	Accuracy
Males					
BMC (TB)	2.87	0.41	--	--	--
BMC (HB)	2.87	0.39	0.97	0.97	0.99
FM (TB)	21.01	8.61	--	--	--
FM (HB)	21.09	8.65	0.99	0.99	0.99
LST (TB)	56.67	8.39	--	--	--
LST (HB)	56.4	8.34	0.98	0.98	0.99
%FM (TB)	26.36	7.32	--	--	--
%FM (HB)	26.54	7.26	0.98	0.98	0.99
Females					
BMC (TB)	2.07	0.33	--	--	--
BMC (HB)	2.09	0.33	0.97	0.98	0.99
FM (TB)	25.93	7.3	--	--	--
FM (HB)	26.03	7.53	0.99	0.99	0.99
LST (TB)	40.15	5.07	--	--	--
LST (HB)	40.06	5.23	0.98	0.98	0.99
%FM (TB)	38.68	6.59	--	--	--
%FM (HB)	38.79	6.74	0.98	0.98	0.99

X: mean; SD: standard deviation; CCC: concordance correlation coefficient; BMC: bone mineral content; FM: fat mass; LST: lean soft tissue; %FM: percentage of fat mass.

DISCUSSION

The aim of the study was to verify the accuracy of body composition scanning through HBS DXA scanning compared to standard WBS scanning, using GE Lunar Prodigy DXA.

The results of the study have shown that the half-body scan reflects similar results as the total body scan in the indicators of BMC, FM, LST and %FM. These findings are consistent with some studies that compared both methods (4,7,10,12).

In fact, no bias was observed in the results, even the correlations between both methods were high and almost perfect, ranging from 0.93 to 0.99 as reported by other studies (7,17).

Evidently, HBS scanning has reflected wide concordance and precise and accurate values versus WBS scanning, as this information allows highlighting that the HBS scanning technique supports the use of DXA to scan a larger number of subjects and in less time. It also allows the inclusion of those subjects that are outside the scanning area (7) due to their extreme body dimensions (9).

In fact, DXA has become a popular tool for measuring body composition due to its ease of operation, completeness of analysis and gold standard (18,19). For nowadays WBS and HBS scanning, can be considered as precise and accurate scanning techniques, moreover, some studies have used HBS scanning to predict body composition in weight reduction programs in obese patients who barely fit in the scanning area (20) and even, to verify body composition changes after bariatric surgery in morbidly obese individuals (21).

In that sense, it is important that studies develop a satisfactory technique to scan individuals of all physical types (11), these include patients who present metallic implants in their extremities, as they are often excluded from studies covering body composition analysis (15).

Also, it is widely known that most manufacturers' manuals do not verify the use of DXA for body composition analysis in subjects with a metallic implant (22).

Consequently, having the HBS scanning technique in clinical and epidemiological contexts may avoid excluding some patients who are likely to have extreme physical characteristics, as well as amputations and/or metallic implants in some of their extremities. On the contrary, HBS scanning opens new perspectives and possibilities to be implemented in clinics and laboratories to cover not only conventional but also non-conventional populations.

In general, DXA is a non-invasive, fast, safe and low radiation method equivalent to a day sunbathing (23), in addition, in recent years, DXA equipment have been improving over time in their designs and manufacturing models, for example, they have been reducing scanning times, as well as have ostensibly improved the quality in their images in terms of pixels (24).

This research presents some strengths, given that it is the first study that verified the applicability of the use of HBS scanning in a sample of Chilean adults. In addition, the results obtained in this study can serve for future comparisons, as well as a baseline to verify trends among the adults studied.

Notwithstanding the above, the study has some limitations, for example, the type of sample selection and the number of participants considered were not large enough. These aspects could limit the generalizability of the results to other contexts, so they should be analyzed with caution. Future studies should consider the use of more sophisticated equipment to corroborate our findings.

In conclusion, this study demonstrated that HBS scanning through DXA evidenced concordance and high values of precision and accuracy to assess body composition indicators (BMC, FM, LST and %FM.) in adult patients. The results suggest the use and application in research, clinical and epidemiological contexts.

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ARÁN

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Trabajo Original

Valoración nutricional

Association between adherence to the Mediterranean diet with anthropometric measurements and nutritional status in adolescents

Asociación entre la adherencia a la dieta mediterránea y las medidas antropométricas y el estado nutricional en adolescentes

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Abstract

Background: adolescence is a critical period for developing healthy eating habits. It is crucial to evaluate and encourage adherence to the Mediterranean diet, a sustainable and healthy diet model in this age group.

Objective: this study aimed to evaluate the relationship between adherence to the Mediterranean diet and anthropometric measurements and nutritional status in Turkish adolescents.

Material and methods: the demographic characteristics, health information, nutritional habits, physical activity status, and 24-hour dietary recall of the adolescents were obtained with a questionnaire. Adherence to Mediterranean diet was evaluated with the Mediterranean-Style Dietary Pattern Score (MSDPS).

Results: a total of 1,137 adolescents (mean age 14.0 ± 1.37 years) were included; 30.2 % of the boys and 39.5 % of the girls were overweight/obese. The median (interquartile range) value of the MSDPS was 10.7 (7.7), and this value was 11.0 (7.6) for the boys and 10.6 (7.4) for the girls ($p > 0.05$). The levels of protein, fiber, vitamin A, vitamin C, folate, vitamin B12, iron, magnesium, zinc, and potassium intake increased with adherence to Mediterranean diet ($p < 0.001$). Age, parental education level, body mass index (BMI), waist circumference, and skipping meals affected MSDPS.

Conclusion: adolescents' adherence to the Mediterranean diet was low and correlated with some anthropometric measures. Increasing adherence to the Mediterranean diet may contribute to preventing obesity and adequate and balanced nutrition in adolescents.

Keywords:

Mediterranean diet. Adolescents. Mediterranean-Style Dietary Pattern Score. Body weight. Obesity. Nutritional status.

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Resumen

Introducción: la adolescencia es un periodo crítico para el desarrollo de hábitos alimentarios saludables. Es fundamental evaluar y fomentar la adherencia a la dieta mediterránea, un modelo de alimentación sostenible y saludable en este grupo de edad.

Objetivo: este estudio tuvo como objetivo evaluar la relación entre la adherencia a la dieta mediterránea y las medidas antropométricas y el estado nutricional en adolescentes turcos.

Material y métodos: las características demográficas, la información de salud, los hábitos nutricionales, el estado de actividad física y el recuerdo dietético de 24 horas de los adolescentes se obtuvieron mediante un cuestionario. La adherencia a la dieta mediterránea se evaluó con el Mediterranean-Style Dietary Pattern Score (MSDPS).

Resultados: se incluyó un total de 1.137 adolescentes (edad media 14,0 ± 1,37 años). El 30,2 % de los niños y el 39,5 % de las niñas tenían sobrepeso/obesidad. El valor de la mediana (rango intercuartílico) del MSDPS fue de 10,7 (7,7), siendo este valor de 11,0 (7,6) para los niños y de 10,6 (7,4) para las niñas ($p > 0,05$). Los niveles de ingesta de proteína, fibra, vitamina A, vitamina C, folato, vitamina B12, hierro, magnesio, zinc y potasio aumentaron con la adherencia a la dieta mediterránea ($p < 0,001$). La edad, el nivel de educación de los padres, el índice de masa corporal (IMC), la circunferencia de la cintura y la omisión de comidas afectaron al MSDPS.

Conclusión: la adherencia a la dieta mediterránea de los adolescentes fue baja y se correlacionó con algunas medidas antropométricas. El aumento de la adherencia a la dieta mediterránea puede contribuir a la prevención de la obesidad y a una nutrición adecuada y equilibrada en los adolescentes.

Palabras clave:

Dieta mediterránea. Adolescentes. Puntuación del patrón dietético de estilo mediterráneo. Peso corporal. Obesidad. Estados nutricionales.

INTRODUCTION

Childhood and adolescent obesity is increasing in our country as well as in the world, and growing day by day (1). The last American National Health and Nutrition Examination Survey reported the prevalence of childhood-adolescent obesity between the ages of 2-19 as 16.3 % (2). Recently, the World Health Organization (WHO) European Regional Obesity Report 2022 showed that Turkey has a higher rate of obesity in relation to European countries (3).

Nutrition, which is among the modifiable risk factors, has an important role in the prevention of obesity in adolescents. Different dietary factors contribute negatively or positively to the development and prevention of obesity (4). Decreased adherence to the Mediterranean diet (MD), especially due to the spread of the Western style diet, is related to childhood obesity and an increase in the incidence of adult obesity and other chronic non-communicable diseases in the following years (5).

MD is frequently used to describe the traditional eating habits of societies living around the Mediterranean (6). It is a sustainable diet model in which olive oil is used as the main source of fat, and fruits, vegetables, whole grain foods, legumes and oil seeds are consumed frequently. In this diet, milk and its products, fish, poultry, and wine are moderately consumed, while red meat and its products and sugar are consumed at low levels (7). MD emphasizes the consumption of local and traditional foods suitable for lifestyle and sustainability by ensuring seasonal and nutritional diversity (8).

Consumption of plant foods, especially vegetables, fruits, and legumes, which are among the nutritional behaviors of those adopting the MD, and reducing the consumption of energy-dense foods are important dietary factors in the prevention of obesity (9). It is emphasized that increasing adherence to Mediterranean-style nutrition, especially from childhood, may reduce the risk of non-communicable chronic diseases (10). It has been reported that the MD has positive effects on body weight and health protection (11). A study conducted with adolescents on the relationship between body mass index (BMI) and MD compliance found a negative relationship (11). Also, one multicenter study covering eight European countries revealed that waist circumference was negatively associated with MD compliance (12). In addition, adherence to the Mediterranean diet is positively related to physical activity status in adolescents (13). For these reasons, evaluation of MD and adherence to the determinants of this nutritional model in earlier years of life is significant for lifestyle changes and nutritional recommendations to be developed for the implementation of a healthy nutrition model (14).

The evaluation of adherence to the MD is important in the prevention of adolescent obesity. However, it is also recommended to focus on demographic characteristics, anthropometric measurements, body composition, lifestyle habits (especially physical activity), and food and nutrient consumption that may be associated with MD compliance (15). This study aimed to evaluate the relationship between adherence to the MD and anthropometric measurements and nutritional status in adolescents.

MATERIAL AND METHODS

STUDY SETTING AND POPULATION

This cross-sectional study was conducted between November 2021 and May 2022 with middle school and high school students (mean age 14.0 ± 1.37 years) in Turkey. Children who did not have a chronic problem that affects their diet or that requires a special diet, who did not have psychological problems, who were not diagnosed with eating disorders, and who agreed to participate in the study were included in the sample. As a result of the power analysis, it was aimed to reach 1,070 individuals at 5 % type 1 error level and a confidence interval of 80 %. The data were collected through face-to-face interviews using the survey method.

Ethical permission was obtained from Erzurum Technical University Ethics Committee (20.10.2021) and Erzurum Provincial Directorate of National Education (05.11.2021). The study was carried out in accordance with the principles outlined in the Helsinki Declaration. Informed consent in written form was obtained from the parents and child assent was obtained.

MEASURES

The data collection forms included sociodemographic characteristics (age, gender, educational status of students and edu-

cational status of parents), nutritional habits, health information, physical activity status, anthropometric measurements and body composition, and 24-hour dietary recall. Energy and nutrient intakes of adolescents were evaluated using the Nutrition Information System (BeBiS) program (version 7) (16). The Mediterranean-Style Dietary Pattern Score was used to determine the degree of adherence to the Mediterranean Diet (17).

Adherence to Mediterranean diet

Adherence to the Mediterranean diet was assessed using the MSDPS and the score calculated based on the food consumption information obtained from the 24-hour dietary recall. Children's food consumption record was obtained with the help of their parents by the researchers. The MSDPS, a useful score for measuring overall diet quality according to Mediterranean diet, was developed by Rumawas et al. (2009) (17). The MSDPS was developed based on adherence to recommended intakes of 13 food groups (dairy products, fruits, vegetables, wine, whole-grain cereals, olives/legumes/nuts, fish and other seafood, poultry, meat, potatoes and other starchy roots, sweets, eggs, and olive oil) in the Mediterranean diet pyramid. In the present study, scores from only 12 groups were obtained since alcohol consumption was not asked due to adolescents' age, cultural, and religious beliefs. The score was calculated based on the recommended amounts of foods in the Mediterranean pyramid to be consumed daily or weekly. The score evaluates the negative effects of excessive consumption as well as insufficient consumption, and takes into account the foods that are not included in the Mediterranean pyramid. Except for olive oil, other MSDPS components were scored on a scale from 0 to 10. For participants whose number of consumed servings was over the recommended number, a penalty score was assigned. The aim of applying a penalty was to prevent one from attaining higher scores solely by overconsumption. Exclusive olive oil intake was scored as 10, olive oil intake besides the intake of other vegetable oils was scored as 5, and no olive oil intake was scored as 0 (17). Total MSDPS was determined by summing the 12 components of MSDPS, which were weighted in accordance with the ratio of total energy intake from the Mediterranean dietary pyramid and standardized on a 0-100 scale. All components of the MSDPS were evaluated according to intake recommendations as below the recommended intake (BRI), met the recommended intake (MRI), and exceeded the recommended intake (ERI). The calculation of the MSDPS is explained in Rumawas et al. (2009) in detail (17).

Anthropometric measurements

The researchers performed the measurements of weight and body fat (%) using a Tanita BC532 device. Waist circumference was measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest at minimum respiration with an inelastic flexible tape in a standing position (18). A stadiometer was used to measure height (18). The BMI (kg/m^2) value was evaluated according to the WHO growth standards (19). BMI-for-age Z-scores were computed using the WHO AnthroPlus software (version 1.0.4, February 2011). Z-score junctions were used to categorize the measurements (19).

Physical activity

The Turkish validity and reliability study of the International Physical Activity Questionnaire-Short Form (IPAQ-SF) was conducted by Saglam et al. (2010) (20). Individuals are classified according to their physical activity level as low (< 600 MET-min/week), moderate (600-3,000 MET-min/week), and high (> 3,000 MET-min/week) (20).

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (version 22.0) software was used for all analyses. Descriptive statistical variables (median, interquartile range [IQR] 5th-95th percentile values, mean, and standard deviation) were used to analyze the data, which was divided into four tertiles according to the MSDPS. Intergroup differences were assessed using the t-test, Mann-Whitney U test, one-way ANOVA or Kruskal-Wallis test. The relationship between the variables was evaluated using the correlation coefficient. In addition, linear regression analysis was performed for MSDPS prediction. The level of statistical significance was set at $p < 0.05$.

RESULTS

A total of 1,137 adolescents (45.2 % boys; 54.8 % girls; 14.0 ± 1.37 years) were included in the study. The frequency of those whose mother and father had an education period of eight years or more was found to be 58.0 %. It was revealed that 83.0 % of the adolescents skipped at least one main meal or snack (data not shown). More than half of the male students (55.1 %) were categorized as normal according to the BMI classification based on age, while 30.2 % were categorized as overweight/obese. As regards female adolescents, 46.9 % had normal BMI, while 39.5 % were considered to be overweight/obese according to the BMI classification. In addition, 20.4 % of the male students and 21.0 % of the female students were found to have low physical activity (< 600 MET-min/week). The rate of those with moderate physical activity was 55.1 % for the male students and 55.8 % for the female students (data not shown).

The median MSDPS of the adolescents was found to be 10.7 (7.7) out of a maximum possible score of 100. This score was 11.0 (7.6) for the male students and 10.6 (7.4) for the female students ($p > 0.05$). Among the 12 Mediterranean food groups, the median component score was the highest for olive oil consumption, followed by fruit intake. The score for fruits, vegetables, eggs, potatoes, and other starchy roots was higher in girls than boys ($p < 0.05$). The correlation between the total MSDPS and its components was the lowest for the consumption of fish and other seafood (correlation coefficients [r] = 0.031) and the highest for the whole grain group (correlation coefficients [r] = 0.368). The consumption of foods that are part of the Mediterranean-style dietary pattern contributed to 53.4 % of the total energy intake (Table I).

[Nutr Hosp 2023;40(2):368-376]

Table I. Evaluation of Mediterranean-Style Dietary Pattern Score and intake amount of its components according to gender

MSDPS components	Boys			Spearman's rank correlation to total MSDPS†	Girls			Spearman's rank correlation to total MSDPS†	Total			Spearman's rank correlation to total MSDPS†	p‡
	Intake amount*	Serving amount*	Score*		Intake amount*	Serving amount*	Score*		Intake amount*	Serving amount*	Score*		
Intake/day													
Whole grains	60.0 (0, 186.0)	2.0 (0, 6.2)	2.5 (0, 7.25)	0.316	60.0 (0, 200.8)	2.0 (0, 6.69)	2.5 (0, 8.28)	0.411	60.0 (0, 200.0)	2.0 (0, 6.67)	2.5 (0, 7.87)	0.368	0.629
Fruits	51.5 (0, 506.3)	0.51 (0, 5.06)	0.91 (0, 9.32)	0.332	120.0 (0, 433.0)	1.2 (0, 4.33)	3.33 (0, 9.46)	0.403	100.0 (0, 455.0)	1.0 (0, 4.55)	2.66 (0, 9.34)	0.366	0.001
Vegetables	167.0 (0, 493.3)	1.67 (0, 4.93)	2.78 (0, 8.14)	0.322	143.0 (0, 459.0)	1.43 (0, 4.59)	2.33 (0, 7.23)	0.351	155.0 (0, 470.2)	1.55 (0, 4.70)	2.58 (0, 7.53)	0.342	0.006
Dairy	160.0 (0, 512.5)	3.68 (0, 11.52)	0 (0, 10.0)	0.160	175.0 (0, 550.0)	4.0 (0, 11.50)	0 (0, 9.0)	0.118	170.0 (0, 535.1)	3.98 (0, 11.50)	0 (0, 9.33)	0.138	0.343
Intake/week													
Fish and other seafood	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.001	0 (0, 4.0)	0 (0, 0.04)	0 (0, 0.06)	0.055	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.031	0.142
Poultry	0 (0, 150.0)	0 (0, 1.5)	0 (0, 3.75)	0.104	0 (0, 150.0)	0 (0, 1.50)	0 (0, 3.75)	0.115	0 (0, 150.0)	0 (0, 1.50)	0 (0, 3.75)	0.112	0.128
Olives, legumes and nuts	15.0 (0, 104.3)	0.5 (0, 3.47)	1.25 (0, 7.5)	0.297	15.0 (0, 89.0)	0.5 (0, 2.96)	1.25 (0, 6.67)	0.272	15.0 (0, 100.0)	0.5 (0, 3.33)	1.25 (0, 7.08)	0.283	0.315
Potatoes and other starchy roots	0 (0, 200.0)	0 (0, 2.0)	0 (0, 6.66)	0.194	0 (0, 174.0)	0 (0, 1.74)	0 (0, 5.66)	0.243	0 (0, 200.0)	0 (0, 2.0)	0 (0, 5.99)	0.224	0.002
Eggs	36.0 (0, 115.0)	0.72 (0, 2.3)	2.24 (0, 7.65)	0.301	13.0 (0, 100.0)	0.26 (0, 2.0)	0.86 (0, 6.67)	0.273	16.0 (0, 107.1)	0.32 (0, 2.14)	1.06 (0, 6.79)	0.289	0.012
Sweets	2.5 (0, 70.5)	0.1 (0, 2.82)	0.26 (0, 7.39)	0.148	3.0 (0, 74.6)	0.12 (0, 2.98)	0.39 (0, 7.93)	0.189	3.0 (0, 72.0)	0.12 (0, 2.88)	0.39 (0, 7.75)	0.169	0.641
Meat	0 (0, 142.7)	0 (0, 1.42)	0 (0, 9.0)	0.273	0 (0, 146.2)	0 (0, 1.46)	0 (0, 9.0)	0.218	0 (0, 143.2)	0 (0, 1.43)	0 (0, 9.0)	0.246	0.053
Olive oil	0 (0, 15.0)	0 (0, 1.5)	5.0 (5.0, 5.0)	.	0 (0, 15.0)	0 (0, 1.50)	5.0 (5.0, 5.0)	.	0 (0, 15.0)	0 (0, 1.5)	5.0 (5.0, 5.0)	.	.
MSDPS (median [IQR])	11.0 (7.6)				10.6 (7.4)				10.7 (7.7)				
Total energy intakes attributed to consumption of Mediterranean diet foods, %	53.6 % (28.6, 85.2)				53.2 % (27.9, 85.6)				53.4 % (28.3, 85.2)				

*MSDPS: Mediterranean-Style Dietary Pattern Score; IQR: interquartile range. *Data are median (5th, 95th percentiles). †Spearman's rank correlation to total MSDPS, correlation coefficients. ‡Score differences between genders.*

Table II. Distribution of MSDPS components according to the recommended intake

	Boys			Girls			Total		
	BRI (%)	MRI (%)	ERI (%)	BRI (%)	MRI (%)	ERI (%)	BRI (%)	MRI (%)	ERI (%)
Whole grains	84.4	1.8	13.8	81.5	0.8	17.1	82.8	1.2	15.9
Fruits	85.6	-	14.4	83.3	-	16.7	84.3	-	15.7
Vegetables	98.8	-	1.2	98.2	-	1.8	98.5	-	1.5
Dairy	28.8	5.8	65.4	28.7	3.5	67.7	28.8	4.6	66.7
Fish and other seafood	100.0	-	-	100.0	-	-	100.0	-	-
Poultry	99.8	-	0.2	99.8	0.2	-	99.8	0.1	0.1
Olives, legumes, and nuts	96.5	0.2	3.3	97.0	0.5	2.6	96.7	0.4	2.9
Potatoes and other starchy roots	98.6	-	1.4	99.5	-	0.5	99.1	-	0.9
Eggs	99.2	-	0.8	99.0	-	1.0	99.1	-	0.9
Sweets	96.1	-	3.9	95.3	-	4.7	95.7	-	4.3
Meat	85.4	2.3	12.3	88.9	1.0	10.1	87.3	1.6	11.1
Olive oil*	100.0	-	-	100.0	-	-	100.0	-	-

*BRI: below the recommended intake; MRI: met the recommended intakes; ERI: exceeded the recommended intake. *All participants used olive and other vegetable oils. Therefore, all participants score were "5".*

The "met the recommended intake" (MRI) score obtained from the MSDPS for each component was very low, and among the 12 food groups, the highest MRI score was achieved in the dairy group (male 5.8 %; female 3.5 %). For the other eleven components, the rate of "below the recommended intake" (BRI) was found to be over 80 %. The highest "exceeded the recommended intake" (ERI) score was dairy products (male 65.4 %; female 67.7 %) (Table II).

Table III shows the median daily intakes of macro and micronutrients across the quartile categories of the MSDPS. While there was no difference between quartiles in terms of dietary energy, carbohydrates (CHO) and fat intakes, and vitamin E and calcium intakes in both boys and girls, the level of protein, fiber, vitamin A, vitamin C, folate, vitamin B12, iron, magnesium, zinc, and potassium intake increased with adherence to MD ($p < 0.001$) (Table III). A difference was observed in waist circumference in both boys and girls according to the MSDPS quartiles ($p < 0.05$). The majority of the underweight and overweight girls (31.5 % and 34.7 %, respectively) were in Q1 (Table IV).

When the factors that could affect the MSDPS (age, parental education level, gender, BMI, body fat, waist circumference, skipping meals) were evaluated with regression analysis, the model was important (R2: 0.036, $p < .001$). It was determined that gender and body fat did not affect the MSDPS ($p > 0.05$), while age, parental education level, BMI, waist circumference, and skipping meals had an effect on the model ($p < .05$) (Table V).

DISCUSSION

In this study, the participants showed low adherence to the Mediterranean diet. The findings revealed that the older adolescents and those whose mothers had higher education and who did not skip meals were more likely to adhere to the Mediterranean diet. Also, BMI and waist circumference had a negative effect on MSDPS in regression model. Adolescents with high adherence to MD (Q4) had higher macro-micro nutrients intake levels.

MD has been accepted as a nutritional model with protective effects for childhood and adolescent obesity and related chronic diseases (10). However, the positive effects of MD on health have mostly been studied in adult population, and studies on children and adolescents are limited. In a study evaluating adherence to MD in adults in the United States, the mean MSDPS score was 24.8 (3.1-60.7) (17). The contribution of the nutrients in the MD to total energy was found to be 73.1 % (54.5-85.8), higher than the finding of our study (10.7 [7.7]) and 53.4 %, respectively (Table I). This difference may be attributed to the age difference of the sample of two studies.

One study conducted with school-aged children and adolescents in European countries with a high tendency to the MD, such as Spain, Greece, and Cyprus, found that adherence to the MD was low (21). In one study conducted with adolescents in Iran, the MSDPS score was found to be low (15.9 ± 5.6) (22). The reasons for the low MSDPS score were listed as preference for refined product consumption in the society instead of whole

Table III. Daily intakes of macro and micronutrients associated with the Mediterranean diet according to quartile categories of the MSDPS

MSDPS Quartiles	Boys				p*	Girls				p*
	Q1 (0.2-7.4)	Q2 (7.5-10.7)	Q3 (10.8-15.1)	Q4 (15.2-40.5)		Q1 (0.2-7.4)	Q2 (7.5-10.7)	Q3 (10.8-15.1)	Q4 (15.2-40.5)	
Energy, kcal	1,551.9 (704.3)	1,685.8 (682.8)	1,656.6 (789.4)	1,616.0 (643.8)	0.643	1,512.2 (646.7)	1,613.1 (568.3)	1,621.1 (620.9)	1,630.9 (632.8)	0.143
Protein, g	52.0 (25.9)†	58.0 (29.4)†,‡	60.4 (39.9)‡	63.4 (30.6)‡	*0.001*	50.1 (20.3)†	52.2 (27.6)†,‡	59.1 (28.1)§	55.9 (29.4)‡	*< 0.001*
Fat, g	62.3 (38.9)	67.9 (36.2)	70.9 (31.6)	71.3 (39.8)	0.372	65.3 (36.8)	67.9 (32.9)	69.8 (38.1)	69.2 (35.4)	0.449
Carbohydrate, g	184.6 (88.4)	196.5 (109.5)	182.3 (110.7)	178.2 (79.1)	0.246	163.9 (81.8)	187.3 (78.8)	176.7 (98.9)	180.3 (104.5)	0.219
Fiber, g	13.0 (8.4)†	15.9 (8.0)‡	17.2 (10.4)‡	17.7 (12.5)§	*< 0.001*	13.1 (7.7)†	15.4 (7.7)‡	15.9 (8.9)‡	18.2 (8.6)§	*< 0.001*
SFA, g	24.3 (19.1)	24.4 (15.5)	23.8 (14.2)	24.8 (13.8)	0.980	22.8 (16.9)	23.9 (12.3)	23.9 (14.8)	21.9 (13.7)	0.418
MUFA, g	20.6 (13.7)	22.6 (12.3)	22.9 (13.1)	23.9 (12.4)	0.060	21.2 (11.9)	21.8 (9.8)	23.2 (15.2)	23.8 (14.1)	0.089
PUFA, g	14.8 (10.9)	13.6 (11.4)	16.3 (14.7)	14.7 (14.1)	0.711	14.2 (12.9)	14.8 (14.5)	14.7 (13.7)	14.8 (11.6)	0.767
Omega-6, g	13.6 (12.0)	12.5 (11.2)	15.2 (13.9)	13.0 (12.8)	0.794	12.8 (12.3)	13.3 (13.1)	13.4 (13.2)	13.4 (11.7)	0.933
Omega-3, g	1.0 (0.8)	0.9 (0.8)	1.0 (0.9)	1.1 (0.8)	0.138	0.9 (0.8)†	0.9 (08)†,‡	0.9 (0.8)†	1.2 (0.8)‡	*< 0.001*
Vitamin A (µg/d)	519.1 (522.2)†	588.7 (432.9)†	718.7 (563.7)‡	715.3 (560.5)‡	*< 0.001*	505.4 (422.6)†	522.5 (492.7)†	621.5 (480.2)‡	689.9 (621.9)‡	*< 0.001*
Vitamin C (mg/d)	33.5 (44.3)†	57.0 (52.7)‡	68.1 (66.0)‡	97.0 (96.8)§	*< 0.001*	37.8 (54.6)†	47.4 (59.8)‡	78.0 (67.4)‡	102.1 (85.9)§	*< 0.001*
Vitamin E (mg/d)	13.4 (11.5)	14.1 (10.1)	15.2 (13.2)	14.4 (13.4)	0.345	13.4 (12.9)	13.9 (13.8)	14.7 (14.8)	14.2 (13.2)	0.297
Folate (µg/d)	183.9 (107.4)†	220.5 (103.5)‡	222.7 (108.5)‡	261.7 (147.5)§	*< 0.001*	168.8 (126.7)†	188.9 (117.4)‡	226.7 (109.8)‡	243.4 (128.7)§	*< 0.001*
Vitamin B12 (µg/d)	2.9 (2.6)†	3.0 (3.3)†,‡	3.6 (3.5)‡	4.3 (3.9)§	*< 0.001*	2.6 (2.1)†	3.0 (2.9)†,‡	3.5 (2.8)‡	3.5 (2.7)‡	*< 0.001*
Calcium (mg/d)	574.9 (444.6)	595.4 (360.4)	601.9 (324.8)	574.6 (344.2)	0.959	544.4 (433.9)	585.5 (402.7)	574.4 (417.3)	532.9 (327.8)	0.392
Iron (mg/d)	6.4 (3.8)†	8.2 (4.7)‡	8.5 (4.4)§	9.4 (5.5)§	*< 0.001*	6.5 (4.3)†	7.6 (4.7)‡	8.4 (4.5)§	8.9 (4.4)§	*< 0.001*
Magnesium (mg/d)	177.6 (101.6)†	198.0 (109.9)†	218.7 (118.2)‡	221.9 (120.5)‡	*< 0.001*	170.1 (90.9)†	186.5 (108.9)†	206.9 (99.5)‡	219.9 (115.2)‡	*< 0.001*
Zinc (mg/d)	6.9 (4.5)†	7.5 (5.1)†,§	8.1 (5.5)‡,§	9.3 (4.7)‡	*< 0.001*	6.5 (3.3)†	6.9 (4.2)†,§	7.8 (3.7)‡,§	7.9 (3.5)‡	*< 0.001*
Potassium (mg/d)	1,394.2 (930.0)†	1,795.6 (822.3)‡	1,968.2 (967.4)‡	2,213.7 (1082.4)§	*< 0.001*	1,356.1 (745.5)†	1,731.6 (879.2)‡	1,957.3 (850.3)‡	2,196.9 (1,029.4)§	*< 0.001*

*MSDPS: Mediterranean-Style Dietary Pattern Score; SFA: saturated fatty acid; MUFA: monounsaturated fatty acid; PUFA: polyunsaturated fatty acid. *Kruskal-Wallis test. †,‡,§The groups with the same letters within a row are not significantly different according to pairwise comparisons.*

Table IV. Evaluation of adolescents demographic characteristics, obesity and physical activity status according to quartile categories of the MSDPS

	Boys (n: 514)				p	Girls (n: 623)				p
	Q1 (0.2-7.4)	Q2 (7.5-10.7)	Q3 (10.8-15.1)	Q4 (15.2-40.5)		Q1 (0.2-7.4)	Q2 (7.5-10.7)	Q3 (10.8-15.1)	Q4 (15.2-40.5)	
n (%)	116 (22.6)	129 (25.1)	131 (25.5)	138 (26.8)		168 (27.0)	155 (24.9)	154 (24.7)	146 (23.4)	
Age (years)	13.0 (1.0)	13.0 (2.0)	14.0 (2.0)	13.0 (3.0)	0.675	14.0 (2.0)	14.0 (2.0)	14.0 (2.0)	13.0 (2.0)	0.063
BAZ classification (n, %)										
Underweight (< -1SD)	15 (21.4)	17 (24.3)	17 (24.3)	21 (30.0)	0.175	29 (31.5)	17 (18.5)	21 (22.8)	25 (27.2)	0.628
Normal (≥ -1 +1 SD)	53 (22.0)	64 (26.6)	52 (21.6)	72 (29.9)		80 (23.3)	88 (25.7)	94 (27.4)	81 (23.6)	
Overweight (> +1SD)	31 (24.8)	29 (23.2)	38 (30.4)	27 (21.6)		50 (34.7)	38 (26.4)	27 (18.8)	29 (20.1)	
Obesity (> +2SD)	17 (21.8)	19 (24.4)	24 (30.8)	18 (23.1)		9 (20.5)	12 (27.3)	12 (27.3)	11 (25.0)	
Body fat (%)	18.2 (12.7)	17.3 (12.4)	16.6 (11.1)	15.9 (16.1)	0.890	25.1 (11.7)	24.8 (10.0)	24.4 (9.3)	23.7 (9.5)	0.479
Waist circumference (cm)	77.0 (16.3)*	74.0 (16.0)*	73.0 (12.0)†	72.0 (17.0)†	*0.025*	70.0 (12.0)*	70.0 (12.5)*	70.0 (10.8)†	68.0 (11.0)†	*0.021*
MET (minutes/week)	2,520.0 (2,828.5)	2,028.0 (2,310.0)	2,100.0 (2,261.6)	2,175.0 (2,220.0)	0.495	1,533.0 (2,340.0)	2,100.0 (2,280.0)	1,680.0 (2,265.0)	2,100.0 (2,100.0)	0.433
MET classification (n, %)										
Inactive < 600	17 (14.7)	29 (22.5)	23 (17.6)	23 (16.7)	0.284	37 (22.0)	32 (20.6)	26 (16.9)	21 (14.4)	0.080
Moderate active 600-3,000	66 (56.9)	75 (58.1)	79 (60.3)	91 (66.0)		100 (59.5)	90 (58.1)	95 (61.7)	94 (64.4)	
Very active > 3,000	33 (28.4)	25 (19.4)	29 (22.1)	24 (17.3)		31 (18.5)	33 (21.3)	33 (21.3)	31 (21.2)	

*MSDPS: Mediterranean-Style Dietary Pattern Score; BAZ: BMI-for-age Z score. *†The groups with the same letters within a row are not significantly different according to pairwise comparisons.*

Table V. Regression analysis for MSDPS prediction

Model	MSDPS		
	Beta	t	p
Age (years)	0.115	2.333	*0.020*
Gender	0.032	0.793	0.428
Parental education level*	0.180	3.562	*< 0.001*
BMI (kg/m^2)	-0.149	-2.075	*0.038*
Body fat (%)	-0.036	-0.610	0.542
Waist circumference (cm)	-0.151	-2.812	*0.005*
Skipping meals†	-0.103	-3.499	*< 0.001*
	$R^2 = 0.036$; $p < 0.001$		

*MSDPS: Mediterranean-Style Dietary Pattern Score; BMI: body mass index. *Description of parental (both father and mother) education level: "0" was ≤ 8 years, "1" was > 8 years. †Description of skipping meals: "0" was "no", "1" was "yes".*

grain products, low levels of consumption of olive oil and fish, and fruit consumption exceeding the recommended amount (22). In this study, alcohol consumption was not evaluated in the MSDPS score due to age group, similar to the study in Iran. The low score in our study is due to the fact that whole grains, fruits, vegetables, olives, legumes and nuts, and eggs are consumed below and dairy products consumption exceeding the recommended amounts (Table II). Turkey is a Mediterranean country. However, it has undergone significant demographic and socio-economic changes in recent years, which affected dietary habits and adherence to the MD. Globalization and food advertisements also lead to changes in eating behaviors. In particular, the media and advertising sector can affect young individuals more and lead to the formation of unhealthy eating habits. Interactions between peers, especially the increasing popularity of fast-food restaurants, have a significant impact on food preferences (23).

Among the MSDPS score components, olive oil has the highest score, followed by whole-grain products. It can be said that olive oil is widely used in diets in Turkey (24). In addition, milk consumption was found to be above the recommended levels in adolescents, which negatively affected the MSDPS score. Milk consumption is encouraged within our country's scope of the School Milk Program.

The MD is rich in vitamins and minerals because it contains vegetables and fruits, whole grains, nuts, olive oil and fish, and it is stated that the risk of insufficient micronutrient intake is quite rare (25). In our study, consumption of foods that are part of the Mediterranean-style dietary pattern contributes to 53.4 % of total energy intake. The increase in adherence to MD contributes to the intake of recommended food groups and nutrients in recommended amounts. Our study revealed that the components of the MSDPS could not meet the reference intake recommendations, and among the 12 components, the consumption of dairy products was found to have the highest rate of consumption, meeting the intake recommendations. In addition, adolescents with high adherence to MD had higher protein, fiber, vitamin A, vitamin C, folate, vitamin B12, iron, magnesium, zinc, and potassium intake levels ($p < 0.001$). Therefore, it is important to popularize the Mediterranean-style diet model in order to meet the nutrient requirements and food group intake recommendations in the adolescence period and to ensure adequate and balanced nutrition.

Generally, young individuals are more prone to unhealthy food consumption, and as they age, they attach more importance to choosing healthier foods in order to lead a healthy life and maintain body weight (22). Some studies showed that the MSDPS score is positively associated with age (26). Similarly, our study revealed a positive relationship between age and MSDPS. People have started to eat out and tended to skip breakfast, lunch or dinner. In addition, intense and long working hours of parents, and therefore less frequent family meal times, have a significant impact on adolescents' nutritional transitions, especially on meal skipping (27). Our study also revealed that skipping meals had a negative effect on adherence to MD. The availability of healthy foods at home and habits such as eating with parents are thought to play an important role in improving the diet quality of adolescents.

MD has positive effects on body weight and health protection (28,29). Some studies conducted with adolescents on the relationship between BMI and MD compliance found a negative or no relationship (11,30). Similarly, studies investigating the relationship between MD compliance and waist circumference, which is an indicator of abdominal obesity, found different results (22,29). One multicenter study covering eight European countries revealed that waist circumference was negatively associated with MD compliance (12). Our study found that the waist circumference of girls in Q4 was lower than that of the girls in Q1 and Q2, and there was no difference between tertiles in terms of physical activity (Table IV). The majority of underweight and overweight girls had low adherence to MD. Another finding was that both BMI and waist circumference had a negative effect on the MSDPS score in the regression model (Table V). These results support that adherence to MD may contribute to the maintenance of healthy body weight. Higher adherence to the MD is generally associated with healthier food choices and healthier lifestyles, namely being physically active. Although a previous study has shown that physical activity is associated with high adherence to the MD, no effect of physical activity was found in our study (11). This may be due to the fact that the majority of the sample had moderate physical activity.

It is generally thought that individuals with a high level of education are more conscious about healthy nutrition and therefore will have a healthier diet. In addition to the environment in which people live (friends, family and school environment), easy access to information about healthy nutrition through mass media can affect nutritional behavior (26). Families also play a major role in the development of eating behaviors. It should be noted that a family member's eating behaviors are not independent of the influence of other members. As the family systems theory suggests, familial factors influence children's behaviors (31). A study

shows that children of parents with a high level of education have higher adherence to the MD (32). Similar to the literature, our study revealed that high educational status of parents contributes positively to adherence to MD (Table V).

The limitation of this study was to exclude assessment alcohol due to adolescents' age, cultural, and religious beliefs.

CONCLUSION

In conclusion, adherence to MD was found to be low in adolescents. Adherence to the MD may contribute significantly to the prevention of obesity and adequate and balanced nutrition in adolescents. Since healthy eating behaviors start in childhood and adolescence, it is very important to provide healthy nutrition education for this group and to encourage adherence to MD within the scope of early intervention in obesity. Increasing adherence to MD and extending physical activity in adolescents are important for body weight maintenance and a healthier and better-quality life as well as sustainability.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Epidemiología y dietética

Association of coffee intake and its polyphenols with mammographic findings in women who visited the Brazilian Public Health Service

Asociación de la ingesta de café y sus polifenoles con hallazgos mamográficos en mujeres atendidas en el Servicio de Salud Pública de Brasil

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Abstract

Objective: this study aimed to evaluate if there is an association of intake of coffee and its polyphenols with mammographic findings in women treated at a breast care service unit of the Unified Health System (SUS), Brazil.

Research methods and procedures: this was a cross-sectional study with 532 women treated at a health service. The participants were divided according to their mammographic reports into two groups: without and with altered findings. Two 24-h dietary recalls were applied and coffee consumption was categorized into three groups (less than 1 cup, 1 to 3 cups, and more than 3 cups). Phenolic acids were determined using the Phenol Explorer program. The intake of polyphenols was calculated by adding the values obtained from the total amount of coffee consumed during the day. The Multiple Source Method (MSM) was applied to analyze the usual intake.

Results: of the 532 women, 178 (33.5 %) had altered mammographic findings. The participants' average daily coffee intake was 193.4 mL. No significant association was found between coffee consumption and mammographic findings. However, it was found that the second tertile of polyphenols was a protective factor for breast changes.

Conclusion: coffee polyphenols are protective against breast changes in the group evaluated and, thus, can help prevent breast cancer.

Keywords:

Coffee. Polyphenols. Phenolic acids. Mammographic findings. Women.

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Resumen

Objetivo: este estudio tuvo como objetivo evaluar si existe una asociación de la ingesta de café y sus polifenoles con los hallazgos mamográficos de mujeres tratadas en una unidad de patología mamaria del Sistema Unificado de Salud (SUS), Brasil.

Métodos y procedimientos de investigación: este fue un estudio transversal con 532 mujeres tratadas en un servicio de salud. Las participantes se dividieron de acuerdo con sus informes mamográficos en dos grupos: sin y con hallazgos alterados. Se aplicaron dos registros dietéticos de 24 horas y el consumo de café se clasificó en tres grupos (menos de 1 taza, 1 a 3 tazas y más de 3 tazas). Los ácidos fenólicos se determinaron utilizando el programa Phenol Explorer. La ingesta de polifenoles se calculó sumando los valores obtenidos de la cantidad total de café consumido durante el día. Se aplicó el método de fuentes múltiples (MSM) para analizar la ingesta habitual**.**

Resultados: de las 532 mujeres, 178 (33,5 %) tenían hallazgos mamográficos alterados. La ingesta diaria promedio de café de los participantes fue de 193,4 ml. No se encontró una asociación significativa entre el consumo de café y los hallazgos mamográficos. Sin embargo, se encontró que el segundo tercil de polifenoles era un factor protector para los cambios mamarios.

Conclusión: los polifenoles del café son protectores contra los cambios mamarios en el grupo evaluado y, por lo tanto, podrían ayudar a prevenir el cáncer de mama.

Palabras clave:

Café. Polifenoles. Ácidos fenólicos. Hallazgos mamográficos. Mujeres.

INTRODUCTION

Chronic noncommunicable diseases, such as cancer, are serious public health problems and are prevalent worldwide and in Brazil. Diet, nutritional status, and physical activity are indicated as protective or triggering elements of cancer development and progression (1,2).

Nutritional risk factors involved in this process include low consumption of whole grains, vegetables, and fruits; excessive consumption of fast foods, processed foods, and sugary drinks; high consumption of red and processed meats; consumption of alcoholic beverages; and overweight or obesity (3).

A dietary habit as described above can lead to oxidant and proinflammatory properties directly related to carcinogenesis, including in the breast (4-6). On the other hand, a diet rich in phytochemicals can exert antioxidant and anti-inflammatory effects (7). Phytochemicals are bioactive compounds present in foods of plant origin. In the human organism, in addition to the effects mentioned, they can prevent angiogenesis and reduce cell proliferation (8-10).

Coffee is one of the most widely consumed non-alcoholic beverages globally. Brazil is one of the largest coffee consumers in the world, second only to Finland. There are several components present in coffee, such as caffeine, fibers (mainly insoluble fibers, however, with antioxidant capacity due to the presence of polyphenols), and minerals. Brazilian coffee (Arabica) has an average of 0.8 to 1.4 % (2.6 to 8.7 mg/g) of caffeine and 0.59 to 8.74 mg/g of phenolic acids. However, despite the known role of caffeine in health (stimulant of the central nervous system and smooth muscle, in addition to acting on cell differentiation and inhibition of carcinogenesis), studies show that the main benefits of coffee come from phenolic compounds (11-15).

Phenolic acids are phytochemicals belonging to the polyphenol class. Among the acids found in coffee, the notable ones are the hydroxycinnamic acids (caffeoylquinolic acid, feruloylquinolic acid, and caffeic acid), which act as antioxidants, cardioprotectants, and inhibitors of breast cancer tumor cells (16-23).

Many studies investigated the associations of phytochemicals with breast cancer, but few studied their role in mammographic alterations that may or may not become malignant.

Thus, the objective of the present study was to evaluate whether there is an association between coffee polyphenols and mammographic findings in women assisted at a mastology service under the Brazilian Unified Health System (SUS).

MATERIALS AND METHODS

STUDY DESIGN AND SAMPLE

This was a cross-sectional, quantitative and analytical study. The sampling was by convenience and included 532 patients seen at a health service linked to the SUS that specializes in mastology, from April 2015 to February 2017. The individuals included in the research were women aged ≥ 18 years on the date of collection, under the care of the SUS, with mammographic reports, without breast cancer, and without evidence of psychiatric disease that might preclude their participation in the research. All women were included without established inclusion criteria, adopting only pregnancy and lactation exclusion criteria, because under these conditions coffee consumption is often already limited (24).

CLINICAL AND ANTHROPOMETRIC DATA

The *Breast Imaging-Reporting and Data System* (BI-RADS) has been adopted as a model to standardize mammographic findings and was used to assess the participants' mammographic findings to stratify the participants into two groups. Group 1 had altered mammographic findings, which presented as categories 0, 3, 4, and 5 (category 6 was excluded because it was indicative of breast neoplasia). Group 2 exhibited normal mammographic findings, which included categories 1 or 2. Category 0 is considered to be of inconclusive interpretation. Category 1 is considered negative for malignancy and with a 0% risk of breast cancer. Category 2 is considered benign and also has a 0% risk of breast cancer. Category 3 is probably benign and up to a 2% risk of cancer. Category 4 presents a suspicious diagnosis and 2 to 95% of malignancy. Category 5 is considered highly sugges-

tive of malignancy and with a probability greater than 95% risk of cancer. Category 6 is considered a proven malignant lesion. Category 0 was included in Group 1 because the mammographic findings demanded additional tests, and category 3, because the findings could not rule out non-benign alteration (25,27,28).

Each participant's weight was obtained using calibrated anthropometric scales (Filizola®, São Paulo, Brazil) with a capacity of 200 kg. Height was determined using a coupled stadiometer with a capacity of 2 meters (29). The Body Mass Index (BMI) was calculated according to the ratio of weight (BP) to height (H) squared (BMI = BP/A²), and the results were expressed in kilograms per square meter (kg/m²). The BMI classification criteria used were those proposed by the World Health Organization (30) for adults and by PAHO or the elderly (31).

Calculation of coffee intake and its polyphenols

Food intake, including coffee e caloric intake, was collected through two 24-hour recordings (R24h). For the research, two R24h were used, the first collected on the day of the interview and the other by telephone, totaling one on the week and the other on the weekend. In the presence of any intercurrence that prevented the performance of the second 24hR, it was ensured that at least 40 % of the sample had availability of two recalls, so that the habitual consumption of the individual could be estimated (32). The data were analyzed using the Brasil Nutri program, with later inclusion in the Statistical Analysis System (33). The *Multiple Source Method* (MSM) was used in the analysis of usual intake to minimize intrapersonal differences (34).

All participants reported the amount of coffee infusion (mL) consumed, the coffee blend used (Arabic), and if there were additional ingredients, such as milk, sugar, or sweetener. Arabic coffee has a lower amount of caffeine compared to robusta coffee. The protein content in dry grains ranges from 11 to 15 %, lipids from 7 to 16 %, and insoluble fiber is preferable. In relation to chlorine acids, they have an average of 4.5 % after roasting (15).

Coffee consumption was categorized into three groups: less than 1 cup/day, 1 to 3 cups/day, and more than 3 cups/day, with 1 cup corresponding to 50 mL (35). The intake of phenolic acids present in coffee was determined by the Phenol Explorer program (available at www.phenol-explorer.ue) (36). It was calculated by adding the values obtained from each phenolic acid present in the daily amount of coffee ingested. The phenolic acids analyzed in this study were those found in coffee in general: hydroxycinnamic acids (3-caffeoylquinic acids, 4-caffeoylquinic acids, 5-caffeoylquinic acids, 5-feruloylquinic acids and caffeic acid), alkylmethoxyphenols (4-ethylguaiacol and 4-vinylguaiacol), and other polyphenols (catechol, pyrogallol, and phenol) (15,37-39).

STATISTICAL ANALYSIS

The statistical analysis was performed using the SPSS Statistics 20.0 software (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to verify the normality of quantitative variables. The chi-squared test was utilized for categorical variables, and Spearman's correlation test was utilized for continuous variables. Analysis of variance, Kruskal-Wallis, Mann-Whitney U, and logistic regression tests adjusted for age, race, income, smoking, caloric intake, physical activity, and BMI were used to determine the association between mammographic findings, phenolic acids, and coffee consumption. In all tests, $p < 0.05$ was considered statistically significant. All variables were collected on the first day of the survey using a structured form.

The present study was approved by the Ethics Committee of the Universidade Estadual do Ceará, under CAAE number: 18054613.0.0000.5534, with Opinion number 314351, and all participants signed a free and informed consent form.

RESULTS

The study comprised women with a mean age of 52.1 ± 9.1 years, most of them married (52.4 %) and with at least an incomplete high school education (52.1 %). Of the 532 women, 178 (33.5 %) presented with altered mammographic findings.

The mean daily coffee intake of the participants was 193.4 mL, and 86.5 % of the women consumed coffee daily. In terms of their BMI, the average value was 28.7 kg/m^2, and 71.2 % of the women were found to be overweight.

Table I shows the distribution of women according to mammographic findings and demographic, socioeconomic, clinical, and dietary variables, associated with coffee consumption. The variables are: smoke, physical activity, breastfeeding, BMI, age, schooling, race, and family income.

A significant association was found between coffee intake and age group, wherein the higher the coffee consumption, the lower the mean age of the participants ($p = 0.022$).

Table II shows the distribution of polyphenols associated with coffee intake. The average intake of total polyphenols was 375.59 mg/day, divided into: hydroxycinnamic acids (371.5 mg/day), alkylmethoxyphenols (2.12 mg/day), and other polyphenols (2.05 mg/day). A positive association was observed between polyphenols and coffee intake categories, in that the higher the coffee intake, the higher the consumption of phenolic acids and other polyphenols ($p < 0.001$). Moreover, an association between coffee consumption and caloric intake was observed, with a higher caloric intake for those who ingested more than 3 cups of coffee per day ($p = 0.018$).

In logistic regression performed between coffee consumption and mammographic findings according to BI-RADS, no significant association was found, even after adjustment for age, race, income, education attainment level, smoking habit, and BMI stratification. There was also no statistically significant trend that evidenced increased consumption of polyphenols reducing the risk for breast changes.

However, when the coffee components were analyzed in their tertiles, the second tertile of polyphenols was found to be a protective factor for breast alterations (Table III).

Table I. Distribution of the women evaluated according to risk variables for breast cancer and coffee consumption categories. Fortaleza, Brazil, 2020

Variables	Coffee consumption, cups/day*			p†
	< 1 (n = 44)	1-3 (n = 69)	≥ 3 (n = 419)	
Clinical variables				
Mammographic findings, altered‡	14 (31.8)	18 (26.1)	146 (34.8)	0.350
Smoke, yes‡	7 (15.9)	6 (8.7)	36 (8.6)	0.278
Practice of physical activity, no	33 (75.0)	50 (72.4)	320 (76.4)	0.805
Breastfeeding, no	30 (68.2)	36 (52.2)	246 (58.7)	0.599
BMI, overweight‡	30 (75.0)	47 (70.1)	303 (74.9)	0.704
Socioeconomic variables				
Age, years‖	54,5 (9.7)	54.0 (9.7)	51,5 (8.9)	0.022
Schooling, ≤ 8 years‡	21 (47.7)	36 (52.2)	194 (46.3)	0.934
Race, not Caucasian‡	41 (93.2)	56 (81.1)	325 (77.6)	0.089
Family income, < 1 SM‡,§	34 (85.0)	54 (80.6)	330 (81.7)	0.842

Cup equivalent to 50 mL; †Kruskal-Wallis test; ‡Values expressed as n (%); §n = 511; ‖Values expressed as mean (dp).

Table II. Distribution of women assessed according to caloric intake, classes and subclasses of coffee polyphenols, and coffee consumption categories. Fortaleza, Brazil, 2020

Variables	Coffee consumption, cups/day*			p†
	< 1 (n = 44)	1-3 (n = 69)	≥ 3 (n = 419)	
Energy, kcal‡	1563.2 (1282.5-1781.1)	1492.5 (1297.9-1735.0)	1622.6 (1382.1-1852.7)	*0.018*
Phenolic acids, mg‡	0.00 (0.0-0.0)	194.2 (145.6-194.2)	412.8 (388.5-582.7)	*< 0.001*
Hydroxycinnamic acids, mg‡	0.00 (0.0-0.0)	193.2 (144.7-193.2)	410.4 (386.2-579.5)	*< 0.001*
3-Caffeoylquinic acids,mg‡	0.00 (0.0-0.0)	57.5 (57.5-68.3)	111.7 (92.9-136.3)	*< 0.001*
4-Caffeoylquinic acids, mg‡	0.00 (0.0-0.0)	66.2 (66.2-78.6)	128.5 (107.0-156.9)	*< 0.001*
5-Caffeoylquinic acids, mg‡	0.00 (0.0-0.0)	77.8 (77.8-92.3)	151.0 (125.7-184.3)	*< 0.001*
5-Feruloylquinic acid, mg‡	0.00 (0.0-0.0)	12.9 (12.9-15.4)	25.2 (20.9-30.7)	*< 0.001*
Caffeic acid, mg‡	0.00 (0.0-0.0)	0.036 (0.03-0.04)	0.07 (0.05-0.08)	*< 0.001*
Alkylmethoxyphenols, mg‡	0.00 (0.0-0.0)	1.1 (0.82-1.1)	2.33 (2.2-3.3)	*< 0.001*
4-Ethylguaiacol, mg‡	0.00 (0.0-0.0)	0.71 (0.7-0.8)	1.38 (1.1-1.6)	*< 0.001*
4-Vinylguaiacol, mg‡	0.00 (0.0-0.0)	0.51 (0.51-0.6)	0.99 (0.82-1.2)	*< 0.001*
Other polyphenols, mg‡	0.00 (0.0-0.0)	1.06 (0.79-1.06)	2.26 (2.13-3.19)	*< 0.001*
Phenol, mg‡	0.00 (0.0-0.0)	0.45 (0.4-0.5)	0.87 (0.7-1.06)	*< 0.001*
Catechol, mg‡	0.00 (0.0-0.0)	0.13 (0.13-0.15)	0.25 (0.2-0.3)	*< 0.001*
Pyrogallol, mg‡	0.00 (0.0-0.0)	0.60 (0.6-0.7)	1.16 (0.9-1.4)	*< 0.001*
Total polyphenols, mg‡	0.00 (0.0-0.0)	195.3 (146.5-195.3)	415.0 (390.6-585.9)	*< 0.001*

**Cup equivalent to 50 mL; †Kruskal-Wallis test; ‡Values expressed as median (p25-p75).*

Table III. Odds ratio (OR) and confidence interval (CI) corresponding to coffee consumption and polyphenol tertiles in relation to mammographic findings in women. Fortaleza, Brazil, 2020

	OR (95 % CI)	
	Model 1	**Model 2**
Coffee consumption		
< 1	Reference	Reference
1-3	0.69 (0.29-1.64)	0.37 (0.10-1.29)
≥ 3	1.03 (0.52-2.06)	0.67 (0.27-1.66)
p-trend*	0.504	0.835
Total polyphenols		
1 tertile	Reference	Reference
2 tertile	*0.61 (0.38-0.96)*	0.73 (0.38-1.40)
3 tertile	0.97 (0.60-1.56)	0.52 (0.24-1.13)
p-trend*	0.938	0.098

1 x cup/day. Model 1: altered mammographic findings (BI-RADS 0, 3, 4, and 5). Model 2: altered mammographic findings (BI-RADS 3, 4, and 5). Variables adjusted for age, race, income, smoking, caloric intake, physical activity, and BMI. Test performed: logistic regression (trend test).

DISCUSSION

The participants' mean coffee and mean coffee polyphenol intake were 193.4 mL/day and 375.59 mg/day, respectively. A study conducted with the Japanese population found that the average amount of coffee consumed was 426 mg/day, and that polyphenols from coffee accounted for 50 % of total consumption of polyphenols in the Japanese diet. In a study published by the same author in 2020, consumption of coffee polyphenols was 655 mg/day, which amounted to 53 % of total consumption of polyphenols in the Japanese diet (40-42).

On the other hand, a study conducted with 557 Brazilians found that the average coffee consumption of Brazilians was 143.4 mL/day, and the average consumption of polyphenols from coffee, 247 mg/day (35). In a study conducted in Fortaleza with 498 college students, the average coffee consumption was 199 mL/day, much closer to that found in this study (43).

Coffee is one of the most consumed beverages in the world and has several health benefits, including a high level of antioxidant activity (44,45).

In the present study, the group of women with lower coffee consumption (less than 1 cup/day) showed a higher percentage of participants with breast changes, according to the BI-RADS; however, this association did not present a statistical significance ($p = 0.345$). However, when the coffee components were analyzed, the second tertile of coffee polyphenols was found to be protective against breast changes (CI: 0.38-0.96).

Studies show that one effect of polyphenols, specifically phenolic acids, is the neutralization of the free radicals produced by the body that are associated with chronic diseases, such as cancer and cardiovascular diseases. Thus, polyphenols can act preventively in breast cancer by acting on breast changes, even without cell malignancy (46-48).

This is the first study to focus on the association of the consumption of coffee and its polyphenols with mammographic findings, though there have been several previous studies that show the relationship between coffee consumption and a lower risk of breast cancer (49,50). In a study by Lowcock and colleagues (2013), a significant 29 % reduction in the risk of breast cancer was found in those who consumed more than 5 cups/day of coffee. A meta-analysis published in 2013 showed an inverse association between coffee consumption and the risk of breast cancer, even in those with a mutation in the BRCA1 gene (51).

Another benefit attributed to coffee is related to caffeine. It is involved in the metabolism and is one of the best markers of human cytochrome P450 1A2, which is involved in estrogen metabolism and thus has a key role in breast cancer etiology (52,53). However, despite the several benefits of caffeine, studies show that even decaffeinated coffees can aid in the prevention of several chronic diseases due to being rich in polyphenols (54-56). These phytochemicals inhibit the oxidation process, in addition to acting as detoxifiers and repairers. One of the mechanisms involved in this process is the activation of the NF-E2-related factor 2 system that induces the expression of cell defense genes (44,45,57).

A study conducted in Spain with 10,812 women found no association between coffee consumption and the overall risk of breast cancer. However, it was also found that postmenopausal women who consumed more than 1 cup of coffee/day had a lower risk of the disease (58).

In the same study, it was found that those with greater coffee consumption (more than 1 cup/day) had a higher mean age (35.9 years) (58). Conversely, in the present study, the mean age was lower (51.5 years) for those with greater coffee consumption (more than 3 cups/day). In a study conducted with the elderly that evaluated the relationship between coffee and longevity, a lower mean age was found in those with higher coffee consumption (more than 4 cups/day) (59).

The data from our study coincided with the findings of a study conducted in Brazil (ELSA-Brazil). ELSA is a cohort study conducted in six Brazilian cities with 4,426 participants, and one of the objectives was to verify the association of coffee consumption with clinical and demographic variables related to the risk of cardiovascular disease. The authors found a significant association between coffee consumption and mean age, with a lower mean age (49 years) of individuals with greater coffee consumption (more than 3 cups/day). Thus, it can be concluded that young adult women have the greatest coffee intake (60). In a study by Camargo et al. (61), it was also detected that there was a progressive increase in coffee consumption in the 30-39 age group and a decline in the elderly.

In the study by Miranda et al. (60), a higher caloric intake was found in individuals who consumed more coffee (more than 3 cups/day), which is similar to this study's findings. This association of coffee consumption with caloric intake was also verified in another study, which evaluated the association between coffee intake and the risk of hypertension (62). One of the hypotheses attributing to this is that coffee consumption is often accompanied by snacks and more caloric foods, such as bread, cookies, and pasta. Sugar, which is often used to sweeten coffee, also contributes to the increase in daily caloric intake. This association between coffee consumption and caloric intake may also contribute to the association of coffee polyphenols with breast changes (63).

In the present study, it was not verified whether the intake of coffee was accompanied by foods of higher energy density, which can be cited as one of its limitations; like this the consumption of antioxidants from other sources was not collected.

The findings of this study indicate that coffee consumption can be recommended in addition to a healthy diet as a strategy for the prevention of chronic diseases.

CONCLUSIONS

Coffee polyphenols (second tertile) were protective against breast alterations in the evaluated group and may help in the prevention of breast cancer.

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Trabajo Original

Epidemiología y dietética

The effect of social media use on orthorexia nervosa: a sample from Turkey

El efecto del uso de las redes sociales en la ortorexia nerviosa: una muestra de Turquía

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Abstract

Objectives: the current study evaluated the orthorexic tendencies of social media users and the factors affecting these tendencies.

Methods: a total of 2526 adult participants (696 male and 1830 female, 28.4 ± 10.3 years) completed a questionnaire that includes personal information, the Orthorexia Nervosa Scale (ORTO-11), the Social Media and Eating Behavior Scale (SMEB), and the International Physical Activity Questionnaire Short Form (IPAQ). Body mass index (BMI) was calculated from the reported weight and height of the participants. Independent-sample t-tests or chi-square tests were computed to evaluate various information of the participants according to the ON tendency. A binary logistic regression analysis was used to identify risk factors.

Results: according to ORTO-11, 56.1 % of the participants had a tendency to ON, and the trend to ON increased with age and BMI ($p < 0.05$). People without ON tendency spent more time (172.2 ± 119.9 min/day) on social media. Participants who followed webpages with healthy nutrition and sport-exercise recommendations had an increased ON risk when compared to those who did not follow those pages ($p < 0.05$). In addition, although there was a significant difference between participants in physical activity level according to the ON tendency, this relationship was not significant in the regression model ($p > 0.05$).

Conclusion: this study indicates that increasing social media usage, especially web pages that include health and nutrition recommendations, may boost the tendency to ON. Thus, raising awareness of social media may be beneficial to people who have a tendency to ON.

Keywords:

Orthorexia nervosa. Social media. Eating behavior. Eating disorders.

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Ethics approval: this study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Ankara University (14.06.2021/No:09/113). All participants were informed about the study before enrollment, and an online informed consent was obtained from all individuals included in the study.

Data statement: the datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Resumen

Objetivos: el presente estudio evaluó las tendencias ortoréxicas de los usuarios de las redes sociales y los factores que afectan a estas tendencias.

Métodos: un total de 2526 participantes adultos (696 hombres y 1830 mujeres, 28,4 ± 10,3 años de edad) completaron un cuestionario que incluye información personal, la escala de ortorexia nerviosa (ORTO-11), la escala de redes sociales y conducta alimentaria (SMEB) y el cuestionario internacional de actividad física en formato corto (IPAQ). El índice de masa corporal (IMC) se calculó a partir del peso y la estatura declarados por los participantes. Se realizaron pruebas t o pruebas del chi cuadrado de muestras independientes para evaluar la diversa información de los participantes según la tendencia a la ortorexia nerviosa. Se utilizó un análisis de regresión logística binaria para identificar los factores de riesgo.

Resultados: según el ORTO-11, el 56,1 % de los participantes tenían tendencia a la ortorexia nerviosa y esta tendencia aumentaba con la edad y el IMC ($p < 0,05$). Las personas sin tendencia a la ortorexia nerviosa dedicaban más tiempo (172,2 ± 119,9 min/día) a las redes sociales. Los participantes que seguían páginas web con recomendaciones sobre alimentación saludable y deporte/ejercicios tenían un mayor riesgo de ortorexia nerviosa que los que no seguían esas páginas ($p < 0,05$). Además, aunque había una diferencia significativa entre los niveles de actividad física de los participantes según la tendencia a la ortorexia nerviosa, esta relación no era significativa en el modelo de regresión ($p > 0,05$).

Conclusión: este estudio indica que el incremento del uso de las redes sociales, especialmente de las páginas web que incluyen recomendaciones sobre salud y alimentación, podría favorecer la tendencia a la ortorexia nerviosa. Por lo tanto, concienciar a las personas con tendencia a la ortorexia nerviosa sobre las redes sociales puede tener un efecto beneficioso.

Palabras clave:

Ortorexia nerviosa. Redes sociales. Conducta alimentaria. Trastornos alimentarios.

INTRODUCTION

Orthorexia nervosa (ON), first described by Bratman in 1997, is a term used for a possible new eating disorder characterized by extreme obsessive anxiety about healthy eating (1). Obsession with health and healthy food as seen in individuals with ON can cause negative effects such as malnutrition and deterioration in social or academic functioning (2). Healthy eating in orthorexic individuals becomes an indicator of self-respect and control of themselves, and because of their obsession they have rather strict rules of food selection and preparation (3). Individuals who spend most of their days searching for healthy foods or making the food preparation process the healthiest are affected both physically and mentally by the fact that they cannot enjoy eating over time (2). Orthorexia nervosa is not defined as an eating disorder in the DSM-V. However, scales that recently allowed for a more detailed assessment of ON began revealing the relationship between ON and eating disorders (4).

Today, both the developing technology and the lockdown during the COVID-19 pandemic have caused daily habits to change and the Internet to enter our lives more. In the Digital 2021 report of "We are social" and "Hootsuite", it is stated that the time spent on the Internet in 2020 increased by 16 minutes compared to 2019, and reached 6 hours 54 minutes. In addition to the use of the Internet, the use of social media has also become widespread. In the same report, it is stated that more than 53 % of the world population are social media users, and individuals between the ages of 16 and 64 years spend an average of 2 hours and 25 minutes a day on social media (5). However, the widespread and increasing use of social media has started to affect users both physically and mentally (6).

The relationship shown between social media use and eating disorders and body image is important (7). The incidence of body dissatisfaction, body image disorders, and eating disorders is increasing, especially among children and young adults, among whom social media use is more common (6). A study evaluating the relationship between social media addiction and ON has shown that high social media addiction increases the risk of ON (8). Furthermore, among social media platforms, Instagram is the most commonly preferred by individuals with eating disorders (8,9). Quettiana et al. evaluated the relationship between intensity of social media use and eating disorders in their study of female university students, and showed that the increase in daily use of social media platforms, especially Instagram, was associated with a deterioration of eating behavior (9). Another recent study with university students also showed a high rate of social media addiction; however, social media addiction did not increase the risk of eating disorders (10).

Since orthorexia nervosa is an obsession with healthy eating, it was hypothesized that social media users who have a tendency to orthorexia might follow health-related webpages more frequently. This study aimed to determine the orthorexic tendencies of social media users and the factors affecting these tendencies.

MATERIALS AND METHODS

This cross-sectional study was conducted online between July and August 2021. Data were collected with an online questionnaire (via Google Forms). The ethics committee approval of the study was obtained from the Ankara University Ethics Committee (14.06.2021; 09/113). Before starting the study, the participants were informed about the study and work started if they declared their acceptance online. While preparing the study questions, it was ensured that the participants were able to easily understand and answer them on their own. The questionnaire form was announced on various social media platforms (Instagram, Facebook, WhatsApp, Twitter), and volunteers were allowed to participate in the survey during the 8 weeks between July 1st and August 25th, 2021. The population of this study consisted of Internet users between the ages of 19 and 65 living in Turkey. The data about the total number of Internet users in Turkey was obtained from the Turkish Statistical Institute. Accordingly, it was calculated that at least 663 individuals should participate in the study according to a 5 % margin of error and 99 % confidence level (11).

PARTICIPANTS AND DATA COLLECTION

A total of 3105 participants completed the online questionnaire. Duplicate submissions and incomplete or inconsistent data were excluded from the study (Fig. 1). After data cleaning, a total of 2526 volunteers between the ages of 18 and 65, without any known psychological diseases and who declared that they used at least one of the social media applications, were included in the study. The online questionnaire form prepared for collecting research data consisted of six parts. In the first two parts of the questionnaire participants filled in their general information and health information. In the third part of the questionnaire, the current body weight (kg) and height (cm) values of the individuals were recorded based on their self-report, and body mass index (BMI) values were calculated using the formula "kg/m^2". According to the classification of the World Health Organization, the BMI value was evaluated as: < 18.5 equals underweight, 18.5-24.99 equals normal, 25.00-29.99 equals overweight, and ≥ 30.0 equals obese (12). The other parts of the questionnaire included the "Orthorexia Nervosa Scale (ORTO-11)," "Social Media and Eating Behavior Scale (SMEB)," and "International Physical Activity Questionnaire Short Form (IPAQ)."

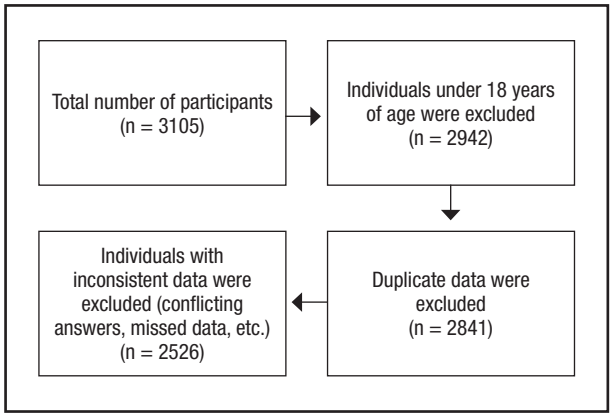

Figure 1.
Data cleaning.

The ORTO-11 scale used to determine the ON trends of the participants was created as a result of the Turkish validity-reliability study of the ORTO-15 test developed by Donini et al. (13). As a result of the study conducted by Arusoğlu et al. (14), it was determined that the Turkish use of ORTO-11 was more appropriate by removing 4 out of 15 questions from ORTO-15. Therefore, the ORTO-11 test was used in this study. In the scoring of ORTO-11 the sixth question was scored reversely, and the remaining questions were scored normally; an increase in the score indicates a decrease in the risk of ON. The cut-off point of the study was determined as 26 points at 25 %, and below this value it was evaluated as an orthorexic tendency.

The effect of social media on nutritional behavior was evaluated using the Social Media Eating Behavior Scale (SMEB) developed and validated by Keser et al. (15). The scale consists of 18 questions and is of a 5-point Likert type. As the score obtained from the scale increases, the effect of social media on eating behavior also increases.

The IPAQ short form has been used to determine the participants' physical activity level. Calculations were made as suggested and three levels (low, medium, and high) of physical activity were identified (16). The validity of the IPAQ short form has been shown in previous studies (17).

STATISTICAL ANALYSES

Statistical analyses were performed using the SPSS (IBM SPSS Statistics 21) software package. The Shapiro-Wilk goodness-of-fit test was used to examine whether the distributions of numerical variables fit a normal distribution, and descriptive statistics such as mean and standard deviation were provided for numerical variables with normal distribution. Percentage values and frequency tables were used for categorical variables. Risk factors affecting the ON tendency of the individuals were determined by binary logistic regression analysis. Before performing a binary logistic regression analysis, a univariate logistic regression analysis was performed on the independent variables used in the study. Independent variables with a p-value of up to 0.25 were included in the binary logistic regression model as possible risk factors. Variables with a p-value greater than 0.25 were excluded from the analysis. The Backward Elimination Method (Backward: LR) was used to determine the statistically significant variables. A Hosmer-Lemeshow test was also administered to evaluate the goodness of fit on the model obtained. Statistical significance was accepted at $p < 0.05$.

RESULTS

It was determined that 27.6 % of the individuals who participated in this study were male, 83.7 % had a university degree, 68.1 % were single, and 56.8 % were not working. The mean BMI of the participants was 23.6 ± 4.3 kg/m^2, and 60.6 % of them had normal body weight. Daily social media usage time was 167.4 ± 141.2 minutes, SMEB scale score was 46.3 ± 21.3, and ORTO-11 score was 25.6 ± 5.4. The general characteristics of the participants are given in table I.

The evaluation of various information on the participants according to their ON tendency is given in table II. It was found that 74.6 % of the participants with orthorexia nervosa tendency were female, and both mean age and BMI were significantly higher than for those without ON tendency (29.3 ± 10.7 years, 27.2 ± 9.5 years; 23.9 ± 4.2, 23.2 ± 4.4; $p < 0.05$). When the social media usage of the individuals participating in the research was evaluated, it was found that those without ON tendency spent 172.2 ± 119.9 minutes daily, while those with the tendency spent 161.1 ± 117.9 minutes on social media ($p < 0.05$), and individuals with ON tendency followed recipes, diet

meals, healthy nutrition recommendations, dietitian/nutrition specialist advice, sports/exercise recommendations, and mother-child education pages more than those without ON tendency ($p < 0.05$). The scores obtained from the SMEB scale applied to evaluate the effect of social media on eating behavior did not differ between the groups ($p > 0.05$). The number of individuals with moderate and high activity levels was significantly higher in the group determined to have orthorexia nervosa tendency ($p < 0.05$).

The ON trend of the individuals participating in the study increased 1.01 times with increasing age and 1.04 times with increasing BMI ($p < 0.05$, %CI: 1.003-1.024; $p < 0.05$, % CI: 1.013-1.062). It was found that the risk of ON was higher in individuals who followed the pages with healthy nutrition recommendations (OR: 2.441, %CI: 1.930-3.088), and sports-exercise recommendations (OR: 1.680, %CI: 1.369-2.060) on social media than in those who did not follow them ($p < 0.05$). However, the tendency to ON was found to be higher in those who did not follow restaurant (OR: 1.600, %CI: 1.216-2.105) and entertainment pages (OR: 1.268, %CI: 1.048-1.534) (Table III).

DISCUSSION

This study aimed to evaluate the use of social media by determining the demographic characteristics of individuals with ON tendencies. Sex, age, and BMI are some of the demographic characteristics that are thought to be related to ON, known as preoccupation with healthy eating. In this study, it was found that the risk of ON tendency was significantly higher in women than in men ($p < 0.05$) (Table III). This result, which has also been shown in various studies (18-21), may be due to the importance women attach to the relationship between health and nutrition (22,23). The greater attention paid to body weight and shape in women may also increase the tendency toward ON (24). However, in a meta-analysis conducted on this subject, it was determined that the difference between sexes varies according to the tool used in the assessment of ON status (25).

Another risk factor thought to be associated with ON tendency is age. In a study conducted with 801 participants in Turkey, it was shown that individuals aged 50 years and over had an increased tendency towards ON (22). In this study, it was determined that there was a significant relationship between age increase and ON tendency ($p < 0.05$). It is estimated that, with increasing age, more attention is paid to health, which leads individuals to pursue a healthy diet. However, there are different results in the literature regarding this subject (18,26,27). In their study, Varga et al. (26) found a positive but weak correlation between age and ON, while Fidan et al. (19) found that the risk of ON increased with younger age. However, it should be noted that participant education levels may affect the results, especially in studies with people who are educated in health or nutrition, such as in Fidan et al. (19,20).

It was determined in this study that ON tendency increased with increase in BMI ($p < 0.05$) (Table III). Oberle et al. (21) showed an increase in ON symptoms with increased BMI in their study in

Table I. General characteristics of the participants

	n (%) / mean ± SD
Sex	
Male	696 (27.6)
Female	1830 (72.4)
Age (years)	28.4 ± 10.3
18-24	1299 (51.4)
25-44	968 (38.3)
45-65	259 (10.3)
Education level	
Primary graduate	89 (3.5)
High school graduate	323 (12.8)
Bachelor's/Master's/PhD	2114 (83.7)
Marital status	
Single	1719 (68.1)
Married	807 (31.9)
Working status	
Working	1091 (43.2)
Not working	1435 (56.8)
Income status	
Less income than expenditure	411 (16.3)
Income equals expenditure	1334 (52.8)
More income than expenditure	781 (30.9)
Smoking	
Yes	554 (21.9)
No	1771 (70.1)
Chronic disease presence	
Yes	580 (23.0)
No	1946 (77.0)
BMI (kg/m^2)	23.6 ± 4.3
BMI classification	
Underweight	192 (7.6)
Normal	1531 (60.6)
Overweight	583 (23.1)
Obese	220 (8.7)
ORTO-11 score	25.6 ± 5.4
ON tendency	
With tendency (< 26)	
Without tendency (> 26)	1416 (56.1)
Time spent on social media	1110 (43.9)
(min/d)	165.9 ± 118.9
SMEB score	46.3 ± 21.3
Physical activity level (n = 2240)	
Low activity	875 (39.1)
Moderate activity	783 (34.9)
High activity	582 (26.0)

BMI: body mass index; ON: orthorexia nervosa; SMEB: Social Media and Eating Behavior Scale.

459 college students. In another study, a positive correlation was found between ON and BMI (28). It is possible that the reasons for this relationship between ON and BMI include the instinct to protect against the health risks caused by obesity by eating completely healthy. Studies on this subject show that the primary motivation of individuals with ON is to "maintain health" instead of losing weight (29). Additionally, focusing more and more on foods perceived as healthy while dieting also increases the risk of ON (4). However, Depa et al. (30) differentiated ON from healthy orthorexia, revealed the difference in dietary motivations of the two groups, and showed that weight loss and visual anxiety were substantial in ON. The interest in body structure or shape of individuals with ON tendency has been shown in various studies (28,31). A study conducted with university students has shown an association between muscle mass, instead of BMI, and ON (31). The perfectionist features in these individuals play an essential role in weight control and body satisfaction (4). Barnes and Caltabiano (32) state that body image dissatisfaction is higher in individuals with ON tendency, which increases the risk of developing an eating disorder. The use of healthy eating in orthorexia nervosa for maintaining body weight and changing body image or shape indicates that ON is associated with other eating disorders (4,30).

Table II. Evaluation of various parameters of the participants according to ON tendency

	Without ON tendency n (%) / mean ± sd	With ON tendency n (%) / mean ± sd	p
Sex			
Male	336 (30.3)	360 (25.4)	*0.007*
Female	774 (69.7)	1056 (74.6)	
Age (years)	27.2 ± 9.5	29.3 ± 10.7	*< 0.001*
Working status			
Working	459 (41.4)	623 (44.6)	0.098
Not Working	651 (58.6)	784 (55.4)	
BMI (kg/m^2)	23.2 ± 4.4	23.9 ± 4.2	*< 0.001*
BMI classification			
Underweight	106 (9.5)	86 (6.1)	
Normal	688 (62.0)	843 (59.5)	*< 0.001*
Overweight	218 (19.6)	365 (25.8)	
Obese	98 (8.8)	122 (8.6)	
Time spent on social media (min/d)	172.2 ± 119.9	161.1 ± 117.9	*< 0.05*
Content followed on social media			
Recipe pages (taste priority)	433 (39.0)	614 (43.4)	*0.028*
Diet recipe pages (health priority)	131 (11.8)	306 (21.6)	*< 0.001*
Healthy nutrition recommendation pages	180 (16.2)	504 (35.6)	*< 0.001*
Restaurant suggestion pages	158 (14.2)	156 (11.0)	*0.015*
Dietitian/nutritionist specialist pages	158 (14.2)	332 (23.4)	*< 0.001*
Sports/exercise pages	256 (23.1)	499 (35.2)	*< 0.001*
News/newspaper pages	680 (61.3)	856 (60.5)	0.679
Celebrity pages	296 (26.7)	343 (24.2)	0.161
Entertainment pages	669 (60.3)	717 (50.6)	*< 0.001*
Family education pages	139 (12.5)	229 (16.2)	*0.01*
SMEB score	46.8 ± 22.3	45.9 ± 20.5	0.295
Physical activity level (n: 2240)			
Low activity/Sedentary	411 (42.0)	464 (36.8)	
Moderate activity	332 (33.9)	451 (35.7)	*0.031*
High activity	235 (24.1)	347 (27.5)	

ON: orthorexia nervosa; BMI: body mass index; SMEB: Social Media Eating Behavior Scale.

Table III. Risk factors affecting participants' tendency toward ON

	B	S.E.	Wald	p	Exp (B)	95 % CI
Age	0.014	0.005	6.778	0.009	1.014	1.003-1.024
BMI	0.036	0.012	9.289	0.002	1.037	1.013-1.062
Sex	0.251	0.109	5.282	0.022	1.285	
Following healthy nutrition recommendation pages	0.893	0.120	55.380	0.000	2.441	2.009-3.199
Following restaurant suggestion pages	-0.470	0.140	11.250	0.001	0.625	0.468-0.810
Following sport/exercise pages	0.519	0.104	24.747	0.000	1.680	1.330-1.992
Following entertainment pages	-0.237	0.097	5.957	0.015	0.789	0.642-0.939

Social media has become an important communication and interaction tool that is used by everyone, regardless of demographic characteristics such as age, sex, or education level, where both true and false information is available. In the Digital 2021 report prepared by "We Are Social" and "Hootsuite," it is stated that individuals between the ages of 16 and 64 in Turkey used social media for an average of 177 minutes a day in 2020 (5). In this study, it was found that participants with ON tendencies spent an average of 161.1 ± 117.9 minutes per day on social media and followed pages with dietary meals, healthy eating, and sports-exercise recommendations more frequently ($p < 0.05$) (Table II). As a result of their study, Turner and Lefevre (8) showed that there is a significant relationship between the use of Instagram, with more visual content, and the ON tendency. Moreover, the higher tendency of individuals with ON to follow advice in social media rather than the suggestions of therapists is another result that shows the effect of social media on individuals with ON (33).

The lockdowns/quarantines implemented during the COVID-19 pandemic increased the use of both the Internet and social media (5). Nowadays, social media is also used as a platform where visual sharing of foods, nutritional recommendations, and recipes are given (34). Especially young individuals are open-minded about healthy eating and getting recipes from social media (35). It was found in this study that the risk of ON was 2.4 times higher in those who followed the pages with healthy nutrition recommendations and 1.68 times higher in those who followed the pages with sports-exercise recommendations ($p < 0.05$) (Table III). Tricas-Vidal et al. (36) determined in their study that women follow food-related social media accounts more than men and millennials from the z-generation. Additionally, it was found that the participants showed more interest in posts based on product/supplement promotion rather than scientific evidence (36). Therefore, health-related posts such as nutrition and exercise must also contain accurate information and be interesting in order to increase the number of followers. An exemplary study on this subject was conducted by Grantham et al. to raise awareness among the public about healthy nutrition during the pandemic. In the research, the social media campaign carried out with the hashtag #eatwellcovid19 with experts in the field managed to increase the number of interactions and participants on all social media platforms within four months (37).

Greater use of social media can increase depressive symptoms (38), body-perception disorder, and eating disorder symptoms (39). Individuals with a tendency toward ON during the pandemic stated that they felt pressure to diet and lose weight on social media (40). Furthermore, individuals with eating disorders, including ON, prefer to follow the recommendations of social media influencers rather than health professionals, which hinders their treatment (7,33). In this study, it was found that individuals with ON tendencies had a higher BMI average, and that increases in BMI significantly increased the risk of ON. With this result, it is thought that the pages/contents that individuals with ON tendency prefer to follow on social media may cause the existing ON symptoms to progress further. All of these contributed to the fact that ON has started to be seen as an individual and social disorder (33). When these results are considered, health- and nutrition-related posts on social media should be shared carefully to prevent individuals with ON tendency to further progress, or to prevent the emergence of another eating disorder.

Although the high number of participants in this cross-sectional study is the study's strength, there are some limitations. It should also be noted that the male subset, often observed in voluntary survey studies, is underrepresented. The inability to collect data face to face caused that anthropometric measurements and time spent on social media were self-reported by the participants. Moreover, the ORTO-11 test was used since no other test had validity and reliability in Turkish for evaluating ON. Therefore, no differentiation could be made between the sub-dimensions of ON or between healthy orthorexia and orthorexia nervosa.

In conclusion, this study showed that the risk of tendency to ON could be affected by increased BMI, age, gender, and following certain web pages. Further studies are needed to understand the effects of social media on behavioral health concerns like ON.

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ARÁN

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Trabajo Original

Epidemiología y dietética

Inequalities in the association between adherence to the Mediterranean diet and physical fitness in the young population during the COVID-19 lockdown

Desigualdades en la asociación entre la adherencia a la dieta mediterránea y la condición física en la población joven durante el confinamiento de la COVID-19

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Abstract

Objective: this study analyzed the association between adherence to the Mediterranean diet and proxy-reported physical fitness among Spanish and Brazilian youths during the COVID-19 lockdown according to several inequality indicators.

Methods: we conducted a cross-sectional study with parents and guardians of children and adolescents from Spain and Brazil. The evaluation process was through the use of online questionnaires. Adherence to the Mediterranean diet was assessed using the Mediterranean Diet Quality Index in Children and Adolescents. Proxy-reported physical fitness was determined using the International Fitness Scale. Inequality indicators (gender, nationality, socioeconomic status, and parents/guardians' education level) were evaluated with a survey completed by the participants' parents/guardians. Binary logistic regression models estimated the association between adherence to the Mediterranean diet and proxy-reported physical fitness, with stratification according to inequality variables. A total sample of 1099 Spanish and Brazilian individuals (47.6% girls, aged 3 to 17 years) were included in the analysis.

Results: compared to the "improvement needed to Mediterranean diet" category, the "optimal Mediterranean diet" group was significantly associated with "very good" physical fitness in boys (OR = 1.5; 95 % CI: 1.0-2.1) and in participants with parents/legal guardians' education level without university studies (OR = 1.5; 95 % CI: 1.0-2.4).

Conclusions: gender and parents/guardians' education level plays a significant role in the association between the "optimal Mediterranean Diet" and "very good" physical fitness level in Spanish and Brazilian children and adolescents. Future prospective studies are needed to investigate the role of inequality indicators in this relationship.

Keywords:

Young population. Pandemic. Behavior. Obesity. Socioeconomic status.

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Resumen

Objetivo: este estudio analizó la asociación entre la adherencia a la dieta mediterránea y la aptitud física autoinformada entre jóvenes españoles y brasileños durante el confinamiento de COVID-19 según varios indicadores de desigualdad.

Métodos: se realizó un estudio transversal con padres y tutores de niños y adolescentes de España y Brasil. El proceso de evaluación fue a través del uso de cuestionarios online. La adherencia a la dieta mediterránea se evaluó mediante el Índice de Calidad de la Dieta Mediterránea en Niños y Adolescentes. La aptitud física declarada por los padres se determinó mediante la Escala Internacional de Aptitud Física. Los indicadores de desigualdad (género, nacionalidad, estatus socioeconómico y nivel educativo de los padres/tutores) se evaluaron con una encuesta completada por los padres/tutores de los participantes. Los modelos de regresión logística binaria estimaron la asociación entre la adherencia a la dieta mediterránea y la aptitud física informada por los progenitores, estratificando según las variables de desigualdad. Se incluyó en el análisis una muestra total de 1099 individuos españoles y brasileños (47,6 % niñas, de 3 a 17 años).

Resultados: en comparación con la categoría de "necesidad de mejorar la dieta mediterránea", la de "dieta mediterránea óptima" se asoció significativamente con una aptitud física "muy buena" en los chicos (OR = 1,5; IC del 95 %: 1,0-2,1) y en los participantes con nivel educativo de los padres/tutores sin estudios universitarios (OR = 1,5; IC del 95 %: 1,0-2,4).

Conclusiones: el género y el nivel educativo de los padres/tutores legales desempeñan un papel significativo en la asociación entre la "dieta mediterránea óptima" y el nivel de condición física "muy bueno" en niños y adolescentes españoles y brasileños. Se necesitan futuros estudios prospectivos para investigar el papel de los indicadores de desigualdad en esta relación.

Palabras clave:

Población joven. Pandemia. Comportamiento. Obesidad. Estatus socioeconómico.

INTRODUCTION

Physical fitness (PF) is considered a powerful marker of health for children and adolescents due to its benefits for several health outcomes (1). The scientific literature suggests that cardiorespiratory fitness (2), and muscular fitness (3) are the main indicators of health in children and youth. Besides the benefits that PF provides to children and adolescents during their development, the scientific literature has reported a prospective negative association between muscular fitness and adiposity and cardiometabolic parameters in later life (4). Also, strong evidence supports that higher levels of cardiorespiratory fitness during the childhood and adolescence are associated with a healthier cardiovascular profile later in life (5).

The relationship between PF and adherence to the Mediterranean diet (MD) has been previously studied and a recent meta-analysis has concluded that an improvement of dietary habits towards those proposed by MD is associated with higher PF in children and adolescents (6). Although the relevance of adhering to MD over PF in children has been suggested (7), it seems that MD does not overcome the effect that fitness could have in the relationship with cardiovascular risk, as it was found in a study with 2477 adolescents (8).

The pandemic caused by COVID-19 has impacted negatively in children and adolescents' movement behaviors (9); it is well known that a reduction in physical activity and an increase in sedentary behavior have negative effects on PF (10). Regarding the dietary habits, the population in general reported an increase in the number of snacks consumed and also an increase in meal numbers and frequency; however studies reporting these dietary habits in younger population are scarce (11).

These indicators, associated with obesity and metabolic health, are elevated in people with low socioeconomic status and in some ethnicities, therefore it is suggested that solutions should be provided to facilitate this situation (12). In addition, it is recognized that social determinants of health have presented an even bigger effect during the COVID-19 pandemic (13), hence it is necessary to provide new insights on the role of these determinants in relation with PF and MD. Given that a reduction of PF during the COVID-19 pandemic has been estimated (14), there is a lack of information about its association with MD and the role of social determinants on this relationship. Thus, the aim of this study was to assess the association between adherence to MD and proxy-reported general PF among Spanish and Brazilian children and adolescents during the COVID-19 lockdown, according to several inequality indicators (gender, nationality, socioeconomic status, and parents/guardians' education level).

METHODS

STUDY DESIGN AND PARTICIPANTS

Parents and guardians of children and adolescents aged between 3 and 17 years old were contacted through different dissemination ways to be enrolled in an online survey. The online survey was administrated during 15 days in Spain and Brazil (between March and April 2020). It required 15 minutes to be completed and contained an informed consent at the beginning. They were asked to complete the survey in case they had been at home with restrictions of going out during the previous week. In total, 1263 participants completed the online survey, but 164 were removed for different reasons (outside the age range or missing values). The STROBE statement for nutritional epidemiology was used for reporting this study supplementary table I.

ETHICS

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Ethical Committee of the Catholic University of Murcia in Spain (Registration: CE112001) and the Technical University of Paraná in Brazil (Registration: 4.275.232). Written informed consent was obtained from all participants.

Table I. Descriptive characteristics of participants (n = 1099)

Variables	Values*
Age (years)	11.5 ± 4.5
BMI (z-score)	0.9 ± 2.0
Gender (%)	
Boys	52.4 (49.4-55.4)
Girls	47.6 (44.6-50.6)
Nationality (%)	
Spanish	55.0 (52.0-57.9)
Brazilian	45.0 (42.1-48.0)
SES (%)	
Low SES	32.9 (30.2-35.8)
Medium SES	48.1 (45.1-51.1)
High SES	18.9 (16.7-21.4)
Parents/legal guardians' education level (%)	
No university studies	51.0 (48.0-54.0)
University studies	49.0 (46.0-52.0)
Adherence to the MD (%)	
Optimal MD	44.3 (41.3-47.3)
Improvement needed MD	55.7 (52.7-58.7)
General PF (%)	
Very good PF	26.8 (24.2-29.5)
Rest PF categories	73.2 (70.5-75.8)

*BMI: body mass index; MD: Mediterranean diet; PF: physical fitness; SES: socioeconomic status. *Age and BMI are presented as mean (standard deviation). Categorical variables are presented as percentage (95 % confident interval).*

SOCIODEMOGRAPHIC INFORMATION

General sociodemographic information from the parents/guardians was requested in the first part of the online survey, including information about nationality, socioeconomic status (SES) (assessed by the Family Affluence Scale III) (15), parents/guardians' education level, and children and adolescents' age and gender.

ANTHROPOMETRIC PARAMETERS

Weight and height were proxy-reported by parent/guardians about their children. Body mass index (BMI) was calculated following standard procedures and then BMI (z-score) was computed (16).

PROXY-REPORTED PHYSICAL FITNESS

The International Fitness Scale (IFIS) was used to assess proxy-reported PF (17). This scale is a short, self-administered scale that assess PF. The IFIS is composed of five Likert-scale questions asking the perceived overall fitness, cardiorespiratory, muscular fitness, speed-agility, and flexibility in comparison with their friends. For the current study, only the overall fitness item was selected.

Even though the Likert-scale is composed of five categories ("very poor", "poor", "average", "good" and "very good"), the results of the current study were collapsed into two new categories as follows: "very good" PF category and the other PF categories ("very poor"; "poor"; "average" and "good"). This categorization was done to increase the statistical power and to focus the analysis on the "very good" category.

ADHERENCE TO THE MEDITERRANEAN DIET

To assess adherence to MD the Mediterranean Diet Quality Index in Children and Adolescents was used (18). It was completed by the participants' parents/guardians, and it is composed by 16 dichotomic questions, 12 of them about positive aspects and 4 of them about negative aspects related to MD. Answering in the affirmative to positive questions adds 1 point, while answering in the affirmative to negative questions detracts 1 point. Negative answers to all the questions are coded as zero. The total score of the Mediterranean Diet Quality Index in Children and Adolescents index ranges from 0 to 12 points.

The results were organized in three categories: "Optimal MD" (> 8 points); "improvement needed to adjust intake to

Mediterranean patterns" (4-7 points); and "very low diet quality" (< 4 points). The last two categories were collapsed into one category, which was defined as "improvement needed to MD". This categorization was done to increase the statistical power and focusing the analysis on the "optimal MD" category.

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences v.25 (SPSS, IBM Corp., Armonk, NY, USA) was used to perform all the analyses. Data were expressed as mean (standard deviation) for continuous variables, while categorical variables were expressed as absolute frequency (percentage).

The Chi-squared test was used to test the association of different categorized variables of inequality with exposure and outcome.

To determine the odds ratio of proxy-reported "very good" PF in relation to adherence to MD, a binary logistic regression was performed stratifying the sample according to inequality variables (gender, nationality, SES, and parents/guardians' education level). Interaction between inequality indicators (nationality, SES, and parents/guardians´ education level), proxy-related PF and adherence to the MD were tested. A *p* value ≤ 0.05 was set for statistical significance.

RESULTS

The interaction between inequality variables in the association between proxy-reported PF and adherence to MD was reported with a statistically significant interaction in nationality, SES, and education level ($p < 0.05$ for all), while no statistically significant interaction was found for gender ($p > 0.05$).

Descriptive characteristics of the sample are presented in table I. Of the total sample of participants, 1099 in total, a higher percentage were boys (52.4 %), Spanish (55.0 %), medium SES (48.1 %), and with parents/legal guardians without university studies (51.0 %). Most of the sample need improving MD adherence (55.7 %) and only 26.8 % of participants reported "very good" PF.

The proxy-reported general PF stratified by inequality indicators is presented in table II. A lower proportion of participants reported "very good" PF. Most of the participants reporting "very good" PF in each inequality indicator were boys (32.6 % vs 20.3 % of girls; $p < 0.001$), participants from Brazil (28.1 % vs 25.7 % from Spain; $p > 0.05$), also more classified in the high SES level (31.7 % vs 29.1 and 20.4 % in medium and low SES, respectively; $p < 0.05$), or with parents/legal guardians' education level with university studies (31.4 % vs 22.3 % without university studies; $p = 0.001$).

The adherence to MD stratified by inequality indicators is presented in table III. A lower proportion of participants reported an "optimal" MD. Most of the participants reporting "optimal" MD were boys (46.0 % vs 42.4 % of girls; $p > 0.05$), participants from Spain (47.2 % vs 40.8 % from Brazil; $p < 0.001$), classified as high SES level (53.8 % vs 46.9 and 35.1 % of medium and low SES, respectively; $p < 0.05$), and with parents/legal guardians with university studies (47.4 % vs 41.4 % without university studies; $p < 0.05$).

Figure 1 and supplementary table II shows the odds ratio of reporting "very good" PF in accordance with the reporting an "optimal MD" level of adherence to the MD. Each part of the figure shows comparisons by the social determinants described previously (gender, nationality, SES, and parents/guardians' education level). A higher odd of presenting a "very good" PF was found in both boys and girls with "optimal" adherence to the MD (OR = 1.5; 95 % CI: 1.0-2.1; $p < 0.05$ vs OR = 1.1; 95 % CI: 0.7-1.8; $p > 0.05$) in comparison with the reference category, but only in boys the association was statistically significant. Both nationalities (Spanish and Brazilian) presented higher odds of reporting "very good" PF when also reporting "optimal" MD (OR = 1.4; 95 % CI: 0.9-2.1 and OR = 1.3; 95 % CI: 0.8-1.9, respectively), but the odds were not statistically significant. Regarding the SES, when participants were classified in the low and medium SES level, they presented higher odds of reporting a "very good" PF with an "optimal" MD (OR = 1.7; 95 % CI: 0.9-2.9 and OR = 1.4; 95 % CI: 0.9-2.1, respectively), but not for participants classified in the "high SES" level (OR = 0.8; 95 % CI: 0.4-1.4); however, the odds were not statistically significant. Finally, participants with parents/legal guardians' education level without university studies presented statistically significant odds of reporting "very good" PF with an "optimal" MD (OR = 1.5; 95 % CI: 1.0-2.4; $p = 0.05$) in comparison with those with university studies (OR = 1.2; 95 % CI: 0.8-1.7; $p > 0.05$).

DISCUSSION

The aim of the current study was to analyze the association between adherence to MD and proxy-reported general PF in a sample of children and adolescents from Spain and Brazil during the COVID-19 lockdown according to gender, nationality, SES, and parents/guardians' education level. The main results show that boys reporting "optimal" MD are more likely to report "very good" PF when compared to girls. In addition, those participants whose parents/legal guardians reported no university studies were more likely to report "very good" PF when reporting "optimal" MD in comparison with the university studies category. Regarding the rest of inequalities analyzed, although nationality and/or SES were associated to proxy-reported PF and adherence to MD, no statistically significant odds ratio of reporting "very good" PF was observed when participants reported "optimal" MD.

Overall, previous evidence has observed a positive relationship between MD and cardiorespiratory/muscular fitness, and a negative relationship with speed-agility, suggesting that an improvement of the MD pattern could be associated with higher PF in the youth (6). A study with results based on PF field test with data before the COVID-19 pandemic also observed the association between adherence to MD and PF level (19). In this sense, the relationship between physical activity and MD (6,20) is well known, as well as between physical activity and PF in children (21). Therefore, those participants with higher standards of lifestyle (physical activity and high adherence to MD) could be more likely to score higher in PF test (reported or field-based).

Table II. Proxy-reported general physical fitness according to inequality indicators (n = 1099)

Variables	Very good PF (n = 294)	Rest of PF categories (n = 805)	p*
Gender (%)			
Boys (n = 576)	32.6 (28.8-36.6)	67.4 (63.4-71.2)	< 0.001
Girls (n = 523)	20.3 (16.9-24.0)	79.7 (76.0-83.1)	
Nationality (%)			
Spanish (n = 604)	25.7 (22.2-29.3)	74.3 (70.7-77.8)	0.368
Brazilian (n = 495)	28.1 (24.2-32.3)	71.9 (67.7-75.8)	
SES (%)			
Low SES (n = 362)	20.4 (16.4-25.0)	79.6 (75.0-83.6)	0.003
Medium SES (n = 529)	29.1 (25.3-33.2)	70.9 (66.8-74.7)	
High SES (n = 208)	31.7 (25.5-38.5)	68.3 (61.5-74.5)	
Parents/legal guardians' education level (%)			
No university studies (n = 561)	22.3 (18.9-26.0)	77.7 (74.0-81.1)	0.001
University studies (n = 538)	31.4 (27.5-35.5)	68.6 (64.5-72.5)	

*PF: physical fitness; SES: socioeconomic status. *Statistical significance at* $p < 0.05$*. Values are presented as percentage (95 % confidence interval).*

Table III. Adherence to Mediterranean diet according to inequality indicators (n = 1099)

Variables	Optimal MD (n = 487)	Improvement needed in MD (n = 612)	p
Gender (%)			
Boys (n = 576)	46.0 (41.9-50.2)	54.0 (49.8-58.1)	0.235
Girls (n = 523)	42.4 (38.2-46.8)	57.6 (53.2-61.8)	
Nationality (%)			
Spanish (n = 604)	47.2 (43.1-51.3)	52.8 (48.7-56.9)	0.034
Brazilian (n = 495)	40.8 (36.4-45.3)	59.2 (54.7-63.6)	
SES (%)			
Low SES (n = 362)	35.1 (30.2-40.2)	64.9 (59.8-69.8)	< 0.001
Medium SES (n = 529)	46.9 (42.6-51.2)	53.1 (48.8-57.4)	
High SES (n = 208)	53.8 (46.8-60.8)	46.2 (39.2-53.2)	
Parents/legal guardians' education level (%)			
No university studies (n = 561)	41.4 (37.2-45.6)	58.6 (54.4-62.8)	0.044
University studies (n = 538)	47.4 (43.1-51.7)	52.6 (48.3-56.9)	

*MD: Mediterranean diet; SES: socioeconomic status. *Statistical significance at* $p < 0.05$*. Values are presented as percentage (95 % confidence interval).*

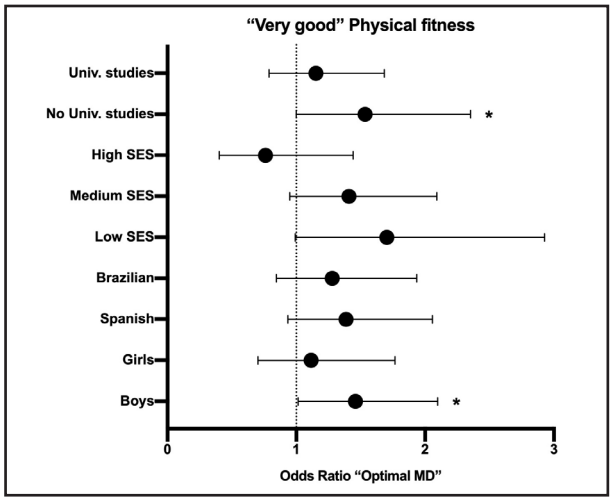

Figure 1.

Odds ratio of having very good physical fitness in relation to an optimal level of adherence to Mediterranean diet, stratified by gender, nationality, socioeconomic status, and parents/guardians' education level (Univ.: university; SES: socioeconomic status. **p*-value ≤ 0.05).

GENDER

The current study shows differences between boys and girls regarding proxy-reported PF and adherence to MD. Boys are represented in a higher proportion in the "very good" level of PF and in the "optimal" level of adherence to MD when compared with girls. Also, males who have a "very good" level of PF are more likely to have good MD. However, this association was not present in females. In this line, gender disparities in PF have been extensively informed by the scientific literature. A recent observational study (22) reported that boys presented higher odds to meet aerobic capacity fitness standards than girls in a sample of 15,052 children (average age, 10.7 years). Although the differences observed in the current study were obtained using proxy-reported data collected during the COVID-19 lockdown, results are consistent with the previous knowledge.

Also, it is important to highlight that a higher proportion of boys reported "very good" PF in comparison with girls ($p < 0.001$), while no differences between the proportion of boys and girls that reported "optimal MD" was observed ($p = 0.235$). A previous study suggests that an optimal adherence to MD is not enough to reduce cardiometabolic risk and it might be combined with higher levels of PF (8). Therefore, even though the proportion of girls with "optimal MD" in the current study is similar to the proportion of boys, this proportion of girls might not be sufficiently protected against cardiometabolic risk due to the level of PF reported.

NATIONALITY

Similar proportions of participants from both countries reported "very good" PF, while a higher proportion of Spanish participants reported "optimal MD" in comparison with their Brazilian counterparts. In line with this, the analysis of MD in Brazil is scarce yet, and the translation and cultural adaptation of the tool used in the current study is recent (23). Generally, Spain is one of the European countries reporting the lowest adherence to MD in both children and adolescents (20); however, the current study report almost half of Spanish participants with an "optimal" level of adherence to MD. Brazil is located in a different latitude and altitude, and their dietary patterns could differ from those related to MD in accordance with previous knowledge (24). Then, mixing these two countries in this study might have led to controversial results respect those expected for Mediterranean and not Mediterranean countries (25).

SOCIOECONOMIC STATUS AND PARENTAL EDUCATION LEVEL

The lower odds of reporting "very good" PF by reporting "optimal MD", the higher SES has been observed among the participants in the current study. However, participants with higher SES represent a higher proportion reporting "very good" PF ($p = 0.003$) and "optimal MD" ($p < 0.001$) with respect to the other two SES. These two facts are in accordance with previous studies reporting a lower performance in PF tests in children with lower SES (26) and also higher SES associated with higher adherence to MD (27). Also, due to the well-known relationship between SES and education level, it was expected to find similar results regarding parental education level. Hence, those participants with parents/legal guardians holding "university studies" reported a higher statistically significant proportion of participants with "very good" PF ($p = 0.001$) and a higher statistically significant proportion of participants with "optimal MD" ($p = 0.044$). However, participants with parents/legal guardians with "no university studies" had higher odds of "very good" PF when they reported "optimal MD" (OR = 1.5; 95 % CI, 1.0-2.4, $p = 0.05$) in comparison with the odds observed in the category "university studies" (OR = 1.2; 95 % CI, 0.8-1.7, $p = 0.464$). It is well-known the role of the mothers' education level in relationship with children and adolescents' dietary habits (27), and this fact could have influenced the observed results, but the current study did not register which of the parents completed the survey, therefore these results must be interpreted with caution. In addition, parental educational level mediates the association between adherence to MD and obesity (28), therefore this social factor must be considered in these relationships.

STRENGTHS AND LIMITATIONS

The current study presents the strength of analyzing the association during the COVID-19 lockdown, when social inequalities have been shown as strong factors affecting differences between people. Also, it is relevant to highlight that this study used a questionnaire to report PF and results are in accordance with a previous study using field tests (22), which could be relevant to test larger sample size since the use of questionnaires requires less time in comparison with field tests.

Also, there are limitations to be recognized. This is a cross-sectional study; therefore, conclusions should be interpreted with caution. Also, each country adopted different restrictions that could have affected in different ways to the workers in each SES. Besides, due to the impossibility to assess PF using field test, the current study used a proxy-reported PF questionnaire, which has limitations to report the real PF status. In addition, we recorded only the education level of the person that completed the survey when it has been observed that mother's education is a determinant of the MD (20).

CONCLUSIONS

There was more likely to report a "very good" PF during the COVID-19 lockdown when the participant was classified as "optimal MD" in boys in comparison with the odds observed in girls. In addition, an association between "very good" PF and "optimal MD" was observed in participants with parents/legal guardians with "no university studies".

These results must be considered with caution because there is controversy with the scientific literature before the COVID-19

pandemic; however, the new situation observed during the lockdown could have affected these relationships.

FUNDING

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Supplementary Table I. STROBE checklist

	Item No.	Recommendation	Page No.
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	391
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	391
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	392
Objectives	3	State specific objectives, including any prespecified hypotheses	392
Methods			
Study design	4	Present key elements of study design early in the paper	392
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	392
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	392
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	393
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	393
Bias	9	Describe any efforts to address potential sources of bias	393
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	393
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	393
		(b) Describe any methods used to examine subgroups and interactions	393
		(c) Explain how missing data were addressed	-
		(d) If applicable, describe analytical methods taking account of sampling strategy	-
		(e) Describe any sensitivity analyses	393
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	392
		(b) Give reasons for non-participation at each stage	392
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	393
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers of outcome events or summary measures	393-5
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95 % confidence interval). Make clear which confounders were adjusted for and why they were included	393-5
		(b) Report category boundaries when continuous variables were categorized	393
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	393-4

(Continues on next page)

Supplementary Table I (Cont.). STROBE checklist

	Item No.	Recommendation	Page No.
Discussion			
Key results	18	Summarise key results with reference to study objectives	396-7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	397
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	397
Generalizability	21	Discuss the generalizsability (external validity) of the study results	397
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	391

Supplementary Table II. Odds ratio of having very good physical fitness in relation to an optimal level of adherence to Mediterranean diet, stratified by inequality indicators

Parameter		Very good PF
Boys		
MD adherence	Optimal MD	1.4 (1.0-2.1)*
	Improvement needed in MD	1
Girls		
MD adherence	Optimal MD	1.1 (0.7-1.8)
	Improvement needed in MD	1
Spanish		
MD adherence	Optimal MD	1.4 (0.9-2.0)
	Improvement needed in MD	1
Brazilian		
MD adherence	Optimal MD	1.3 (0.8-1.9)
	Improvement needed in MD	1
Low SES		
MD adherence	Optimal MD	1.7 (0.9-2.9)
	Improvement needed in MD	1
Medium SES		
MD adherence	Optimal MD	1.4 (0.9-2.1)
	Improvement needed in MD	1
High SES		
MD adherence	Optimal MD	0.8 (0.4-1.4)
	Improvement needed in MD	1
No university studies		
MD adherence	Optimal MD	1.5 (1.0-2.3)*
	Improvement needed in MD	1
University studies		
MD adherence	Optimal MD	1.1 (0.8-1.7)
	Improvement needed in MD	1

*MD: Mediterranean diet; SES: socioeconomic status. Values are odds ratios and 95 % confidence intervals. *p-value ≤ 0.05.*

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Trabajo Original

Epidemiología y dietética

Lifestyle and cardiometabolic risk factors in the ethnic and non-ethnic population > 15 years of age: results from the National Chilean Health Survey 2016-2017

Estilo de vida y factores de riesgo cardiometabólico en la población étnica y no étnica > 15 años: resultados de la Encuesta Nacional de Salud de Chile 2016-2017

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Abstract

Background: lifestyle and cardiometabolic risk factors information is scarce regarding youth and adults of Latin-American ethnics.

Objective: the primary aim was to describe the lifestyle and cardiometabolic risk factors for arterial hypertension (HTN) and diabetes in ethnic Latin-American groups (Mapuche and Aymara) and other non-ethnics > 15 years of age in the Chilean population. A secondary aim was to determine the association between physical activity 'intensity' with HTN and diabetes markers.

Material and methods: a representative sample from the National Chilean Health Survey 2016-2017, included Mapuche (EG-Map; women n = 166, men n = 300; total n = 466), Aymara (EG-Aym; women n = 96, men n = 55; total n = 151), and a non-ethnic population group (No-EG; women n = 2057, men n = 3445; total n = 5502). The main outcomes were; systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (GL), and secondary outcomes were other anthropometric, lipid profile, and lifestyle parameters.

Results: GL was significantly associated with nutrition (0.9 %, $p < 0.0001$), tobacco and alcohol habits (0.6 %, $p < 0.0001$). SBP was significantly associated with nutrition (whole-grains 0.04, $p = 0.001$; water consumption 0.07, $p < 0.0001$), sleep hygiene (week 0.04, $p = 0.030$; on weekends -0.04, $p = 0.026$), and alcohol consumption (-0.06, $p < 0.0001$).

Conclusion: in conclusion, lifestyle differences among Mapuche and Aymara ethnic groups in comparison with non-ethnic Chilean peers > 15 years are significantly associated with blood pressure and glycemia.

Keywords:

Obesity. Physical inactivity. Healthy lifestyle. Ethnicity.

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Informed consent statement: all participants who participated provided their written informed consent.

Data availability statement: all information, files and database are freely available from the Chilean Health Minister at http://epi.minsal.cl/bases-de-datos/.

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

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Resumen

Antecedentes: la información sobre estilos de vida y factores de riesgo cardiometabólico es escasa en jóvenes y adultos de etnia latinoamericana.

Objetivo: el objetivo principal fue describir el estilo de vida y los factores de riesgo cardiometabólico para la hipertensión arterial (HTA) y la diabetes en grupos étnicos latinoamericanos (Mapuche y Aymara) y otros no étnicos > 15 años de la población chilena. Un objetivo secundario fue determinar la asociación de la "intensidad" de la actividad física con la HTA y los marcadores de diabetes.

Material y métodos: muestra representativa de la Encuesta Nacional de Salud de Chile 2016-2017, compuesta por mapuches (EG-Map; mujeres n = 166, hombres n = 300; total n = 466), aymaras (EG-Aym; mujeres n = 96, hombres n = 55; total n = 151) y un grupo poblacional no étnico (No-GE; mujeres n = 2057, hombres n = 3445; total n = 5502). Las principales evaluaciones fueron la presión arterial sistólica (PAS), la presión arterial diastólica (PAD) y la glucosa plasmática en ayunas (GL), y los resultados secundarios fueron otros parámetros antropométricos, del perfil lipídico y del estilo de vida.

Resultados: la GL se asoció significativamente a los hábitos nutricionales (0,9 %, $p < 0,0001$) y los hábitos de tabaco y alcohol (0,6 %, $p < 0,0001$). La PAS se asoció significativamente con la nutrición (cereales integrales 0,04, $p = 0,001$; consumo de agua 0,07, $p < 0,0001$), higiene del sueño (semana 0,04, $p = 0,030$; fines de semana -0,04, $p = 0,026$) y consumo de alcohol (- 0,06, $p < 0,0001$).

Conclusión: en conclusión, las diferencias de estilo de vida entre las etnias mapuche y aymara en comparación con sus pares chilenos no étnicos mayores de 15 años se asocian significativamente con la presión arterial y la glucemia**.**

Palabras clave:

Obesidad. Inactividad física. Estilo de vida saludable. Etnicidad.

INTRODUCTION

The lifestyle of the population is highly associated with the current increase in the prevalence of cardiometabolic disease *(i.e.,* diseases that compromise both cardiovascular and metabolic systems) in young and adult populations, including arterial hypertension (HTN) (1) and diabetes (2). Physical activity (PA) and healthy nutrition are key environmental factors to preserve good cardiometabolic health in adolescents and adults (3-5). On the other hand, sleep hygiene (*i.e.,* sleeping a sufficient amount of hours per each 24 h cycle) (6,7), and avoiding tobacco and alcohol consumption have been described additionally as important modifiable risk factors contributors to HTN and diabetes in adolescents and adults (8). More recently, it was reported a 26.9 % of HTN prevalence, and 11.2 % prevalence of diabetes in the non-ethnic Latin American adult population (1). On the other hand, ethnic young cohorts have shown recently a worrying 35.9 % prevalence of HTN in comparison with their non-ethnic peers (11.6 %) (9).

Following this, and as a relevant component of a healthy lifestyle, PA practice at different 'intensities' (*i.e.*, vigorous, moderate, or low) has been associated with lower cardiovascular risk in young (9) and adult populations (10,11), but also with better physical fitness (10,12). Additionally, fruit and vegetable intake frequency (*i.e.,* healthy nutrition) as well as water consumption is also a key modifiable element in avoiding HTN and diabetes in adolescents and adult Latin American populations (13). In this sense, although there is important evidence in the Chilean population about lifestyle and its relationship with cardiometabolic disease markers of HTN (*i.e.,* systolic [SBP], diastolic [DBP] blood pressure), and diabetes (fasting glycemia [GL]) in both adolescents and adults, there is a scarcity of evidence about these markers in the population of ethnic Latin American groups such as the Mapuche —*people of the land* in the Mapudungun language— and Aymara —*the language of many years* in the Jayamararu language. From a demographic perspective of the national Chilean survey, there are around 2,185,729 individuals in the Chilean population who declare themselves to be of some native ethnic group, this amount representing 12.8 % of the total Chilean population. Of this percentage (*i.e.*, 12.8 %), 79.8 % correspond to Mapuche, and 7.2 % to Aymara ethnicity, among others (14), both being the major representatives of ethnicity in the country. Along this line, previous studies have suggested a worrying increase in insulin resistance in the adult Mapuche population (15), and other reports have shown higher levels of blood pressure (16), and fasting glucose (17), thus increasing the risk of HTN and diabetes. Epidemiologically, preliminary studies have described that adults of Mapuche ethnic origin in Chile report a 24.5 % of HTN prevalence (18), while 18.5 % was described for the Aymara ethnic group (19). Other reports describe the diabetes prevalence in Mapuche ethnicity as 8.2 %, and 6.9 % for Aymara (17). On the other hand, despite lifestyle factors such as PA and nutrition and their known association with HTN and diabetes markers, other evidence has suggested that ethnic groups who are living in urban areas show a major cardiometabolic risk in comparison with their rural peers, with living in urban areas being attributed a greater role than lifestyle factors for these diseases (15); it is of great interest to study these groups in terms of increasing health prevention strategies.

Unfortunately, these previous studies are isolated, have been developed in one or another of the 15 geographic regions of Chile, and do not contain major representative data of the whole country. Thus, there is a scarcity of studies reporting a representative sample of these groups (*i.e.,* at least from a geographical perspective) including ethnic adolescents and adult populations such as the Mapuche and Aymara groups, describing lifestyle (*i.e.,* PA 'intensity', nutritional, water consumption, sleep hygiene, tobacco, and alcohol habits), and testing their association with HTN and diabetes markers. Thus, the primary aim of this study was to describe the lifestyle and cardiometabolic risk factors for arterial hypertension (HTN) and diabetes in ethnic Latin American Mapuche, Aymara, and other non-ethnic Chilean individuals > 15 years of age. A secondary study was to determine the association between physical activity intensity with HTN and diabetes markers.

MATERIALS AND METHODS

STUDY DESIGN

A cross-sectional national secondary study was developed with the National Health database surveys (NHS) 2016-2017 of Chile. The NHS is a prevalence, and multi-stage national study that includes representatives of the Chilean geographical country, and is applied in multi-stages, in person at home with families using a cross-sectional random, stratified-by-conglomerates survey with inclusion of the population ≥ 15 years old, with or without an ethnic origin, and living in particular homes, from urban to rural areas of the 15 geographical regions of this country.

Of 6,233 thousand participants included in the NHS 2016-2017 (*i.e.,* all of this population are part of the Chilean public health system), a total of $n = 731$ participants belonged in some of the major eight ethnic groups, including Aymara $n = 151$, Rapa-Nui $n = 1$, Quechua $n = 14$, Mapuche $n = 466$, Atacameño Linkánanta $n = 36$, Coya $n = 17$, Kawésqar Alacalufes $n = 3$, and Diaguita $n = 43$), with the rest of participants being identified as a non-ethnic adolescent (≥ 15 years)/adult population ($n = 5.502$) ascribed to the Chilean public health system. The present study included and analyzed the information related only to the Mapuche ethnic group (EG-Map; men $n = 166$, women $n = 300$), Aymara ethnic group (EG-Aym; men $n = 55$, women $n = 96$), and the population of non-ethnic origin (No-EG; men $n = 2,057$, women $n = 3,445$). The study protocol was approved by the Ethical Committee of the Escuela de Medicina de la Pontificia Universidad Católica de Chile (16-019), and all participants signed an informed consent (20).

LIFESTYLE PARAMETERS

Characterization of physical activity and sedentary time

To determine PA levels, the "*Global Physical Activity Questionnaire*" version 2 was applied (GPAQ v2) (20). Thus, PA was described according to its intensity as follows; *i*) PA of 'vigorous'-intensity (PA_{VI}); *ii*) PA of 'moderate'-intensity (PA_{MI}), and finally *iii*) PA of 'light'-intensity (PA_{LI}), which corresponded to all those activities such as walking, transport, or cycling.

Determination of nutrition frequency

The NHS 2016-2017 includes the GABA criteria as follows; *i)* fish consumption 2 times/week (*fish and seafood*), *ii*) dairy products in 3 servings/day (*milk, cheese, or yogurt*), *iii*) legumes consumption 2 times/week (*legumes/beans*), *iv*) consumption of fruits/vegetables 5 servings/day, and finally *vi*) drinking water 6 glasses/day (21). This information was obtained from the three Mapuche, Aymara, and non-ethnic adult groups by self-report.

Determination of sleep hygiene, tobacco habit, and alcohol consumption

Other lifestyle parameters were registered and reported as sleep time using the following categorization; sleep hygiene (< 7 h/day; 7 to 9 h/day; and > 9 h/day), tobacco (*Yes, 1 or more cigarette/day; Yes, occasionally, < 1 cigarette/day; No, I stopped smoking; and No, I have never smoked*), and alcohol consumption (*Never;* ≤ 1 *cups/week; 2 to 3 cups/week; and* ≥ 4 *cups/week*).

All information on nutrition frequency, sleep hygiene, tobacco habit, and alcohol consumption was obtained by self-report, using the validated questionnaire of the Chilean NHS 2016-2017.

Measurement of blood pressure (main outcome)

As HTN markers, SBP and DBP were measured in both arms twice during 30 sec, and in different days (at least 1 day between measurements) by the professional nursing staff of the public health center. In this study, these measurements were averaged and registered for subsequent analyses. After that, both SBP/DBP values were used to classify HTN prevalence in % considering categories of 'normotension, elevated blood pressure, HTN stage 1 (SBP ≥ 140, or PAD ≥ 90 mmHg), and HTN stage 2, following standard current procedures (22).

Measurement of fasting glycemia (main outcome), and lipid profile outcomes

As diabetes marker, fasting plasma glucose (GL) was used. This outcome was measured in conditions of at least 8 hrs of fasting state and applied similarly to previous studies (21), following the Chilean clinical guide (23).

Additionally, we also included the metabolic markers of dyslipidemia (total cholesterol (Tc), low-density lipid cholesterol (LDL-c), high-density lipid cholesterol (HDL-c), and plasma triglycerides (Tg) as additional information. As categorical information, we also included the metabolic syndrome diagnoses.

Anthropometric measurements

To assess the body weight, there was used a digital scale OMRON® (model HN 289 OMRON Corporation, Kioto, Japon) with a sensitivity of 100 g, and a maximum weight register of 150 kg). Height was measured by a metal tape, a square, and adhesive tape (*i.e.*, to secure in a wall or gate). Waist circumference was measured using inextensible and flexible tape. The nutritional state was established by body mass index (BMI) following adult recommendations as follows; underweight < 18.5 kg/m^2; normal weight: 18.5-24.9 kg/m^2; overweight: 25.0-29.9 kg/m^2 and ≥ 30.0 kg/m^2 to obesity. There was also included informa-

tion regarding the nutritional state, (*underweight, normal weight, overweight, obesity*) (24).

STATISTICAL ANALYSES

Data of socio-demographic and cardiometabolic characteristics are shown as means (95 % confidence interval [CI]) for continuous variables, and numbers (proportion, %) for categorical variables. To continuous outcomes, the univariate test was applied to establish the significance of interaction by groups and to compare the difference between groups, Sidak's *post-hoc* was used to compare both ethnic EG-Map and EG-Aym *versus* the non-ethnic group. Age, BMI, sex, height, and region were used as co-variables for continuous outcomes. For categorical outcomes Pearson's *Chi*-squared test was applied to determine differences in frequencies, and Somer's d-test. Additionally, the association between lifestyle factors of PA 'intensity', as well as the nutrition, sleep hygiene, and other secondary outcomes were associated with SBP, DBP, and GL using linear regression analyses by 4-models; model 1 (PA_{LI}, PA_{MI}, PA_{VI}, min/day), model 2 (seafood consumption, dairy products, whole grains, legumes, greens and vegetables, and water consumption), model 3 (sleep time in the week, and the weekends), and model 4 (tobacco and alcohol habits). These analyses were applied independently to describe PA 'intensity', nutrition, sleep hygiene, tobacco, and alcohol consumption predictive weight. All analyses were carried out using the SPSS version 28 software. All procedures described were developed following the technical recommendations of the Guideline of Application F2 of the NHS 2016-2017 (25).

RESULTS

COMPARISON OF DESCRIPTIVE DATA ACCORDING TO GROUPS

The characteristics of the Mapuche, Aymara, and non-ethnic groups are shown in table I. For continuous outcomes, there were significantly different values of age, body weight, height, BMI, waist circumference, fasting glycemia, SBP/DBP, Tc, LDL-c, HDL-c, and Tg between EG-Map, and EG-Aym versus (*vs.*) the No-EG group (Table I). For categorical outcomes, there were significant differences in the area of living (urban, rural), educational level, and nutritional state in EG-Map, and EG-Aym *vs.* No-EG (Table I).

Table I. Descriptive characteristics of the > 15-year-old Chilean population of ethnic Mapuche, Aymara, and non-ethnic peers from the National Health Survey 2016-2017

Outcomes	EG-Map[a]	EG-Aym[b]	No-EG[x]	Sample size (EG-Map, EG-Aym, No-EG)	*p*-value interaction
Sex					
Women, *n* = (%)	166 (35.6 %)	96 (63.6 %)	2057 (37.4 %)		$p = 0.748^{\#}$
Men, *n* = (%)	300 (64.4 %)	55 (36.4 %)	3445 (62.6 %)		
Area of living					
Urban, *n* = (%)	320 (68.7 %)	122 (80.8 %)	4711 (85.6 %)		$p < 0.0001^{\#}$
Rural, *n* = (%)	146 (31.3 %)	29 (19.2 %)	791 (14.4 %)		
Educational level					
< 8 years, *n* = (%)	124 (26.7 %)	22 (15.2 %)	1308 (24.0 %)		$p = 0.025^{\#}$
8 to 12 years, *n* = (%)	266 (57.2 %)	80 (55.2 %)	2907 (53.3 %)		
≥ 13 years, *n* = (%)	75 (16.1 %)	43 (29.7 %)	1237 (22.7 %)		
Anthropometry					
Age, years	41.7 (39.8; 43.6)[x]	44.8 (41.4, 48.2)	49.8 (49.3; 50.4)	(*n* = 408; *n* = 128; *n* = 4895)	$p = 0.011^{\dagger}$
Body weight, kg	72.9 (72.2; 73.5)[x]	72.7 (71.5; 73.9)	74.1 (73.9; 74.3)	(*n* = 408; *n* = 128; *n* = 4895)	$p < 0.0001^{\dagger}$
Height, cm	158.6 (157.9; 159.3)	158.2 (157.0; 159.5)	159.7 (159.5; 159.9)	(*n* = 408; *n* = 128; *n* = 4895)	$p < 0.0001^{\dagger}$
BMI, kg/m^2	29.8 (29.3; 30.3)[x]	29.2 (28.2; 30.2)	28.8 (28.7; 29.0)	(*n* = 408; *n* = 128; *n* = 4895)	$p < 0.0001^{\dagger}$

(Continues on next page)

Table I (Cont.). Descriptive characteristics of the > 15-year-old Chilean population of ethnic Mapuche, Aymara, and non-ethnic peers from the National Health Survey 2016-2017

Outcomes	EG-Map[a]	EG-Aym[b]	No-EG[x]	Sample size (EG-Map, EG-Aym, No-EG)	*p*-value interaction
Nutritional state					
Underweight, *n* = (%)	4 (1.0 %)	1 (0.8 %)	64 (1.3 %)	(*n* = 408; *n* = 128; *n* = 4895)	*p = 0.004*[#]
Normal weight, *n* = (%)	89 (21.8 %)	27 (21.1 %)	1087 (22.4 %)		
Overweight, *n* = (%)	123 (30.1 %)	55 (43.0 %)	1867 (38.5 %)		
Obesity, *n* = (%)	192 (47.1 %)	45 (35.2 %)	1827 (37.7 %)		
Waist circumference (cm)	92.5 (91.7; 93.9)[x]	92.5 (91.1; 93.9)[x]	93.7 (93.5; 93.9)	(*n* = 403; *n* = 128; *n* = 4833)	*p = 0.003*[†]
Blood glucose					
Fasting glycaemia, mg/dL	96.3 (92.6; 99.9)	98.1 (91.5; 104.7)	100.3 (99.2; 101.3)	(*n* = 383; *n* = 120; *n* = 4474)	*p* = 0.349[†]
Diabetes prevalence					
Normoglycaemia, %	300 (77.5 %)	92 (76.7 %)	3331 (73.8 %)		*p* = 0.172[#]
Prediabetes, %	63 (16.3 %)	20 (16.7 %)	798 (17.7 %)		
Diabetes, %	24 (6.2 %)	8 (6.7 %)	385 (8.5 %)		
Blood pressure					
SBP, mmHg	122 (120.7; 124.9)[x]	119.5 (115.8; 123.2)[x]	127.7 (127.1; 128.3)	(*n* = 408; *n* = 128; *n* = 4841)	*p = 0.005*[†]
DBP, mmHg	73 (72.0; 74.0)[x]	70.0 (68.2; 71.8)[x]	78.4 (74.5; 75.1)	(*n* = 408; *n* = 128; *n* = 4841)	*p = 0.003*[†]
Hypertension prevalence					
Normotension, %	190 (46.3 %)	86 (66.7 %)	2037 (41.8 %)		
Elevated BP, %	96 (23.4 %)	18 (14.0 %)	982 (20.1 %)		*p < 0.0001*[#]
HTN stage 1, %	56 (13.7 %)	11 (8.5 %)	652 (13.4 %)		
HTN stage 2, %	68 (16.6 %)	14 (10.9 %)	1203 (24.7 %)		
Lipid profile					
Tc, mg/dL	173.6 (168.7; 178.6)[x]	180 (171.7; 189.0)	182.1 (180.7; 183.5)	(*n* = 260; *n* = 86; *n* = 3253)	*p = 0.034*[†]
LDL-c, mg/dL	100.4 (96.3; 104.6)[bx]	106.0 (98.6; 113.3)	105.1 (103.9; 106.3)	(*n* = 259; *n* = 85; *n* = 3230)	*p = 0.003*[†]
HDL-c, mg/dL	48.0 (46.5; 49.6)[b]	45.8 (43.0; 48.5)	47.8 (47.4; 48.3)	(*n* = 260; *n* = 86; *n* = 3253)	*p = 0.002*[†]
Tg, mg/dL	131.0 (119.7; 142.4)[bx]	149.6 (129.7; 169.9)	145.0 (141.1; 148.1)	(*n*=263; *n*=86; *n*=3286)	*p = 0.002*[†]
Metabolic syndrome					
Yes, *n* = (%)	149 (61.8 %)	46 (58.2 %)	1675 (54.2 %)		*p* = 0.174[#]
No, *n* = (%)	92 (38.2 %)	33 (41.8 %)	1417 (45.8 %)		

Data are shown as means and 95 % confidence intervals (95 % CI) for continuous outcomes and as number (n) *and percentages (%) for categorical outcomes. Groups are described as: EG-Map: Mapuche ethnic group; EG-Aym: Aymara ethnic group; No-EG: no ethnic group. Outcomes are described as: BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; Tc: total cholesterol; LDL-c: low-density lipid cholesterol; HDL-c: high-density lipid cholesterol; Tg: triglycerides.* [†]*Data analyzed by univariate test. aSignificantly different* versus *EG-Map at* p < *0.05, bSignificantly different* versus *EG-Aym at* p < *0.05. xSignificantly different* versus *No-EG at p < 0.05 by Sidak's* post-hoc. [#]*Categorical data analyzed by Pearson's* Chi-*squared test at* p < *0.05. Italics values denote significant between-group interaction at* p < *0.05.*

DESCRIPTION AND COMPARISON OF LIFESTYLE DATA ACCORDING TO GROUPS

In the characteristics of the PA 'intensity' (measured by the GPAQ-v2 questionnaire), there were significant differences among groups in the PA_{VI}, PA_{MI} (Table II). In the nutritional parameters, there were significant differences in the frequency of 'milk, cheese, or yogurt', 'whole grains, bread, foods with whole-meal flours', 'legumes/beans', 'fruits' and 'vegetables', as well as in 'water consumption' (Table II). There were significant differences in the sleep hygiene (hours of sleep on weekends, the adherence to sleep hygiene, and tobacco habit and alcohol consumption between EG-Map, and EG-Aym *versus* No-EG (Table II).

Table II. Lifestyle parameters (physical activity, diet, water consumption, sedentary time, sleep hygiene, and tobacco/alcohol habits in the Chilean > 15-year-old population of ethnic Mapuche, Aymara, and non-ethnic peers from the National Health Survey 2016-2017

Outcomes	EG-Map	EG-Aym	No-EG	*p*-value
PA 'intensity'				
PA_{VI}				
Yes, n = (%)	79 (17.0 %)	17 (11.3 %)	740 (13.4 %)	$p = 0.341^{\#}$
No, n = (%)	387 (83.0 %)	134 (88.7 %)	4762 (86.6 %)	
PA_{MI}				
Yes, n = (%)	123 (26.4 %)	21 (13.9 %)	1496 (27.2 %)	$p = 0.002^{\#}$
No, n = (%)	343 (76.6 %)	130 (86.1 %)	4006 (72.8 %)	
PA_{LI}				
Yes, n = (%)	312 (67.0 %)	88 (58.3 %)	3530 (64.2 %)	$p = 0.014^{\#}$
No, n = (%)	154 (33.0 %)	63 (41.7 %)	1972 (35.0 %)	
Nutrition				
'Fish'				
> 1 time/week, n = (%)	46 (9.9 %)	21 (13.9 %)	539 (9.8 %)	
1 time/week, n = (%)	128 (27.5 %)	45 (29.8 %)	1838 (33.4 %)	$p = 0.244^{\#}$
< 3 times/month, n = (%)	114 (24.5 %)	36 (23.8 %)	1234 (22.4 %)	
< 1 time/month, n = (%)	178 (38.2 %)	49 (32.5 %)	1891 (34.4 %)	
'Milk, cheese, or yogurt'				
≥ 3 times/day, n = (%)	27 (5.8 %)	7 (4.6 %)	340 (6.2 %)	
< 3 times/day, n = (%)	30 (6.4 %)	9 (6.0 %)	432 (7.9 %)	
1 time/day, n = (%)	134 (28.8 %)	35 (23.2 %)	2001 (36.4 %)	$p < 0.0001^{\#}$
Every 3 days, n = (%)	88 (18.9 %)	50 (33.1 %)	974 (17.7 %)	
At least 1 time/week, n = (%)	100 (21.5 %)	35 (23.2 %)	1023 (18.6 %)	
At least 1 time/month, n = (%)	42 (9.0 %)	9 (6.0 %)	288 (5.2 %)	
Never, n = (%)	45 (9.7 %)	6 (4.0 %)	444 (8.1 %)	

(Continues on next page)

Table II (Cont.). Lifestyle parameters (physical activity, diet, water consumption, sedentary time, sleep hygiene, and tobacco/alcohol habits in the Chilean > 15-year-old population of ethnic Mapuche, Aymara, and non-ethnic peers from the National Health Survey 2016-2017

Outcomes	EG-Map	EG-Aym	No-EG	*p*-value
Nutrition				
'Whole-grain cereals, whole-grain bread, foods with whole-grain flours'				
≥ 1 time/month, n = (%)	8 (1.7 %)	2 (1.3 %)	136 (2.5 %)	
Everyday, n = (%)	49 (10.5 %)	15 (9.9 %)	782 (14.2 %)	
Every 3 days, n = (%)	35 (7.5 %)	16 (10.6 %)	428 (7.8 %)	*p < 0.0001*[#]
At least 1 time/week, n = (%)	44 (9.4 %)	15 (9.9 %)	663 (12.1 %)	
At least 1 time/month, n = (%)	40 (8.6 %)	20 (13.2 %)	467 (8.5 %)	
Never, n = (%)	290 (62.2 %)	83 (55.0 %)	3026 (55.0 %)	
'Legumes/beans'				
≥ 2 times/week, n = (%)	113 (24.2 %)	43 (28.5 %)	1455 (26.4 %)	
At least 1 time/week, n = (%)	236 (50.6 %)	80 (53.0 %)	2741 (49.8 %)	*p = 0.046*[#]
1-3 times/week, n = (%)	58 (12.4 %)	20 (13.2 %)	625 (11.4 %)	
< 1 time/week, n = (%)	59 (12.7 %)	8 (5.3 %)	681 (12.4 %)	
'Fruits'				*p < 0.0001*[†]
Days/week	3.9 (3.7; 4.1)[x]	4.0 (3.6; 4.4)	4.4 (4.3; 4.4)	
'Vegetables'				*p < 0.0001*[†]
Days/week	5.1 (4.9; 5.3)	5.4 (5.1; 5.7)	5.4 (5.4; 5.5)	
'Water consumption'				*p < 0.0001*[†]
Number of water glasses, glasses/day	3.8 (3.5; 4.1)[x]	4.3 (3.7; 4.8)	4.1 (4.0; 4.2)	
Adherence to sleep hygiene time				
< 7 h/day, n = (%)	95 (20.4 %)	38 (25.2 %)	1559 (28.3 %)	*p = 0.008*[#]
7 to 9 h/day, n = (%)	265 (56.9 %)	92 (60.9 %)	2928 (53.2 %)	
> 9 h/day, n = (%)	106 (22.7 %)	21 (13.9 %)	1015 (18.4 %)	
Tobacco habit				
Yes, 1 or more cigarette/day, n = (%)	83 (17.8 %)	18 (11.9 %)	1209 (22.0 %)	
Yes, ocationally, < 1 cigarette/day, n = (%)	39 (8.4 %)	10 (6.6 %)	374 (6.8 %)	*p < 0.0001*[#]
No, I stopped smoking, n = (%)	121 (26.0 %)	19 (12.6 %)	1304 (23.3 %)	
No, never, n = (%)	223 (47.9 %)	104 (68.9 %)	2615 (47.5 %)	
Alcohol consumption				
Never, n = (%)	138 (33.7 %)	42 (32.6 %)	1774 (36.4 %)	
≤ 1 glass/week, n = (%)	174 (42.5 %)	58 (45.0 %)	1719 (35.2 %)	*p < 0.0001*[#]
2 a 3 glasses/week, n = (%)	20 (4.9 %)	4 (3.1 %)	250 (5.1 %)	
≥ 4 glasses/week, n = (%)	6 (1.5 %)	2 (1.6 %)	128 (2.6 %)	

Data are shown as number (n) and percentage (%). Groups are described as: EG-Map: Mapuche ethnic group; EG-Aym: Aymara ethnic group; No-EG: No-ethnic group. Outcomes are described as: PAVI: physical activity of vigorous intensity; PAMI: physical activity of moderate intensity; PALI: physical activity of light intensity. [#]Denotes categorical data analysed by Pearson's Chi square test at p < 0.05. Italics values denote significant between-group interaction at p < 0.05. [†]Analysed by univariate test at p < 0.05. Italics values denote significant between-group interaction at p < 0.05.

ASSOCIATION OF PA 'INTENSITY' WITH HTN AND DIABETES OUTCOMES

For predicting blood pressure from PA 'intensity', lineal regression analyses revealed only PA of 'moderate' intensity predicted significantly DBP in model 1 (PA_{MI}, $p = 0.008$) (Table III). The diabetes marker of GL was significantly associated with model 2 (nutrition 0.9 %, $p < 0.0001$), and model 4 (tobacco and alcohol habits 0.6 %, $p < 0.0001$). In another lifestyle, SBP has significantly associated with model 2 nutrition (whole grains, water consumption), model 3 sleep hygiene, and model 4 tobacco, all $p < 0.001$), DBP was significantly associated with model 2 nutrition (whole-grains, legumes, and water consumption), model 3 sleep hygiene (sleep time in the week, and weekends), and model 4 tobacco, all $p < 0.001$) (Table III). Fasting plasma glucose was significantly associated with model 2 nutrition (whole-grain, water consumption, $p < 0.001$), model 3 sleep hygiene (sleep time on weekends, $p = 0.026$), and model 4 alcohol habits, $p < 0.0001$) (Table III).

Table III. Association of four models of lifestyle outcomes with hypertension and diabetes markers (SBP, DBP, and GL) in Chileans of ethnic Mapuche, Aymara, or non-ethnic background > 15 years old, from the National Chilean Health Survey 2016-2017

Models 'SBP' β (95 % CI)		***p*-value**
Model 1: PA 'intensity'		
PA_{VI}, min/wk	0.17 (-0.26; 2.29)	$p = 0.152$
PA_{MI}, min/wk	0.23 (-0.03; 4.84)	$p = 0.053$
PA_{LI}, min/wk	-1.11 (-4.23; 1.48)	$p = 0.341$
Model 2: Nutrition		
Fish and seafood, times/wk	0.002 (-0.52; 0.61)	$p = 0.883$
milk, cheese, or yogurt, times/wk	-0.006 (-0.46; 0.29)	$p = 0.655$
whole-grain cereals, whole-grain bread, foods with whole-grain flours, times/wk	0.12 (1.37; 2.10)	*p < 0.0001*
Legumes/beans, times,wk	-0.06 (-2.16; -0.92)	*p < 0.0001*
Fruits/vegetables, times/wk	-0.01 (-0.40; 0.14)	$p = 0.339$
Water consumption, glasses/day	-0.04 (-0.48; -0.12)	*p = 0.001*
Model 3: Sleep hygiene		
Sleep time in the week, h	0.12 (1.23; 2.18)	*p < 0.0001*
Sleep time on weekends, h	-0.15 (-2.22; -1.40)	*p < 0.0001*
Model 4: Tobacco/alcohol		
Tobacco, cig/day	0.09 (1.27; 2.26)	*p < 0.0001*
Alcohol, glasses/wk	0.002 (-0.53; 0.64)	$p = 0.865$
'DBP' β (95 % CI)		***p*-value**
Model 1: PA 'intensity'		
PA_{VI}, min/wk	0.16 (-0.22; 1.27)	$p = 0.165$
PA_{MI}, min/wk	0.31 (0.51; 3.24)	*p = 0.008*
PA_{LI}, min/wk	-0.14 (-2.58; 0.63)	$p = 0.230$
Model 2: Nutrition		
Fish and seafood, times/wk	-0.01 (-0.47; 0.09)	$p = 0.186$
milk, cheese, or yogurt, times/wk	0.05 (0.19; 0.56)	*p < 0.0001*
whole-grain cereals, whole-grain bread, foods with whole-grain flours, times/wk	0.08 (0.35; 0.71)	*p < 0.0001*
Legumes/beans, times,wk	-0.02 (0.57; 0.04)	$p = 0.089$
Fruits/vegetables, times/wk	-0.01 (-0.18; 0.08)	$p = 0.481$
Water consumption, glasses/day	-0.03 (-0.42; -0.10)	*p = 0.001*

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Table III (Cont.). Association of four models of lifestyle outcomes with hypertension and diabetes markers (SBP, DBP, and GL) in Chileans of ethnic Mapuche, Aymara, or non-ethnic background > 15 years old, from the National Chilean Health Survey 2016-2017

Models 'SBP' β (95 % CI)		***p*-value**
Model 3: Sleep hygiene		
Sleep time in the week, h	0.01 (-0.15; 0.31)	$p = 0.505$
Sleep time on weekends, h	-0.06 (-0.59; -0.19)	*$p < 0.0001$*
Model 4: Tobacco/alcohol		
Tobacco, cig/day	0.007 (-0.17; 0.30)	$p = 0.594$
Alcohol, glasses/wk	0.08 (0.62; 1.19)	$p < 0.0001$
Predictors GL β (95 % CI)		***p*-value**
Model 1: PA 'intensity'		
PA_{VI}, min/wk	0.08 (-1.34; 2.63)	$p = 0.519$
PA_{MI}, min/wk	-0.01 (-4.12; 3.59)	$p = 0.891$
PA_{LI}, min/wk	-0.10 (-6.13; 2.48)	$p = 0.400$
Model 2: Nutrition		
Fish and seafood, times/wk	-0.005 (-1.18; 0.82)	$p = 0.722$
milk, cheese, or yogurt, times/wk	0.02 (-0.15; 1.19)	$p = 0.130$
whole-grain cereals, whole-grain bread, foods with whole-grain flours, times/wk	0.04 (0.41; 1.69)	*$p = 0.001$*
Legumes/beans, times,wk	-0.03 (-2.49; -0.31)	$p = 0.012$
Fruits/vegetables, times/wk	-0.02 (-0.83; 0.13)	$p = 0.158$
Water consumption, glasses/day	0.07 (0.53; 1.15)	*$p < 0.0001$*
Model 3: Sleep hygiene		
Sleep time in the week, h	0.04 (0.09; 1.77)	*$p = 0.030$*
Sleep time on weekends, h	-0.04 (-1.52; -0.09)	*$p = 0.026$*
Model 4: Tobacco/alcohol		
Tobacco, cig/day	0.01 (-0.43; 1.29)	$p = 0.331$
Alcohol, glasses/wk	-0.06 (-3.55; -1.49)	*$p < 0.0001$*

Data are shown as beta coefficient and 95 % CI. All analyses were adjusted by age, BMI, sex, height, and region. PAVI: physical activity of vigorous intensity; PAMI: physical activity of moderate intensity; PALI: physical activity of light intensity. Italics values denote a significant association between the independent outcome and the dependent outcome at $p < 0.05$.

DISCUSSION

The primary aim was to describe the lifestyle and cardiometabolic risk factors for HTN and diabetes in ethnic Latin American Mapuche, Aymara, and other non-ethnic > 15-year-old Chilean adolescents/adults. A secondary study was to determine the association between physical activity 'intensity' with HTN and diabetes markers. The main finding of this study related to the first aim is that; *i*) there are significant differences in some anthropometric, nutritional state, waist circumference, blood pressure, and lipid profile outcomes between EG-Map and EG-Aym in comparison with peers of No-EG, *ii*) being also significantly different the practice of different PA intensities, as PA of 'moderate', and 'light' intensity among groups, and to the second study aim concerns, *iii*) DBP was significantly associated with PA of 'moderate' intensity. These results were displayed with other lifestyle outcomes associated with SBP such as nutrition, sleep hygiene, and tobacco, or by contrast, DBP was also associated with nutrition, and sleep hygiene, and finally, GL was significantly associated with nutrition, and sleep hygiene and alcohol. Overall, there was a significant prevalence of HTN in the adolescents/adults who does not pertain to ethnic groups, who show higher SBP levels in relationship with ethnic peers of EG-Map and EG-Aym.

Although lifestyle parameters such as PA, and nutrition play a key role in health, in Chile evidence is scarce from adolescents and adult ethnic groups such as those of Mapuche and Aymara ethnicity that represent an important amount population (12.8 %) (14). Due to from > 15 years old young adolescents have autonomy in

their environmental behavior (*i.e.,* they take their PA patterns, nutrition, and sleep hygiene independently of adults), to increase the information about lifestyle and cardiometabolic risk factors from these ages could increase the approach for future public politics in terms of early education and prevention of HTN and diabetes.

Following this, increasing the information regarding these minorities through representative studies could increase their knowledge to prevent HTN and diabetes in minorities that live in urban environments that usually left their cultural lifestyle patterns. For example, in the present study, the main findings indicated that DBP was significantly associated with PA of 'moderate' intensity (Table III). In this sense, it is relevant to mention that Aymara ethnic groups are located in the north of Chile, which is characterized by higher temperatures, Mapuche groups are endemic in the central to southern portions of this country, characterized by a higher amount of rain and cold climate, and the non-ethnic population is located throughout the country's geography, where we presume that these climate factors are involved in the intensity of daily PA practice. On the other hand, in the PA of transport, usually termed also as 'active commuting', the main part of PA of low to moderate intensity can be achieved by active commuting in more developed countries, where it is well known that using vehicles as a means of transport, is highly associated to sedentary lifestyles and cardiometabolic risk factors (26). Thus, it could be relevant to increase public politics for a major promotion of active commuting using bikes or walking in urban environments, where road security and street infrastructure could increase the health promotion in ethnic and non-ethnic adolescents and adults.

Due to there were differences in the frequency of nutrition among groups, particularly in dairy products, cereals, legumes, fruits, vegetables, and water consumption (Table II), we presume that independent of cultural or ethnic factors, there have been reported that the daily nutrition is also modified due to residence at rural/urban areas, the socio-economic income (27), and including the educational level (28). On the other hand, it is well known that both tobacco (29) and alcohol consumption promotes dangerous health risks whereas preventive public health mechanisms are strongly known (30). Additionally, other more recently known risk factors such as low sleep hygiene (*e.g.,* 28.3 % of No-EG, reported to sleep < 7 hrs/day, where we presume that as this cardiometabolic risk indicator has been recently included in public health systems, there is low awareness in the adult population of this concern. For example, a low sleep time has been related to a wide variety of cardiometabolic alterations such as higher blood pressure or HTN (31), and higher fasting glucose levels of diabetes (32,33).

We observed that the No-EG group showed higher levels of SBP than ethnic groups EG-Map and EG-Aym. There are controversial findings in the literature, from the point of view that previous Latin-American studies have shown that ethnic minorities show elevated risk factors when these groups are living in urban contexts (15). Thus, we also presume that more than the 'ethnicity' factor, the 'urban living' could be a better factor explaining those markers of HTN and diabetes, due to the major possibilities of acquiring westernized habits (*i.e.*, spending sedentary time in jobs, to be physically inactive, to consume more sugar, salt, and poor fruits, vegetates and water, together with poor sleep hygiene [34]) are more characteristic of the city context. Additionally, urbanization has been previously associated with lower possibilities of active commuting as we have mentioned, which is related to more diabetes prevalence for example (5,35). Due to these concerns, is that it has been proposed better neighbourhood regulations that favour more active living in communities, including more green areas, and better possibilities for active commuting (36). However, by contrast, other studies have reported that more than living in urban or rural areas, job occupation is a major factor associated with the prevalence of risk factors for HTN and diabetes in the adult population (37).

From a more general point of view, higher SBP levels in Chilean population are not new, because different isolated previous studies developed in ethnic young (9,38), adults (15,39), and non-ethnic populations have alerted this situation (1,2). For example, our research team has previously shown that schoolchildren of Mapuche ethnicity showed higher levels of SBP, and thus also a higher prevalence of HTN (38), being more recently these findings corroborated and complemented with sex differences in major risk of ethnic groups (40). The significance of our findings is that this is the first Chilean national study that includes lifestyle and cardiometabolic risk factors for HTN and diabetes including the two major ethnic groups, the Mapuche and Aymara populations, having our findings of characterization relevance for future more complex studies.

On the other hand, we observed that SBP, DBP, and GL were significantly associated with model 3 sleep hygiene. In this line, sleep is an important factor in blood pressure, neuroendocrine function, and glucose metabolism. Low sleep quality, for example, has been related to more metabolic and endocrine alterations, such as decreased insulin sensitivity, and increased appetite (41). Sleep restriction worse the hormonal system that regulates energy balance involving different hormones such as cortisol, insulin, ghrelin, leptin, and melatonin, that all are related to an increased risk of diabetes (42) and mortality (43). A low amount of sleep hours has been associated with all-cause mortality, obesity, and cardiovascular events ref. In addition, a reduced, sleep duration is a risk factor for both obesity and cardiovascular disease and represents a common complication that could contribute to worsening complications in metabolic and cardiovascular diseases (44).

Part of our secondary results included that alcohol consumption was also negatively associated with GL. In this regard, it is well known that a higher dose of alcohol consumption is related to more HTN, and moderate consumption per week is highly related to pancreatic cancer in subjects with prediabetes (45). However, there's also evidence that a light alcohol intake also reports minimal association with cardiometabolic risk, but when the analyses are adjusted by a beneficial lifestyle this minimal risk is attenuated, playing a critical role in the level of alcohol intake (46). Future studies should include the association between different amounts of sleep by adolescents/adults, including sleep quality with other cardiometabolic health markers.

STRENGTHS AND LIMITATIONS

The present study has the following limitations; *i*) the significant associations reported do not denote causality, *ii*) the PA levels (*i.e.*, in terms of 'intensity' were obtained from self-report by a standard the GPAQ v2 PA questionnaire, where it could be supra- or- underestimated, *iii*) despite the several ethnic groups information part of the NHS 2016-2017, we included only that related with Mapuche and Aymara ethnicity, but unfortunately, due to socio-politician concerns of some geographical regions, it could be possible that the instrument used here as the NHS 2016-2017 could not include all those ethnic populations considering that not all these groups are in the public health system, *iv*) we included a population > 15 years old including adolescents/adults with information of the NHS 2016-2017 that is recommended to interpret with rigor for future comparisons, *v*) around 80 % of the > 15-year-old participants in the NHS 2016-2017 were adolescents/adults living in urban areas, that may induce a predominant urban (*i.e.,* westernized) lifestyle, and *vi*) the sample size among ethnics and non-ethnic groups were different. A strength of this study is that; *i*) the study contains representative data of the Chilean adult population (*i.e.,* the NHS is applied in multi-stages, in person at home with families using a cross-sectional random, stratified by conglomerates), including lifestyle, and cardiometabolic risk factors outcomes of the two major ethnic groups of this country.

CONCLUSIONS

In conclusion, there are differences in lifestyle between ethnic Mapuche, Aymara, and non-ethnic Chilean adolescents/adults (> 15 years of age), where PA of 'moderate' intensity, and other modifiable lifestyle factors are also associated with blood pressure and fasting glycemia.

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AUTHOR CONTRIBUTIONS

Conceptualization, C.A. and P.D-F.; methodology, CA and P.D.-F.; software, C.A.; validation, C.A., R.R.-C., C.M., P.I.-S., C.C.-J., C.C.-M., E.M.-S., C.C.-M. and P.D.-F.; formal analysis, C.A.; investigation, C.A. and P.D-F.; resources, C.A., and P.D-F.; data curation, C.A. and P.D-F.; writing-original draft preparation, C.A. and P.D-F.; writing-review and editing, C.A. and P.D-F.; visualization, C.A.; supervision, C.A. and P.D-F.; project administration, C.A and P.D.-F. All authors have read and agreed to the published version of the manuscript.

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Trabajo Original

Otros

Vitamin D status and biomarkers of renal graft function after kidney transplantation: a longitudinal study

Estado de la vitamina D y biomarcadores de función del injerto renal después del trasplante de riñón: un estudio longitudinal

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Abstract

Introduction: low 25-hydroxyvitamin D [25(OH)D] levels occur after kidney transplantation (KTx), and can be associated with increase the risk of graft loss. This longitudinal study aimed to evaluate the vitamin D status and association with biomarkers of the renal graft function after KTx.

Methods: this longitudinal study included 42 patients evaluated at baseline, 3 and 6 months after KTx. Biodemographic, clinical, and biochemical parameters such as 25(OH)D and parathyroid hormone (PTH), and biomarkers of renal graft function, such as creatinine, estimated glomerular filtration rate (eGFR), and urinary albumin/creatinine ratio (ACR), were assessed. Sun exposure was also evaluated. Patients were categorized according to their 25(OH)D levels.

Results: at baseline, 25(OH)D levels < 30 ng/mL were found in 43 % patients, and 38 % of these patients failed to improve their 25(OH)D levels by 6 months after KTx. Low 25(OH)D levels occurred regardless of sun exposure. Further, 44 % patients developed albuminuria at 6 months. An increased ACR was observed in patients with 25(OH)D levels < 30 ng/mL ($p = 0.002$) compared to that in patients with 25(OH)D > 30 ng/mL. Additionally, 25(OH)D levels were negatively correlated with ACR at 6 months post-KTx ($r = -0.444$; $p = 0.003$). Twelve (28.6 %) patients with 25(OH)D levels < 30 ng/mL showed no eGFR recovery until 6 months after KTx.

Conclusion: low vitamin D levels and increased albuminuria were observed at 6 months after KTx, even in a region with high sun exposure. The association between vitamin D status and biomarkers of renal graft function after KTx should be explored in further studies.

Keywords:

Kidney transplantation. 25-Hydroxyvitamin D. Hypovitaminosis D. Albuminuria. Urinary albumin/creatinine ratio.

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Resumen

Introducción: los bajos niveles de 25-hidroxivitamina D [25(OH)D] ocurren después del procedimiento de trasplante de riñón (KTx) y pueden estar asociados con un aumento del riesgo de pérdida del injerto. Este estudio longitudinal tuvo como objetivo evaluar el estado de la vitamina D y la asociación con los biomarcadores de función del injerto renal después del KTx.

Métodos: este estudio longitudinal incluyó a 42 pacientes que fueron evaluados al inicio del estudio, y 3 y 6 meses después del KTx. Se evaluaron los parámetros biodemográficos, clínicos y bioquímicos, como 25(OH)D y hormona paratiroidea (PTH), y los biomarcadores de función del injerto renal, como creatinina, tasa de filtración glomerular estimada (eGFR) y relación albúmina/creatinina (ACR). También se evaluó la exposición al sol. Los pacientes se clasificaron según sus niveles de 25(OH)D.

Resultados: al inicio del estudio se encontraron niveles de 25(OH)D < 30 ng/ml en el 43 % de los pacientes, mientras que el 38 % de estos pacientes no lograron mejorar sus niveles de 25(OH)D a los 6 meses después del KTx. También se produjeron niveles bajos de 25(OH)D independientemente de la exposición al sol. Asimismo, el 44 % de los pacientes desarrollaron albuminuria a los 6 meses. Se observó un aumento de la ACR en los pacientes con niveles de 25(OH)D < 30 ng/mL (p = 0,002) en comparación con los pacientes con 25(OH)D > 30 ng/mL. Además, los niveles de 25(OH)D se correlacionaron negativamente con la ACR a los 6 meses después del KTx (r = -0,444; p = 0,003). Doce (28,6 %) pacientes con niveles de 25(OH)D < 30 ng/ml no mostraron recuperación de la TFGe hasta 6 meses después del KTx.

Conclusión: se observaron niveles bajos de vitamina D y un aumento de la albuminuria a los 6 meses después del KTx, incluso en una región con alta exposición solar. La asociación entre el estado de la vitamina D y los biomarcadores de función del injerto renal después del KTx debe explorarse en estudios adicionales.

Palabras clave:

Trasplante de riñón. 25-Hidroxivitamina D. Hipovitaminosis D. Albuminuria. Cociente albúmina/creatinina.

INTRODUCTION

Kidney transplantation (KTx) is the most effective treatment for patients with end-stage renal disease because it increases survival rates, lowers morbidity, improves the quality of life, and reduces healthcare costs (1). Although KTx improves patient prognosis, conditions that occur after KTx may lead to a decreased micronutrient status, including lower vitamin D levels, which increase the risk of graft failure and premature death (2).

Vitamin D deficiency, typically defined as a 25-hydroxyvitamin D [25(OH)D] level of < 20 ng/mL (3), is commonly observed in patients after KTx and can be attributed to several factors, such as decreased food intake, reduced sun exposure, and 1-alpha-hydroxylase deficiency in the kidneys (4). Yin et al. (5) demonstrated that 52 % of recipients had vitamin D deficiency after KTx. The incidence of vitamin D deficiency at 3 and 6 months after KTx has been reported to be 34 % and 23 %, respectively.

A previous study has revealed that vitamin D deficiency is associated with increased albuminuria, which decreases renal function and increases the risk of graft loss (6). In a recent meta-analysis, patients with vitamin D deficiency had an 82 % greater chance of acute rejection than those without vitamin D deficiency, suggesting that an adequate vitamin D status a few days before and after KTx can reduce the chance of acute rejection.

Low 25(OH)D levels cause changes in the renin-angiotensin-aldosterone system, leading to increased blood pressure, modulation of the immune response, and loss of the podocytes, the components of the glomerular filtration barrier (8,9). Therefore, maintaining 25(OH)D levels > 30 ng/mL is beneficial in this population (3). A longitudinal study evaluated albuminuria in 230 patients after KTx according to their vitamin D status and revealed increased albuminuria in patients with lower vitamin D levels (10).

Although the clinical relevance of vitamin D status in renal graft function has been demonstrated, more studies are needed to clarify the time after KTx at which low vitamin D levels may be associated with renal function decline. Therefore, this longitudinal study aimed to evaluate the hypothesis that vitamin D status could be associated with biomarkers of renal graft function in patients at baseline and at 3 and 6 months after KTx.

METHODS

STUDY DESIGN AND PATIENTS

This longitudinal study was conducted at the Nephrology Outpatient Clinic of Onofre Lopes Hospital of the Federal University of Rio Grande do Norte, Natal, Rio Grande do Norte, Brazil, between August 2015 and January 2017. Patients of both sexes aged > 20 years who had undergone KTx were included. The exclusion criteria were as follows: patients administered vitamin D supplements, patients diagnosed with focal segmental glomerulosclerosis, patients with diabetes *mellitus* or diabetic kidney disease, cases in which cytomegalovirus infection occurred in the donor or recipient, patients with residual diuresis after KTx, and patients who experienced humoral or cell rejection.

Among the 156 recipients who underwent KTx, 45 met the eligibility criteria and agreed to participate. After initiating the study, one patient died, one patient dropped out, and two patients experienced graft loss; thus, the remaining 42 patients were analyzed.

As immunosuppressive therapeutic regimens, patients were administered mycophenolate mofetil, tacrolimus, and prednisone or mammalian target of rapamycin inhibitors, such as everolimus or sirolimus.

All patients were followed up at baseline and at 3 and 6 months after KTx. They were categorized into two groups according to their 25(OH)D levels—patients with 25(OH)D levels > 30 ng/mL and patients with 25(OH)D levels ≤ 30 ng/mL (3). At each follow-up examination, fasting blood and first morning void urine samples were obtained.

The study was conducted in accordance with the guidelines of the Ethics in Research Committee of Federal University of Rio Grande do Norte and complies with the Declaration of Helsinki (protocol number 1.144.405). All patients provided their written informed consent to participate.

DATA COLLECTION

The following information was obtained from the patients' medical records: age, sex, ethnicity, etiology of renal disease,

presence of comorbidities, duration of hemodialysis, time of hospitalization after KTx, immunosuppressive therapy, donor type, donor age, donor cause of death, creatinine level of donor, estimated glomerular filtration rate (eGFR) of donor, and cold ischemia time of maintaining the organs before KTx.

Sun exposure was assessed based on an adapted questionnaire proposed by Hanwell et al. (11). A sun exposure score was calculated for healthy adults using a recall questionnaire assessing daily time in the sun (< 5 min, 5-30 min, > 30 min) and skin exposure (face/hands, face/hands and arms, face/hands and legs, and "bathing suit") for 1 week. Skin color was self-classified according to the five categories adopted by the Brazilian Institute of Geography and Statistics (12). Weight and height were measured to calculate body mass index (BMI),which was classified according to the World Health Organization guidelines (13).

BIOCHEMICAL ANALYSIS

Fasting blood samples were collected for biochemical analysis. Serum creatinine levels were measured using the Wiener kit and CMD-800 automatic biochemistry analyzer (Wiener Laboratories, Rosario, Argentina). Parathyroid hormone (PTH) levels were measured using the UniCel® Dxl 800 Immunoassay System (Beckman Coulter, Brea, CA, USA). Circulating 25(OH) D levels were measured by chemiluminescence with ABBOTT® kits using the ARCHITECT i2000SR Immunoassay Analyzer (ABBOTT Diagnostics, Lake Bluff, IL, USA). The cutoff points used for 25(OH)D levels were defined by the Endocrine Society (as follows: "adequate" ≥ 20 ng/mL and "deficiency" ≤ 20 ng/mL. In this study, patients were classified according to 25 (OH)D levels > 30 ng/mL or ≤ 30 ng/mL, as recommended by the Brazilian Society of Endocrinology and Metabolism, which suggests that in some clinical situations, such as chronic kidney disease, 25(OH) D levels > 30 ng/mL can be beneficial (3).

eGFR was evaluated using the Chronic Kidney Disease Epidemiology Collaboration equation (14). Urinary albumin/creatinine ratio (ACR) was assessed using the first morning urine samples. Albumin and creatinine levels in the urine were determined using the Wiener kit and CMD-800 automatic biochemistry analyzer. The cut-off points used for albuminuria, as defined by the Kidney Disease: Improving Global Outcomes (15), were as follows: normal-to-mild, < 30 mg/g of creatinine; moderate, 30-300 mg/g of creatinine; and severe, > 300 mg/g of creatinine.

STATISTICAL ANALYSIS

The distribution of variables was analyzed using the Kolmogorov–Smirnov test. The data are presented as the average or median, when appropriate. Differences among continuous variables at different time points, at baseline and at 3 and 6 months after KTx, were analyzed using the Friedman test, followed by the post hoc Wilcoxon signed-rank test with Bonferroni correction. Variables were also analyzed according to the vitamin D status at each collection time. Data with parametric distribution were analyzed using Student's t-test, whereas variables showing a non-parametric distribution were analyzed using the Mann-Whitney test. Correlations were assessed using Pearson's or Spearman's rank test when appropriate. Differences between categorical variables were tested using the χ^2 test. Categorical data are presented as frequencies (percentages). Data were analyzed using Statistical Package for the Social Sciences version 15.0 (SPSS Inc., Chicago, IL, USA) and Graph Pad Prism, version 5.0 software (Graph Pad, Inc., San Diego, CA, USA). Significance level was set at $p < 0.05$.

RESULTS

The mean participant age was 41.8 ± 12.3 years; most participants were male and had mixed skin. Glomerulonephritis has been considered the main cause of chronic kidney disease. More than half of the patients had no comorbidities. The median duration of hemodialysis was 3 (1.8-7) years and that of hospital stay after KTx was 16.5 (11-32) days. Furthermore, the most widely used therapeutic regimen was that with the immunosuppressants mycophenolate mofetil, tacrolimus, and prednisone. Most donated kidneys were obtained from deceased donors, with a mean age of 38.2 ± 13.9 years. Head trauma was the main cause of death of the donors. The median creatinine level of the donors was 0.9 (0.8-1.5) mg/dL, eGFR was 84.4 ± 40.8 mL/min/1.73 m², and cold ischemia time was 14.7 ± 11.6 h (Table I).

When evaluating vitamin D status of patients who underwent KTx, 43% had 25(OH)D levels < 30 ng/mL at baseline. Moreover, 26 % of these patients had 25(OH)D levels < 20 ng/dL during this period, indicating vitamin D deficiency. At the 6-month study follow-up, 38 % patients with 25(OH)D levels < 30 ng/dL at baseline failed to show improvement in their vitamin D status.

There was no significant difference between the BMI values of patients with 25(OH)D levels < 30 ng/mL and those with 25(OH) D levels > 30 ng/mL who underwent KTx. Sun exposure was significantly higher in patients with 25(OH)D levels > 30 ng/dL at 6 months after KTx compared to that in patients with 25(OH)D levels < 30 ng/mL ($p = 0.008$), which was possibly associated with increased production of vitamin D through exposure of the skin to sunlight. A significant increase in PTH levels was observed at 3 months after KTx($p = 0.008$) in patients with 25(OH)D levels < 30 ng/mL compared to that in patients with 25(OH)D levels > 30 ng/mL (Table II), with higher medians than reference values.

There was no significant difference between creatinine levels in the different groups; however, the median values at baseline and at 3 months tended to be higher in patients with 25(OH)D levels < 30 ng/mL than in those with 25(OH)D levels < 30 ng/mL. Reflecting this result, eGFR tended to be decreased in patients with 25(OH)D levels < 30 ng/mL at baseline and at 3 months after KTx, although the results were not significant. Twelve (28.6 %) patients with 25(OH)D levels < 20 ng/mL showed no eGFR recovery until 6 months after KTx.

ACR decreased in both groups within 3 months, demonstrating an improvement in post-KTx renal function. How-

ever, there was a significant increase at 6 months in patients with 25(OH)D levels < 30 ng/mL compared to that in patients with 25(OH)D levels > 30 ng/mL (p = 0.002; Table II). We found that 44 % patients developed albuminuria after 6 months.

The following variables were associated with 25(OH)D levels. There was a correlation between 25(OH)D levels and ACR (r = -0.444; p = 0.003) at 6 months after KTx, supporting the previous results that demonstrated a worsening of albuminuria during this period in patients with low vitamin D levels. The eGFR correlated with 25(OH)D levels over the 3 months (r = 0.305; p = 0.049), corroborating the comments made in table II that there was a trend toward worse renal function in patients with 25(OH)D levels < 30 ng/mL in this period of the study. Cold ischemia time correlated with 25(OH)D levels at baseline (r = -0.369; p = 0.019) and at 6 months (r = -0.394; p = 0.012).

Table I. Characteristics of patients and donors who underwent KTx

Variables	n = 42	95 % CI
Patients undergoing KTx		
Age, mean (SD), *years*	41.8 ± 12.3	37.9-45.6
Sex		
Male, *n* (%)	29 (69)	54.2-81.6
Female, *n* (%)	13 (31)	18.4-45.8
Skin color		
Mixed, *n* (%)	34 (81)	67.4-90.8
White, *n* (%)	6 (14.3)	5.9-26.9
Black, *n* (%)	2 (4.8)	0.8-14
Etiology of renal disease		
Glomerulonephritis, *n* (%)	15 (35.7)	22.4-50.7
Hypertension, *n* (%)	13 (31)	18.4-45.8
Not specified, *n* (%)	7 (16.7)	7.5-29.7
UTI, n (%)	3 (7.1)	1.8-17.5
Lithiasis, n (%)	2 (4.8)	0.8-14
Polycystic kidney, n (%)	2 (4.8)	0.8-14
Comorbidities		
Not present, n (%)	35 (83.3)	70.3-92.5
Hypothyroidism, n (%)	4 (9.5)	3.1-20.8
Coronary artery disease, n (%)	3 (7.1)	1.8-17.5
DH, median (IQR), *years*	3 (1.8-7)	3.5-6.4
TH after KTx, median (IQR), *days*	16.5 (11-32)	18.3-30.2
Immunosuppressant medication		
Tacrolimus + MMF + PRD, n (%)	26 (61.9)	49.3-77.6
Tacrolimus + Sirolimus + PRD, n (%)	9 (21.4)	9.2-32.6
Tacrolimus + Everolimus + PRD, n (%)	7 (16.7)	7.5-29.7
Kidney donors		
Donor type		
Deceased, n (%)	36 (85.7)	73.1-94.1
Living, n (%)	6 (14.3)	5.9-26.9
Donor age, mean (SD), *years*	38.2 ± 13.9	33.8-42.6
Donor cause of death		
Head trauma, n (%)	18 (42.9)	28.6-57.9
Stroke, n (%)	12 (28.6)	16.5-43.2
Living donor, n (%)	6 (14.3)	5.9-26.9
IH, n (%)	4 (9.5)	3.1-20.8
Encephalopathy, n (%)	1 (2.4)	0.1-10.1
Hydrocephalus, n (%)	1 (2.4)	0.1-10.1
Creatinine of donor, median (IQR), *mg/dL*	0.9 (0.8-1.5)	0.1-1.3
eGFR, mean (SD), *mL/min/1.73 m²*	84.4 ± 40.8	71.7-97.1
Cold ischemia time, mean (SD), *h*	14.7 ± 11.6	11-18.4

Results are expressed as the mean ± standard deviation or median (interquartile range), except otherwise indicated. 95 % CI: 95 % confidence interval; DH: duration of hemodialysis; eGFR: estimated glomerular filtration rate; IH: intracerebral hemorrhage; IQR: interquartile range; KTx: kidney transplantation; MMF: mycophenolate mofetil; n: number of individuals; PRD: prednisone; SD: standard deviation; TH: time of hospitalization; UTI: urinary tract infection.

Table II. Anthropometric data, sun exposure profile, and biochemical parameters of patients who underwent KTx according to 25(OH)D status considering collection time

Variables	25(OH)D > 30 ng/mL			25(OH)D < 30 ng/mL					
	Baseline n = 19	3 months n = 9	6 months n = 15	Baseline n = 23	3 months n = 33	6 months n = 27	p-value 1	p-value 2	p-value 3
BMI, mean (SD), *kg/m²*	22.9 ± 2.8	21.9 ± 3.8	23.4 ± 2.6	24.8 ± 4.8	23.2 ± 3	23.2 ± 4.2	0.144	0.265	0.883
Sun exposure, median (IQR), *score*	0 (0-18)	0 (0-0.1)	12 (3-21)	3 (0-20)	0 (0-14)	0 (0-14)	0.464	0.133	0.008†
25(OH)D, mean (SD), *ng/dL*	35.1 ± 6.4	33.2 ± 4.5	38 ± 6.8	20.5 ± 5.3	23.4 ± 4.7	24.1 ± 3.8	< 0.001†	< 0.001†	< 0.001†
PTH, median (IQR), *pg/mL*	154.6 (117.4-286)	66.6 (47.5-79.5)	90 (58.7-175.7)	141 (66.8-325.7)	129.5 (79.6-245)	102.6 (69.3-212.7)	0.626	0.008†	0.551
Creatinine, median (IQR), *mg/dL*	1.6 (1.4-4.5)	1.3 (1.1-1.5)	1.5 (1.4-1.6)	2.1 (1.5-4.6)	1.6 (1.3-1.8)	1.4 (1-1.9)	0.535	0.056	0.443
eGFR, mean (SD), *mL/min/1.73 m²*	41.3 ± 26.3	69 ± 16.7	57.6 ± 13.8	37.5 ± 27.4	54 ± 19.8	59.9 ± 24.8	0.648	0.045†	0.703
ACR, median (IQR), *mg/g of creatinine*	27.5 (14.5-123.5)	1.8 (0.3-3.4)	3.4 (1.3-9.4)	64.7 (42-136)	1.7 (0.2-8.1)	15.9 (5.3-63)	0.146	0.570	0.002†

*Results are expressed as the mean ± standard deviation or median (interquartile range). IQR: interquartile range; SD: standard deviation; n: number of individuals; BMI: body mass index; eGFR: estimated glomerular filtration rate; ACR: urinary albumin/creatinine ratio; 5(OH)D: 25-hydroxyvitamin D; PTH: parathyroid hormone. Friedman and Wilcoxon signed-rank tests were used to compare repeated measures with post-hoc Bonferroni correction. *Significant vs. 3 months (p < 0.008). Student's t-test or the Mann-Whitney U-test was used to compare groups, as appropriate—p-value 1: baseline [25(OH)D < 30 ng/mL] vs. baseline [25(OH)D > 30 ng/mL]; p-value 2: 3 months [25(OH)D < 30 ng/mL] vs. 3 months [25(OH)D > 30 ng/mL]; p-value 3: 6 months [25(OH)D < 30 ng/mL] vs. 6 months [25(OH)D > 30 ng/mL]—†Significant p-values.*

DISCUSSION

This longitudinal study evaluated vitamin D status in patients who underwent KTx residing in a region of high solar incidence. We found a high frequency of 25(OH)D levels < 30 ng/mL at baseline, which was sustained until the end of the study. The presence of albuminuria at 6 months after KTx was also observed in almost half of the patients who had this vitamin D status profile.

The high percentages of patients with 25(OH)D levels < 30 ng/mL at baseline are consistent with those reported in a previous study, indicating that only 12 % of patients had 25(OH)D levels > 30 ng/mL after KTx. A fact that caught our attention even in our study was that 38 % patients were unable to improve their 25(OH)D status at 6 months (16).

This high frequency of hypovitaminosis D after KTx can be attributed to several factors, such as low sun exposure. Our study demonstrated that patients with 25(OH)D levels > 30 ng/dL had greater sun exposure at 6 months after KTx than those with 25(OH)D levels < 30 ng/mL, which confirms that the incidence of solar radiation increases endogenous vitamin D production.

Although Brazil receives a large amount of solar radiation during the year, specifically in Natal/Rio Grande do Norte, which is a coastal city with the highest solar radiation, there was a considerable frequency of low 25(OH)D levels at 6 months after KTx in our study. These results can be explained by the limitations to sun exposure imposed on this group of patients due to the increased risk of skin tumors (18). Another study conducted in south-eastern Brazil also showed the prevalence of vitamin D deficiency among patients who underwent KTx, even in geographic areas with high exposure to ultraviolet rays (17).

The other factors that may be associated with low vitamin D levels are decreased food intake and 1-alpha-hydroxylase deficiency in the kidneys (4). Progressive loss of the kidney function results in a reduction in the kidney's ability to synthesize active vitamin D. Further, immunosuppressive therapy has been shown to alter vitamin D metabolism, as in the case of the patients in our study. Steroids, for example, express enzymes involved in vitamin D catabolism. Other immunosuppressive agents, such as calcineurin inhibitors, have also been implicated in dysregulation of vitamin D metabolism observed after KTx (19,20).

An important finding of this study is the negative correlation between 25(OH)D levels and albuminuria at 6 months after KTx. During this period, 44 % patients had albuminuria, suggesting the period during which renal function declines. In similar studies, the prevalence of post-KTx albuminuria varied considerably from 7.5 % to 45 % (21). In addition, mild albuminuria (< 500 mg/24 h) at 1 year after KTx was associated with a four-fold increased risk of transplant graft failure (22).

Although this association between vitamin D and renal graft function decline was noted at 6 months, Bienaimé et al. (23) showed that low 25(OH)D levels at 3 months after KTx were associated with worse outcomes in allograft function at 1 year after transplantation. Keyzer et al. (2), in a 7-year follow-up cohort study, also showed that low 25(OH)D levels were significantly

associated with decreased renal function and increased mortality. In addition, clinical studies have demonstrated the therapeutic efficacy of vitamin D analogues in reducing proteinuria after KTx (10).

Vitamin D has been shown to protect the kidney by regulating pathways involved in kidney injury, including the renin-angiotensin system and filtration slit diaphragm protein pathways (9,10). In cell culture and mice, Deb et al. (8) demonstrated that podocytes expressing the vitamin D receptor are strongly induced by 1,25-dihydroxyvitamin D3 to stimulate the transcription of nephrin, a key protein in the slit diaphragm synthesized by podocytes. Thus, vitamin D receptor signaling plays a critical role in maintaining the integrity of the slit diaphragm.

Therefore, one of the main extra-osseous effects of vitamin D is represented by its antiproteinuric effect primarily mediated by dysregulation of the renin-angiotensin-aldosterone system. The inverse correlation between calcitriol and renin is an idea consolidated in the literature. Patients with low levels of 25(OH)D (< 30 ng/mL) have been shown to have high levels of renin and angiotensin II due to an inappropriate activation of the renin–angiotensin system (24). These data demonstrate the use of vitamin D due to antiproteinuric function, and it is considered safe in patients with chronic kidney disease and after KTx (25).

This can be explained by the fact that vitamin D exerts potent renoprotective activity that increases graft survival by reducing albuminuria, a major risk factor for renal failure, cardiovascular events, and death (26). Similar to our study, a cross-sectional analysis of the Third National Health and Nutrition Examination Survey database revealed an association between vitamin D deficiency and an increased prevalence of albuminuria in the adult population (27), suggesting that vitamin D has intrinsic antiprotein activity.

The presence of genetic polymorphisms encoding vitamin D binding protein and vitamin D receptor has been recently discussed and is also a factor that may explain the association between vitamin D andrenal function. It is suggested that these polymorphisms can modulate the immune response after allograft transplantation, which can lead to an increased risk of graft rejection and viral infections (28).

The tendency to increase PTH levels in patients with 25(OH)D levels < 30 ng/mL observed in our study corroborates with the findings another study that point out that it is well established that PTH levels are inversely associated with circulating 25(OH)D levels (29). The role of vitamin D is classically associated to the action of PTH on the bone physiology and mineral homeostasis, regulating calcium and phosphate metabolism in different target organs, such as the bones, kidneys, liver, and gastrointestinal tract. Its deficiency often results in bone mineral disorders and development of secondary hyperparathyroidism (30). Thus, studies have demonstrated that vitamin D supplementation can be considered a well-accepted preventive therapy against post-KTx bone loss (31).

In our study, we also observed a negative correlation between 25(OH)D levels and cold ischemia time (Fig. 1). A high cold ischemia time can be associated to the greatest podocyte loss, which is associated with the onset of albuminuria after KTx. This alteration that impairs the integrity of the glomerular filtration membrane (32) and increases blood pressure via negative regulation of the renin–angiotensin system contributes to increased urinary protein excretion. Furthermore, the protective effect of vitamin D as a recognized immunomodulator cannot be offered to recipients with low 25(OH)D levels who underwent KTx in a previous study (9).

There are some limitations to our study. It was not possible to obtain food consumption data, thus compromising the association of these parameters with vitamin D status. Thus, large-scale studies on the population who underwent KTx are needed to determine the association between vitamin D levels and renal graft function.

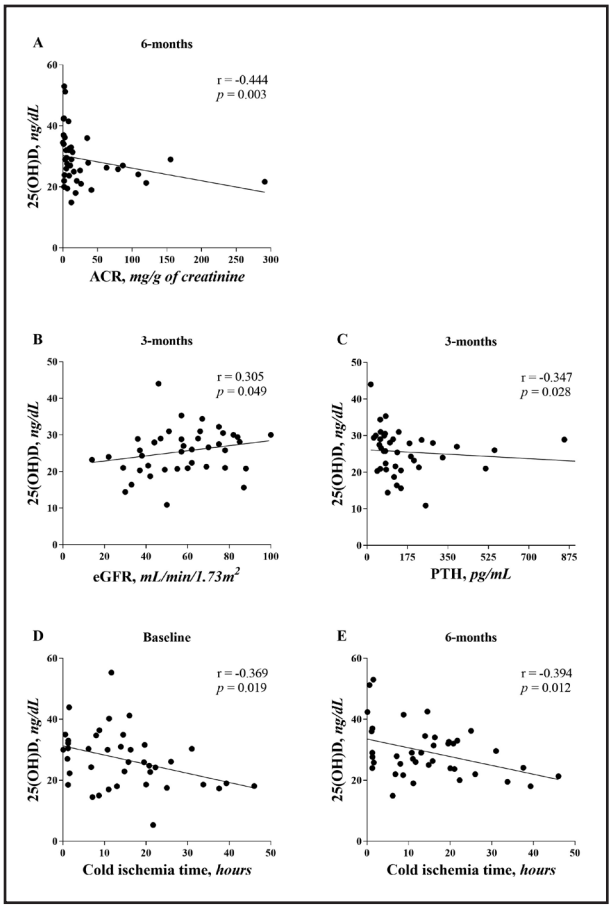

Figure 1.

Correlation between 25(OH)D levels, cold ischemia time, estimated glomerular filtration rate, and urinary albumin/creatinine ratio (eGFR: estimated glomerular filtration rate; ACR: urinary albumin/creatinine ratio).

CONCLUSION

Patients frequently have 25(OH)D levels < 30 ng/mL after KTx, even in a region with high sun exposure, with no recovery of this profile within 6 months after KTx in most patients. The biomark-

ers of renal graft function seem to recover up to 3 months after KTx, but show changes such as the appearance of albuminuria at 6 months, suggesting the period during which renal function declines. These results appear to have a relationship with the vitamin D status of these patients and should be explored in further studies. In the future, we would like to present more comprehensive research results. In addition, randomized clinical trials are needed to assess the effect of vitamin D supplementation on long-term survival outcomes after KTx.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Otros

Food intake behaviors change as a function of maternal diet and time-restricted feeding

Las conductas de ingesta de alimentos se alteran en función de la dieta materna y la alimentación limitada en el tiempo

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Abstract

Introduction: changes in dietary/energetic composition during the critical period of development (pregnancy/lactation) or even during mealtimes may contribute to changes in metabolic and behavioral parameters such as feeding behavior.

Objective: the study aimed to examine the repercussions of time-restricted feeding on feeding behavior and on some parameters of glycemic and lipemic metabolism of the offspring of adult rats whose mothers were fed a westernized diet during pregnancy and lactation.

Methods: initially, 43 male Wistar rats were used. At 60 days of life, the rats were divided into 4 groups: C: control group; RC: control group with time-restricted feeding; W: westernized diet during pregnancy/lactation group; RW: westernized diet group during pregnancy/lactation group with time-restricted feeding. The following parameters were evaluated: behavioral sequence of satiety (BSS), biochemical parameters, and abdominal fat.

Results: findings highlighted a high level of abdominal fat in the groups whose mothers were submitted to a westernized diet, as well as hypertriglyceridemia, and clear differences in feed rate and meal length. This study showed that the westernized diet ingested by mothers during pregnancy and lactation induced hyperlipidemia and changes in the feeding behavior of their adult offspring.

Conclusions: these changes may be responsible for eating disorders and risk factors for metabolism disturbance-related diseases.

Keywords:

Feeding behavior. Wistar rats. Time-restricted feeding. Food deprivation. Western diet.

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Ethical standards: the authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on the care of laboratory animals (CONCEA) and have been approved by the institutional committee (Ethical Committee of the Federal University of Pernambuco).

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Resumen

Introducción: los cambios en la composición dietética/energética durante el período crítico de desarrollo (embarazo/lactancia) o incluso durante las comidas pueden contribuir a cambios en los parámetros metabólicos y conductuales como el comportamiento alimentario.

Objetivo: el estudio tuvo como objetivo examinar las repercusiones de la alimentación restringida en el tiempo sobre el comportamiento alimentario y sobre algunos parámetros del metabolismo glucémico y lipémico de crías de ratas adultas cuyas madres fueron alimentadas con una dieta occidentalizada durante el embarazo y la lactancia.

Métodos: inicialmente se utilizaron 43 ratas Wistar macho. A los 60 días de vida, las ratas se agruparon en 4 grupos: C: grupo de control; RC: grupo de control con alimentación restringida en el tiempo; W: grupo de dieta occidentalizada durante el embarazo/lactancia; RW: grupo de dieta occidentalizada durante el embarazo y la lactancia con alimentación restringida en el tiempo. Se evaluaron los siguientes parámetros: secuencia conductual de saciedad (BSS), parámetros bioquímicos y grasa abdominal.

Resultados: destacó una grasa abdominal elevada en los grupos cuyas madres fueron sometidas a una dieta occidentalizada, así como hipertrigliceridemia y una diferencia evidente en la tasa de alimentación y la duración de la comida. Este estudio demostró que la dieta occidentalizada ingerida por las madres durante el embarazo y la lactancia induce hiperlipidemia y cambios en el comportamiento alimentario de las crías adultas.

Conclusiones: estos cambios pueden ser responsables de trastornos alimentarios y factores de riesgo de enfermedades relacionadas con alteraciones del metabolismo.

Palabras clave:

Comportamiento alimentario. Ratas Wistar. Alimentación restringida en el tiempo. Privación de alimentos. Dieta occidental.

INTRODUCTION

The eating habits found in the majority of the population are mainly influenced by lifestyle in the contemporary world regarding the increasing intake of processed foods. This dietary pattern is composed mostly of saturated fatty acids and trans-fat, sodium, and simple carbohydrates, among which fructose stands out. The set of these components characterizes the westernized diet (1,2). Previous studies have shown that the westernized diet used in experimental trials with rodents during pregnancy and lactation favors the onset of chronic diseases in adulthood. These characteristics are related to increased body fat and weight, dyslipidemia, preference for palatable foods, insulin resistance, and/or glucose intolerance; besides, changes in the expression of neuropeptides responsible for appetite regulation have been documented (3).

More recently, not only the quality or quantity of what is ingested but at which times or intervals of the day it is ingested has also been shown to be of interest as a predictive factor of health or metabolic disorders (4). Homeostatic hunger has a daily cycle with peak times defined in humans (5) and animals (6). The establishment of this rhythm is associated with a central pacemaker at the suprachiasmatic nucleus (SCN) located in the hypothalamus. The SCN regulates physiological rhythms and peripheral structures. However, the physiological rhythms of peripheral structures are influenced not only by the central pacemaker but also by exogenous factors such as nutritional composition (7) and feeding time (8,7).

Feeding behavior is a complex process that involves endogenous interactions of each organism and species with its environment (9), going beyond the endogenous rhythm of feeding. In rats specifically, feeding behavior involves a sequence of procedures expressed by the animal that can be modified by factors such as perinatal malnutrition (9) or dietary composition, usually increased by greater lipid intake (10,11). The study of feeding behavior in rodents is carried out from the study of the Behavioral Satiety Sequence (BSS). This test allows to analyze the feeding behavior of the rat (12). Although it has been reported that malnutrition (10), early weaning (13), and acute consumption of the westernized diet (7) alters feeding behavior, it is still unknown whether this behavior is altered due to the association of a maternal westernized diet with time-restricted feeding in the adult life of rats.

Therefore, male rats were submitted to a feeding window of 16 hours (4 hours of the dark phase and 12 hours of the light phase) of the 24 hours cycle. This experimental model tries to mimic the lifestyle of the humans known as “night eaters”. We hypothesize that dietary restriction by itself and/or the westernized diet ingested by the mother during pregnancy and lactation can cause excess weight and body fat, hyperglycemia, hyperlipidemia, and changes in the feeding behavior of the adult offspring. The exploratory aim of this study was to examine the repercussions of time-restricted feeding on feeding behavior and on some parameters of glycemic and lipemic metabolism of the offspring of adult rats whose mothers were fed a westernized diet during pregnancy and lactation.

MATERIALS AND METHODS

ANIMALS

The research was developed in the Department of Nutrition of the Center for Health Sciences of the Federal University of Pernambuco - UFPE, and in the Laboratory of Metabolic and Nutritional Diseases of the Department of Veterinary Medicine located in the Federal Rural University of Pernambuco - UFRPE. All experimental procedures were submitted to analysis and approval by the Ethics Committee on Animal Experimentation of the Federal University of Pernambuco (UFPE) under protocol number 0036/2016, and abide by the resolutions and guidelines determined by CONCEA (National Council for Animal Experimentation Control) (14).

Sixteen virgin females and eight adult males (Wistar rats, *Rattus norvegicus*) from the colony of the Department of Nutrition were mated in the proportion of 2:1 (female: male). After confirming pregnancy by vaginal smear and monitoring weight gain, pregnant rats were packed in individual cages and divided into 2 groups according to the diet received: control (standard chow diet) and westernized (experimental diet). The animals were

maintained at room temperature (22 ± 1 °C) with controlled 12 hours dark/light cycle, and they had free access to a commercial diet and water *ad libitum* until the experiments began.

On the 21th day the offspring were weaned. Male pups were included in the experiment and started to receive a standard chow diet. On the 30th day of life, the animals were placed in individual cages for adaptation, and at 45 days of life the experiments were performed with the formation of the groups according to maternal diet and the dietary restriction (control = C, westernized = W, restricted control = RC, and restricted westernized = RW). From 60 days of life, the animals of the RC and RW groups were deprived of feed for the first 8 hours of the dark period (from 8 am to 4 pm of an inverted circadian cycle) and the groups C and W received a standard chow diet *ad libitum* throughout the experimental period. After 8 weeks of daily food restriction, a test of behavioral satiety sequence (BSS) was performed and the animals were euthanized by an overdose of anesthetics (ketamine, 80 mg/kg and xylazine, 10 mg/kg). Abdominal fat and the liver were removed and weighed. The experimental design is outlined in figure 1.

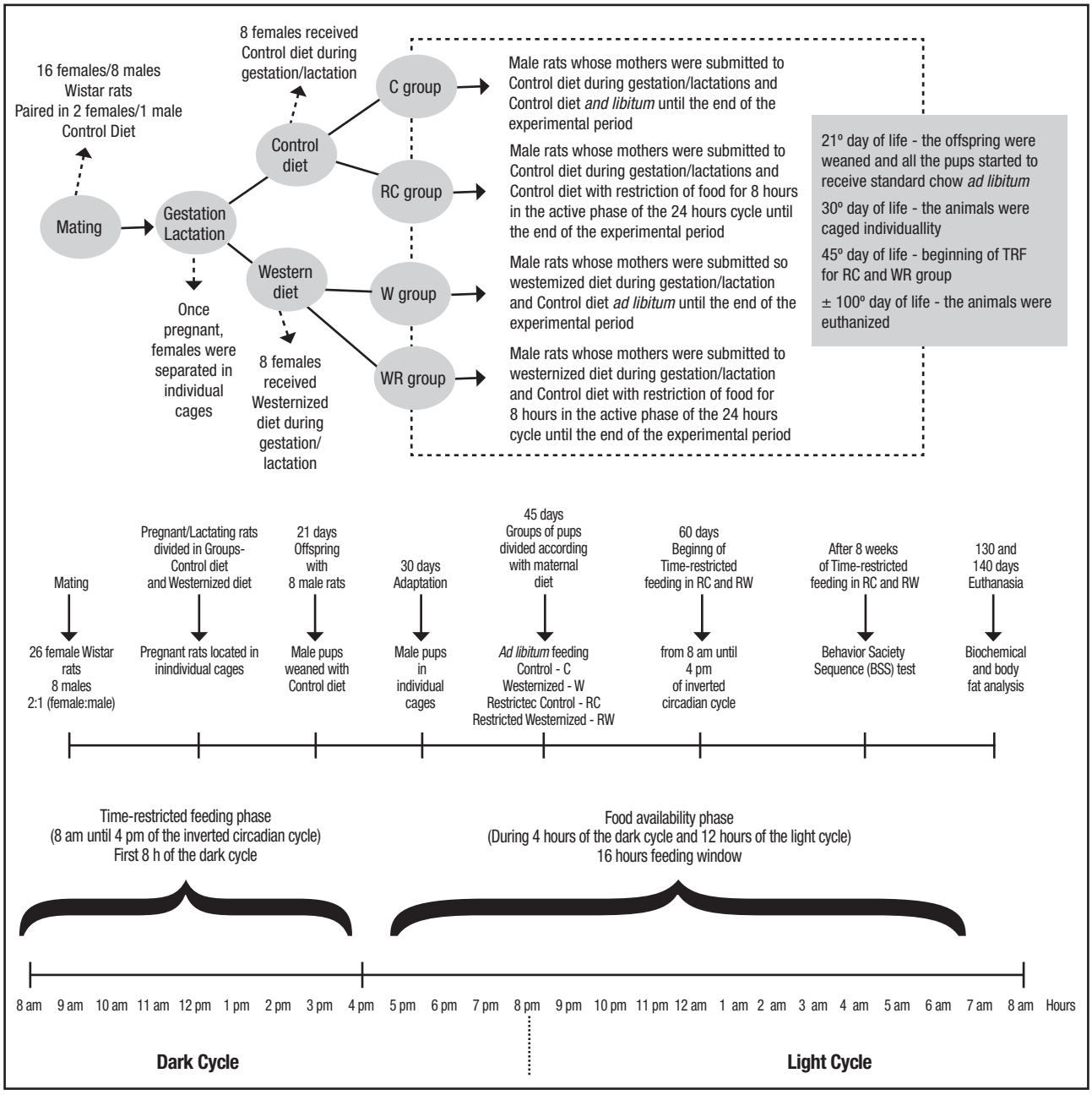

Figure 1.

Experimental design (C: control; W: westernized; RC: restricted control; RW: restricted westernized).

BODY WEIGHT AND FOOD INTAKE

Body weight evolution was recorded weekly for 10 weeks. The standard chow diet offered to the control group progenitors had 23 % proteins, 63 % carbohydrates, and 11 % lipids totaling 3.6 kcal/g throughout the experimental period. The westernized group received an experimental westernized diet formulated from an adaptation of the study by Ferro-Cavalcante et al. (2013) (15) until the end of the lactation period (21 days postpartum), composed of 21 % proteins, 45 % carbohydrates, and 34 % lipids, totaling 4.6 kcal/g. After weaning (postnatal day 22), all puppies were fed a commercial diet *ad libitum*. The amount of feed offered to the restricted groups was the same as in the control and westernized groups. Food intake (g) was obtained by the difference between the amount of food offered and the rejected food (4).

BEHAVIORAL SATIETY SEQUENCE

The analysis of the behavioral satiety sequence followed the method determined by Halford, Wanninayake, and Blundell (1998) (12). The animals were submitted to behavioral tests (BSS) after the feeding restriction period of 8 hours daily for 8 weeks when the animals presented an average of 120 days of life. The tests were conducted in animals submitted to 2 hours of fasting after turning off the lights of the experimentation room. The rats were monitored under low-intensity red light (< 5 lux) in the dark phase of the 24-hour photoperiod. A test meal was offered and feeding, cleaning, and other activities were observed over 60 minutes by a trained individual and recording the time in which each behavior predominated. All 60 minutes were recorded on a video camera to be subsequently examined by a second observer.

Behaviors were categorized as feeding (ingesting food, gnawing, chewing, or holding food in paws), drinking, active (exploring movements around the cage, rearing), grooming (body care movements with the mouth and paws), and resting (sitting or lying in a resting position or sleeping). Other measures scored from the behavioral observation of feeding were: meal duration (time in minutes over the entire monitoring period the animal was eating food), and feeding rate (amount of food or energy consumed/meal duration), that were relativized by kg/kcal of kg of body weight. To promote feeding, food was removed from the home cages at the beginning of the dark cycle (active cycle for rodents) and the presentation of the diet took place during 1 hour after this period registering all behaviors mentioned above. Food was weighed at the beginning and the end of each session.

BIOCHEMICAL AND BODY FAT ANALYSES

After BSS, between 130 and 140 days of life, the animals were euthanized. After fasted overnight, the animals were sacrificed by excess anesthetic to perform a median laparotomy. After reaching deep anesthesia, a vertical incision in the abdominal region was performed to collect blood samples (5 mL) through intracardiac puncture. Each blood sample was centrifuged at 2500 G/20 min to obtain the serum and then stored in a freezer at -20 °C for further analysis. Serum samples were obtained to determine biochemical variables (fasting glycemia, total cholesterol, low-density lipoprotein (LDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatinine). Biochemical analyses were performed at the Department of Metabolic and Nutritional Diseases of the Federal Rural University of Pernambuco through the use of an automatic Labmax 400® analyzer and Latest reagents®. The abdominal fat was removed and weighed on a mass scale® (model AL200 Marte; Rio de Janeiro, Brazil).

STATISTICAL ANALYSIS

For statistical analysis, the Shapiro-Wilk test was performed to evaluate data homogeneity; a one-way or two-way analysis of variance (ANOVA) test was performed followed by Holm Sidak´s or Tukey´s *post-hoc* test. The Graph Pad Prism 7 for Windows (GraphPad Software Inc., La Jolla, Calif., USA) was used for all groups and the values are presented as mean and standard deviation (SD); p-values < 0.05 were considered to be statistically significant.

RESULTS

BODY MASS AND FOOD INTAKE

At 60 days old the bodyweight of the animals before time-restricted feeding showed a difference between western groups (an increase of 13 %) and control groups (C = 246.8 ± 8.5; RC = 258.8 ± 32.2; W = 279.5 ± 24.6; RW = 278.6 ± 23.4 g, p = 0.0149) indicating the effect of maternal diet. At the end of the experimental period, body weight gain (g) was similar between control groups and westernized groups. However, we found differences between the RC (58.0 ± 23.5) and W groups (W = 94.5 ± 28.0; RW = 71.6 ± 29.7) (p = 0.047). Even so, the final body weight (g) of the W group was 17 % and 18 % greater than that of the C and RC groups, respectively (C = 319.4 ± 22.7; RC = 316.8 ± 28.8; W = 374.0 ± 25.4; RW = 350.2 ± 30.4 g, p = 0.0001). The RW group also showed greater body weight compared to C and RC in the 7th and 10th week, respectively (Fig. 2). The RM two-way ANOVA test showed interactions between diet and time ($F(9, 99) = 2.4$, $p = 0.016$), and isolated effects of diet ($F(3, 33) = 9$, $p = 0.0002$)) and time ($F(3, 99) = 181$, $p < 0.0001$). Therefore, regardless of the time elapsed, there was an effect of maternal diet from the first week of intervention until the end of the experimental period.

Before the time restricted-feeding, the groups did not show any differences in total diet intake, neither in the light phase nor in the dark phase of the 24-hour cycle. However, during the restriction period, the restricted groups reduced the food intake

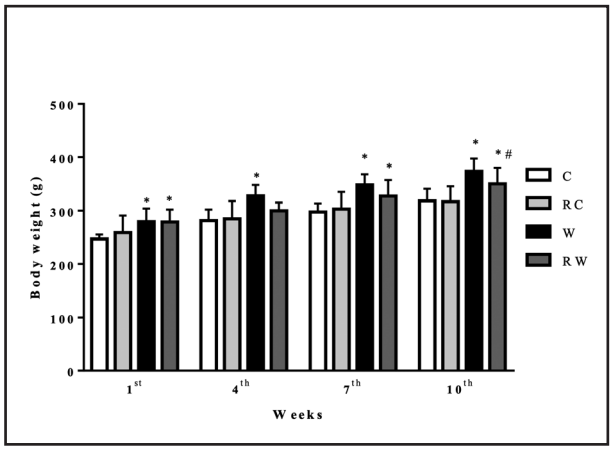

Figure 2.

Weekly body weight of offspring according to maternal diet and time-restricted feeding in adult life (Groups [n = 10 per group]: C: control group; RC: restricted control; W: westernized group; RW: restricted westernized. RM two-way ANOVA followed by Holm Sidak´s *post-hoc* C test. *Versus C group, #Versus RC group [$p < 0.05$]).

(by 46 % for both restricted groups) during the 24-hour cycle (C = 26.9 ± 2.1 g; RC = 14.7 ± 2.5 g; W = 27.1 ± 2.4 g; RW = 14.7 ± 2.7 g, $p < 0.001$). This reduction was likely from the total amount ingested in the dark period (C = 6.1 ± 1.5 g; RC = 2.2 ± 3.8 g; W = 6.5 ± 0.7 g; RW = 2.4 ± 4.2 g, $p < 0.001$), since no changes were observed in the amount of food ingested in the light period (C = 2.9 ± 0.9 g; RC = 2.7 ± 0.8 g; W = 2.5 ± 1.42 g; RW = 2.5 ± 0.8 g, $p > 0.05$). However, it is highlighted that immediately after diet replacement, the restricted groups showed a "temporary hyperphagia", increasing by 29 % the intake of diet in the RC group compared to C (C = 5.1 g; RC = 6.6 g) and by 22 % in the RW group compared to W (W = 5.9 g; RW = 7.2 g), but this was insufficient to generate a total increase in the daily amount of energy.

BEHAVIORAL SATIETY SEQUENCE

The BSS was performed after 8 weeks of time-restricted feeding allowed to identify whether the nutritional manipulation at the beginning of life and/or the restriction of food in the dark phase altered the pattern of frequency, size, and duration of a meal of adult animals.

It was observed that the restriction of food and/or the maternal diet did not cause loss of the natural structure of the eating behavior characterized by an initial state of feeding followed by a transition between rest periods mediated by cleaning and exploration behaviors (Fig. 3). However, comparing RC with C, a phase advance was observed in the satiety point that occurred at 38 min in the RC group against 45 min in the C group (Fig. 3 C and D). However, this difference was not statistically significant when analyzed by sequence by time-bin (Fig. 3 B and D) — e.g., the comparison between RC and C did not show any significance ($F(1, 16) = 3.3$, $p = 0.0891$). However, significant mother western diet x time bin interactions were evident for the duration of eating in W group versus the C group during the fourth, sixth, seventh, eighth time-bins ($F(1, 16) = 61$, $p < 0.0001$) causing an advance in the transition from eating to resting (Fig. 3 E and F). Thus, the time spent in rest was increased in the W group compared to the C group during the seventh and eighth time-bins (($F(14, 154) = 3.3$; $p = 0.0002$) (Fig. 3E). The comparison with other groups (RC, RW, W) did not show any differences between RC and RW, but a phase delay was observed in RW compared to C in the sixth time-bin ($F(1, 12) = 46$, $p < 0.0001$) (Fig. 3 G and A). The set of changes related was accompanied by an increase in feed rate and a decrease in meal duration relativized by body weight in all groups compared to control, and between the RW x W and between RW x RC groups (Table I).

Together, it was evidenced that both the maternal diet and the restriction of food caused alterations in eating behavior when compared with the control groups (C and W, reference). Thus, it can be inferred that the maternal westernized diet itself modifies in the long term the feeding behavior of the offspring, and that the changes in eating behavior due to temporal restriction varied differently between groups and were influenced by the maternal diet.

BIOCHEMICAL PROFILE AND ABDOMINAL FAT

The statistical analysis revealed a difference in fasting glycemia as a function of the gestation/lactation diet, but without effect due to dietary temporal restriction or in association with gestation/lactation dietary intervention (Table II). For triglyceride values, both groups with westernized diets (W and RW) showed high rates. Regarding the other biochemical parameters evaluated, there was no alteration either due to the perinatal diet or the temporal restriction of food. Regarding enzymes associated with liver damage, only ALT, more specific to liver tissue, was altered due to temporal restriction associated with perinatal diet (Table II).

Table II also shows that the relative gonadal, retroperitoneal and total abdominal fat were higher in the westernized group compared to the control group, and the RW group exhibits a higher total amount of abdominal fat, but not compartmentalized between retroperitoneal and gonadal fat. No difference was observed in relative liver weight.

DISCUSSION

Eating behavior is a fundamental component in the control of the overweight/obesity processes because it can impact eating disorders (15) and physiometabolic disorders (16). The experimental model analyzed caused higher body weight and abdominal fat in the westernized groups. Interestingly, the time-restricted feeding did not promote weight or abdominal fat reduction between the restricted groups compared to their peer's *ad libitum,* even with restricted groups ingesting less food during the 24-h cycle. However, we highlighted the temporary hyperphagia found in both groups immediately after the end of the restriction period, and an alteration of the satiety point in animals from mother-fed westernized diet during pregnancy and lactation.

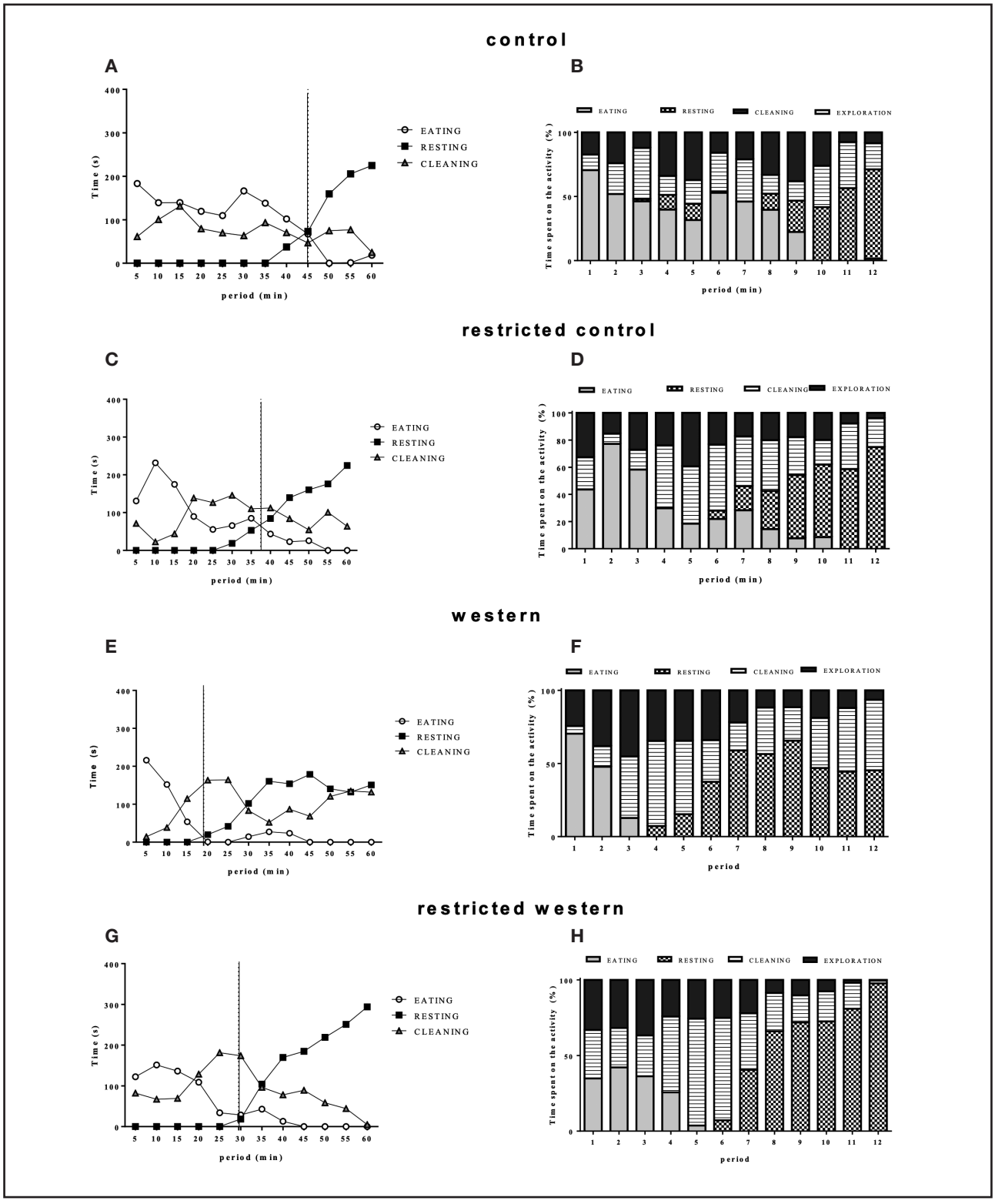

Figure 3.

Behavioral sequence of satiety of adult offspring from dams exposed to westernized diet or control in pregnancy and lactation, and with temporal restriction of food. Each period (12 times) of 5 min quantifies the duration of the behavior during total test time intervals (60 min). Columns represent the proportion of the total number of behavior observations per time interval (C [AB]: control group; RC [CD]: control group with temporal restriction of food; W [EF]: westernized diet group in pregnancy and lactation; RW [GH]: westernized diet group in pregnancy and lactation with temporal restriction of food. The line of intersection between resting and eating behavior signifies the point of satiety; RM two-way ANOVA followed by Holm-Sidak´s *post-hoc* test; $p < 0.05$).

Table I. Meal microstructure parameters of adult rats from mothers exposed to a westernized diet or controls during pregnancy and lactation and time-restricted feeding

Variables		C	RC	W	RW
Meal size	(kcal/kg of weight)	65.33 (± 15.81)	46.15 (± 15.91)	50.00 (± 19.80)	67.46 (± 9.78)
Feed rate	(kcal/min)	1.14 (± 0.24)	1.03 (± 0.28)*	2.30 (± 0.57)*	3.63 (± 0.69)*†‡
	(g/min)	0.31 (± 0.06)	0.28 (± 0.08)*	0.63 (± 0.16)*	1.00 (± 0.19)*†‡
Meal duration	(min)	18.97 (5.48)	15.41 (6.15)*	6.54 (2.84)*	7.14 (1.43)*

*C: control group (n = 9); RC: control group with temporal restriction of food (n = 10); W: westernized diet group during pregnancy and lactation (n = 11); RW: westernized diet group during pregnancy and lactation with temporal restriction of food (n = 7). One-way ANOVA followed by Tukey's post-test (p < 0.05). *Versus C; †Versus RC; ‡Versus W.*

Table II. Serum biochemical profile and abdominal fat pad of adult rats from mothers fed a westernized diet during pregnancy and lactation, submitted or not to time-restricted feeding

Biochemical parameters	C	RC	W	RW
Glycemia (mg/dL)	138.70 (± 20.75)	146.90 (± 25.88)	183.10 (± 32.0)*	164.20 (± 30.03)
Triglycerides (mg/dL)	27.10 (± 8.48)	35.66 (± 12.64)	45.97 (± 11.73)*	46.8 (± 14.47)*
Cholesterol (mg/dL)	56.93 (± 9.98)	61.73 (± 16.73)	62.54 (± 11.59)	58.31 (± 11.34)
Fat pad (g/100 g of body weight)	**C**	**RC**	**W**	**RW**
Abdominal fat	1.88 (± 0.82)	2.36 (± 1.05)	3.56 (± 1.16)*	3.12 (± 0.64)*
Gonadal fat	0.88 (± 0.36)	1.13 (± 0.45)	1.64 (± 0.76)*	1.52 (± 0.48)
Retroperitoneal total fat	0.99 (± 0.52)	1.22 (± 0.73)	1.77 (± 0.56)*	1.46 (± 0.14)

C: control group; RC: control group with temporal food restriction; W: westernized diet group during pregnancy and lactation; RW: westernized diet group during pregnancy and lactation with temporal restriction of food. One-way ANOVA followed by Tukey's post-hoc *test. *Versus C versus RC (p < 0.05). Values expressed as mean ± DPM.*

Similar responses to the weight increase of the adult offspring from mothers fed a westernized or high-fat diet were observed in previous studies (17,18). Possible changes in the energetic homeostasis of the offspring may be due to the phenomenon described as fetal programming, which shows that the conditions of the mother during the critical period of development will reverberate in the homeostasis of the offspring during adulthood (19). Disturbances in the energetic homeostasis of the offspring were later confirmed by other studies based on the use of a low-protein maternal diet (10), or high-fat diet (20) proving the consequences of the long-term maternal diet on the metabolic homeostasis of the adult offspring (21).

Food intake control involves a complex network of orexigenic and anorexigenic neuropeptides. TRF stimulates the secretion of orexigenic factors and causes animals to eat faster, suggesting that those factors act on mechanisms at the beginning and end of the meal (22). In rats, a high-fat maternal diet may result in changes in metabolic regulation and feeding behavior, resulting from a greater proliferation of orexigenic neurons (23) of the hypothalamus (24,25). These morphofunctional changes that occur in hypothalamic functions impact the body composition and glycemic control of the offspring (23).

The responses to the feeding behavior of the groups submitted to temporal food restriction varied according to the maternal diet. The group submitted to restriction from control mothers had an advanced point of satiety. On the other hand, the group of westernized mothers delayed the point of satiety when compared to their respective pairs of non-restricted controls. The behavioral analysis demonstrated that both the restriction of control and westernized diet affects the state of satiety observed by means

of the feeding rate. This result can be explained by changes in the secretion of hormones related to hunger and satiety (25) with long-term effects on controlling food intake among other factors. In other fetal programming models such as low-protein maternal diet, the study of feeding behavior in the offspring demonstrated a delay in the firing of the satiety point in adulthood (10), similar to that found in young animals submitted to early weaning (13), whose models and results are opposed to those of the present study —i.e., the descending group of mothers fed a westernized diet (W or RW) demonstrated advancements in the firing of the satiety point, but both ate with more speed or a higher feeding rate. On the other hand, the RC group showed a slower feeding rate compared to the C group.

Altogether, we can infer that either due to lack or excess nutrients, the system of control of food intake in the adult offspring is strongly influenced by the maternal diet, and that deprivation time interferes differently according to composition diet. Moreover, we highlight that the results of our experimental design are pioneer in showing the influence of the westernized maternal diet on the feeding behavior of the offspring in the long term.

A cafeteria diet during lactation increases food intake in the adult offspring (26). The increase in food intake and consumption speed can be observed in our results. Westernized groups (W and RW) during BSS increased the speed of food intake by 100 % and 218 %, respectively compared to group C. The results of the maternal westernized diet also favor, in the adult offspring, an increase in ectopic fat deposits in the abdominal region, hyperglycemia, and hypertriglyceridemia, similar to those observed by Ferro-Cavalcante et al. (2013) (15). The increase in white adipose tissue deposits resulting from fetal programming has been translated by reduced fat oxidation in tissues such as skeletal muscle and brown adipose tissue (27,28). Therefore, there is a reduction in energy expenditure due to lower lean mass and altered mitochondrial metabolism (33-35). In part, this change seems to be associated with a reduction in the expression of decoupling proteins (UCPs) in brown adipose tissue, which plays a fundamental role in the thermogenesis process (30,31).

The increase in fat in the W group can be explained by metabolic programming, but the small fat reduction in the RW group was not expected. However, evidence from the literature has also shown that an increase in fat in the diet attenuates the amplitude of the clock genes and that temporal restriction restores this amplitude. A study conducted in 2012 showed that fasting at the beginning of the dark phase in mice resulted in an increase in the amplitude of lipogenic genes, resulting in new lipid synthesis in the liver, which is consistent with little reduction in abdominal fat and the hypertriglyceridemia (36) observed in our results in the RW group. However, it was observed in the present study that TRF seems to have minimized some negative metabolic effects generated by the maternal diet in the offspring, such as the restoration of glycemia, and not an elevation of retroperitoneal and epididymal fat.

In our study, a westernized diet caused changes in glycemia and lipidemia in line with the results found by Ferro-Cavalcante et al. (2013) (15), which constitute metabolic risk factors for associated diseases. Therefore, the nutritional composition of the dietary model used, associated or not with time-restricted feeding, is favorable to the development of disorders observed in the feeding behavior and metabolism of adult offspring. The westernized diet is characterized among other factors by having a high amount of lipids and fructose. The increase in fructose in the diet of rats is associated with the presence of glucose intolerance and hepatic steatosis (7,34,35). When present early in life, it seems to modulate epigenetic changes that predispose the individual to long-term metabolic diseases (36).

We recognize as a limitation of the study the absence of more in-depth molecular analyses such as the peptides related to feeding behavior, or the expression of clock genes. However, we revealed that this is a pioneering study in demonstrating the influence of both factors, maternal westernized diet and time-restricted feeding, on the risk of feeding disorders. This contributes to the establishment of links between obesity, eating disorders, and comorbidities. We also suggest that the results obtained herein can serve as a basis for subsequent studies to investigate the associated molecular machinery.

The set of results of the present study demonstrates that maternal diet and time-restricted feeding independently alter glucose and lipid metabolism and aspects of feeding behavior. From the BSS findings, it can be inferred that maternal diet influences in the long term the feeding behavior of the adult offspring, and that the time-restricted feeding affects the parameters of feeding behavior independently of the diet.

The importance that maternal diet during pregnancy and lactation has in the long term on the health of the offspring is well documented. This study shows that the feeding schedules of the adult offspring whose mothers had an obesogenic diet during pregnancy/lactation can impact the metabolic outcome and feeding behavior of these offspring in the long term. It is necessary that human studies be carried out to analyze the intensity of these effects on human health and, in this way, manage the consequences of a westernized maternal diet.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Otros

Vitamina D y su efecto positivo sobre el eje PTH/vitamina D/calcio-FGF23/klotho/fósforo en pacientes con trasplante renal

Vitamin D and its positive effect on the PTH/vitamin D/calcium-FGF23/klotho/phosphorus axis in kidney transplant recipients

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Resumen

Introducción: la hipovitaminosis D es frecuente en los receptores de trasplante renal (RTR) y se asocia con efectos deletéreos tanto a nivel óseo como extraóseo. El tratamiento con colecalciferol es eficaz para la normalización de la 25(OH)D, demostrándose un efecto benéfico sobre el eje calciotrópico; sin embargo, su efecto sobre el eje fosfotrópico no se ha reportado. El objetivo de este estudio fue evaluar el efecto de la normalización de las concentraciones séricas de 25(OH)D sobre el eje PTH/vitamina D/calcio-FGF23/klotho/fósforo en RTR tratados con colecalciferol, así como la asociación entre sus componentes.

Métodos: estudio prospectivo en 23 RTR con hipovitaminosis D y antecedente de nefropatía primaria tratados con colecalciferol, en quienes se evaluó el eje PTH/vitamina D/calcio y FGF23/klotho/fósforo durante el estado de hipovitaminosis D y a la normalización de la 25(OH)D.

Resultados: a la normalización de la 25(OH)D se evidenció una reducción de la PTH [103 (58,5-123,9) *vs.* 45,6 (30,1-65,1) pg/mL; p = 0,002] y un aumento del fósforo sérico [3,1 (2,3-3,5) *vs.* 3,3 (3-3,6) mg/dL; p = 0,01], sin diferencias en las concentraciones de calcio, klotho y FGF23. El tiempo para lograr la normalización de la 25(OH)D fue de 12 semanas (4-12), con una dosis de 5000 UI/día (4000-6000). Se corroboró una asociación positiva entre klotho y PTH (r = 0,54; p = 0,008; regresión lineal, β = 0,421; IC 95 %: 0,003-0,007; p = 0,045).

Conclusiones: el tratamiento con colecalciferol es eficaz para la normalización de la 25(OH)D con un efecto benéfico sobre el metabolismo calcio-fosfotrópico caracterizado por una reducción de la PTH y un incremento de la fosfatemia, sin modificaciones de calcemia, calciuria, FGF23 o klotho.

Palabras clave:

Trasplante renal. Calcio. Fósforo. Factor de crecimiento fibroblástico 23. Klotho. Vitamina D.

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Aspectos éticos: este protocolo se desarrolló de acuerdo a las recomendaciones nacionales e internacionales en materia de investigación.

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Abstract

Background: hypovitaminosis D is frequent in kidney transplant recipient (KTR) patients and is associated with deleterious effects both at the bone and extraosseous levels. Treatment with cholecalciferol is effective for the normalization of 25(OH)D, demonstrating a beneficial effect on the calcium-tropic axis in other populations; however, its effect on the PTH/vitamin D/calcium and FGF23/klotho/phosphorus axis in RTR has not been reported. The aim of this study was to evaluate the effect of normalization of serum 25(OH)D concentrations on the PTH/vitamin D/calcium-FGF23/klotho/phosphorus axis in KTR treated with cholecalciferol, as well as the association between the components of this axis.

Methods: a prospective study in 23 KTR with hypovitaminosis D, with evolution from 1 to 12 months post-transplantation, an estimated glomerular filtration rate > 60 mL/min/1.73 m^2 and a history of primary nephropathy treated with cholecalciferol, in whom the PTH/vitamin D/calcium and FGF23/klotho/phosphorus axis was evaluated during the state of hypovitaminosis D and at normalization of 25(OH)D.

Results: at the normalization of 25(OH)D, a reduction in PTH [103 (58.5-123.9) vs 45.6 (30.1-65.1) pg/mL; p = 0.002] and an increase in serum phosphorus [3.1 (2.3-3.5) vs 3.3 (3-3.6) mg/dL; p = 0.01] were evident, with no differences in calcium, klotho and FGF23 concentrations. The time to achieve normalization of 25(OH)D was 12 weeks (RIC, 4-12), with a dose of 5000 IU/day (RIC, 4000-6000). A positive association between klotho and PTH was corroborated (r = 0.54; p = 0.008; linear regression, β = 0.421; B = 0.004; 95 % CI, 0.003-0.007; p = 0.045).

Conclusions: treatment with cholecalciferol is effective for the normalization of 25(OH)D, with a beneficial effect on calcium-phosphotropic metabolism characterized by a reduction in PTH concentration, without significant changes in calcemia or calciuria, as well as an increase in phosphatemia, without modifications in FGF23 or klotho concentrations.

Keywords:

Kidney transplantation. Calcium. Phosphorus. Fibroblast growth factor 23. Klotho. Vitamin D.

INTRODUCCIÓN

A pesar de los efectos benéficos del trasplante renal (TR), las alteraciones del metabolismo del calcio y el fósforo son frecuentes en los receptores de trasplante renal (RTR), condicionando un aumento en la morbimortalidad (1). La enfermedad metabólica ósea (EMO) en RTR se caracteriza por alteraciones en la formación y mineralización ósea, con reducción de la osteoblastogénesis y aumento de la apoptosis del osteoblasto. Dentro de los factores asociados a la EMO en RTR se encuentran: a) las alteraciones del eje FGF23 (factor de crecimiento fibroblástico 23)/PTH (hormona paratiroidea)/vitamina D; b) la terapia de inmunosupresión; c) la presencia de EMO pre-TR; d) las alteraciones de la función del injerto; y e) la hipofosfatemia. Dentro de estos factores, los más importantes son la hipovitaminosis D, el hiperparatiroidismo persistente y el uso de fármacos inmunosupresores (2).

La hipovitaminosis D, definida como la disminución de las concentraciones de 25-hidroxivitamina D [25(OH)D] por debajo de 30 ng/mL según la *Endocrine Society* (3), se encuentra hasta en el 97 % de los RTR antes del primer año, persistiendo en el 94 % después del primer año post-TR (4). Aproximadamente, el 30 % se encuentran en rangos de deficiencia y el 81-85 % en insuficiencia (5,6). La hipovitaminosis D se asocia con un aumento de la morbimortalidad (2,7) y una reducción de los efectos benéficos del TR (6). Dentro de los mecanismos propuestos en la etiopatogenia de la hipovitaminosis D en los RTR destacan: a) la deficiente suplementación de vitamina D antes y después del TR; b) el aumento del catabolismo de 25(OH)D inducido por los fármacos inmunosupresores (6); c) la conversión acelerada de la 25(OH)D en 1,25(OH)2D ante la hipofosfatemia y la elevación de la PTH (8,9); y d) la reducción de la exposición solar para la prevención del cáncer de piel (6).

Se ha reportado que las adecuadas concentraciones de 25(OH)D en los RTR tienen un efecto positivo sobre el metabolismo mineral óseo, la función cardiovascular, la función del injerto, la prevención de infecciones, la antiproteinuria, la disminución de la incidencia del cáncer *de novo* y la disminución de la mortalidad (10). El tratamiento con colecalciferol es eficaz para la normalización de las concentraciones de 25(OH)D, demostrándose un efecto benéfico sobre el eje PTH/vitamina D/calcio en individuos aparentemente sanos y en pacientes con diálisis peritoneal o hemodiálisis, caracterizado principalmente por la disminución de las concentraciones de PTH (11-17); sin embargo, los estudios acerca del efecto del colecalciferol sobre el eje PTH/vitamina D/calcio y FGF23/klotho/fósforo en los RTR, sobre todo al lograr el efecto terapéutico de normalización de las concentraciones de 25(OH)D, son escasos.

El objetivo principal de este estudio fue evaluar el efecto de la normalización de las concentraciones séricas de 25(OH)D sobre el eje PTH/vitamina D/calcio y FGF23/klotho/fósforo en RTR tratados con colecalciferol. El objetivo secundario fue evaluar las asociaciones entre los componentes del eje PTH/vitamina D/calcio y FGF23/klotho/fósforo a la normalización de las concentraciones de 25(OH)D.

MÉTODO

PACIENTES

Se realizó un estudio prospectivo en RTR con hipovitaminosis D atendidos en la clínica de metabolismo mineral óseo del departamento de endocrinología de un hospital de tercer nivel de atención. Se incluyeron hombres y mujeres mayores de 18 años de edad, con evolución de más de un mes pero menos de 1 año post-TR, con una tasa estimada de filtrado glomerular (TFGe) > 60 mL/min/1,73 m^2, sin datos de disfunción o rechazo del injerto y con antecedente de enfermedad primaria como causa de enfermedad renal crónica (ERC). Se excluyeron los pacientes con datos de disfunción o rechazo del injerto, TFGe < 60 mL/min/1,73 m^2, hipercalcemia, hipersensibilidad conocida al fármaco y enfermedades crónico-degenerativas como diabetes, hipertensión arterial, hepatopatía, obesidad, enfermedades autoinmunes, infecciosas o neoplasias, esto con el propósito de disminuir los sesgos generados por el efecto deletéreo directo de dichos factores sobre el metabolismo mineral.

Se definió la hipovitaminosis D como una concentración de 25(OH)D en sangre inferior a 30 ng/mL (3). Se consideró que había deficiencia de vitamina D cuando la concentración de 25(OH) D era < 20 ng/mL e insuficiencia cuando se encontraron entre 21 y 29 ng/mL (3). Se realizó la evaluación clínica y bioquímica del eje PTH/vitamina D/calcio y FGF23/klotho/fósforo antes del inicio del colecalciferol y al lograr la normalización de las concentraciones de 25(OH)D.

TRATAMIENTO CON COLECALCIFEROL

El tratamiento de la hipovitaminosis D consistió en la administración de colecalciferol a dosis de 4000 unidades internacionales por día (UI/d), con medición de la 25(OH)D sérica mensualmente, hasta lograr la normalización (> 30 ng/mL). Se indicó un aumento de 2000 UI/d cada mes cuando el paciente continuaba con 25(OH)D por debajo de 30 ng/dL. La dosis máxima de colecalciferol fue de 10,000 UI/d (3). Una vez lograda la normalización de la 25(OH)D, la dosis de mantenimiento fue de 2000-4000 UI/d [2000 UI/d si las concentraciones de 25(OH)D eran > 40 ng/mL y 4000 UI/d si las concentraciones de 25(OH)D estaban entre 30 y 39 ng/mL]. Se cuantificó en semanas el tiempo en que se logró la normalización de la 25(OH) D. Solo se incluyeron en el análisis los pacientes que lograron la normalización de las concentraciones de 25(OH)D. Las reacciones adversas medicamentosas (RAM) investigadas fueron: hipercalcemia, hiperfosfatemia, hipercalciuria, litiasis renoureteral e hipersensibilidad. Se utilizó el método de recuento de píldoras para evaluar la adherencia terapéutica. Esta medida indirecta y objetiva contó el número de píldoras que se habían tomado entre dos visitas a la clínica en comparación con el número total de píldoras recibidas por el paciente (número de píldoras dispensadas - número de píldoras restantes) / (número prescrito de píldoras por día × número de días entre 2 visitas); el resultado se multiplicó por 100 para obtener el porcentaje de adherencia. La adherencia exitosa se definió como la toma del 90-100 % de las píldoras durante el seguimiento. La función renal se evaluó midiendo las concentraciones de urea y creatinina, así como la tasa de filtración glomerular estimada (TFGe) por CKD-EPI.

EVALUACIÓN BIOQUÍMICA

Se realizó la toma de una muestra de 5 mL de sangre a través de venopunción después de 8 horas de ayuno. Se utilizaron métodos automatizados basados en ensayos colorimétricos y espectrofotométricos (COBAS, Roche, EE. UU.) para la medición del calcio (suero y orina), el magnesio (suero), el fósforo (suero y orina), la albúmina (suero), la urea (suero), la creatinina (suero) y la fosfatasa alcalina (suero). El rango normal (RN) de cada una de estas fue: calcio sérico: 8,4-10,2 mg/dL; calcio urinario de 24 horas < 300 mg/día; fósforo sérico: 2,7-4,5 mg/dL; fósforo urinario de 24 horas: 400-1300 mg/día; magnesio: 1,6-2,6 mg/dL; urea: 10-50 mg/dL; creatinina: 0,40-1,2 mg/dL; albúmina: 3,5-5,2 g/dL; y fosfatasa alcalina: varones: 40-129 U/L; mujeres: 35-104 U/L. Las concentraciones de calcio sérico corregido (mmol/L) se obtuvieron mediante la siguiente fórmula: 4 g/dL - concentración de albumina sérica (g/dL)) × 0,8 + calcio sérico total medido (mg/dL). La relación calcio urinario/peso corporal fue el cociente de la división entre el calcio urinario de 24 horas y el peso en kg (RN < 4 mg/kg de peso corporal por día). Se utilizó un ensayo quimioluminiscente específico para medir la PTH (DiaSorin Inc, EE. UU.), con una sensibilidad de 1 pg/mL y un coeficiente de variación (CV) inter e intraensayo del 5,3 % y 3,5 %, respectivamente, con RN de 15-65 pg/mL. Las concentraciones séricas de 25(OH)D se midieron por quimioluminiscencia (DiaSorin Inc., EE. UU.) con una sensibilidad de 4 ng/mL y unos CV inter e intraensayo del 5,1 % y 8,6 %, respectivamente. Para las mediciones de las concentraciones séricas de FGF23 y klotho se empleó un ensayo inmunoenzimático (ELISA). Para el FGF23 se utilizó el kit "Human FGF23 ELISA" (Aviva Systems Biology, Corp. San Diego, CA, EE. UU.), con RN de 15,6-1000 pg/mL y sensibilidad de 10 pg/mL, con CV intraensayo del 4 % e interensayo del 6,4 %. Para la klotho se utilizó el *kit* de ELISA "Human KL" (Aviva Systems Biology, Corp. San Diego, CA, EE. UU.), con un RN de 7,8-500 pg/mL y una sensibilidad de 2,4 pg/mL, y un CV intra e interensayo del 4,7 % y 7,1 %, respectivamente.

INMUNOSUPRESIÓN

Todos los pacientes recibieron tratamiento inmunosupresor con prednisona, micofenolato mofetilo y tacrolimus, los cuales fueron reportados como dosis en mg/día.

ANÁLISIS ESTADÍSTICO

Las variables categóricas se informaron como frecuencias absolutas y porcentajes. Las variables cuantitativas se describieron como media ± desviación estándar (DE) o mediana y rango intercuartílico (RIC), según su distribución. La relación entre las variables categóricas se evaluó mediante la prueba del χ^2; las variables cuantitativas se analizaron mediante las pruebas T, de Wilcoxon o U de Mann-Whitney, según su distribución. Las correlaciones de las variables cuantitativas se realizaron con el coeficiente de correlación de Spearman. La regresión lineal se utilizó para explicar la relación entre una variable dependiente y una o más variables independientes. Se utilizó la transformación logarítmica en los datos no paramétricos para incluirlos en el modelo de regresión lineal. Todas las pruebas estadísticas se calcularon a dos colas; el valor $p < 0,05$ se consideró estadísticamente significativo. El tamaño de la muestra tuvo un valor $\alpha = 0,05$, un $b = 0,1$ y una potencia estadística $1 - \beta = 0,9$ (G*Power). Se utilizaron los programas estadísticos IBM SPSS Statistics v.25.0 (IBM SPSS, EE. UU.) y STATA v.13 (StataCorp, EE. UU.) para el análisis.

ASPECTOS ÉTICOS

Este protocolo fue desarrollado de acuerdo a las recomendaciones nacionales e internacionales en materia de investigación y fue aprobado por el Comité Local de Ética e Investigación. Se obtuvo del consentimiento informado de todos los pacientes previamente a su inclusión en el estudio.

RESULTADOS

CARACTERÍSTICAS BASALES DE LA POBLACIÓN

De un total de 26 RTR con hipovitaminosis D tratados con colecalciferol se incluyeron en el análisis 23 pacientes que lograron la normalización de las concentraciones séricas de 25(OH) D. De los 3 pacientes que no lograron normalizar la 25(OH)D, dos tuvieron un inadecuado apego terapéutico y en un paciente se diagnosticó síndrome de malabsorción intestinal (Fig. 1). El 52,2 % (n = 12) fueron hombres, con una mediana de edad de 28 años (RIC: 25-33,5). Todos los pacientes eran latinos. Las características basales de los pacientes se resumen en la tabla I.

Después del inicio del colecalciferol, el tiempo para lograr la normalización de las concentraciones séricas de 25(OH)D fue de 12 semanas (RIC: 4-12). La dosis de colecalciferol requerida para lograr la normalización de la 25(OH)D fue de 5000 UI/día (RIC: 4000-6000). Durante el tratamiento con colecalciferol no se evidenciaron reacciones adversas medicamentosas o sospecha de las mismas.

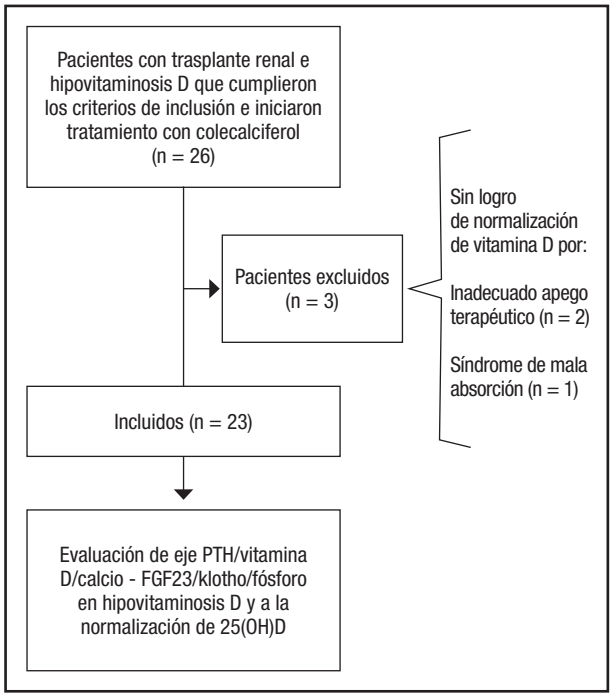

Figura 1.

Diagrama de flujo sobre la metodología del estudio.

Tabla I. Características basales de los receptores de trasplante renal incluidos en el estudio (n = 23)

Variable	Resultado
Edad (años)	28 (25-33,5)
IMC (kg/m^2)	21,7 (19,8-24)
Distribución corporal (%)	
Masa muscular	31,4 (29,8-32,3)
Masa grasa	17,8 (16,4-21,25)
Tabaquismo, % (n)	Antes del trasplante renal: 26,1 (6) Después del trasplante renal: 0
Consumo de alcohol, % (n)	Antes del trasplante renal: 26,1 (6) Después del trasplante renal: 0
Etiología de la enfermedad renal crónica, % (n)	Hipoplasia renal: 52,2 (12) Idiopática: 30,5 (7) Glomerulonefritis (membranosa, proliferativa, focal y segmentaria): 13 (3) Cistinosis: 4,3 (1)
Tipo de tratamiento sustitutivo de la función renal antes del trasplante, % (n)	Diálisis peritoneal: 56,5 (13) Hemodiálisis: 13 (3) Diálisis peritoneal y posteriormente hemodiálisis: 30,5 (7)
Tipo de trasplante renal, % (n)	Donador vivo relacionado: 47,8 (11) Donador vivo no relacionado: 30,4 (7) Donador fallecido: 21,7 (5)

IMC: índice de masa corporal. Variables cualitativas reportadas en porcentajes y frecuencia. Variables cuantitativas reportadas en mediana y rango intercuartílico.

EFECTO DE LA NORMALIZACIÓN DE LAS CONCENTRACIONES SÉRICAS DE 25(OH)D SOBRE EL EJE PTH/VITAMINA D/ CALCIO EN RECEPTORES DE TRASPLANTE RENAL TRATADOS CON COLECALCIFEROL

Cuando se logró la normalización de la 25(OH)D se evidenció el aumento de las concentraciones de 25(OH)D [13 (9,3-17,1) *vs.* 37,6 (32-45,2) ng/mL; p = 0,000] y la reducción de la PTH [103 (58,5-123,9) *vs.* 45,6 (30,1-65,1) pg/mL; p = 0,002] con respecto al estado de hipovitaminosis D. Se evidenció una reducción del 56 % en las concentraciones de PTH. No se encontraron diferencias estadísticamente significativas en las concentraciones de calcio, calcio urinario de 24 h e índice CaU/kg (Tabla II). En el 96 % (n = 22) de los pacientes, las concentraciones de PTH se normalizaron.

EFECTO DE LA NORMALIZACIÓN DE LAS CONCENTRACIONES SÉRICAS DE 25(OH)D SOBRE EL EJE FGF23/KLOTHO/ FÓSFORO EN RECEPTORES DE TRASPLANTE RENAL TRATADOS CON COLECALCIFEROL

Al evaluarse las características del eje FGF23/klotho/fósforo se observó un aumento de las concentraciones de fósforo sérico [3,1 (2,3-3,5) *vs.* 3,3 (3-3,6) mg/dL; p = 0,01]. No se evidenciaron diferencias estadísticamente significativas en las concentraciones de FGF23, klotho y fósforo urinario de 24 h al compararlas durante la hipovitaminosis D y a la normalización de las concentraciones de 25(OH)D (material suplementario).

No se evidenciaron diferencias en las concentraciones de magnesio [1,7 (1,5-1,9) *vs.* 1,7 (1,5-1,8) mg/dL; p = 0,37], fosfatasa alcalina [82 (71-92) *vs.* 75 (68-82,5) U/L; p = 0,22], creatinina [1 (0,8-1,2) *vs.* 1,1 (0,8-1,3) mg/dL; p = 0,15] ni en la TFGe [79,6 (66,8-109,5) *vs.* 78 (63,7-92,3) mg/dL; p = 0,17] con la normalización de las concentraciones de 25(OH)D.

ASOCIACIONES ENTRE LOS COMPONENTES DEL EJE PTH/VITAMINA D/CALCIO Y FGF23/ KLOTHO/FÓSFORO A LA NORMALIZACIÓN DE LAS CONCENTRACIONES SÉRICAS DE 25(OH)D

El análisis de las asociaciones entre los diferentes componentes del eje PTH/vitamina D/calcio y FGF23/klotho/fósforo cuando se logró la normalización de las concentraciones de 25(OH)D corroboró una asociación positiva entre klotho y PTH (r = 0,54; p = 0,008; regresión lineal, β = 0,421; B = 0,004; IC 95 %, 0,003 a 0,007; p = 0,045). No se observaron asociaciones entre el resto de las variables y tampoco se evidenció asociación con la dosis de los fármacos incluidos en el esquema inmunosupresor (Tabla III).

Tabla II. Características del eje PTH/vitamina D/calcio - FGF23/klotho/fósforo en hipovitaminosis D y a la normalización de las concentraciones séricas de 25(OH)D

	Hipovitaminosis D	A la normalización de 25(OH)D	p
25(OH)D (ng/mL)	*13 (9,3-17,1)*	*37.6 (32-45,2)*	*0,0001*
PTH (pg/mL)	*103 (58,5-123,9)*	*45,6 (30,1-65,1)*	*0,002*
Calcio (mg/dL)	9,7 (9,3-10,1)	9,8 (9,4-10)	0,39
Calcio corregido (mg/dL)	9,2 (8,9-9,5)	9,3 (9,1-9,6)	0,30
Albúmina (g/dL)	4,5 (4,3-4,8)	4,8 (4,4-5)	0,52
Calcio urinario de 24 h (mg/día)	94,6 (57,5-125)	110 (90-160)	0,14
Índice calcio urinario/kg peso (mg/kg/día)	1,7 (1,15-2,08)	2 (1,4-2,6)	0,13
FGF23 (pg/mL)	6,2 (5,6-9,6)	6,6 (5,6-11,05)	0,39
Klotho (pg/mL)	18,4 (15,3-23,9)	19,5 (13,8-32,5)	0,09
Fósforo (mg/dL)	*3,1 (2,3-3,5)*	*3,3 (3-3,6)*	*0,01*
Fósforo urinario de 24 h (g/día)	53 (37,7-56,2)	54,2 (44,6-59,3)	0,41
Creatinina (mg/dL)	1 (0,8-1,2)	1,1 (0,8-1,3)	0,15
Tasa estimada de filtrado glomerular (mL/min): CKD-EPI	79,6 (66,8-109,5)	78 (63,7-92,3)	0,17
Dosis de fármacos inmunosupresores (mg/día)			
Prednisona	20 (15-25)	15 (10-20)	0,01
Micofenolato	1500 (1250-2000)	1750 (1250-2000)	0,08
Tacrolimus	6 (5,5-8)	7 (5-8)	0,34

Variables reportadas en mediana y rango intercuartílico.

Tabla III. Asociaciones entre los componentes del eje PTH/vitamina D/calcio - FGF23/klotho/fósforo a la normalización de las concentraciones séricas de 25(OH)D

	Vitamina D	PTH	FGF23	Klotho
Vitamina D		r = -0,08 p = 0,70	r = 0,74 p = 0,73	r = -0,30 p = 0,15
PTH	r = -0,08 p = 0,70		r = -0,10 p = 0,62	*r = 0,54* *p = 0,008*
Calcio sérico	r = 0,01 p = 0,94	r = 0,09 p = 0,66	r = 0,17 p = 0,43	r = 0,20 p = 0,34
Calcio urinario 24 h	r = -0,01 p = 0,95	r = 0,12 p = 0,57	r = 0,32 p = 0,13	r = -0,02 p = 0,91
FGF23	r = 0,74 p = 0,73	r = -0,10 p = 0,62		r = -0,08 p = 0,70
Klotho	r = -0,30 p = 0,15	*r = 0,54* *p = 0,008*	r = -0,08 p = 0,70	
Fósforo	r = -0,25 p = 0,23	r = 0,93 p = 0,67	r = -0,17 p = 0,43	r = 0,14 p = 0,50
Fósforo urinario	r = -0,22 p = 0,30	r = 0,01 p = 0,95	r = -0,02 p = 0,91	r = 0,07 p = 0,73
Mg sérico	r = -0,21 p = 0,32	r = 0,21 p = 0,33	r = 0,96 p = 0,66	r = 0,15 p = 0,48
Prednisona	r = -0,14 p = 0,51	r = 0,22 p = 0,29	r = -0,18 p = 0,39	r = 0,06 p = 0,77
Micofenolato	r = -0,03 p = 0,88	r = -0,04 p = 0,84	r = -0,05 p = 0,81	r = -0,10 p = 0,62
Tacrolimus	r = 0,17 p = 0,41	r = 0,38 p = 0,66	r = -0,06 p = 0,77	r = -0,14 p = 0,50

DISCUSIÓN

En este estudio se evaluó el efecto de la normalización de las concentraciones séricas de 25(OH)D sobre el eje PTH/vitamina D/calcio y FGF23/klotho/fósforo en RTR tratados con colecalciferol, evidenciándose una reducción de la PTH (incluso la normalización de esta hormona en la mayoría de los pacientes) y la optimización de las concentraciones de fósforo con respecto al estado de hipovitaminosis D, sin evidencia de hipercalcemia, hiperfosfatemia, hipercalciuria o modificaciones de la función renal durante el tratamiento. Por otra parte, se encontró como hallazgo relevante la asociación positiva entre klotho y PTH, no descrita previamente en RTR.

El trasplante renal exitoso mejora las alteraciones del metabolismo mineral óseo, principalmente a lo largo del primer año post-TR (18). Como se comentó previamente, a pesar del efecto benéfico del TR, las alteraciones del metabolismo del calcio y fósforo son frecuentes en los pacientes RTR. La hipovitaminosis D, al igual que en la población general, es frecuente en los RTR, condicionando un aumento de la morbimortalidad. La normalización de las concentraciones séricas de 25(OH)D en los RTR es posible con el tratamiento con colecalciferol, lo cual promueve efectos positivos sobre el metabolismo mineral óseo tal y como evidenciamos en este estudio. Algunos estudios han evaluado el efecto de colecalciferol sobre el eje PTH/vitamina D/calcio y FGF23/klotho/fósforo en poblaciones diferentes a la incluida en este estudio.

En individuos aparentemente sanos con hipovitaminosis D, el tratamiento con colecalciferol ha mostrado una reducción de las concentraciones de PTH y, sin embargo, un aumento significativo de 1,25(OH)2D y FGF23 (11); en este estudio controlado con placebo, el tratamiento con colecalciferol condicionó un incremento de las concentraciones de FGF23, el cual se asoció de manera directa con el aumento en las concentraciones de 1,25(OH)2D (11). En los pacientes con obesidad/sobrepeso e hipovitaminosis D, la administración de colecalciferol normalizó las concentraciones de 25(OH)D y disminuyó las concentraciones de PTH (12).

En los pacientes en diálisis peritoneal, el tratamiento con colecalciferol condicionó un aumento exponencial del FGF23 con niveles elevados (> 30.000 pg/mL) en el 74 % de los casos y con reducción hasta valores basales a las 32 semanas de su suspensión (13). En dicho estudio, la elevación de los valores de FGF23 se asoció también al incremento de los valores de 1,25(OH)2D (13). Por otra parte, en una población con ERC y TGFe > 30 mL/min/1,73 m^2 no se evidenciaron modificaciones de las concentraciones de FGF23 y klotho después del tratamiento con colecalciferol (14).

En los pacientes en hemodiálisis, el tratamiento con colecalciferol logró la normalización de la 25(OH)D dentro de los primeros 3 meses de tratamiento, sin modificaciones de las concentraciones de PTH a lo largo de su seguimiento; sin embargo, al compararlos contra un grupo con placebo, se observaron menores concentraciones de PTH (15). Otro estudio de pacientes en hemodiálisis demostró una reducción de las concentraciones de klotho durante el tratamiento con colecalciferol, sin modificaciones de FGF23 (16).

Específicamente en los RTR se ha observado una reducción de la PTH (12 %) a los 12 meses de tratamiento con colecalciferol (17), independientemente de si se logró la normalización de la 25(OH)D; sin embargo, su efecto sobre otros parámetros del eje FGF23/klotho/fósforo no se había descrito hasta este momento. Cabe destacar que, en cada uno de los estudios previamente comentados, los componentes del eje PTH/vitamina D/calcio y FGF23/klotho/fósforo no se evaluaron de manera simultánea, a diferencia de nuestro estudio.

En nuestro estudio corroboramos la disminución de las concentraciones de PTH con un porcentaje mayor al reportado (56 % *vs.* 12 %), observando incluso que la mayoría de los pacientes normalizaron la PTH (96 %); en el paciente en que no se normalizó esta hormona, se evidenció una reducción mayor del 50 % con respecto a su valor pretratamiento. Aunado a lo anterior, evidenciamos una optimización de las concentraciones de fósforo, sin condicionar hiperfosfatemia, aunado al mantenimiento de normocalcemia y, a diferencia de lo evidenciado en otras poblaciones, no se corroboraron diferencias significativas en las concentraciones de FGF23 o klotho.

Por otra parte, resultan interesantes la dosis y el tiempo requeridos para normalizar las concentraciones de 25(OH)D en nuestro estudio. En la población general se recomienda el tratamiento con colecalciferol a una dosis 1500-2000 UI/día para los adultos de entre 19 y 50 años con hipovitaminosis D, con un tiempo aproximado de 4 a 6 semanas para la normalización de las concentraciones séricas de 25(OH)D (3). En nuestro estudio observamos que la dosis de colecalciferol requerida para normalizar la 25(OH)D en los pacientes RTR fue de 5000 UI/día, con un tiempo de 12 semanas, ambos mayores a lo establecido, lo cual puede guardar relación con alteraciones en parámetros farmacocinéticos como la absorción de colecalciferol, las alteraciones en su distribución o el aumento del catabolismo de vitamina D mediado por otros fármacos (glucocorticoides u otros inmunosupresores). En un estudio previo realizado en una población semejante a la de este estudio se mostró un requerimiento de 4000 UI/día para el mantenimiento de concentraciones séricas de 25(OH)D > 30 ng/dL durante el primer año de seguimiento post-TR (18). Este dato puede ser importante para normar la dosis de colecalciferol a largo plazo dentro de los protocolos para la atención y el tratamiento integral de los RTR.

Durante el tratamiento con colecalciferol no evidenciamos RAM ni sospecha de las mismas; sin embargo, es importante mencionar que, debido al diseño y al objetivo de nuestro estudio, el seguimiento fue relativamente corto. Un estudio previo en nuestra población informó que el tratamiento con colecalciferol no produjo RAM como hipercalcemia o hiperfosfatemia a los 12 meses, detectándose solo un caso de hipercalciuria entre los 74 pacientes incluidos (18). En otra cohorte de RTR tratados con colecalciferol se informó una frecuencia de hipercalcemia del 3,2 % sin observarse hiperfosfatemia, litiasis, hipercalciuria, rechazo del injerto, alteraciones de la función renal, ni fracturas (17). Consideramos que, durante el tratamiento con colecalciferol, los estudios de farmacovigilancia a largo plazo para la detección de RAM o sospecha de las mismas son indispensables para evaluar la seguridad del fármaco y la relación riesgo/beneficio en los pacientes con TR; además, los datos proporcionados por dichos estudios podrían servir para sugerir modificaciones de las dosis de mantenimiento de colecalciferol de manera dinámica y personalizada a cada población.

Otro hallazgo relevante en nuestro estudio es la asociación positiva de klotho y PTH. Klotho tiene un papel importante en la regulación del metabolismo del calcio tanto a corto como a medio plazo, en un sistema regulador de "varios pasos". Klotho se une a la Na^+,K^+-ATPasa y regula su reclutamiento en la superficie celular; en respuesta a concentraciones reducidas de calcio extracelular, controla la reabsorción de calcio en las células del túbulo contorneado distal y la secreción de PTH en las glándulas paratiroides. En la "regulación de segundos a minutos", klotho promueve el transporte transepitelial de Ca^{2+} y la secreción de PTH. En la "regulación de minutos a horas" y "de horas a días" regula la homeostasis del calcio a través de la acción de la PTH y de la producción de 1,25(OH)2D mediada por PTH (19). La asociación entre klotho y PTH observada en nuestro estudio puede ser explicada por este mecanismo fisiológico. En la población general con función renal conservada, se ha evidenciado una asociación entre klotho y PTH dependiente del sexo: en hombres se ha visto una asociación positiva entre estas dos variables mientras que en mujeres la asociación es negativa (20). En RTR se ha encontrado una asociación de klotho con la DMO y los niveles de osteocalcina (21); sin embargo, la asociación de klotho y PTH en pacientes RTR no se ha publicado aún, por lo que el hallazgo en nuestro estudio resulta novedoso y original. Cabe destacar que, si bien se demostró una disminución estadísticamente significativa de la dosis de prednisona a la normalización de la 25(OH)D con respecto al estado de hipovitaminosis D, no evidenciamos una asociación de la dosis de este fármaco con alguno de los componentes del eje calcio-fosfotrópico, por lo que las modificaciones de PTH o fósforo no se pueden atribuir a las modificaciones de las dosis de prednisona.

Dentro de las fortalezas de nuestro estudio destacamos la originalidad y relevancia al realizarlo en una población en la cual el efecto del colecalciferol sobre el eje calciotrópico y fosfotrópico aún no se ha estudiado, así como la intervención terapéutica con fines de normalización de las concentraciones de 25(OH)D y no solo de substitución con colecalciferol. Dentro de las limitaciones se encuentra el tamaño de muestra aparentemente reducido derivado de los criterios de inclusión y exclusión establecidos; sin embargo, es importante destacar que con el número de pacientes incluidos se cumplió con un adecuado poder estadístico. Proponemos la realización de estudios futuros para evaluar los efectos de la normalización de las concentraciones de 25(OH)D con colecalciferol sobre el

eje calcio-fosfotrópico a largo plazo, su farmacovigilancia y su efecto sobre otras variables a nivel cardiovascular, renal e inmunológico, así como el efecto sobre el pronóstico y la sobrevida.

CONCLUSIONES

El tratamiento con colecalciferol dentro del primer año post-TR es eficaz para la normalización de las concentraciones de 25(OH) D, con un efecto benéfico sobre el metabolismo calcio-fosfotrópico caracterizado por una reducción de PTH y un incremento de la fosfatemia, sin condicionar hipercalcemia, hipercalciuria, hiperfosfatemia, ni modificaciones de FGF23 o klotho. Aunado a lo anterior, se observa una asociación directa entre klotho y PTH al normalizar la 25(OH)D. El presente estudio demuestra que la normalización de las concentraciones de 25(OH)D en pacientes RTR tratados con colecalciferol conduce al control del hiperparatiroidismo secundario sin inducir elevación de FGF23, siendo aquel un fármaco seguro.

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ARÁN

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Revisión

Application of bioelectrical impedance in newborns: an integrative review

Aplicación de la impedancia bioeléctrica en recién nacidos: revisión integradora

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Abstract

Objective: the objective of this study was to identify the use of bioelectrical impedance in newborns (NB), as this is an easy-to-apply and non-invasive method of measurement that can be used for distinguishing fat-free mass (FFM), fat mass (FM), and total body water (TBW).

Method: this was an integrative review of the literature using the PubMed/MEDLINE, EMBASE, Web of Science, and Virtual Health Library databases to search for original articles between 2010-2020. A total of 900 articles were retrieved; after checking for duplicity and applying the eligibility criteria, 9 were further analyzed.

Results: about the results, five studies used single frequency bioimpedance, with a specific population of neonates, preterm and/or full term, and different clinical conditions. Resistance was the most studied bioelectric indicator, the phase angle is little explored, and four studies investigated body composition (FFM, FM and TBW). Studies found that preterm newborns had lower amounts of TBW, FFM, and FM than term newborns, and there were differences in body composition between sex. The phase angle was lower for preterm newborns. Babies fed with high protein formulas had increases in the FFM.

Conclusion: there is a need for multicenter studies to define standardized methods to be used with this public.

Keywords:

Electric impedance. Infant. Newborn. Body composition. Body water.

Resumen

Objetivo: el objetivo de este estudio fue identificar el uso de la impedancia bioeléctrica en recién nacidos (NB), ya que ese método es de fácil medición y no invasivo para la distinción de masa libre de grasa (MLG), masa grasa (MG) y agua corporal total (ACT).

Método: esta fue una revisión integradora de la literatura utilizando PubMed/MEDLINE, EMBASE, Web of Science y Virtual Health Library para la búsqueda de artículos originales (2010-2020). En total, se encontraron 900 artículos, aunque tras la verificación de duplicidad y aplicación de los criterios de elegibilidad, solo 9 fueron para análisis.

Resultados: cinco estudios utilizaron el dispositivo de monofrecuencia. Cada investigación se aplicó en una población específica de neonatos, prematuros y/o a término y diferentes condiciones clínicas. La resistencia fue el indicador bioeléctrico más estudiado, el ángulo de fase fue poco explorado y cuatro estudios investigaron la composición corporal. Dos estudios encontraron que los recién nacidos prematuros tienen menos cantidades de ACT, MLG y MG que los RNT y se observó diferencia en la composición corporal entre los sexos. El ángulo de fase fue inferior en prematuros. Los lactantes que se alimentaron con una fórmula con mayor contenido proteico tenían una mayor cantidad de MLG.

Conclusión: se observa la necesidad de estudios multicéntricos para definir métodos estandarizados para ser utilizados con este público.

Palabras clave:

Impedancia eléctrica. Bebé. Recién nacido. Composición corporal. Agua corporal.

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INTRODUCTION

Nutritional status assessments of newborns (NBs) use weight as an initial parameter, as it is easy to measure and provides a global assessment of body composition; however, this measure does not distinguish between types of body tissues, e.g., fat-free mass (FFM) and fat mass (FM). An adequate birth weight may be indicative of water retention, as newborns have a high metabolic rate; thus, fluid balance needs to be assessed (1).

In this perspective, the Bioelectrical Impedance Analysis (BIA) test is an alternative method to assess body composition and estimate total body water, as well as to analyze changes in body hydration. It is a simple, safe and non-invasive method based on the passage of a low-intensity alternating electrical current, which flows through the human body owing to the movement of ions. The ease of electrical conduction is directly proportional to the amount of body water and electrolytes in the body tissues (2-4).

BIA enables the measurement of raw bioelectrical values of resistance (R) and reactance (Xc) and the calculation of the phase angle (AF). Resistance refers to the opposition to the passage of electric current through the body; it is inversely proportional to the amount of intra and extracellular fluids. FFM, for example, has high conductivity of electric current, as it has a large amount of water and electrolytes, thus presenting low resistance. Bone and adipose tissue, on the other hand, show high resistance because they have a low amount of water and electrolytes; therefore, they are not good electrical conductors. Reactance, in turn, indicates cell membrane integrity, its value is directly related to the presence of a healthy or diseased membrane, nutritional status or hydration (5).

Based on the values of R and Xc, the values of FFM, FM and total body water (TBW) can be estimated using validated and age group-specific formulas. Phase angle (PA) can also be calculated; it reflects the size, integrity, and quality of the cell membrane. Phase angle can be used as a prognostic marker in different clinical situations; abnormal PA values are related to nutritional status. Individuals with low values may have a deficient nutritional status (6,7).

In NBs, BIA can be used to assess hydration, FFM and FM; it is more accurate for TBW assessment, since water is the main conductor in humans and almost all body water volume is located in FFM. Therefore, TBW and FFM can be estimated by means of sex- and age-specific equations that use impedance values in combination with height and weight (8).

However, there are gaps and challenges to an accurate evaluation of body composition by BIA in younger children — for example, a lack of prediction equations for different pediatric populations; overestimation of TBW; the impossibility of determining FM distribution; and the small number of studies that have addressed the use of BIA in this public (8,9). Therefore, the objective of this study was to describe the use of bioelectrical impedance in newborns.

METHODS

This was an integrative review of the literature, based on the analysis of articles that used BIA to assess newborns. This is the main research question: "How is BIA used for assessing newborns?". This study followed the steps proposed for the development of an integrative review, as discussed by Soares et al. (2014) theme selection; formulation of research question; definition of inclusion and exclusion criteria; search for articles in the databases; data analysis and interpretation; presentation, interpretation, and discussion of results (10).

Original articles were considered as eligible when they presented data on fat-free mass, fat mass, resistance, reactance, phase angle or hydration; were written in Portuguese, English and/or Spanish; and were published in the last 10 years. The following types of publications were excluded from this review of the literature: articles, dissertations, theses, articles published in non-indexed journals, animal studies, *in vitro* studies; genetic, speech-language, cardiac, respiratory studies; studies with schoolchildren or with children in early childhood; studies with pregnant women; studies that used electrical impedance tomography or cardiographic bioimpedance as an evaluation method.

The article search step was carried out in March 2022 in the electronic databases PubMed/MEDLINE, EMBASE, Web of Science and the Virtual Health Library, through the *Portal de Periódico Capes* platform. The search used the descriptors 'bioelectrical impedance' and newborns and their variations according to the databases (DECS – Bireme, MESH TERMS and EMTREE TERMS), combined with the Boolean operators AND and OR, which resulted in the following search strategies (Table I).

Table I. Search strategies

Database	Search strategies
PubMed	(Electric Impedance OR "Bioelectrical Impedance") AND ("Infant, Newborn" OR Neonate)
Web of Science	(Electric Impedance OR "Bioelectrical Impedance") AND ("Infant, Newborn" OR Neonate)
EMBASE	('impedance'/exp OR impedance OR 'bioelectrical impedance' OR 'impedance, electric') AND ('newborn'/exp OR newborn OR neonate)
BVS	("Electric Impedance") AND ("Infant, Newborn")

The results were imported into the Mendeley® reference manager and, after checking for duplications, they were exported to an Excel® spreadsheet. The studies were analyzed by 3 independent evaluators, starting with the analysis of the title and then of the abstract, using a standardized eligibility form, according to the model proposed by the Ministry of Health (11). For this analysis, the following evaluation criteria were established: type of study, use of BIA, age group, description of resistance/reactance/phase angle values and the purpose of using BIA.

Subsequently, the studies selected by the 3 researchers were compared to check for agreement before inclusion in this review. In the case of differences, they were discussed on the basis of the inclusion criteria established and described previously. After this step, the articles were read in full. The methodological approach, data extraction and writing of findings followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines (12). The data were organized and summarized in tables with information about the studies, the participants, and the method.

RESULTS

The initial search resulted in 900 articles, which totaled 760 after exclusion of duplicate documents. After the application of the eligibility criteria, 11 articles were selected for analysis, in addition to another 4 articles included from the reference list of selected articles; thus, there were 15 studies in total. However, after full reading, six documents were excluded, thus resulting in the final analysis of 9 articles (Fig. 1).

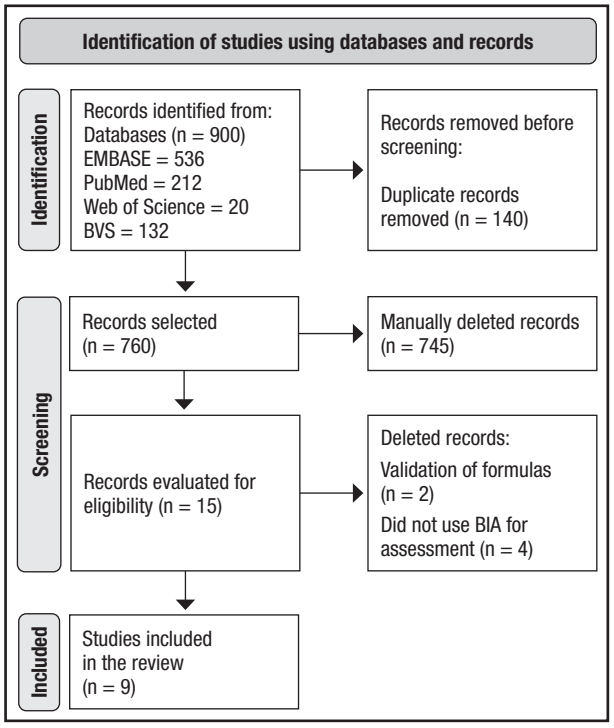

Figure 1.
Flow diagram (PRSMA, 2020).

Table II shows the characteristics of the studies reviewed; objective, design and study location are highlighted. The studies were carried out in four countries: Australia, Brazil, Spain and Poland, with three longitudinal studies evaluating BIA at two or more times (13-15). When considering the objectives of the studies, only three compared body composition with other indicators, e.g., type of diet offered to NBs, which was evaluated in two studies (16,17) and analysis of the specific mortality indicator, which was evaluated in only one study (15).

All the characteristics of the population of the studies (Table III) were stable at the time of evaluation, and some newborns (n = 4) had VLBW (16-18). Three studies included term and preterm newborns (14,17,18), another three only full-term NBs (13,19,20) and three focused on premature infants (15,16,21). All of them were up to 15 days old at the beginning of the studies and the number of participants ranged from 11 to 154 NBs; there was a similar number of male and female infants.

Table IV shows that R was the most studied bioelectric indicator; it was not evaluated in only one study (17). Body composition, both FFM and FM were investigated in four of the studies (13,16-18). TBW was also an indicator addressed in these studies (n = 3) and Bioelectrical Impedance Vector Analysis (BIVA) was used in three studies (19-21).

Table V shows the methodology and the main results of the studies, with the majority (n = 5) using a single-frequency bioimpedance analyzer (15,16,19-21). To analyze TBW, two studies used the formula by Tang (1997) (14,16), which includes the newborn's weight, foot length and the R value. Two studies found higher R and R/H among girls (19,20).

DISCUSSION

The main findings in the reviewed articles showed that BIA can be used to assess the amount of TBW, body composition (FFM and FM), and the resistance, reactance and PA values in newborns; R was the most assessed indicator. However, there were some comparative limitations between the results of these studies, since each study uses a specific population of neonates with different gestational ages, and different BIA devices.

As described in the literature, BIA is a simple and non-invasive method to estimate TBW, FM and FFM both in term and preterm infants; it is a useful tool to assess abnormal values in TBW and body composition (18). Another way of evaluating BIA data is using BIVA, which allows detecting changes in hydration status and cell mass in newborns. Vector displacements along the major axis of the tolerance ellipses reflect variations in hydration status, and the displacements in relation to the minor axis show changes in body cell mass (20). The three studies that evaluated BIVA between 2010 and 2020 enable a better comparison of results, since the devices being used had the same frequencies (single frequency/50 kHz), and the NBs were the same age (in days of life) in the evaluation and showed similar gestational ages. In a study by Margutti et al. (2012) (21) PT-NBs presented vector distribution above the 95 % tolerance intervals available in the literature for TNBs — equivalent to a state of lower TBW and lower FFM/FM ratio in comparison to TNBs.

Table II. Characteristics of the studies included in the review

Authors/year of publication	Objective	Study design	Study site
Margutti; Monteiro; Camelo (2010)	To determine R and Xc values and build BIVA curves for healthy neonates aged 7 to 28 days, born at term, and suitable for gestational age, as well as to establish PA values	Cross-sectional	Maternity hospital Ribeirão Preto, Brazil
Costa-Orvay et al. (2011)	To determine the effects of a high-protein diet on growth and body composition in VLBW	Randomized clinical trial	Neonatal Intensive Care Unit Barcelona, Spain
Margutti et al. (2012)	To observe the behavior of the PTNB vectors plotted in the RXc reference graphs related to the neonatal period and to the PA values	Cross-sectional	Intermediate care unit Ribeirão Preto, Brazil
Lingwood et al. (2012)	To evaluate the use of BIA to estimate FFM and %BF over the first 4 months of life in healthy term infants	Longitudinal	Maternity hospital Brisbane, Australia
Villela et al., (2015)	To analyze the growth and body composition of preterm newborns whose gestational age at term was corrected, and when they weighed between 3.0 and 3.5 kg	Longitudinal	ICU - Neo Rio de Janeiro, Brazil
Mól; Kwinta (2015)	To assess whether there is a difference in the values of bioelectrical impedance and body composition between preterm and full-term newborns in the first 3 months of life	Non-randomized clinical trial	ICU - Neo Krakow, Poland
Mól; Zasada; Kwinta (2019)	To evaluate the body composition of VLBW according to type of diet and compared to the control group TNB	Non-randomized clinical trial	ICU - Neo Krakow, Poland
Redondo-del-Río et al. (2019)	To determine the impedance vector distribution for a group of healthy Spanish newborns	Cross-sectional	Maternity hospital Valladolid, Spain
Coradine; Lima; Sarquis (2020)	To check if phase angle could be a better indicator of mortality and prognosis than SNAP in newborns admitted to the ICU - Neo	Longitudinal	ICU - Neo Curitiba, Brazil

BIA: bioelectrical impedance analysis; ICU-Neo: neonatal intensive care unit; VLBW: very low birth weight; NBs: newborns; PTNBs: preterm newborns; TNBs: term newborns; BF: body fat; FFM: fat-free mass; PA: phase angle; SNAP: Score for Neonatal Acute Physiology; BIA: bioelectrical impedance analysis; BIVA: bioelectrical impedance vector analysis; Xc: capacitance; R: resistance.

Table III. Characteristics of the population evaluated in the studies

Authors/year of publication	Clinical condition	Gestational age - weeks ($\bar{X}$ ± SD)	Days of life at the beginning of the study ($\bar{X}$ ± SD)	Sample (n)	Sex	
					M	F
Margutti; Monteiro; Camelo (2010)	Stable	39.8	13 ± 3.6	109	57	52
Costa-Orvay et al. (2011)	VLBW	29.0 ± 1.7	Not described	38	-	-
Lingwood et al. (2012)	Stable	40 ± 1.1	2.1 ± 1.1	77	36	41
Margutti et al. (2012)	Stable	35 ± 1.6	2.56 ± 1.35	68	-	-
	Stable	32.2 ± 2.0	14.70 ± 7.22	40	-	-
Villela et al. (2015)	Stable	≥ 37	Up to 48h	32	-	-
	Stable	29.7 ± 2.2	Up to 24h	39		
Mól; Kwinta (2015)	VLBW	30.5 (26-33)	4.7 ± 2.8	26	-	-
	Adequate weight	39 (37-41)	4.6 ± 1.6	12		
Mól; Zasada; Kwinta (2019)	VLBW*	29 (28-31.75)	Up to 7 days	34	-	-
	VLBW†	29 (28-32)	Up to 7 days	11	-	-
	Adequate weight	39 (37-40)	Up to 7 days	19	-	-
Redondo-del-Río et al. (2019)	Stable	37-41	1.1 ± 0.75	154	75	79
Coradine; Lima; Sarquis (2020)	Stable	33.7 ± 3.1	Up to 48 h	93	51	42

*VLBW: very low birth weight; SD: standard deviation; n: number; F: female; M: male; h: hours. *Formula-fed VLBW; †Breastfed very low birth weight infants.*

Table IV. Summary of the variables analyzed in the studies

BIA assessment	Criterion assessed	Articles between 2010 and 2020								
		Margutti; Monteiro; Camelo (2010)	Costa-Orvay et al. (2011)	Lingwood et al. (2012)	Margutti et al. (2012)	Villela et al. (2015)	Mól; Kwinta (2015)	Redondo-del-Río e t al. (2019)	Mól; Zasada; Kwinta, (2019)	Coradine; Lima. Sarquis (2020)
Resistance	Yes	X	X	X	X	X	X	X		X
	No								X	
Reactance	Yes	X		X	X		X	X		X
	No		X			X			X	
Phase angle	Yes	X			X		X	X		X
	No		X	X		X			X	
Fat free mass	Yes		X	X			X		X	
	No	X			X	X		X		X
Fat mass	Yes		X	X			X		X	
	No	X			X	X		X		X
Total body water	Yes		X			X	X			
	No	X		X	X			X	X	X
BIVA	Yes	X			X			X		
	No		X	X		X	X		X	X
Comparison with another BC assessment method	Yes			X		X				
	No	X	X		X		X	X	X	X

BC: body composition; BIA: bioelectrical impedance analysis; BIVA: bioelectrical impedance vector analysis.

Table V. Methods and main results of the studies included in the review

First author (year)	BIA frequency	Formulas/Indicators	Main results
Margutti; Monteiro; Camelo (2010)	Monofrequency *50* kHz	BIVA and PA ([Xc/R] x 180°/π)	The girls had significantly higher R and R/H values than boys, and Xc, Xc/H, or PA values were not different between sexes. A statistically significant difference was obeserved between the impedance vectors for girls and boys
Costa-Orvay et al. (2011)	Monofrequency *50* kHz	TBW = ([0.016 + 0.674 x weight – 0,038 x weight² + 3.84 - foot length²] / resistance) (Tang et al., 1997) FFM = (TBW / water percentage of the FFM)	The VLBW groups with high protein formulas displayed higher increases in FFM compared to newborns who did not receive supplementation
Margutti et al. (2012)	Monofrequency *50* kHz	BIVA; PA ([Xc / R] x 180°/π); R/H and Xc/H	PTNBs had higher R/H and Xc/H values than TNBs. However, the BIVA analysis found a lower TBW in the PTNBs

(Continues on next page)

Table V (Cont.). Methods and main results of the studies included in the review

First author (year)	BIA frequency	Formulas/Indicators	Main results
Lingwood et al. (2012)	Multifrequency R_{inf}, Z_c, R_0 and *50* kHz	FFM and %BF	The bioimpedance analysis did not show the advantages predicted for FFM and %BF at birth and at 6 weeks of age by the formulas used according to weight, sex, and length. However, this prediction improves after 3 months of age
Villela et al. (2015)	Monofrequency *50* kHz	TBW = (0.016 + 0.674 x weight – 0,038 x weight² + 3-84 -foot length²) / resistance) (Tang et al.,1997)	PTNBs and TNBs had different body compositions with bigger %BF and smaller TBW% in the preterm newborns
Mól; Kwinta (2015)	Multifrequency 5 kHz, 50 kHz and 100 kHz	R, Xc, PA, TBW, FFM and FM	PTNBs showed higher R and Xc at the first examination; lower FFM and FM at the age of 3 months and lower TBW in all the period. There was a change in TBW% throughout the observational period, with similar values between PTNBs and TNBs at the age of 3 months
Mól; Zasada; Kwinta (2019)	Multifrequency 5 at 1000 *kHz*	FFM and FM	VLBW preterm newborns fed with formula had significantly lower amounts of FFM and increased FM compared to the control group. No difference was observed in the body composition of newborns when they were fed breast milk
Redondo-del-Río et al. (2019)	Monofrequency *50* kHz	BIVA, R, Xc, PA, R/H, Xc/H	The bioelectrical characteristics (R, R/H e Xc/H) and the BIVA were significantly different between sexes. The girls had significantly higher R, R/H e Xc/H values than boys
Coradine; Lima; Sarquis (2020)	Monofrequency *50 kHz*	PA ([Xc/R] x 180°/π)	The PA values were not different between preterm and term newborns in the first 24 hours. However, the PTNBs showed a significant decrease at 7 days of life and PA values were lower in the group of newborns who died

BIVA: bioelectrical impedance vector analysis; PA: phase angle; R: resistance; R/H: resistance/length; Xc: reactance; Xc/H: reactance/length; TBW: total body water; FFM: fat-free mass; FM: fat mass; VLBW: very low birth weight infants; R_{inf}: resistance at infinite frequency; Z_c: resistance at the characteristic frequency; R_0: resistance at zero frequency; %BF: percentage of body fat; PTNBs: preterm newborns; TNBs: term newborns.

Body water in neonates is variable and can account for 78 % of their birth weight. Loss of body water occurs in the NB's first weeks of life and the main reason is the mobilization of water from the extracellular space. In preterm infants, such loss may be greater, as breastfeeding is often not well established and the evolution of feeding is gradual (22,23). Mól & Kwinta (2015) (18) have corroborated these findings when they found that there was a decrease in TBW percentage during the first 3 months of life of TNBs and PTNBs; at the end of this period, the values were similar in both groups.

Lingwood et al. (2012) (13) stressed that the use of BIA to compare groups of neonates is adequate; however, caution is necessary in the analysis of the results, especially as regards FM, since it is more vascularized in this group, which results in a greater volume of water in fat cells and can interfere with resistance values.

Villela et al. (2015) (14) conducted a study to compare TNBs and PTNBs, and they found that body composition is different in the corrected gestational age of PTNBs, and that this group had a lower percentage of TBW, which suggests lower FFM percentage. Mól & Kwinta (2015) (18) also confirmed this finding: TBW was significantly lower in PTNBs in the first week of life compared to TNBs. In a study by Margutti et al. (2012) (21), the results were similar in the first weeks of life, as PTNBs had a lower absolute amount of TBW, FFM and FM when compared to TNBs.

The analysis of R and Xc data showed that the values were significantly higher in PTNBs in their first week of life; thus, it can be inferred that FFM and FM values are lower in these newborns.

PA behaved differently, with a significant increase after 7 days of life in PTNBs, which may be indicative of improvement in clinical conditions (18,21). Coradine et al. (2020) (15) showed that decreases in PA values at different times of assessment were a good marker of severity. Vector analysis also showed significant differences in these data, as female infants showed higher values of R, R/C and Xc/C than male ones (19,20).

In addition to these results, the reviewed studies sought to analyze the relationship between body composition and the diet provided to neonates. Costa-Orvay et al. (2011) (16) found that the type of diet interferes with the body composition of VLBW infants; there was a greater increase in FFM in those who received a high-protein diet. Mól & Kwinta (2019) (17), when comparing the body composition of PTNBs fed with infant formula and TNBs at three months of age, found that the former had a significantly lower percentage of FFM and a higher percentage of FM. In that study, there was no difference in body composition between preterm infants fed with breast milk and infant formula; however preterm infants fed with breast milk had similar body composition to that of TNBs.

The comparative analysis between these two studies is limited because the former evaluated neonates using BIA in a single-frequency analyzer while the latter used a multi-frequency analyzer, which made up to 50 measurements. Currently, there are both single-frequency devices (50 kHz), which are the most used, and multi-frequency devices, whose frequencies range from 5 to 1,000 kHz. At different frequencies, an analyzer calculates the amount of total body water and its intra and extracellular distribution, assuming constant hydration, unlike the single-frequency analyzer (24).

Despite the articles found for this review, there were few studies on BIA in NBs, and they have limited practical applicability, as studies differ in terms of the formulas and devices that they use, BIA frequencies and the clinical conditions of the neonates. Therefore, an in-depth analysis should be made of body composition, using BIA in newborns in longitudinal, multicenter and representative research, because the assessment of body weight gain in NB, alone, is not enough to assess body composition. According to Lyons-Red et al. (2021) (25), the use of BIA in neonates needs to be standardized, since the existing equations are methodologically limited; thus, it cannot be inferred that using them is better than collecting data by means of anthropometric equations.

Knowing the body composition of NBs is important at different gestational ages at birth, as it can support interventions (for example, the type of diet offered) aimed at the clinical evolution of patients. It is also important to assess whether other variables e.g., genetics and environmental factors, are associated with changes in the body composition of neonates.

One of limitations of the present study is the delimitation of time — the most updated articles (last ten years) were included; the delimitation of language; and the proposal of a mini review, even though the researchers followed most of the steps of a systematic review.

CONCLUSION

BIA in newborns is commonly used to assess body composition and hydration and to compare these values between groups of neonates. The reviewed studies found that PTNBs have a lower amount of body water and FFM than TNBs. Studies using BIVA showed a statistically significant difference in body composition between male and female infants, with FM being higher among female ones. The diet provided to newborns interferes with their body composition, and some findings have shown that a high-protein diet can benefit PTNBs in FFM gain. The evaluation of the phase angle is still little explored in this population, but its increase after 7 days of life seems to be related to the improvement of clinical conditions. Another study found that its reduction was associated with the risk of mortality. There are still limitations for comparisons between studies, given the differences between the samples, and the adoption of different ways to characterize the results.

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ARÁN

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Revisión

Influencia de la dieta en el riesgo de infección y de gravedad de la COVID-19: una revisión sistemática

Influence of diet in COVID-19 infection and severity risk: a systematic review

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Resumen

Introducción: el riesgo y/o el pronóstico de la COVID-19, causado por el virus SARS-CoV-2, se han relacionado con enfermedades crónicas como obesidad, diabetes *mellitus* y enfermedades cardiovasculares, siendo la dieta de mala calidad un factor predisponente para estas enfermedades.

Objetivo: sintetizar la evidencia científica sobre el efecto de la dieta en el riesgo de infección por SARS-CoV-2 y de COVID-19 grave.

Métodos: revisión sistemática realizada siguiendo las guías PRISMA. La búsqueda bibliográfica se hizo en las bases de datos Web of Science, Scopus y Medline (a través del buscador PubMed). El análisis del riesgo de sesgo se realizó mediante las escalas *Newcastle-Ottawa* y *Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies*.

Resultados: se incluyeron 14 estudios. Una buena adherencia a la dieta mediterránea se asoció con una disminución del riesgo de infección por SARS-CoV-2 (razón de momios RM = 0,44; IC 95 %: 0,22-0,88, para adherencia alta *versus* baja, y RM significativas de 0,88 y 0,95 en los estudios que analizaron la adherencia de forma cuantitativa) pero no con la gravedad de la COVID-19. Una dieta basada en plantas presentó una asociación protectora frente a la infección y la enfermedad grave. Concretamente, un alto consumo de verdura, legumbres y cereales, y una baja ingesta de lácteos y carnes rojas mostraron un efecto protector frente a la infección y/o la COVID-19 grave, según el estudio. Los suplementos vitamínicos y probióticos también disminuyeron el riesgo de infección.

Conclusión: la evidencia disponible sugiere que una dieta saludable, basada en un patrón de dieta mediterránea o en alimentos vegetales, con consumo de lácteos y carnes rojas moderado, ejerce un efecto protector frente a la COVID-19.

Palabras clave:

Dieta. Dieta mediterránea. COVID-19. SARS-CoV-2. Nutrientes.

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Abstract

Introduction: the risk and/or prognosis of COVID-19, caused by the SARS-CoV-2 virus, have been related to chronic diseases such as obesity, diabetes *mellitus,* and cardiovascular diseases, with poor-quality diet being a predisposing factor for these diseases.

Objective: to synthesize the scientific evidence on the effect of diet on the risk of SARS-CoV-2 infection and severe COVID-19.

Methods: a systematic review was carried out following the PRISMA guidelines. The bibliographic search was made in the databases Web of Science, Scopus and Medline (through the PubMed search engine). Risk of bias analysis was performed using the Newcastle-Ottawa and Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies scales.

Results: 14 studies were included. Good adherence to the Mediterranean diet was associated with a decreased risk of SARS-CoV-2 infection (OR = 0.44; 95 % CI, 0.22-0.88, for high versus low adherence, and significant ORs of 0.88 and 0.95 in studies that analyzed adherence quantitatively) but not with the severity of COVID-19. A plant-based diet also had a protective association against both COVID-19 infection and severity. Specifically, a high consumption of vegetables, legumes and cereals, and a low intake of dairy products and red meat showed a protective effect against infection and/or COVID-19 severity, depending on the study. Vitamin and probiotic supplements also lowered the risk of infection.

Conclusion: the available evidence suggests that a healthy diet, based on a Mediterranean or plant-based diet, with moderate consumption of dairy and red meat, exerts a protective effect against COVID-19.

Keywords:

Diet. Mediterranean diet. COVID-19. SARS-CoV-2. Nutrients.

INTRODUCCIÓN

La pandemia de COVID-19 causada por el virus SARS-CoV-2 se encuentra todavía en curso, afectando a la salud y economía de las personas, y modificando el estilo de vida en todo el mundo. Desde el 31 de diciembre de 2019 que se comunicó el primer brote de COVID-19 a la Organización Mundial de la Salud (OMS) (1) hasta la fecha de septiembre de 2022, la pandemia ha causado más de 603 millones de casos y 6,49 millones de fallecidos (2).

Para la primera variante del SARS-CoV-2, durante la primera onda epidémica, la letalidad de la infección se estableció en un 6-7 % a nivel global, llegando a superar el 10 % en España, Italia y Suecia (3). Los principales factores de riesgo de enfermedad grave y/o fallecimiento que se han descrito son el sexo (masculino), la edad y ciertas comorbilidades como la obesidad, la hipertensión, la diabetes y el cáncer (4-6).

Aunque la aparente menor virulencia de las nuevas variantes del virus, junto con la inmunidad (natural y artificial) adquirida por la población, parece haber disminuido la morbimortalidad de la enfermedad (7), siguen produciéndose ondas epidémicas con resultados adversos, especialmente en las poblaciones envejecidas y con elevada prevalencia de obesidad y sus enfermedades cardiometabólicas asociadas.

Una dieta inadecuada es un factor predisponente a enfermedades crónicas como obesidad, diabetes *mellitus* y enfermedades cardiovasculares (8,9). Estas patologías presentan un estado proinflamatorio crónico (10) que posiblemente contribuye al aumento de la cascada de citoquinas que se ha detectado en casos graves de COVID-19 (11,12), ofreciendo una explicación al peor resultado de salud en los pacientes con dichas comorbilidades (6). Además, la desnutrición afecta al sistema inmunológico (13,14), por lo que una dieta insuficiente podría ser también un factor de riesgo para el desarrollo de infecciones respiratorias como la COVID-19 (15).

La dieta mediterránea (DMed) es un patrón dietético saludable que se ha relacionado con bajas tasas de enfermedades crónicas (16-19). De hecho, ha demostrado reducir la inflamación y mejorar el perfil lipídico (20), por lo que se ha postulado que una mayor adherencia a la DMed podría representar un factor protector frente a la infección por COVID-19 y/o el agravamiento de la enfermedad (21). De la misma manera, otros patrones de dieta saludables podrían proteger frente a la COVID-19 grave. Por este motivo, el objetivo de este trabajo fue sintetizar la evidencia científica sobre el efecto de la dieta en el riesgo de infección por SARS-CoV-2 y de COVID-19 grave mediante la realización de una revisión sistemática.

MATERIALES Y MÉTODOS

La realización de la revisión sistemática se basó en la guía para la publicación de revisiones sistemáticas PRISMA *(Preferred Reporting Items for Systematic reviews and Meta-Analysis)* (Tabla suplementaria I). La pregunta de investigación se formuló siguiendo el formato PECO: P) Población/Paciente: personas de cualquier edad; E) Exposición: una dieta saludable u óptima; C) Comparación: dieta no saludable; O) Resultados (*outcome*): riesgo y pronóstico de la infección por COVID-19, medida mediante gravedad, parámetros analíticos, mortalidad, complicaciones, duración de la hospitalización y/o salida/entrada en la unidad de cuidados intensivos.

La búsqueda se realizó independientemente por dos autores (MMM y MGP) el 24/02/2022. Se usaron tres bases de datos, Web of Science, Scopus y Medline (a través del buscador PubMed). Para la estrategia de búsqueda se usaron los operadores booleanos "AND" y "OR" y los siguientes términos o sus equivalentes: *diet, mediterranean diet, nutrional status, food quality, SARS-CoV-2, COVID-19, Coronavirus, 2019-new coronavirus, incidence, risk, relative risk, odds ratio, prognosis, evolution, mortality, lethality, severity, hospitalization, intensive care unit, death*. El algoritmo completo de búsqueda para cada base de datos está detallado en la tabla suplementaria II. Por último, se realizó una búsqueda basada en el principio de bola de nieve.

Los criterios de inclusión de los artículos fueron: a) artículos escritos en inglés o español; b) artículos publicados después del 2020. Se excluyeron las revisiones narrativas, revisiones sistemáticas o metaanálisis, estudios de casos, comentarios, cartas al editor, estudios realizados en animales, estudios que abordaban otros factores del estilo de vida que no incluían la dieta, y estudios en los que se medía exclusivamente la ingesta dietética

sin determinar su calidad. Los artículos se seleccionaron primero por título y resumen, y en una segunda criba, por la lectura del texto completo.

La selección de artículos la realizaron dos autores de manera independiente (MMM y MGP); en caso de discrepancia, se resolvió la duda consultando con un tercer autor (PR). Se extrajeron los siguientes datos: título, primer autor, lugar de realización del estudio, tipo de diseño epidemiológico del estudio, tamaño muestral, método de medición de la dieta, principales características de la muestra, tiempo de seguimiento, método de medición de la variable resultado, resultados principales, realización o no de análisis ajustado y variables de ajuste, así como las principales conclusiones y limitaciones del estudio. En caso de existir varios modelos analíticos, se escogió aquel con mayor nivel de ajuste por variables confusoras. Y en caso de existir varias definiciones de infección, se escogió la más objetiva, es decir, aquella basada en pruebas analíticas o historias clínicas. La extracción de datos la realizaron tres autores de manera independiente (ELD, MMM y MGP) en una hoja Excel; en caso de discrepancia, se resolvió la duda consultando con un tercer autor (PRM).

El riesgo de sesgo, también llamado calidad metodológica, de los estudios individuales incluidos se evaluó mediante las herramientas "Newcastle-Ottawa Scale" (NOS) (22), para los estudios longitudinales observacionales, y la escala "Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies" (JBI) para los estudios transversales analíticos (23). La escala NOS contiene ocho ítems divididos en tres dimensiones: selección, comparabilidad y, según el tipo de estudio, resultado (estudios de cohortes) o exposición (estudios de casos y controles). Se utiliza un sistema de puntos para proporcionar una evaluación semicuantitativa de la calidad del estudio, de modo que los estudios de mayor calidad reciben un máximo de un punto por cada ítem, con la excepción del ítem sobre comparabilidad, que permite la concesión de dos puntos. Así, la puntuación final oscila de cero a nueve puntos. La escala JBI utiliza ocho criterios para evaluar la calidad metodológica general de un estudio. Los criterios incluyen: criterios de inclusión de la muestra; descripción de temas y escenarios; medida de exposición válida y fiable; medida objetiva y estándar de la condición; identificar factores de confusión; estrategias para hacer frente a los factores de confusión; medida de resultado válida y fiable; y análisis estadístico adecuado. La puntuación final oscila entre 0 y 8 puntos.

No existe un criterio de clasificación para la calidad de los estudios. Para facilitar la interpretación, se clasificó el resultado de la calidad metodológica, independientemente de la escala usada, como: baja (0-3 puntos), media (4-6 puntos) y alta (> 6 puntos).

RESULTADOS

CARACTERÍSTICAS DE LOS ESTUDIOS

El proceso detallado de los resultados de búsqueda y selección de artículos se recoge en la figura 1. Se identificaron 5137 estudios en las bases de datos consultadas. Tras la eliminación de duplicados, quedaron 3155 artículos para el análisis del título y del resumen. De estos, 3055 fueron eliminados tras la lectura del título/resumen por no corresponder con la pregunta PECO o no cumplir los criterios de selección. De los 100 artículos restantes, que fueron evaluados por texto completo, 13 estudios (24-36) fueron seleccionados por cumplir con los criterios de selección. A través de la estrategia de búsqueda en bola de nieve se añadió un artículo, por lo que el número total de artículos seleccionados fue de 14 (29).

De los 14 estudios, en 4 se abordó la relación entre la DMed y la COVID-19; en 3 estudios, otros patrones dietéticos; en 9 se estudió la asociación entre grupos de alimentos o nutrientes específicos y la COVID-19; y en 2 se analizó el efecto del uso de suplementos dietéticos y la COVID-19. No se encontró ningún estudio experimental y hubo 3 estudios ecológicos. Los 11 estudios no ecológicos incluyeron 1465256 participantes (rango desde 206 a 592571 pacientes), con 6 estudios de cohortes, 2 de casos y controles, y 3 transversales. La calidad de los estudios individuales se valoró como media en 7 estudios y como alta en 4 estudios (Tablas I, II y III). La puntuación detallada (para cada ítem) del análisis de calidad de los artículos evaluados se describe en las tablas suplementarias III, IV y V.

PATRONES DIETÉTICOS Y COVID-19

Efecto de la adherencia a la DMed en el riesgo de COVID-19

En 4 de los estudios se analizó la asociación entre la adherencia a la DMed y el riesgo de infección por SARS-CoV-2 (24-27); además, uno de ellos también determinó el riesgo de mortalidad asociada (26). Dos de ellos fueron estudios de cohortes (24,27), uno transversal (25) y uno ecológico (26). Sus características se describen en la tabla I.

Los resultados recogidos en los 3 estudios individuales indican que la adherencia a la DMed tiene una asociación protectora frente a la infección por SARS-CoV-2, con una razón de momios (RM, también conocida por el término inglés *odds ratio*) = 0,44; IC 95 %: 0,22-0,88 (27) cuando se compara la alta adherencia con la baja; y con RM = 0,88; IC 95 %: 0,81-0,97 (24) y RM = 0,95; IC 95 %: 0,91-0,99 (25) por cada punto de más en la escala de adherencia. Cabe destacar que, en el último estudio, los autores calculan la RM de no estar infectado; aquí se ha calculado el inverso, es decir, la RM de estar infectado, para mejor comparabilidad con el resto de estudios. Ninguno de los tres estudios encontró asociación entre la adherencia a la DMed y la gravedad de la COVID-19.

El análisis de la calidad de los artículos demostró que estos tres artículos tenían una calidad media, debido principalmente al uso de cuestionarios autoadministrados para la medición de la exposición (dieta) y del resultado (COVID-19), y de la falta de comparabilidad con la población general al usar cohortes con características muy específicas o bien omitir información sobre los criterios de selección.

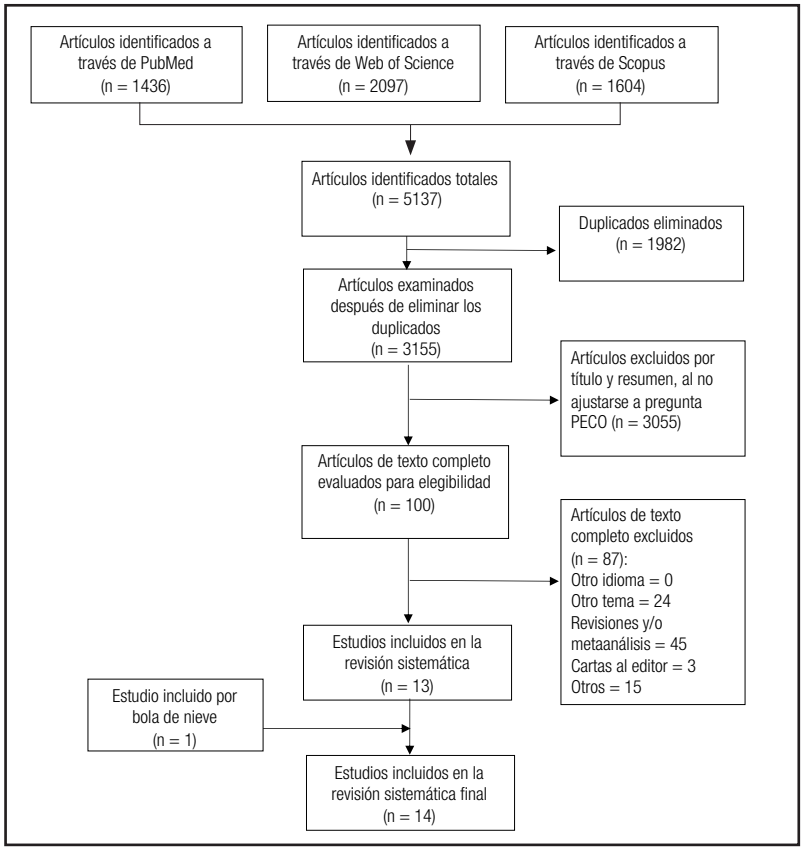

Figura 1.
Diagrama de flujo de la revisión sistemática.

Tabla I. Características de los estudios que miden la adherencia a la dieta mediterránea (DM)

Referencia / País	Tipo de estudio / Tamaño muestral	Medición dieta-escala adherencia DM / Medición COVID-19	Análisis ajustado / Variables de ajuste	Calidad Puntuación
Pérez-Araluce et al., (2022) / España (26)	Cohortes, prospectivo / 9485	CFA autoadministrado – *Mediterranean diet score* / Cuestionario autoadministrado	Sí / Edad, sexo, años de estudios universitarios, estado civil, hábito tabáquico, IMC, actividad física, tiempo de seguimiento, comorbilidades	Media 5
El Khoury et al., (2021) / Líbano (24)	Transversal / 399	CFA autoadministrado – *MedDiet score* / Cuestionario autoadministrado	Sí / Edad, comorbilidades	Media 4
Ponzo et al., (2021) / Italia (23)	Cohortes, retrospectivo / 900	CFA autoadministrado – *Medi-lite score* / Cuestionario autoadministrado	Sí, variables significativas (regresión *stepwise*) / *Modelo 1* – Medi-lite score: ingesta carbohidratos, ingesta grasas saturadas, ingesta proteica, ingesta fibra. *Modelo 2* – componentes DM: ingesta carbohidratos, ingesta grasas saturadas, ingesta proteica, ingesta fibra, ingesta fruta, ingesta verdura, ingesta cereales, ingesta aceite de oliva	Media 5
Greene et al., (2021) / Múltiples países, CC. AA. España (25)	Ecológico / CC. AA. España y 24 países	*Mediterranean Adequacy Index score* / Diferentes bases de datos para cada país	Sí / *Modelo Regiones España:* ingresos económicos del hogar, nivel educativo, número de habitaciones por persona en hogar, exposición a contaminación aire, escala satisfacción personal autopercibida. *Modelo 24 países:* ingresos económicos del hogar, nivel educativo, número de habitaciones por persona en hogar, exposición a contaminación aire, escala satisfacción personal autopercibida, actividad física	NA

CFA: cuestionario de frecuencia de consumo de alimentos. IMC: índice de masa corporal. NA: no aplicable.

Tabla II. Características de los estudios que miden otros patrones, grupos de alimentos y/o nutrientes

Referencia / País	Tipo de estudio / Tamaño muestral	Medición dieta / Medición COVID-19	Análisis ajustado / Variables de ajuste	Calidad Puntuación
Deschasaux-Tanguy et al., (2021) / Francia (29)	Cohortes, retrosprospectivo / 7766	Registro dietético 24 h (6 en dos años previos a pandemia) / Anticuerpos anti-COVID-19	Sí / Sexo, edad, nivel educativo, situación laboral, hábito tabáquico, presencia de hijos y/o nietos en el hogar, zona residencial, actividad física, comorbilidades, área geográfica, IMC, tiempo de seguimiento, número registros dietéticos, ingesta calórica, consumo de alcohol	Media 6
Tavakol et al., (2021) / Irán (35)	Transversal / 206	CFA mediante entrevista / Historias clínicas	No	Media 5
Kim et al., (2021) / Múltiples países (37)	Casos y controles / 2884	CFA autoadministrado / Cuestionario autoadministrado	Sí / Edad, sexo, raza/etnia, país, especialidad médica, hábito tabáquico, actividad física, IMC, comorbilidades	Alta 7
Merino et al., (2021) / Reino Unido y EE. UU. (34)	Cohortes, prospectivo / 592571	CFA autoadministrado / Cuestionario autoadministrado	Sí / Edad, sexo, raza/etnicidad, país, fecha reclutamiento, deprivación socio-económica, densidad de población, contacto pacientes COVID-19, comorbilidades, IMC, hábito tabáquico, actividad física	Media 6
Abdulah et al., (2020) / Múltiples países (32)	Ecológico / 158 países	*Global Dietary Database* / Registro Organización Mundial de la Salud	No	NA
Li et al., (2021) / Múltiples países (33)	Ecológico / 155 países	Registros estatales de consumo de alimentos / Registro *Johns Hopkins Coronavirus Resource Center*	No	NA
Ahmadi et al., (2021) / Reino Unido (33)	Cohortes, prospectivo / 468569	CFA autoadministrado / registro estatal	Sí / Edad, sexo, deprivación socio-económica, etnia, IMC, uso de corticoides, comorbilidades	Alta 8
Mohseni et al. (2021) / Irán (28)	Casos y controles, retrospectivo / 505	CFA mediante entrevista / Historias clínicas	Sí / Actividad física, IMC, ingesta calórica, consumo suplementos dietéticos	Alta 7

CFA: cuestionario de frecuencia de consumo de alimentos. IMC: índice de masa corporal. NA: no aplicable.

Tabla III. Características de los estudios que miden suplementos dietéticos

Referencia / País	Tipo de estudio / Tamaño muestral	Medición dieta / Medición COVID-19	Análisis ajustado / Variables de ajuste	Calidad Puntuación
Louca et al., (2021) / Reino Unido (30)	Cohortes, retrospectivo / 372720	Cuestionario autoadministrado / Cuestionario autoadministrado	Edad, sexo, IMC, etnia, comorbilidades, hábito tabáquico, deprivación socio-económica, estado de salud	Media 6
Aldwihi et al. (2021) / Arabia Saudita (31)	Transversal / 738	Entrevista telefónica / Registro estatal	Edad, sexo, IMC, estado civil, comorbilidades	Alta 8

IMC: índice de masa corporal.

Por otro lado, en el estudio ecológico (26), usando un modelo ajustado por factores de bienestar, se observó que la adherencia a la DMed se asoció negativamente tanto con los casos de COVID-19 (β = –0,032; error estándar –EE– = 0,014; p = 0,045) como con las muertes relacionadas con la enfermedad (β = –0,003; EE = 0,001; p = 0,043) en 17 regiones de España. Sin embargo, al estudiar los 23 países de la OCDE, solo se encontró una asociación negativa significativa con el riesgo de mortalidad por COVID-19 (β = -0,597; EE = 0,176; p = 0,010) pero no con el de infección.

Otros patrones dietéticos y COVID-19

Otros tres estudios abordaron el efecto de un patrón dietético saludable en la COVID-19 (Tabla II). Un estudio de cohortes de calidad alta (28) no encontró asociación entre la dieta y la mortalidad por COVID-19. Los otros dos estudios, de calidad media y alta, encontraron que una dieta basada en el consumo de productos vegetales reduce el riesgo de padecer COVID-19 (35,37). Así, en un estudio de casos y controles dirigido a los trabajadores sanitarios de 6 países diferentes se observó que la dieta vegetariana o a base de plantas reducía en un 72 % (RM = 0,28; IC 95 %: 0,10-0,82) la probabilidad de padecer COVID-19 moderada o grave, y la dieta a base de plantas y pescado reducía el riesgo en un 59 % (RM = 0,41; IC 95 %: 0,16-0,99) (37). Estos resultados son avalados por el otro estudio de cohortes, donde se observó que una dieta de calidad basada en el consumo de productos vegetales disminuyó el riesgo de padecer COVID-19 (HR = 0,91; IC 95 %: 0,88-0,94) y COVID-19 grave (HR = 0,59; IC 95 %: 0,47-0,74) (35).

Grupos de alimentos, nutrientes y COVID-19

Se han encontrado un total de 8 artículos que analizan el efecto del consumo de grupos de alimentos y/o nutrientes específicos en la COVID-19, cuyas características se describen en la tabla II. La calidad de estos artículos fue media o alta. Además, algunos de los artículos que medían el efecto de la adherencia a la DMed también estudiaron grupos específicos de alimentos y/o nutrientes.

En sintonía con los dos estudios que evaluaron patrones dietéticos basados en plantas, un estudio de cohortes prospectivo observó que el consumo de frutas y verduras se asociaba con un menor riesgo de infección por SARS-CoV-2 (RM = 0,85; IC 95 %: 0,74-0,97) (30). Igualmente, en un estudio ecológico (llevado a cabo en 154 países más los 50 estados de Estados Unidos) se vio una asociación significativa e inversa entre el consumo de verdura y el riesgo de COVID-19 y muertes asociadas ($\beta = -7{,}2 \times 10^{-4}$ y $\beta = -3{,}1 \times 10^{-3}$, respectivamente; variables seleccionadas en una regresión Lasso, valores p o intervalos de confianza no indicados) (34). No obstante, aunque no se han hallado estudios que encuentren una asociación positiva (de riesgo) entre el consumo de verdura y el COVID-19, 5 estudios no encontraron una asociación significativa (ni negativa ni positiva) entre ambas variables (24,25,27,29,36).

Con respecto al consumo de fruta, en dos estudios ecológicos (33,34) se encontró una asociación positiva entre el consumo de frutas y el riesgo de COVID-19 ($\beta = 0{,}237$; $p = 0{,}006$ y $\beta = 0{,}003$; regresión Lasso, valor p no proporcionado) pero una asociación negativa entre la mortalidad por COVID-19 y el consumo de frutas ($\beta = -0{,}226$; $p = 0{,}047$). Estos resultados van en sintonía con los de Tavakol y cols., que relacionaron el consumo de fruta con la reducción de la severidad en la enfermedad ($p = 0{,}020$) (36). Por último, otros estudios llevados a cabo por Pérez-Araluce y cols., El Khoury y cols., Mohseni y cols., Ponzo y cols. y Kim y cols. no encontraron ninguna relación entre el consumo de frutas y la COVID-19 (24,25,27,29,37).

En línea con los resultados descritos sobre los grupos de alimentos vegetales, la alta ingesta de legumbres se ha relacionado con una disminución en la tasa tanto de infección ($\beta = -0{,}145$; $p = 0{,}038$) como de mortalidad ($\beta = -0{,}176$; $p = 0{,}046$) (33), si bien Pérez-Araluce y cols. (27), Deschasaux-Tanguy y cols. (30), El Khoury y cols. (25), Ponzo y cols. (24) y Mohseni y cols. (29) no encontraron relación entre el consumo de legumbres y la COVID-19.

Otro grupo de alimentos de origen vegetal que puede tener un efecto protector en la COVID-19 por los nutrientes que contienen son los cereales. Ponzo y cols. detectaron que el consumo de cereales está inversamente relacionado con el riesgo de infección por SARS-CoV-2 (RM = 0,64; IC 95 %: 0,45-0,90) (24). Esta asociación no fue comprobada en otros dos estudios que analizaron este grupo de alimentos (25,27).

Con respecto a las grasas de adición, destaca el papel del aceite de oliva; en dos estudios, los casos de COVID-19 consumían menos aceite oliva que los controles sin dicha enfermedad (consumo de aceite de oliva en infectados = 1,59 ± 0,66 y en no infectados = 1,74 ± 0,55, sobre una puntuación máxima de 2 puntos, $p = 0{,}004$; y consumo diario de aceite de oliva: infectados = 18,7 % y no infectados = 33,3 %, $p = 0{,}004$) (24,25). No obstante, Pérez-Araluce et al. no encontraron ningún efecto asociado al aceite de oliva (27).

Entre los alimentos que se han relacionado con un aumento del riesgo de infección por COVID-19 se encuentran los de origen animal. Así, en el estudio de Kim y cols. (37), la dieta con mayor consumo de carne roja y procesada y de aves fue más frecuente en los casos de COVID-19 graves (21,7 %) que en los leves (14,2 %, $p = 0{,}040$). Sin embargo, no está claro el efecto de la carne de ave sobre la COVID-19. En un estudio transversal, el consumo elevado (≥ 17 veces al mes) fue más frecuente en los casos de COVID-19 (17,3 %) que en los controles (7,2 %, $p = 0{,}014$) (25); por el contrario, en otro estudio transversal, el consumo elevado de carne de ave (≥ 3 veces por semana) fue más frecuente en las personas con enfermedad moderada (53 %) que en aquellas con enfermedad grave (29 %, $p = 0{,}050$) (36). Por otra parte, otros 2 trabajos que han examinado el consumo de carne no han encontrado relación con la COVID-19 (24,29).

Otro grupo de alimentos de origen animal que se ha asociado con un aumento del riesgo de infección por COVID-19 son los productos lácteos (RM = 1,19; IC 95 %: 1,06-1,33) y, por ende, elementos como el calcio (RM = 1,16; IC 95 %: 1,01-1,35) (30). Igualmente, Pérez-Araluce y cols. (27) observaron que el menor consumo de productos lácteos enteros disminuyó el riesgo de infección por COVID-19 (RM = 0,65; IC 95 %: 0,33-0,94), del mismo modo que el yogur, aunque en este caso el resultado no fue significativo. Estos resultados son avalados por los dos estudios ecológicos, en los que se determinó que la leche y el calcio ($\beta = 0{,}045$; $p = 0{,}010$ y $\beta = 0{,}113$; $p = 0{,}003$, respectivamente) (33) o los productos lácteos en general ($\beta = 0{,}001$; regresión Lasso, valor p no proporcionado) (34) aumentaron el riesgo

de infección y/o de mortalidad asociada. Por el contrario, Mohseni y cols. encontraron un efecto protector entre la ingesta de yogur (RM = 0,74; IC 95 %: 0,56-0,98) pero no de leche (RM = 0,78; IC 95 %: 0,52-1,17) y la aparición de sintomatología de COVID-19 (29). Por último, cabe mencionar que otros estudios no han encontrado relación entre la COVID-19 y los productos lácteos (24,25,36,37).

En otro grupo de artículos se analizó el efecto de nutrientes específicos en la COVID-19. Concretamente, la probabilidad de infección por SARS-CoV-2 disminuyó con un consumo alto de vitamina B9 (RM = 0,84; IC 95 %: 0,72-0,98), vitamina C (RM = 0,86; IC 95 %: 0,75-0,98), vitamina K (RM = 0,86; IC 95 %: 0,74-0,99) y fibra (RM = 0,84; IC 95 %: 0,72-0,98) (30). En otro estudio ecológico se observó que, aunque la vitamina D y la vitamina K estaban asociadas a menores tasas de infección y/o de fallecimientos debidos a la COVID-19, la vitamina C y B se relacionaban con un aumento de dichas tasas (34).

Por último, en un estudio ecológico se asoció el elevado consumo de bebidas azucaradas con un mayor riesgo de infección por COVID-19 ($\beta = 0,340$; $p < 0,001$) (33). Del mismo modo, las dietas a base de vegetales en las que se observó un menor consumo de bebidas azucaradas ($p = 0,010$) se relacionaron con una menor gravedad de la COVID-19 (37).

Utilización de suplementos dietéticos frente al COVID-19

Dos artículos analizaron la utilización de suplementos dietéticos en el desarrollo de COVID-19 (Tabla III). El primero es un estudio de cohortes, de calidad media (6 puntos), donde se evaluaba de forma retrospectiva y autorreferida el consumo de suplementos en los 3 meses previos y el riesgo de infección por SARS-CoV-2 (31). El segundo estudio, de carácter transversal y calidad alta (8 puntos), evaluó el consumo de suplementos durante la infección y el riesgo de hospitalización, recogiéndose la información mediante entrevista e historia clínica, respectivamente.

El consumo de complejos vitamínicos generales disminuyó el riesgo de infección (RM = 0,87; IC 95 %: 0,84-0,90) (31). Entre las vitaminas, los dos estudios mostraron datos relativamente contradictorios con respecto a los suplementos de vitamina D; uno de ellos encontró una asociación negativa para el riesgo de hospitalización (RM = 0,91; IC 95 %: 0,88-0,94) (32) y el otro, asociación positiva para el riesgo de infección (RM = 1,89; IC 95 %: 1,20-2,98) (31). Otra vitamina suplementada de manera individual que mostró una asociación negativa con el riesgo de hospitalización por COVID-19 fue la vitamina C (RM = 0,51; IC 95 %: 0,33-0,79) (32). En sintonía con este resultado, la suplementación natural con limón y la naranja (alimentos ricos en vitamina C) también mostró un efecto protector frente a la hospitalización (RM = 0,54; IC 95 %: 0,33-0,88) (32).

Otros suplementos cuyo consumo mostró una asociación estadísticamente significativa con la COVID-19 fueron los probióticos (RM = 0,86; IC 95 %: 0,81-0,92) y los ácidos grasos omega-3 (RM = 0,88; IC 95 %: 0,84-0,92). Ambos mostraron una reducción del riesgo de infección por SARS-CoV-2 (31) y, a su vez, el consumo de menta (RM = 0,53; IC 95 %: 0,31-0,90) se asoció con una menor hospitalización de los pacientes con COVID-19 (32).

DISCUSIÓN

En esta revisión sistemática se ha buscado sintetizar la evidencia científica disponible sobre la asociación de la dieta, estudiada como patrón dietético, grupos de alimentos, nutrientes específicos y suplementos dietéticos, con el riesgo y/o pronóstico de la COVID-19.

Los resultados encontrados sobre el efecto de la DMed sobre el número de casos de COVID-19 son consistentes, mostrando un efecto protector de la misma en los 4 estudios. Estos resultados pueden explicarse de dos maneras. Por un lado, la DMed podría tener un efecto directo sobre el sistema inmune, ayudando a combatir la infección. En este sentido, la DMed tiene componentes inmunomoduladores y antiinflamatorios como vitaminas, polifenoles, fibra y ácidos grasos no saturados e insaturados como el omega-3 (23-26) que podrían tener un papel importante en la respuesta inmunitaria (23,24,26,36). Una fuente importante de estos nutrientes en la DMed es el aceite de oliva y cabe destacar que dos de los tres estudios individuales asociaron un mayor consumo de este alimento con un menor riesgo de COVID-19 (23,24), lo que podría deberse a su contenido en vitamina E, además de a sus propiedades antioxidantes y antiinflamatorias.

Por otro lado, el efecto de la DMed podría ser indirecto y deberse al conocido efecto protector de este patrón sobre las comorbilidades que se asocian a un peor pronóstico de la COVID-19, como obesidad, diabetes y enfermedad cardiovascular (15-18). A la luz de los resultados de los estudios encontrados, esto parece menos probable, ya que ninguno de los tres estudios individuales encontró asociación entre la adherencia a la DMed y la gravedad de la COVID-19, y dos de ellos realizaron un análisis multivariable controlando precisamente dichas comorbilidades. Pero este efecto de la DMed sobre las comorbilidades podría ser suficiente para disminuir la probabilidad de un diagnóstico, especialmente cuando este se recogió mediante cuestionarios autoadministrados y en la primera onda epidémica, donde los test se realizaban solo a pacientes de COVID-19 graves/sintomáticos.

Se han encontrado otros estudios que abordan la medida de la dieta en su globalidad. Un estudio de cohortes (28) no encontró asociación entre la dieta y la mortalidad por COVID-19. Pese a que fue de calidad alta, cabe destacar que, en este estudio, la dieta se evalúo en el reclutamiento, que aconteció entre 2006 y 2010, por lo que los hábitos alimentarios podrían haber cambiado hasta que aconteció la pandemia. Otros dos estudios encontraron un efecto protector de la dieta a base de plantas frente al riesgo y/o gravedad de la COVID-19. Pese a las limitaciones de estos dos estudios, en los que tanto la dieta como la COVID-19

fueron autorreportadas a través de aplicaciones móviles o páginas web, y donde la población del estudio pudo no ser representativa de la población general, la consistencia de los resultados justifica la necesidad de hacer nuevos estudios con mejor diseño para demostrar esta hipótesis. Las personas que toman dietas basadas en plantas tienen mayor ingesta de ciertos nutrientes, como fibra, vitaminas A, C y E, folato y minerales (hierro, potasio, magnesio) (38). Algunos de estos nutrientes podrían reforzar el sistema inmunitario (39) y, como se ha visto en el último apartado de esta revisión, la suplementación con complejos vitamínicos o ciertas vitaminas también disminuye el riesgo de COVID-19 o de enfermedad grave.

En relación a los estudios que abordaron grupos de alimentos/nutrientes específicos, en general se ha observado bastante consistencia en las asociaciones protectoras entre los alimentos de origen vegetal y el riesgo y/o la gravedad de la COVID-19. Solo se encontró una excepción: dos estudios ecológicos que encontraron un aumento del riesgo de infección entre las personas con alto consumo de fruta, si bien este resultado contradictorio y no esperado debe interpretarse con cautela, puesto que los estudios ecológicos suelen tener menos validez que los estudios individuales y, además, uno de dichos estudios ecológicos y otro transversal encontraron una asociación protectora entre el consumo de fruta y la mortalidad por COVID-19, en línea con lo esperado y descrito para otros alimentos vegetales.

La asociación protectora entre alimentos de origen vegetal y la COVID-19 es consistente con el efecto protector de la dieta vegetariana, y los potenciales mecanismos explicados anteriormente pueden aplicarse también aquí. Parece haber más controversia sobre la asociación entre el consumo de alimentos de origen animal y la COVID-19, con asociaciones positivas o negativas según el estudio, aunque con predominancia de los estudios que encuentran asociaciones de riesgo. La heterogeneidad en los resultados podría deberse a las grandes diferencias existentes entre los distintos estudios, desde el diseño epidemiológico al análisis estadístico, pasando por la definición de COVID-19, o la medición de la exposición y el desenlace. Y aunque la calidad de los estudios puede indicar en cierta medida la validez y la relevancia de los mismos (40), se requiere mayor volumen de evidencia científica para poder confirmar estos resultados que, en cualquier caso, irían en la línea de los estudios que encuentran una asociación protectora de la DMed y la dieta vegetariana con la COVID-19.

Dos artículos analizaron el efecto de la utilización de suplementos dietéticos en el desarrollo de la COVID-19, mostrando una asociación protectora. La presencia de diversos minerales y vitaminas en estos complejos, combinando propiedades antioxidantes y de refuerzo del sistema inmune, podrían explicar el efecto observado. Los dos estudios mostraron datos relativamente contradictorios con respecto a los suplementos de vitamina D, con asociación negativa y positiva para el riesgo de hospitalización y el riesgo de infección, respectivamente. El efecto de los niveles séricos de vitamina D en la COVID-19 ha sido ampliamente estudiado, encontrándose en general un efecto protector frente a infección o la enfermedad grave (41-44). También una dosis elevada y única de calcifediol (derivado de la vitamina D), administrada a pacientes con COVID-19 hospitalizados, ha mostrado una disminución de la mortalidad (45). Por tanto, son necesarios más estudios que ayuden a verificar el efecto de una suplementación con vitamina D a largo plazo sobre la COVID-19.

Otra vitamina suplementada de manera individual que mostró una asociación negativa con el riesgo de hospitalización por COVID-19 fue la vitamina C. Este efecto era posiblemente esperable debido a que son conocidas las propiedades antioxidantes e inmunomoduladoras de dicha vitamina. Igualmente, los probióticos, los ácidos grasos omega-3 y la menta tuvieron una asociación protectora en uno de los estudios. Los probióticos mejoran la microbiota intestinal y pueden generar metabolitos antivirales, lo que podría mejorar el sistema inmunológico (46). Aunque no está claro el mecanismo protector, los omega-3 y la menta podrían reducir el riesgo debido a sus propiedades antiinflamatorias (47-51).

Aunque los estudios recogidos en esta revisión muestran resultados interesantes y consistentes sobre el efecto de la dieta en la COVID-19, hay que tener en cuenta sus limitaciones: a) la calidad metodológica de los estudios, clasificada como "media" en 7 de los 11 estudios evaluados; b) el diseño observacional de todos los estudios incluidos, lo que puede introducir sesgos, ya que no es posible controlar todas las posibles variables confusoras; c) la inclusión de tres estudios ecológicos y tres transversales, lo que impide o dificulta cualquier inferencia causal; y d) el uso de cuestionarios autoadministrados para medir la dieta y, en algunos estudios, también la COVID-19, lo cual puede introducir sesgos de información y de memoria. Además, el proceso de revisión ha tenido *per se* otra limitación: el criterio de incluir solo artículos publicados en español o inglés.

Esta revisión sistemática también tiene importantes fortalezas. Se ha realizado de acuerdo con la guía PRISMA y es, hasta donde hemos podido saber, la primera revisión sistemática que aborda el efecto de la calidad de la dieta sobre la COVID-19.

CONCLUSIONES

La evidencia disponible, aunque escasa, permite sugerir que un patrón de dieta saludable como la DMed o las dietas basadas en plantas ejerce un efecto protector frente al riesgo de COVID-19, aunque no sobre su gravedad. En concreto, puede señalarse un efecto protector para los alimentos de origen vegetal y un efecto negativo de los alimentos de origen animal, y aunque la evidencia actual es muy débil, también para los suplementos vitamínicos. En cualquier caso, el bajo número de artículos encontrados y la limitada calidad de algunos de ellos hacen necesario que se realicen más estudios para poder concluir que la dieta equilibrada tiene un efecto protector sobre la COVID-19. Dado que la buena tasa de inmunidad en la población a fecha de publicación de esta revisión dificulta la realización de nuevas investigaciones, se sugieren estudios retrospectivos en cohortes nutricionales ya reclutadas al inicio de la pandemia.

Tabla suplementaria I. Lista de verificación de las guías PRISMA

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Line 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Line 24
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Lines 102-106
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Lines 106-108
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Lines 128-133
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Lines 120-121
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary information
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Lines 135-136
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Lines 144-146
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Lines 136-144
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Lines 136-144
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Lines 147-162
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Along the Result section
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis [item #5]).	Not applicable
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not applicable
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Not performed, very few articles were included in the review, so each one has been described in the main text
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Not applicable
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable

(Continúa en página siguiente)

Tabla suplementaria I (Cont.). Lista de verificación de las guías PRISMA

Section and Topic	Item #	Checklist item	Location where item is reported
METHODS			
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1 and lines 168-175
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Tables 1, 2 and 3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Tables 1, 2 and 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Not performed, very few articles were included in the review, so each one has been described in the main text
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Along the Result and Discussion section
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Along the Discussion section
	23b	Discuss any limitations of the evidence included in the review.	Lines 394-402
	23c	Discuss any limitations of the review processes used.	Lines 402-403
	23d	Discuss implications of the results for practice, policy, and future research.	Lines 408-412
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not performed
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not performed
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not performed
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Lines 12-15
Competing interests	26	Declare any competing interests of review authors.	Lines 16-17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Tabla suplementaria II. Algoritmos de la búsqueda bibliográfica

Medline/PubMed:
((Diet [Mesh]) OR (Diet, Mediterranean [Mesh]) OR (Nutritional Status [Mesh]) OR (Food Quality [Mesh]) OR (diet, food, and nutrition [Mesh]) OR (diet* [Title/Abstract])) AND ((COVID-19 [Mesh]) OR (SARS-CoV-2 [Mesh]) OR (COVID [Title/Abstract]) OR (COVID19 [Title/Abstract]) OR (coronavirus [Title/Abstract]) OR (COVID 19 [Title/Abstract]) OR (2019-new coronavirus [Title/Abstract]) OR (2019-nCoV [Title/Abstract])) AND ((incidence [Title/Abstract]) OR (risk [Title/Abstract]) OR (relative risk [Title/Abstract]) OR (odds ratio [Title/Abstract]) OR (prognosis [Title/Abstract]) OR (evolution [Title/Abstract]) OR (mortality [Title/Abstract]) OR (lethality [Title/Abstract]) OR (severity [Title/Abstract]) OR (hospitalization [Title/Abstract]) OR (intensive care unit [Title/Abstract]) OR (death [Title/Abstract])).
Web of Science:
("Diet" OR "Diet, Mediterranean" OR "Nutritional Status" OR "Food Quality" OR "diet, food, and nutrition" OR "diet*") AND ("COVID-19" OR "SARS-CoV-2" OR "COVID" OR "COVID19" OR "Coronavirus" OR "coronavirus" OR "COVID 19" OR "2019-new coronavirus" OR "2019-nCoV") AND ("incidence" OR "risk" OR "relative risk" OR "odds ratio" OR "prognosis" OR "evolution" OR "mortality" OR "lethality" OR "hospitalization" OR "intensive care unit" OR "death").
Scopus:
TITLE-ABS-KEY ("Diet" OR "Diet, Mediterranean" OR "Nutritional Status" OR "Food Quality") AND TITLE-ABS-KEY ("COVID-19" OR "SARS-CoV-2" OR "COVID" OR "COVID19" OR "Coronavirus" OR "COVID 19" OR "2019-new coronavirus" OR "2019-nCoV") AND TITLE-ABS-KEY ("incidence" OR "risk" OR "relative risk" OR "odds ratio" OR "prognosis" OR "evolution" OR "mortality" OR "lethality" OR "hospitalization" OR "intensive care unit" OR "death")

Tabla suplementaria III. Detalle de la puntuación del análisis de calidad de los estudios de cohortes. Escala "Newcastle-Ottawa"

Primer autor / Año de publicación (referencia)	Selección				Comparabilidad	Resultado			Puntuación (*)
	Representatividad cohorte expuesta	Selección cohorte no expuesta	Medida de exposición	Demostración resultado no presente inicialmente	Factores de confusión	Medida resultado	Duración seguimiento adecuado	Seguimiento adecuado	
Ahmadi. et al. / 2021 (27)	*	*		*	**	*	*	*	8
Deschasaux-Tanguy et al. / 2021 (29)		*		*	**	*	*		6
Louca S. et al. / 2021 (30)		*		*	**		*	*	6
Merino et al. / 2021 (34)		*		*	**		*	*	6
Perez-Araluce et al. / 2021 (26)		*		*	**		*		5
Ponzo et al. / 2021 (23)		*		*	**		*		5

Tabla suplementaria IV. Detalle de la puntuación del análisis de calidad de los estudios de casos y controles. Escala "Newcastle-Ottawa"

Primer autor / Año publicación (referencia)	Selección				Comparabilidad	Exposición			Puntuación (*)
	Definición de caso adecuada	Representatividad de los casos	Selección de controles	Definición de controles	Factores de confusión	Medida de exposición	Igual método para casos y controles	Tasa de no respuesta	
Kim et al. / 2021 (37)		*	*	*	**		*	*	7
Mohseni et al. / 2021 (28)	*		*	*	**		*	*	7

Tabla suplementaria V. Detalle de la puntuación del análisis de calidad de los estudios transversales. Escala "JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies"

Primer autor / Año publicación (referencia)	Tavakol et al. / 2021 (35)				Aldwihi et al. / 2021 (31)				El Khoury et al. /2021 (24)			
	Sí	No	Poco aplicable	No aplicable	Sí	No	Poco aplicable	No aplicable	Sí	No	Poco aplicable	No aplicable
¿Se definieron claramente los criterios de inclusión en la muestra?	X				X					X		
¿Se describieron en detalle los sujetos del estudio y el entorno?	X				X				X			
¿Se midió la exposición de forma válida y fiable?	X				X					X		
¿Se utilizaron criterios estándares y objetivos para medir la afección?	X				X					X		
¿Se identificaron factores de confusión?		X			X				X			
¿Se establecieron estrategias para tratar los factores de confusión?		X			X				X			
¿Se midieron los resultados de forma válida y fiable?	X				X					X		
¿Se utilizó un análisis estadístico adecuado?		X			X				X			
Total	5				8				4			

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Revisión

Autophagy, a relevant process for metabolic health and type-2 diabetes

Autofagia, un proceso relevante para la salud y la diabetes tipo 2

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Abstract

Autophagy is a very active process that plays an important role in cell and organ differentiation and remodelling, being a crucial system to guarantee health. This physiological process is activated in starvation and inhibited in the presence of nutrients. This short review comments on the three types of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy, as well as different aspects that control autophagy and its relationship with health and degenerative diseases. As autophagy is highly dependent on functional autophagy (ATG) proteins integrating the phagophore, the role of some key ATG genes and epigenes are briefly commented on. The manuscript deepens discussing some central aspects of type-2 diabetes *mellitus* (T2DM) and their relationship with the cell cleaning process and mitochondria homeostasis maintenance, as well as the mechanisms through which antidiabetic drugs affect autophagy. Well-designed studies are needed to elucidate whether autophagy plays a casual or causal role in T2DM.

Keywords:

Autophagy. Types. ATG genes. Degenerative diseases. Type-2 diabetes. Antidiabetic drugs.

Resumen

La autofagia es un proceso muy activo que juega un papel importante en la diferenciación y remodelación de células y órganos, siendo un sistema crucial para garantizar la salud. Este proceso fisiológico se activa en la inanición y se inhibe en presencia de nutrientes. En esta breve revisión se definen los tres tipos de autofagia: macroautofagia, microautofagia y autofagia mediada por chaperonas, y los diferentes aspectos que controlan la autofagia y su relación con la salud y las enfermedades degenerativas. Como la autofagia depende en gran medida de las proteínas funcionales de autofagia (ATG) que integran el fagóforo, se comenta brevemente el papel clave de algunos genes y epigenes de las ATG. El manuscrito profundiza discutiendo algunos aspectos centrales de la diabetes *mellitus* tipo 2 (DMT2) y su relación con el proceso de limpieza celular y el mantenimiento de la homeostasis mitocondrial, así como los mecanismos a través de cuales los fármacos antidiabéticos afectan a la autofagia. Se necesitan estudios bien diseñados para dilucidar si la autofagia juega un papel de casualidad o causalidad en el desarrollo de la DMT2.

Palabras clave:

Autofagia. Tipos. Genes ATG. Diabetes tipo 2. Fármacos antidiabéticos.

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INTRODUCTION

Autophagy is the term (derived from the Greek words "auto" meaning "oneself" and "phagein" meaning "eating") adopted to describe the set of molecular reactions that result in the degradation of intracellular components in lysosomes, a process for which Yoshinori Ohsumi was awarded the Nobel Prize in Physiology or Medicine in 2016 (1). Recycling is one of the bases of cell survival, since it allows to reduce cellular waste, preserve cellular energy, and adapt to different changes by regulating the abundance of intracellular components. Autophagy occurs in cases of low basal metabolic rate (activated in starvation and inhibited in the presence of nutrients) and is elevated during differentiation and remodelling in a wide variety of tissues, such as brain, intestine, kidney, adipose tissue, lung, liver, prostate, skin, thyroid gland (1), also in the control of cell growth and defence (2) and in the prevention and triggering of some pathologies (3). Contrary to what was previously believed, autophagy is not only based on a protein recycling process, but also contributes to maintaining a positive energy balance through the degradation and use of organelles, glycogen or lipids.

TYPES OF AUTOPHAGY

Based on the way substrates reach the lysosomal lumen, three main forms of autophagy have been described in mammalian cells: macroautophagy, chaperone-mediated autophagy, and microautophagy (1,4) (Fig. 1).

MACROAUTOPHAGY

This is the best characterized lysosomal recycling pathway, in which cytosolic elements destined for degradation are sequestered by the phagophore, a double-membrane vesicle of non-lysosomal origin, which delivers the cytosolic material to lysosomes. The phagophore is formed through the assembly of proteins and lipids from different organelles such as the endoplasmic reticulum, Golgi apparatus or plasma membrane. The closure of the vesicle with the cargo inside gives rise to what is known as an autophagic vacuole or autophagosome, which moves through the microtubules to fuse with the lysosomes, organelles that provide the enzymes necessary for the degradation of the components sequestered (5,6).

CHAPERONE-MEDIATED AUTOPHAGY

This was discovered by J. Fred Dice in 1985 and is an autophagic pathway for the selective degradation of proteins that cross the lysosomal membrane through the membrane pro-

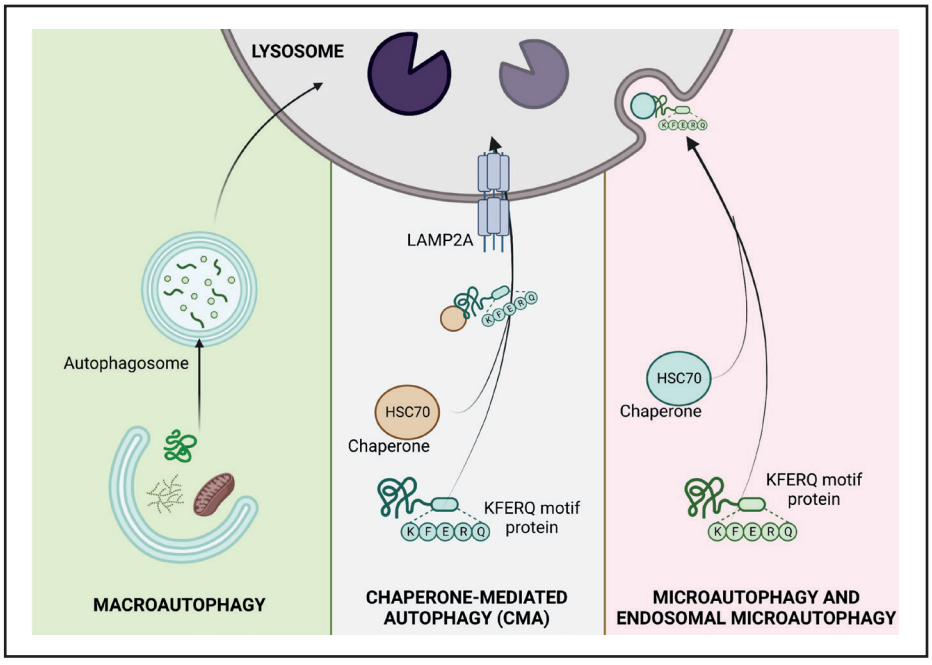

Figure 1.

The three types of autophagy in mammalian cells. Macroautophagy relies on *de novo* formation of cytosolic double-membrane vesicles, autophagosomes, to sequester and transport cargo to the lysosome. Microautophagy involves the direct uptake of cargo through invagination of the lysosomal membrane. Chaperone-mediated autophagy (CMA) transports individual unfolded proteins directly across the lysosomal membrane. All three types of autophagy lead to degradation of cargo and release of the breakdown products back into the cytosol for reuse by the cell. (HSC 70: cytosolic heat shock-related protein of 70 kDa; KFERQ: pentapeptide domain. Modified from Macho-González and Sánchez-Muniz (36).

tein associated with the lysosome type 2A (LAMP-2A) (4). In this process, cytosolic proteins destined for degradation must be recognized by the chaperone cytosolic heat shock-related protein of 70 kDa (HSC 70) through a pentapeptide domain (KFERQ) of the protein's amino acid sequence. Once the chaperone-substrate complex reaches the lysosomal membrane and binds to monomeric LAMP-2A, its multimerization is induced and the substrate protein is transported into the lysosome for degradation. The activation of this type of autophagy, in addition to acting in response to nutritional changes, also functions as a defence mechanism against cellular attacks to eliminate damaged proteins and ensure adequate protein homeostasis (2,4).

MICROAUTOPHAGY

In this type of autophagy the loads are sequestered by direct invagination or protrusion of the lysosome, originating small single-walled vesicles from the lysosomal membrane (7). Recently, a variation of this process called endosomal microautophagy has been found, which takes place in late endosomes and involves selective degradation through recognition of the KFERQ domain of proteins by hsc70, as occurs in CMA. However, substrate internalization is via the transport-required endosomal sorting complex I and III (ESCRTI and III) rather than LAMP-2A.

CENTRAL MOLECULAR ASPECTS OF AUTOPHAGY

The autophagy process can be divided into phases: 1) nucleation, 2) elongation, 3) formation of the mature autophagosome, 4) fusion, 5) degradation, and 6) recycling. The nucleation phase is regulated by the mTORC1 complex, whose regulation depends on the AMP/ATP ratio which, in turn, is related to nutritional and metabolic status. This complex and downstream proteins are regulated by phosphorylation/dephosphorylation. A large part of the process is mediated by proteins of the ATG family (autophagy-initiating proteins), which bind to damaged proteins or organelles, marking them for the formation of phagophores (double-membrane vesicles that contain the material to be recycled). Some ATG proteins bind to phagophores, promoting their maturation and fusion with the lysosome to form the autophagosome (8) (Fig. 2).

The presence of ATG proteins is essential for a proper functioning of the cell recycling process, which has been observed to play roles of indisputable importance in health, and alterations in the autophagic process are implicated in the pathophysiology of cardiovascular diseases, infectious diseases, Crohn's disease and neurodegenerative disorders (9,10).

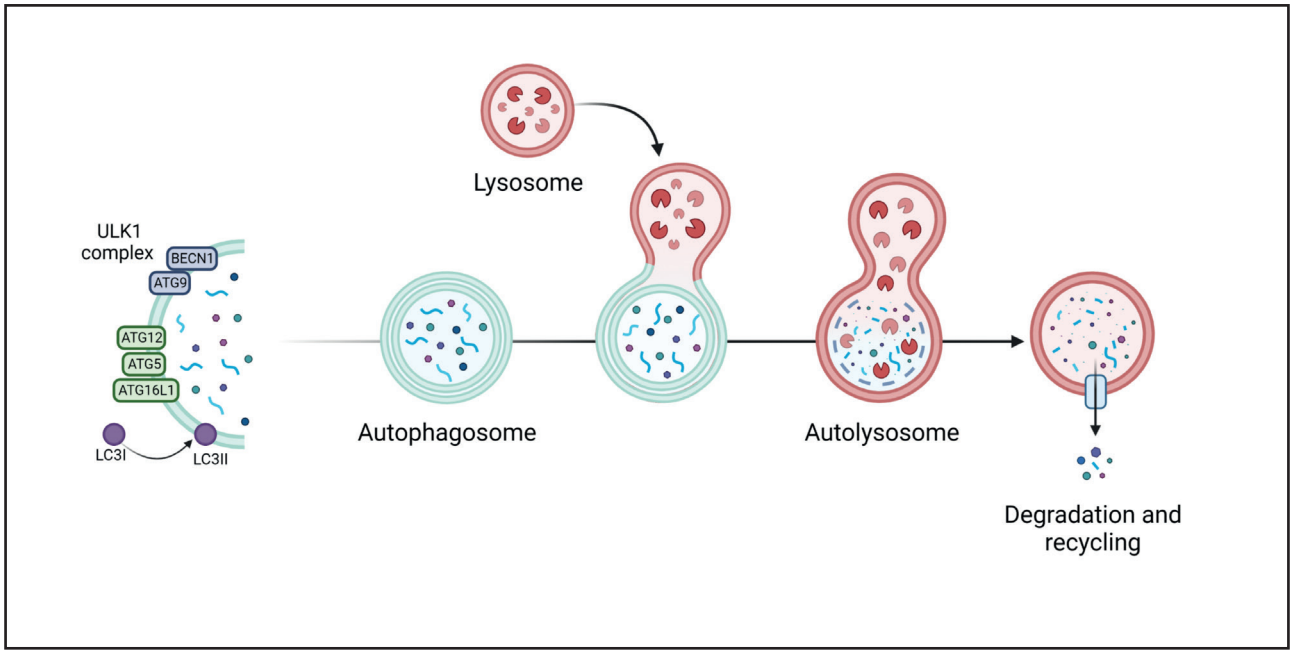

Figure 2.

Genesis and development of the autophagosome and participation of the different ATG proteins in its 6 stages (nucleation, elongation, formation of the mature autophagosome, fusion, degradation, and recycling. It begins by activation of the ULK1/2 kinase-kinase complex (proteins uridine type kinase 1 and 2, respectively), which phosphorylates the Beclin1 protein (BECN1, also known as ATG6) that is part of the phagophore nucleation initiator complex and subsequently its conjugation with the ATG5/ATG12/ATG16 complex (initiator proteins 5, 12 and 16). It, then, continues with the processing of LC3 (microtubule-associated protein light chain 3) and the insertion of the phagophore into the membrane producing the formation of the autophagosome which then fuses with the lysosome (autophagolysosome), where the degradation of the substrate occurs. Finally, degradation products are released into the cytoplasm to be eliminated or recycled. Modified from Costas and Rubio (35).

DIET AND BIOACTIVE DIETARY COMPOUNDS AS MODULATORS OF AUTOPHAGY

Starvation was the first stimulus described to activate the main autophagic pathways (1,2). In the absence of nutrients, autophagy promotes the breakdown of intracellular proteins to ensure the necessary amino acids for protein synthesis. In turn, they also use these pathways to mobilize intracellular lipid and glycogen stores to generate energy when nutrients are scarce.

The communication between nutritional status and autophagy is mediated by intracellular nutrient sensors, the main player of which is the mammalian target of rapamycin (mTOR). This kinase integrates nutritional signals (amino acids, insulin, and ATP levels) and actively suppresses macroautophagy under normal nutritional conditions (11). However, nutrient deprivation increases the AMP/ATP ratio, which activates AMP-activated protein kinase (AMPK), which promotes autophagy and autophagosome formation by inhibiting mTOR and phosphorylating uridin-like-kinase 1 (ULK1). It is well known that mTOR and AMPK nutritional sensors can be modulated by different food components such as polyphenols. It has been suggested that a diet rich in polyphenols can protect against aging by inducing autophagic activity, being one of the mechanisms underlying the beneficial properties attributed to them and favouring the recycling of cellular waste (12). Quercetin and resveratrol increase lifespan in lower eukaryotes by activating sirtuin (SIRT1), a deacetylase that induces autophagy through deacetylation of autophagic genes and its interaction with AMPK (13). However, not all polyphenols show the same action, nor are their bioavailability the same, nor are the effects greater at high concentrations. Polyphenols are showing their therapeutic potential in diseases that occur with alterations in autophagy pathways, since they can modulate key points in degradative processes such as mTOR, AMPK, p62/SQSTM1 or Nrf2. Although the molecular mechanisms involved are still unknown, these compounds represent a promising nutritional strategy (14).

ROLE OF ATG GENE POLYMORPHISMS IN PATHOLOGIES

Since the discovery of genes related to autophagy in yeasts, it is known that the correct functioning of autophagy depends on the presence of polymorphisms in ATG genes, being possible to speak of candidate genes to be studied primarily in errors in autophagy for the ATG 5,12 and ATG16L-1 genes (5,15). The presence of the ATG protein that intervenes in the formation of the phagophore depends on the expression of the ATG genes.

Therefore, the fight against many degenerative diseases, including different types of tumours or cancer, begins with knowledge of the autophagic transcriptome (a set of mRNAs that originate from DNA and are going to be translated on ribosomes), giving rise to the production of a set of proteins (proteome). Unquestionably, gene expression is also modulated by epigenetic effects. In fact, epigenetic alternations of microRNAs and DNA methylation is using for disease diagnosis and treatment (16,17).

Very interesting promising results on gene epigenome and the Mediterranean diet have been recently published, as a higher adherence to the Mediterranean diet is associated with differential DNA-methylation on relevant autophagy related genes and may have a potential effect upregulating autophagy (18).

Discoveries about autophagy have laid the groundwork for knowing its physiological involvement in a variety of physiological and pathological states, having established relationships with Alzheimer's disease, cancer, obesity, T2DM or non-alcoholic fatty liver disease (2,6,15).

ROLE OF AUTOPHAGY IN TYPE-2 DIABETES *MELLITUS*

Insulin resistance in peripheral tissues and decreased insulin production by pancreatic β-cells are the two main diabetogenic factors (19). At the beginning of T2DM, pancreatic β-cells adapt themselves to the situation of insulin resistance by increasing the production and secretion of said hormone. This constant demand has been associated with a greater accumulation of misfolded proteins, especially proinsulin, which cause endoplasmic reticulum stress (20). The continuous glucose uptake by the pancreas and its subsequent metabolism induces a high amount of reactive oxygen species that cannot be counteracted by the antioxidant machinery. Likewise, the arrival of free fatty acids and proinflammatory cytokines from peripheral tissues also contributes to and aggravates cellular stress, causing pancreatic β-cell dysfunction and failure (20). Autophagy can prevent cellular stress by removing misfolded proteins and non-functional organelles such as damaged mitochondria. However, in the diabetic situation, autophagic activity may be reduced or altered though stimulation of mTORC1 by glucose and free fatty acids or though inhibition of lysosomal acidification by free fatty acids and amylin accumulation, leading to destruction of β-cells and contributes to the vicious cycle of T2DM (21).

On the other hand, mitochondria play a central role on cellular metabolic homeostasis; in such a way that the maintenance of a healthy mitochondrial population is essential for cell survival. Metabolic overload of mitochondria clearly influences both muscle insulin resistance and β-cell dysfunction. This overload leads to incomplete β-oxidation, oxidative stress, accumulation of toxic lipid intermediates, and mitochondrial damage (22). Mitophagy, a macroautophagy type consisting in the elimination of aged and altered mitochondria, has been defined to play a protective role against development of insulin resistance and diabetes, as it eliminates oxidative stress and its related pathogenic processes (23). Autophagy also mediates exercise-induced increases in muscle glucose uptake and protects β-cells against ER stress in diabetogenic conditions (21). On the other hand, adipose tissue autophagy promotes adipocyte differentiation, possibly through its role in mitochondrial clearance. Being involved in many aspects, autophagy appears to be an attractive target for therapeutic interventions against obesity and diabetes (22,23).

T2DM is characterized by mitochondrial dysfunction, high production of reactive oxygen species (ROS), and low levels of ATP (24).

Dynamic processes such as mitophagy and mitochondrial biogenesis are also clearly affected in T2DM (24).

As previously discussed, autophagy is clearly dependent of the phagophore formation, whose constituents' proteins are in turn expressed by autophagy genes. Most studies indicate that alterations in the liver, pancreas and adipose tissue participate in T2DM pathophysiology. These alterations are related to modifications in the autophagic process. Thus, knockout mice for Atg7, a gene essential for macroautophagy activity as we have previously discussed, showed structural and functional defects in pancreatic β-cells, leading to glucose intolerance (25). This same deletion in the liver resulted in liver hypertrophy and triglyceride accumulation because of a lipophagy dysregulation, while a lower fat deposition, due to a defective differentiation of adipocytes, is induced in adipose tissue (20).

Similar results have been found for hepatic LAMP-2A knockout mice. These animals presented a phenotype that manifested itself with very high rates of glycolysis and reduced neoglycogenesis and lipolysis, leading to the development of hepatosteatosis (26).

Despite all the indications that associate an alteration of autophagy with T2DM, additional studies are required to know if deregulation of autophagic activity is a cause or consequence of said pathology.

Considering the previous premise, briefly mentioned in this review, there is no doubt that autophagy is a very important new aspect to take into account in the diagnosis, treatment and resolution of very prevalent degenerative conditions. In the very near future, the population should be genotyped according to genes engaged in the encoding of autophagy central proteins (e.g., ATG proteins, necessary for the formation of the phagophore), as a great variability in response to diet has been defined between some individuals and others due to polymorphisms in candidate genes. This will allow to perform a precision nutrition to ensure the greatest possible success in all individuals given the known differences in response between subjects (27).

TYPE-2 DIABETES *MELLITUS* DRUGS AND AUTOPHAGY

Present evidence suggests that antidiabetic agents can affect autophagy pathways and modulate this process. In this section the role of metformin, SGLT2i and DPP-4 inhibitors and GLP-1 receptor agonists (GLP-1RA) on autophagy is reviewed. Metformin hydrochloride is the most common oral glucose-lowering medication. The guidelines published by national and international diabetes associations have supported the use of this drug as first-line therapy together with lifestyle changes for the treatment of adults with newly diagnosed T2DM with or without risk of cardiovascular disease. This reputation has resulted from its effective glucose-lowering capabilities, low cost, weight neutrality, and good overall safety profile (especially the lack of hypoglycemia as an adverse effect) (28-30).

GLP-1RA drugs (e.g., liraglutide) have proven to be highly effective in the treatment of diabetes (31). GLP-1RA result in pharmacological levels of glucagon-like peptide-1 (GLP-1), an incretin produced and secreted by the intestinal enteroendocrine L-cells that can decrease blood sugar levels in a glucose-dependent manner by enhancing the secretion of insulin (32). The DPP-4i inhibitor class drugs (e.g., omarigliptin) have the function of maintaining endogenous levels of GLP-1 by preventing its breakdown and inactivation (33). Sodium glucose cotransporter 2 inhibitors (SGLT2is) (e.g., gliflozins or flozins) help decrease diabetes hyperglycemia by inhibiting glucose reabsorption in the nephron (34).

AMP-activated protein kinase (AMPK) is a key regulator of numerous pathways and metabolic processes, including glucose metabolism, lipid metabolism, and energetic homeostasis, promoting catabolic reactions that generate more ATP and inhibit energy-consuming anabolic pathways, including gluconeogenesis. AMPK is known to be activated by the knockdown of cellular energy status. In addition, the mammalian target of rapamycin (mTOR) is a key component of the so called mTOR complex 1 (mTORC1) that has been found to be a key regulator of metabolism and autophagy. mTORC1 is inhibited in acute response to depletion of cellular energy (35) (Fig. 3). Although mTOR is tightly controlled under physiological conditions, loss of the negative regulation of this pathway can lead to T2DM (36).

Metformin exerts its antihyperglycemic effects through stimulating autophagy in a concentration-dependent manner, mainly by suppressing liver glucose production through AMPK-dependent and AMPK-independent pathways (37). Also, AMPK activation leads to mTORC1 inhibition, which also results in suppression of gluconeogenesis (38).

Autophagy can also be affected by novel antidiabetic agents, including GLP-1RAs, DPP-4is and SGLT2is (39). GLP-1RA may be able to modulate the autophagy process (37,40). Mechanistically, it has been reported that these protective effects are mediated by autophagy stimulation via induction of Beclin-1, microtubule-associated protein light chain 3 (LC-3) II, AMPK, PI3K and Akt and inhibition of mTOR (39) (Fig. 2).

Exenatide (a mimetic of GLP-1) effectively reduced fasting glycemia, cholesterolemia, and triglyceridemia, as well as plasma malondialdehyde levels (41). The increased formation of autophagosomes, and the up-regulation of Beclin-1 and LC3A/B-II/I found, suggested that those metabolic protective results due to GLP-1RA were mediated by the induction of autophagy (41).

Animal models have evidenced that several positive effects of DPP-4i (e.g., sitagliptin, vildagliptin) are produced through autophagy induction (42-46). Results appear primarily related to the effect of DPP-4is on GLP-1 levels, which in turn allow adequate insulin release (47). In fact, the positive effects of sitagliptin on hepatic insulin resistance observed in ob/ob mice with hepatic steatosis and insulin resistance were mainly mediated by autophagy activation through the inhibition of the mTOR signaling pathway and stimulation of AMPK (44). Finally, the present evidence suggests that SGLT2i inhibitors (e.g., empaglyfloxin) are able to modulate the autophagy process to contribute to their anti-diabetic effects (37,48,49). Thus, the effect of empagliflozin on mitochondrial function was tested in diabetic rats that had suffered myocardial infarction (50). Empagliflozin, through promoting autophagy, restored the number and size of the mitochondria observed in this animal model (49).

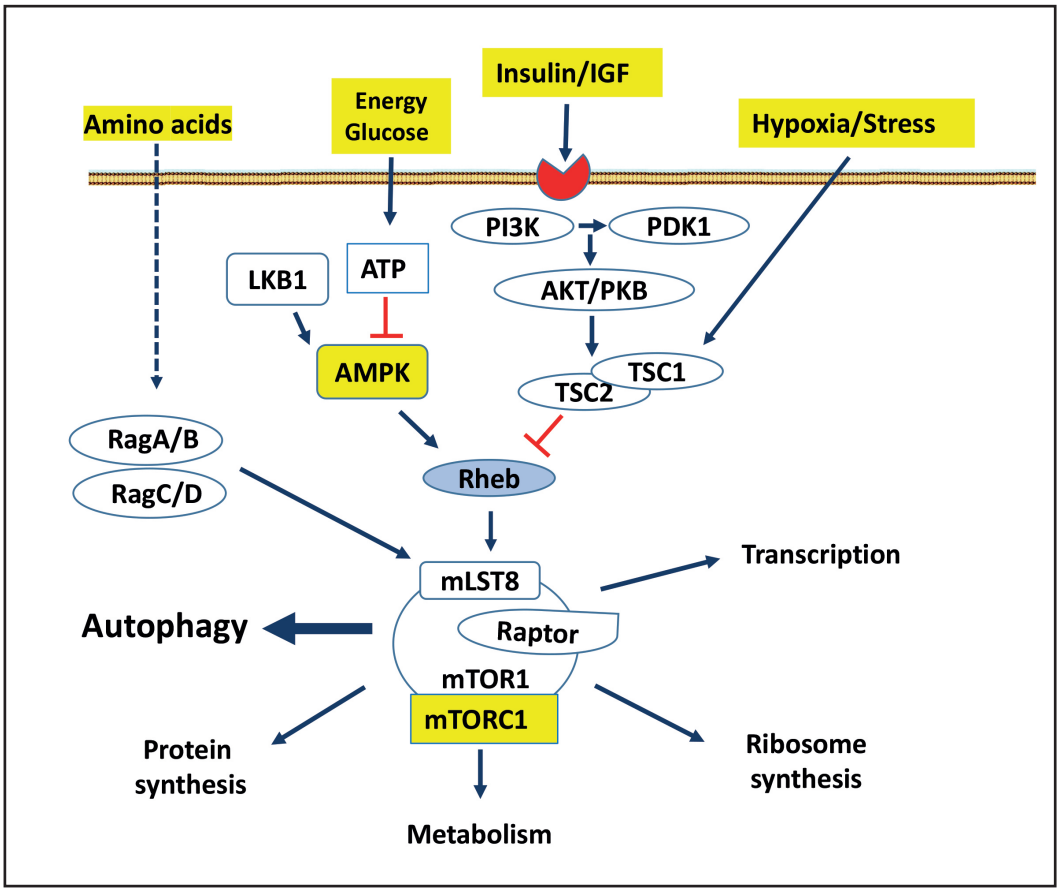

Figure 3.

The rapamycin-sensitive mTORC1 pathway controls several pathways, among them autophagy, that collectively determine cell survive and organ health. mTORC1 responds to growth factors (insulin/IGF), the energy status of cells, nutrients (amino acids) and stress. mTORC1, composed of different proteins, is multimeric, although it is schematized as a monomer. The arrows represent activation, while the bars represent inhibition. Dotted lines represent not totally demonstrated or indirect action (PI3K: phosphatidylinositol 3 kinase; Akt/PKB: protein kinase B; PDK: phosphatidylinositol-dependent protein kinase 1; TSC: tuberous sclerosis complex 1 and 2; LKB1: serine threonine kinase encoded by the LKB1 gene; AMPK: adenosine monophosphate-dependent kinase); Rag: Ras-related small GTPases; Rheb: RAS homologue enriched in brain, a GTPase; mLST8: mammalian lethal protein 8 with SEC13; RAPTOR: regulatory-associated protein of mTOR. Modified from Macho-González and Sánchez-Muniz (36).

CONCLUSIONS AND FUTURE REMARKS

In recent decades several molecular mechanisms of autophagy and their physiological significance have been revealed, with special mention of the studies that led to the Nobel Prize in 2016 and those carried out by other groups. Degradation is a fundamental function of the cell for the maintenance of life. It is necessary to deepen the knowledge of the dynamics of the membranes that constitute autophagy and advance in the development of systems that allow visualizing the dynamic machinery of autophagy with high spatiotemporal resolution. The identification, by Ohsumi, of the ATG genes in yeast represented an enormous advance in the knowledge of autophagy; however, much remains to be done as we are still in the initial stages of understanding this process. More information is needed on the specific role that ATG gene polymorphisms play on autophagosome membrane formation, as well as on the role of the heat shock protein family A member 8 (HSPA8) gene polymorphisms on encoding the central chaperone molecule Hsc70 (Fig. 1). As major evidence on the effects of drug therapy on autophagy came from animal models, it is urgently demanded that studies be carried out in T2DM patients. Finally, considering the role of nutritional status and antidiabetic drugs on autophagy, and the great variability in response to dietary and pharmacological treatments, we think that in the very near future the population at risk for T2DM should be genotyped according to the genes engaged in the three types of autophagy. This will allow to perform a precision nutrition and pharmacotherapy that will ensure the greatest possible success in all individuals given the known differences in response between subjects. It is also important to note that, under conditions

such as stress, autophagy increases to maintain cell survival, as an essential cytoprotective response. Alterations in the autophagic process are implicated in the pathophysiology of several degenerative diseases as T2DM. Autophagy is now recognized as a fundamental process of cell physiology with important implications for health and disease, but the causality or casualty of autophagy on health is still unknown.

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Nutrición Hospitalaria

Crítica de Libros

DIETAS Y ALIMENTOS PARA MI SALUD

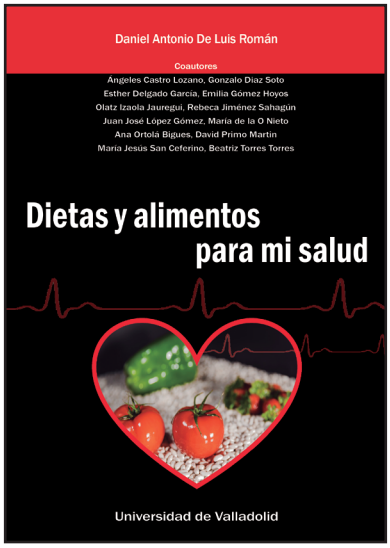
Editor: Daniel A. de Luis Román
Ediciones de la Universidad de Valladolid, 2022. 306 páginas

Tercer libro publicado por el Dr. Daniel de Luis en la línea con los anteriores *21 consejos nutricionales para vivir sano* (2019) y *101 alimentos saludables para tener en casa* (2020), con el fin de divulgar el conocimiento nutricional entre los pacientes, sus familiares y cualquier persona con interés en hacer que su alimentación sea realmente un "motor" de la buena salud.

En este volumen, publicado junto a un buen número de colaboradores: dietistas nutricionistas, endocrinólogos, etc. pertenecientes al área de Endocrinología y Nutrición de la Universidad de Valladolid se desgranan, con un punto de vista eminentemente práctico, ejemplos de dietas para cada uno de los grandes grupos de enfermedades. El libro está articulado en 14 capítulos que van desde "Una dieta sana" (capítulo 1) hasta las "Dietas para vegetarianos" (capítulo 14), incluyendo "dietas para el control de mi diabetes" o "dietas modificadas en texturas para problemas al tragar", entre otras.

Cada capítulo engloba apartados específicos que desarrollan sus contenidos, de tal manera que bajo cada gran epígrafe de un capítulo se agrupan consejos para cada situación clínica (p. ej. dieta para controlar la diarrea o dieta para tratar el estreñimiento).

Como una obra dirigida sobre todo al gran público, los autores usan un lenguaje comprensible y directo y, eminentemente práctico. Todos los capítulos siguen un esquema común: tras una breve introducción que justifica la razón de ser de las recomendaciones dietéticas en cada situación clínica y las líneas generales del consejo nutricional, se detalla primero la composición de la dieta a lo largo de 24 horas y luego una propuesta de menú semanal. En las dietas que lo precisen se acompañan al final de cada capítulo de algunas tablas de equivalencias de raciones o de aclaraciones sobre la composición de los menús sugeridos. Así llegan a constituir un manual práctico de consejos y recomendaciones nutricionales que abarcan la practica totalidad de los problemas de salud en la población adulta enferma.



Es muy de agradecer que los científicos "bajen a la tierra" sus conocimientos y los hagan asequibles al gran público. También que los médicos y los demás profesionales de la salud no solo nos quedemos en dar un consejo, sino que facilitemos cómo llevarlo a la práctica. Estamos convencidos de que este nuevo volumen contribuirá a hacer más sencilla la tarea de los pacientes y sus familias cuando, por razón de su enfermedad, se vean obligados a modificar sus pautas alimentarias. Aprovechamos la ocasión para invitar también al mundo de la Gastronomía, de la cocina, a que con estos mimbres que el equipo del Dr. de Luis nos muestra, hagan posible que además de adecuados sean atractivos. Mi experiencia personal en mi relación con el Departamento de Dietas de la Clínica de la Universidad de Navarra, me confirman que también esto es posible.

José Manuel Moreno Villares
Director de Nutrición Hospitalaria