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Urea en el síndrome de secreción inadecuada de hormona antidiurética crónico: suplemento dietético o fármaco

Urea in chronic syndrome of inappropriate antidiuretic hormone secretion: dietary supplement or drug

La hiponatremia (natremia sérica < 135 mmol/L) es el principal trastorno electrolítico tanto a nivel ambulatorio como a nivel hospitalario. En pacientes con nutrición artificial la frecuencia es aún mayor, alcanzando cifras de un 26 % en pacientes con nutrición enteral (1) y 30 % en pacientes con nutrición parenteral (2) frente al 19 % documentado en población general (3). Este trastorno electrolítico, incluso con cifras de natremia próximas a la eunatremia (natremia > 130 mmol/L) asocia una mayor mortalidad y comorbilidad, afectando a las capacidades cognitivas, la marcha y al riesgo de caídas. En pacientes con nutrición artificial por vía parenteral la presencia de hiponatremia mantenida (75 % de las natremias < 135 mmol) se ha relacionado con un incremento significativo de la mortalidad intrahospitalaria (4). La corrección de la hiponatremia crónica, tras alcanzar cifras mantenidas de eunatremia (> 135 mmol/L), se ha asociado una mejoría significativa en la estabilidad de la marcha y muy probablemente de la mortalidad, según sugiere Corona y cols. en su último metaanálisis (5). Sin embargo, si el incremento de la natremia es muy rápido y excede los límites establecidos, puede originar la aparición del síndrome de desmielinización osmótica (SDO), especialmente en pacientes con hiponatremia crónica y factores de riesgo asociado, como el alcoholismo, la malnutrición, el uso prolongado de diuréticos o la hipopotasemia.

Tanto en pacientes con nutrición artificial como en pacientes sin este soporte, la principal etiología de la hiponatremia es el síndrome de secreción inadecuada de hormona antidiurética (SIADH), representando un 46 % de las hiponatremias en nutrición parenteral (6) y un 67 % en nutrición enteral (7).

El tratamiento del SIADH crónico, en ausencia de clínica neurológica grave, se basa fundamentalmente en cuatro terapias: restricción de líquidos, uso conjunto de suplementos de sal y furosemida, urea y tolvaptán. La eficacia de la restricción de líquidos y de la terapia con furosemida/suplementos de sal, según series de casos y estudios observacionales, es limitada y está condicionada por la capacidad renal de aclaramiento de agua libre y la cifra de osmolalidad urinaria, respectivamente (8). Por otra parte, no es factible su uso en los cuadros de SIADH crónico. Por el contrario, tolvaptán ha demostrado en ensayos clínicos randomizados, seguridad y eficacia en la consecución de precoz de la eunatremia (100 % a los 4 días) y su mantenimiento a largo plazo (4 años). Respecto al riesgo de sobrecorrección (incrementos de natremia > 12 mmol en 24 horas), se ha documentado una frecuencia del 4,6 % en pacientes con SIADH e inicio con dosis 15 mg. Sin embargo, su inicio a dosis 7,5 mg, monitorizando la natremia a las 6 horas del inicio y aplicando suero glucosado en el caso de un incremento mayor de 6, no ha asociado casos de sobrecorrección (9). La aplicación de este protocolo implica iniciar el fármaco a nivel hospitalario y limita su inicio a nivel ambulatorio. Por ello, a este nivel en los últimos años, se ha incrementado sustancialmente el uso de urea. La urea considerada un suplemento dietético actúa a nivel renal como un diurético osmótico facilitando la excreción renal de agua libre. A su vez facilita la reabsorción renal de sodio disminuyendo la natriuresis, favoreciendo por ambos mecanismos el incremento de la natremia en pacientes con SIADH. Según series de casos clínicos y estudios observacionales, recogidos en una revisión sistemática reciente se han objetivado incrementos de natremia de

editorial

5 mmol/l y 10 mmol/L a las 24 horas y a los 5 días, respectivamente y sin documentarse casos de sobrecorrección ni de SDO (10). Obteniéndose mayores tasas de eunatremia con dosis de 30 g/día y una limitación relativa del consumo de líquidos a 1,5 litros al día. En un reciente análisis retrospectivo de 212 pacientes con SIADH, donde se comparó el uso de urea (15 g/día) frente a 1 litro de restricción de líquidos/día el 59,8 % de los pacientes con urea frente al 42 % de los pacientes con restricción de líquidos presentaron eunatremia al alta hospitalaria, lográndolo a los 6 días los pacientes con urea y a los 8 los pacientes con restricción hídrica (11), sin objetivarse tampoco ningún caso de sobrecorrección y registrando como principales efectos adversos la disgeusia y dolor abdominal. Estos efectos adversos han sido descritos también en otros estudios observacionales a consecuencia de la palatabilidad del preparado, atenuada en las últimas formulaciones ya saborizadas. En todos los análisis realizados el incremento de natremia se acompaña de un aumento significativo de las cifras de urea, que no asocian un deterioro de la función renal y ni desarrollo de hipovolemia. Incluso, este incremento de urea plasmática podría interpretarse como un marcador indirecto de adherencia al tratamiento.

En resumen, el SIADH crónico representa un desafío clínico frecuente y relevante, especialmente en pacientes con nutrición artificial. Aunque el tolvaptán ha mostrado eficacia y seguridad en estudios clínicos, su inicio a nivel ambulatorio está limitado. En este contexto, la urea, tradicionalmente considerada un suplemento dietético, emerge como una alternativa terapéutica eficaz, segura y de fácil manejo ambulatorio. Su capacidad para incrementar la natremia sin riesgo de sobrecorrección ni deterioro renal, junto con su bajo coste, refuerza su potencial como fármaco útil en el tratamiento del SIADH. No obstante, se requieren más estudios que avalen su uso prolongado y perfil de seguridad a largo plazo.

Conflicto de intereses: los autores declaran no tener conflicto de interés.

Inteligencia artificial: los autores declaran no haber usado inteligencia artificial (IA) ni ninguna herramienta que use IA para la redacción del artículo.

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Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

Adequacy of financing and prescription of home enteral nutrition. Are things being done right?

Adecuación de la financiación y prescripción de la nutrición enteral domiciliaria. ¿Se están haciendo las cosas bien?

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Abstract

Introduction: this study focuses on Home Enteral Nutrition (HEN), whose use has grown enormously in recent years.

Objective: to analyze the prescriptions and, in addition, determine whether National Health System (NHS) funding criteria are met and to explore whether overcosts exist.

Methods: a retrospective observational study was conducted on 844 patients (895 episodes) who received HEN, using information obtained from the healthcare database. Demographic, clinical, dietary, and economic data were analyzed.

Results: in 9.7 % of the episodes analyzed, the funding criteria were met; in 15.1 %, ≥ 50 % kcal/day required was provided through HEN. During the 3 months of the study an average of 118.1 ± 86.8 units/patient were dispensed, which resulted in an average monthly expenditure of € 69.9 ± 66.3/patient. To go to the hospital to collect HEN, an average of 78.1 ± 69.5 km/patient was traveled, with an associated average monthly fuel cost of € 2.65 ± 2.39/patient. The additional expenditure associated with prescriptions not aligned with the funding criteria was estimated at € 574,259.44/year in the health area analyzed, with a quota of 200,000 inhabitants.

Conclusions. the results of this study show a divergence in the use of HEN compared to the conditions established by the NHS for the funding of this treatment. Given the low compliance rate and the current scientific evidence on the use of HEN, it may be necessary to re-evaluate the funding criteria to make them more representative of clinical evidence and actual practice.

Keywords:

Malnutrition. Enteral nutrition. Economics. Cost. Home care.

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Resumen

Introducción: este estudio se centra en la nutrición enteral domiciliaria (NED), cuyo uso ha crecido enormemente en los últimos años.

Objetivo: analizar las prescripciones y determinar si se cumplen los criterios de financiación del Sistema Nacional de Salud (SNS) explorando la existencia de sobrecostes.

Métodos: se realizó un estudio observacional retrospectivo sobre 844 pacientes (895 episodios) que recibieron NED, utilizando información de la base de datos de asistencia sanitaria. Se analizaron datos demográficos, clínicos, dietéticos y económicos.

Resultados: en el 9,7 % de los episodios analizados se cumplieron los criterios de financiación; en el 15,1 % se proporcionó ≥ 50 % de las kcal/día requeridas a través de NED. Durante los 3 meses del estudio se dispensaron una media de 118,1 ± 86,8 unidades/paciente, lo que supuso un gasto medio mensual de 69,9 ± 66,3 €/paciente. Para acudir al hospital a recoger NED se recorrió una media de 78,1 ± 69,5 km/paciente, con un gasto medio mensual asociado en combustible de 2,65 ± 2,39 €/paciente. El coste adicional asociado con prescripciones no alineadas con los criterios de financiación se estimó en 574.259,44 €/año en el área sanitaria analizada, con un cupo de 200 000 habitantes.

Conclusiones: los resultados de este estudio muestran una divergencia en el uso de NED comparado con las condiciones establecidas por el SNS para la financiación de estos tratamientos. Dada la baja tasa de cumplimiento y la evidencia científica actual sobre el uso de HEN, puede ser necesario reevaluar los criterios de financiación para hacerlos más representativos de la evidencia clínica y la práctica real.

Palabras clave:

Desnutrición. Nutrición enteral domiciliaria. Costo. Económico. Atención domiciliaria.

INTRODUCTION

Enteral nutrition (EN) is a nutritional support technique using chemically defined formulas indicated for patients who cannot meet their nutritional needs with regular oral intake, but who have a functioning gastrointestinal tract capable of digesting and absorbing the formula introduced (1,2). EN is administered orally or through nasoenteral tubes or ostomies (3).

Home enteral nutrition (HEN) involves the administration of these formulas in the patient's home to prevent or correct malnutrition (4). It allows patients to remain in their environment, reducing the likelihood of complications associated with hospital stays, reducing healthcare costs, and increasing health-related quality of life (5). In addition, healthcare professionals must carry out home monitoring of the patient and the correct maintenance of the treatment to ensure nutritional efficacy and avoid possible complications (6). The treatment consists of selecting the enteral formula adapted to the pathology/clinical condition and the access route for each case (2,7,8).

In recent years, an increase in the prescription of HEN has been reported. For example, a study in Italy following 3246 patients over 11 years observed an average incidence of 406 ± 58 patients per million inhabitants per year (9). In the United States, there was a significant increase in the estimated prevalence of patients with HEN rising from 597 per million inhabitants in 1992 to 1385 per million inhabitants in 2013 (10). Another study in France indicates a prevalence of 740 per million inhabitants (11), while in Spain, research carried out in 2015 reports a higher incidence rate of 2290 per million inhabitants per year (12). These figures not only indicate the increase but also the great variability in prescription between different countries.

One of the causes of this variability lies in the fact that funding conditions vary greatly between countries, as therefore do professionals' incentives to prescribe it. In most countries, EN is funded in the hospital setting. However, in community and outpatient settings, funding is lower, limiting coverage to specific diseases or conditions (in Japan, for example, only patients who are fed through nasoenteral tubes or ostomies are funded) or to specific subsets of patients (for example, in Belgium, HEN funding is restricted to patients discharged from hospital and, in Singapore, to low-income patients). In Italy and China, HEN in outpatient patients is not funded, while, in other European countries, including France, Germany, Spain, and the Netherlands, HEN is funded in all 3 settings (hospital, community, and outpatient) (13).

For Spain, HEN is included and regulated in the portfolio of services of the National Health System (NHS) (14). In 15 of the 17 Spanish regions and in the autonomous cities of Ceuta and Melilla, HEN is purchased in pharmacies by the patient or a family member with an official medical prescription and visa from the pharmaceutical inspection. One of the exceptions is in the region of Galicia, where it is issued in hospital pharmacy services (14).

In 2008, the Spanish Ministry of Health published a guide that provides, based on the latest scientific evidence, clear guidelines for the prescription of HEN, the choice of the most suitable diet for each clinical situation, the controls and measures to be adopted in case of complications, the follow-up of the treatment, and the training that the patient and their caregivers must receive (15). Based on the guide, and according to Spanish legislation, patients' treatments must be funded. These funding criteria are set out in the descriptive guide to the provision of dietary products in the National Health System (16).

One of the most restrictive criteria for HEN funding in this guideline is the established calorie threshold, which justifies funding only in patients who do not meet 50% of their daily caloric requirements from ordinary food. However, current scientific evidence supports the use of HEN in certain patients even if their calorie intake from ordinary food is between 60 % and 75 % of their daily requirements (17).

With this background, the main objective of this study is to analyze the degree of compliance with the NHS funding criteria in HEN prescriptions, estimating their costs as well as the excess or defect of costs if inadequate public funding is revealed. Other objectives of this study are to determine the percentage of patients with HEN prescribed for pathologies eligible for treatment funded through the NHS, to determine the percentage of patients who receive at least 50 % of the necessary kcal/day through HEN, and to analyze the adequacy of the HEN prescribed to the patient's clinical situation and to the service responsible for the prescription.

METHODS

STUDY DESIGN AND SAMPLE

This is a retrospective observational study of HEN dispensed to patients who attended the outpatient pharmaceutical care consultation at a tertiary hospital over a three-month period (April 1-June 30, 2023).

The sample size was calculated to achieve a precision of 2.5 % in the estimation of a proportion using a 95 % bilateral asymptotic normal confidence interval. A compliance of 15 % was expected, and so it was necessary to include at least 783 patients. The 3-month period allowed us to meet this objective, and we thus selected the subjects from that period.

All the patients aged over 18 years that came to collect HEN formulas during the study period were included (see the formulas included in Supplementary Table I). Pediatric patients and patients that collected modules (protein module, lipid module, and thickening module) and complete diets indicated in the perioperative environment (Impact®, Optisource®) were excluded.

The data were extracted from the healthcare and management databases of the Complejo Hospitalario Universitario de Lugo (Spain)and were pseudonymized.

Supplementary Table I.
HEN included in the study

Standard HEN formulas:
• High calorie/high protein with fiber
• High calorie/high protein without fiber
• Hypercaloric/normoprotein with fiber
• High calorie/normoprotein without fiber
• Normocaloric/normoprotein with fiber
• Normocaloric/normoprotein without fiber
Specific HEN formulas:
• Intestinal mucosal dysfunction[a]
• Dysphagia[b]
• High-calorie/high-protein diabetes *mellitus* with fiber[c]
• Normocaloric/high protein diabetes *mellitus* with fiber[c]
• Liver failure[d]
• Chronic kidney failure[e]
• Malabsorption syndrome[f]

[a]Normocaloric and normoprotein polymeric formula with 100 % soluble fibre; [b]hypercaloric and hyperproteic formula, moderately thick, with fibre; [c]hypercaloric and hyperproteic formula with fibre, formulated with slow absorption carbohydrates; [d]hypercaloric and normoproteic formula enriched in branched-chain amino acids; [e]hypercaloric formula with low protein content; [f]hypercaloric and hyperproteic oligomeric formula without fibre.

STUDY VARIABLES

The sociodemographic variables of age (years), sex, and place of residence (municipalities in the province of Lugo) were obtained from the database. As for the clinical variables, the indication for HEN (Yes/No), prescribing medical service, *exitus* in the first 90 days from the start of HEN (Yes/No) and death (Yes/No, referring to whether the patient was deceased at the time of data analysis) were extracted. Regarding the diet, the type of HEN prescribed (Standard/Specific; Supplementary Table I), volume and kcal prescribed, route of administration (oral/tubes or ostomies), and number of containers dispensed were obtained.

For the indication of HEN, we analyzed whether the patients met the diagnosis, that is, if they presented any of the pathologies eligible for HEN financed by the NHS. These may be a) patients with mechanical alterations of swallowing or transit, who have aphagia or severe dysphagia and require a tube; b) patients with neuromotor disorders that prevent swallowing or transit and require a tube; c) patients with special energy and/or nutrient requirements; d) patients in clinical situations involving severe malnutrition. For a more detailed description, see the supplementary table II.

Specific HEN prescription was considered appropriate for patients with any of the following clinical conditions: intestinal mucosal dysfunction, dysphagia, diabetes *mellitus*, liver failure, chronic renal failure and/or malabsorption syndrome.

To calculate caloric requirements, a table was created based on the average energy requirements (kcal/day) of the European Food Safety Authority (EFSA), included in the report by the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on Nutritional Intake References for the Spanish population (Supplementary Table III). As for the activity factor (AF), which adjusts the necessary kcal/day based on physical activity performed, since we lacked this data in our patients, an AF of 1.4 was considered, which corresponds to the sedentary group (18).

The variable "meets funding" (Yes/No) was determined based on the HEN funding requirements included in the guide published by the Spanish Ministry of Health (16). As candidates to receive funded HEN, we considered patients who: a) present any of the following pathologies: patients with mechanical alterations of swallowing or transit, who have aphagia or severe dysphagia and require a tube, with neuromotor disorders that prevent swallowing or transit and require a tube, with special requirements of energy and/or nutrients and/or in clinical situations involving severe malnutrition (Supplementary Table II); and b) patients who receive at least 50 % of the necessary kcal/day through HEN (the guide indicates that it should only be financed in patients who, despite the implementation of dietary manipulations, do not reach this 50 %), defining this variable as "meets kcal objective" (Yes/No).

The number of containers dispensed in the study period was obtained by reviewing the records of the healthcare database. The cost per container was obtained from the management data of the Silicon® program. The total cost of HEN dispensed in the study period and the cost of HEN prescribed in patients who did not meet the funding criteria were calculated. It is worth mentioning that the selling prices to hospitals of the different types of HEN are negotiated directly with the distributor and can have average discounts of approximately 60 % compared to pharmacy selling prices.

To evaluate the cost associated with patients traveling to the hospital to collect their HEN, the number of dispensations per patient was obtained and the number of km separating their homes from the hospital was calculated (taking into account that for each dispensation the patients had to make two trips, round trip). These were multiplied by the average price of fuel at the time of travel (€ 1.54/liter). To obtain the estimated expenditure, we took the average car fuel consumption of 7 liters/100 km.

Supplementary Table II. Pathologies eligible for home enteral nutrition financed by the National Health System (Royal Decree 1030/2006, of September 15, which establishes the portfolio of common services of the National Health System and the procedure for its update)

1) Patients with mechanical swallowing or transit disorders, who present with severe aphagia or dysphagia and require a probe: • Head and neck tumors • Tumors of the digestive system (esophagus, stomach) • Otorhinolaryngology and maxillofacial surgery • Non-tumoral esophageal stenosis Exceptionally, in cases of severe dysphagia and if the tube is contraindicated, enteral nutrition without a tube may be used, following a justifying report from the doctor responsible for the indication of the treatment.
2) Patients with neuromotor disorders that prevent swallowing or transit and require a feeding tube: • Neurological diseases that cause aphagia or severe dysphagia: - Multiple sclerosis - Amyotrophic lateral sclerosis - Myastheniform syndromes - Guillain-Barré syndrome - Sequelae of infectious or traumatic diseases of the central nervous system - Severe mental retardation - Severe degenerative processes of the central nervous system • Cerebrovascular accidents • Brain tumors • Cerebral palsy • Neurological coma • Severe intestinal motility disorders: Intestinal pseudo-obstruction, diabetic gastroparesis
3) Patients with special energy and/or nutrient requirements: - Severe malabsorption syndrome - Severe short bowel syndrome - Intractable diarrhea of autoimmune origin - Lymphoma - Postgastrectomy steatorrhea - Pancreatic carcinoma - Wide pancreatic resection - Mesenteric vascular insufficiency - Amyloidosis - Scleroderma - Eosinophilic enteritis • Neurological diseases that can be treated with ketogenic diets: - Refractory epilepsy in children - Glucose transporter type I deficiency - Deficiency of the pyruvate-dehydrogenase complex • Diagnosed allergy or intolerance to cow's milk proteins in infants, up to two years if there is nutritional compromise • Malnourished patients who are to undergo scheduled major surgery or transplants • Patients with chronic hepatic encephalopathy with intolerance to dietary proteins • Patients with X-linked adrenoleukodystrophy, neurologically asymptomatic
4) Clinical situations when patients present with severe malnutrition: • Inflammatory bowel disease: Ulcerative colitis and Crohn's disease • Cancer cachexia due to chronic enteritis caused by chemotherapy and/or radiotherapy treatment • Infectious medical pathology that involves severe malabsorption: AIDS • Cystic fibrosis • Low output enterocutaneous fistulas • Childhood kidney failure that compromises the patient's growth

Supplementary Table III. Average energy requirements (kcal/day) of the European Food Safety Authority (EFSA) included in the report by the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on Nutritional Reference Intakes for the Spanish population, taking into account an activity factor of 1.4 depending on age and sex and kcal below which we consider supplementation (< 50 % of daily caloric requirements)

Age	Average energy requirements (kcal/day) (AF = 1.4) Sedentary group		kcal considered as supplementation (< 50 % of daily requirements)	
	Male	Female	Male	Female
18-29	2,341	1,887	< 1,170	< 943
30-39	2,269	1,815	< 1,134	< 907
40-49	2,221	1,791	< 1,110	< 895
50-59	2,197	1,791	< 1,098	< 895
60-69	2,006	1,624	< 1,103	< 812
70-79	1,982	1,624	< 991	< 812
80-89	1,883	1,543	< 941	< 771
90-99	1,789	1,466	< 894	< 733
100-110	1,700	1,393	< 850	< 696

AF: activity factor.

STATISTICAL ANALYSIS

We conducted a descriptive analysis of the sociodemographic and clinical variables of the study population. Categorical variables were presented using absolute and relative frequencies. In the case of continuous variables, their fit to normality was studied and they were presented using means and standard deviations (SD) or medians and interquartile ranges (IQR), depending on the results. For our comparative analyses, the chi-square test was used for categorical variables, the Mann-Whitney test for comparisons of continuous variables over 2 variables with 2 categories or the Kruskal-Wallis test in case of more than 2 categories.

As for the costs, the average costs per patient of HEN and car fuel consumption were calculated. The total actual costs were obtained by adding both items (HEN and fuel) for all patients. The expected costs were obtained by adding both items for all the patients, according to the following groups: 1) those who met the kcal objective; 2) those who met the diagnostic criterion, and 3) those who met the funding criteria. Finally, the overcosts and the percentage of overcost were obtained through the difference between the total costs and the expected ones as.

$$(C_{overcost} / C_{expected}) \times 100$$

The Ethics Committee for Drug Research of Galicia (CElm-G) approved this study. Registration Code 2023/544. The data obtained were entered in a database in Microsoft Excel®, and used for subsequent statistical analysis with IBM SPSS® Statistics V29 software.

RESULTS

A total of 844 patients were analyzed, generating a total of 895 episodes, given that a small number of patients were given different prescriptions (HEN types and/or guidelines) during the study period, generating more than one episode. The average age of the patients was 79.6 ± 14.1 years (range 22-105). Of the total number of patients included, 409 were men (48.5 %) and 435 were women (51.5 %). Table I shows the main characteristics of the patients. The prescriptions of HEN were issued by 13 different medical services; in 90.6 % of the cases, however, they were concentrated in the endocrinology and geriatrics services.

Table I. Characteristics of patients (*n* = 855) and episodes with home enteral nutrition

	n	%
Sex		
Male	435	51.54
Female	409	48.46
*Age**	79.6 (14.1)	
≤ 80 years	359	43.94
> 80 years	458	56.06
Episodes		
1	795	88.83
2	94	10.5
3	6	0.67
Total episodes	895	

**Mean and standard deviation.*

The 26.4 % of the patients had died at the time of data review, of which 63.2 % corresponded to exitus in the 90 days following the last dispensation of HEN. Regarding the funding criteria of the NHS, these were met in 9.7 % ($n = 87$) of the episodes analyzed. Statistically significant differences were observed between the ≤ 80 years and > 80 years groups, with a compliance with the funding criteria of 13.9 % and 6.3 %, respectively ($p < 0.001$). In 13.6 % ($n = 122$) of the episodes, the patients met the diagnosis. Analyzing this variable by age group, statistically significant differences were also observed between the ≤ 80 years group, with a compliance of 20 % and 13.5 % in those > 80 years ($p < 0.001$) (Table II). In 760 episodes (84.9 %), the HEN prescribed did not reach the kcal objective. These prescriptions generated 1040 dispensations. The median kcal provided in the form of HEN in these patients was 21.4 % (IQR = 18.1-33.5). In 135 episodes (15.1 %) in which this minimum kcal requirement was reached, the patients received a median of 68.5 % (IQR = 54.4-92.3) of kcal ($p < 0.001$) (Table III).

The average kcal provided by the HEN in the prescriptions analyzed was 563 ± 366 kcal, with a median of 420 kcal (IQR = 360). Analyzing separately, depending on whether the kcal objective was met, in the prescriptions where it was reached, the patients received an average of 1223 ± 446 kcal/day, with a median of 1200 (IQR = 700). Meanwhile, the patients that did not reach the kcal objective received an average of 446 ± 178 kcal, with a median of 330 (IQR = 300).

In the analysis by age group, in patients ≤ 65 years, the % of kcal provided by the HEN was 29.9 % of the necessary kcal/day, in patients between 65 and 80 years it was 24.2 %, and in those ≥ 80 years it was 22.5 % ($p = 0.008$).

A total of 9.2 % of the patients were fed through nasoenteral tubes or ostomies. Additionally, 99 % of the patients that did not reach the kcal objective with HEN were able to use the oral route to feed themselves.

The most common pattern in patients that did not reach the kcal objective was 1 container/day (58.7 %). On average, they received 1.59 ± 0.77 containers/day.

Table II. Relationship of prescriptions (*n* episodes) by age, sex and clinical service complying with the SNS funding conditions for HEN*

	Episodes	Meets kcal target ≥ 50 % kcal/día in HEN		Meets the diagnostic		Meets the funding conditions	
	n (%)	*n* (%)	*p*-value	*n* (%)	*p*-value	*n* (%)	*p*-value
Sex							
Males	437 (48.8)	54 (12.3)	0.025	60 (13.7)	0.933	43 (9.8)	0.906
Females	458 (51.2)	81 (17.7)		62 (13.5)		44 (9.6)	
Age							
≤ 80 years	394 (44.0)	70 (17.7)	0.046	79 (20)	< 0.001	55 (13.9)	< 0.001
> 80 years	501 (56.0)	65 (13)		43 (13.5)		32 (6.3)	
Clinical service							
Cardiology	1 (0.1)	0	< 0.001	0	< 0.001	0	< 0.001
Surgery	3 (0.3)	0		0		0	
Digestive	10 (1.1)	0		5 (50)		0	
Endocrinology	377 (42.1)	90 (23.9)		86 (22.8)		65 (17.2)	
Geriatrics	434 (48.5)	39 (9)		28 (6.5)		20 (4.6)	
Home hospitalization	3 (0.3)	0		0		0	
Hematology	1 (0.1)	0		0		0	
Infectious diseases	2 (0.2)	0		0		0	
Internal medicine	36 (4.0)	5 (13.9)		2 (5.5)		2 (5.5)	
Nephrology	2 (0.2)	0		0		0	
Neurology	2 (0.2)	0		0		0	
Oncology	20 (2.2)	1 (5)		1 (5)		0	
Palliative care unit	4 (0.4)	0		0		0	
Total	895	135 (15.1)		122 (13.6)		87 (9.7)	

*HEN: home enteral nutrition; p-value calculated with the chi-square test. *SNS funding conditions for HEN: patients who a) present any of the following pathologies: patients with mechanical alterations of swallowing or transit, who have aphagia or severe dysphagia and require a tube, with neuromotor disorders that prevent swallowing or transit and require a tube, with special requirements of energy and/or nutrients and/or in clinical situations involving severe malnutrition, and b) patients who receive at least 50 % of the necessary kcal/day through HEN.*

Table III. Distribution of patients with HEN prescription based on compliance with the target kcal and % of kcal provided in the form of HEN

	Do not meet target kcal	Meet target kcal	*p*-value
HEN contribution ≥ 50 % kcal/day *n* episodes (%)	760 (84.9)	135 (15.1)	< 0.001
% kcal provided in the form of HEN Median (IQR)	21.4 (18.1 to 33.5)	68.5 (54.4 to 92,3)	< 0.001

IQR: interquartile ranges; p*-value calculated with the Mann-Whitney test. HEN: home enteral nutrition.*

As for the type of HEN dispensed, in 708 episodes (79.1 %), standard formulas were prescribed, compared to 187 in which specific formulas were prescribed (20.9 %). Figure 1 shows the distribution of prescriptions by type of standard HEN prescribed. Of the 187 prescriptions of specific HEN (20.9 %), this was completely consistent with the clinical situation of the patient in 134 (72 %) (Fig. 2).

A total of 99,650 units of HEN were dispensed, with an average of 118.1 ± 86.8 units/patient. The average cost of the HEN dispensed per patient in the study period was € 209.8 ± 198.9 and the total cost, € 177,043.89, corresponding to 67.5 % (€ 119,507.71) of the amount of HEN prescribed without reaching the kcal objective. Meanwhile, the cost of the prescriptions in which the diagnosis was not met was € 129,642.78 (73.2 %). Finally, the cost of the prescriptions that did not meet the funding criteria (i.e., neither diagnosis nor kcal objective), was € 137,245.84 (77.5 %) (Table IV).

The average number of dispensations made per patient in the quarter of the study was 1.4, meaning, therefore, that an average of 2.8 trips per patient was necessary. Taking into account the patients' place of residence, a total of 65,908 km/quarter were traveled, with an average of 78.1 ± 69.5 km/patient.

Based on the average fuel consumption of vehicles at that time, a total fuel cost of € 7,104.88/quarter (€ 7.94 ± 7.18/patient) was estimated. Of the total, € 6,319.02 corresponds to journeys that do not meet the funding criteria. Therefore, added to the costs of the dispensations that do not meet funding criteria, this represents an excess expenditure of € 143,564.86/quarter (Table IV).

Finally, and extrapolating our estimates to an annual level, the excess expenditure derived from the inappropriate prescription of HEN in cases not meeting the funding criteria is € 574,259.44/year in the health area analyzed, which attends to around 200,000 people. This represents an overcost of 353.7 %.

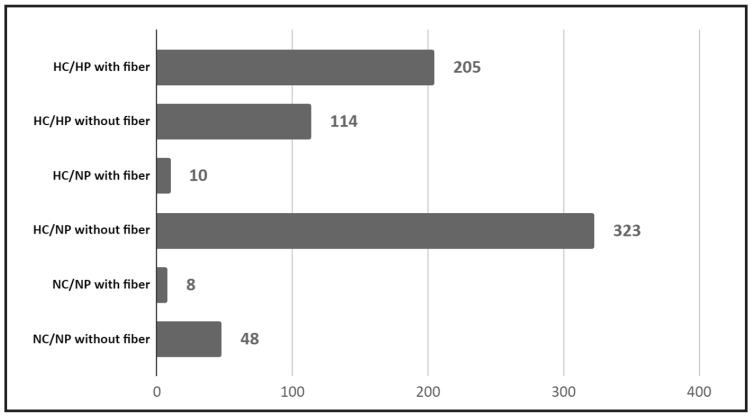

Figure 1.

Number of prescriptions depending on the type of standard HEN prescribed (HC: hypercaloric; HP: hyperproteic; NC: normocaloric; NP: normoproteic. The total number of standard HEN prescriptions in the study period was 708).

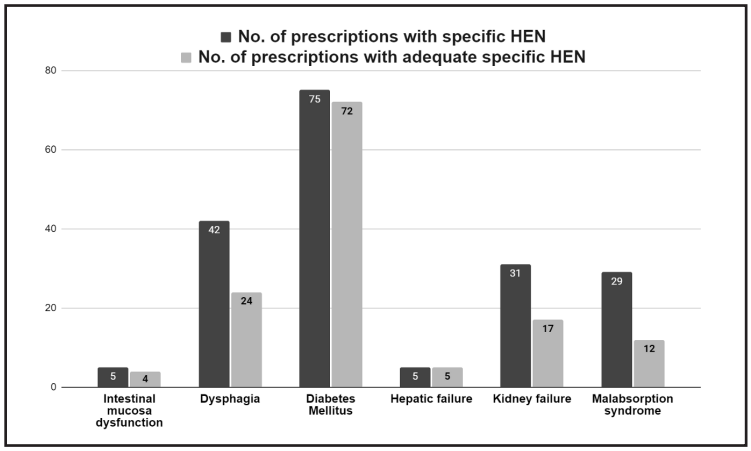

Figure 2.

Number of pathology-specific HEN prescriptions (dark grey) and their relationship to prescriptions completely adequate to the clinical situation of the patients (grey) (HEN: home enteral nutrition. The total number of specific HEN prescriptions in the study period was 187).

Table IV. Overcost, expected costs and percentage of overfinancing in response to compliance with the calorie target, diagnosis, and funding criteria

	HEN	Fuel	Total
Total actual costs (€)	177,043.00	7,104.88	184,147.88
Overcosts (€)*			
kcal target	119,507.71	5,949.48	125,457.19
Diagnosis	129,642.78	5,952.93	135,595.71
Funding criteria	137,000.00	6,319.02	143,319.02
Expected costs† (€)			
kcal target	57,535.29	1,155.40	58,690.69
Diagnosis	47,400.22	1,151.95	48,552.17
Funding criteria	40,043.00	785.86	40,828.86
Overcosts / Expected costs x 100			
kcal target	207.70	514.90	213.80
Diagnosis	273.50	516.80	279.30
Funding criteria	342.10	804.10	351.00

**Costs of episodes in which the kcal or diagnostic objective or the funding criteria are no met. †Costs of episodes in which the kcal or diagnostic target or funding criteria are met. HEN: home enteral nutrition.*

DISCUSSION

The results show that only 9.7 % of patients meet the NHS funding criteria considering the pathology they present and the kcal provided by the HEN. This percentage increases slightly to 13.6 % and 15 %, respectively, if we analyze these two conditions separately. These results indicate a mismatch between the conditions of use of a resource and those funded by the NHS, with an associated health expenditure of € 574,259.44/year for a health area of approximately 200,000 patients (€ 2.87/inhabitant and year).

Various studies carried out in recent years have linked malnutrition to an increase in patient morbidity and mortality (15,19). Due to the high prevalence of malnutrition and the significant advances in the field of nutrition in recent years, the worldwide use of HEN has grown enormously (9-12).

In our study, a notable characteristic of the sample was the elevated age of the population. The median age was 83 years (IQR = 72-90), higher than that in other studies carried out in Spain, where the median was 71 years (IQR = 57-82) (20). This contrasts with the data from a study conducted in China to determine the epidemiology of HEN, in which the median age of the patients was 59 years (IQR = 46-72) (21). The older age in our sample may be attributed to the high percentage of elderly population in the province under study, as well as the possibility that the use of HEN is due to the ageing process itself, perhaps reflecting a misuse of this treatment.

During the study period, 20,405 units of specific HEN were dispensed, 4,257 (20 %) were used in patients who, due to their clinical characteristics, should have used a standard formula. In a study carried out by Ferrer et al. in the Spanish region of Murcia, a reduction in the use of specific formulas of 55 % was observed after the implementation of a program to improve compliance with the NHS rules on the use of HEN (22). Both results show an overuse of these types of formulas. It is important to emphasise that specific formulas tend to have a significantly higher cost compared to standard formulas, which implies that their inappropriate use contributes to unnecessary expenditure in the healthcare system.

In the total of prescriptions analyzed, the median kcal provided by the HEN was 420 (IQR = 360) kcal/day, 1200 (IQR = 700) kcal/day in the patients that reached the kcal objective through HEN and, for the 84.9 % of patients that did not reach that objective, 330 (IQR = 300) kcal/day. These contributions are substantially lower than those obtained by Villar Taibo et al. in a study carried out in the city of Santiago de Compostela (region of Galicia, Spain). In this case, the caloric intake was distributed in two groups, intake of more than 1000 kcal/day (38.8 % of the patients) and less than 1000 kcal/day (61.2 % of the patients). The results show that, in the first group of patients, the median kcal/day provided by the HEN was 1500 (IQR = 1560) kcal while in the second group, it was 600 (IQR = 827) kcal (12). It is important to consider that the differences in caloric intake observed between our study and that of Villar Taibo et al. could be due to several factors. Firstly, there may be differences in the demographic and clinical characteristics of the populations studied, such as age, baseline nutritional status or comorbidities, which may influence caloric requirements. In addition, there may be differences in HEN prescription protocols between hospitals.

As for the route of administration, 90.8 % of the patients were fed orally and 9.2 %, through enteral tubes or ostomies. These results are consistent with those reported by Storck et al. in a study carried out in Switzerland, where 87.1 % received HEN orally and 12.9 % through nasoenteral tubes or ostomies (23). It is important to consider that the percentage of patients who met calorie targets (9.7 %) is comparable to the percentage of patients who received enteral feeding (9.2 %). This may be due to the fact that patients who are exclusively tube or ostomy fed are completely dependent on HEN formulas to meet their calorie requirements.

The average cost of the HEN dispensed per patient in the study period, considering only the price of the formulas, was € 209.8 ± 198.9 and the average monthly cost, € 69.9 ± 66.3/patient. In the study conducted by Villar Taibo et al., a total monthly cost of approximately € 266/patient was obtained, but in this case, the costs of the necessary materials for administration were also included, and so their obtaining a higher cost is logical (12).

In our study, only 13.6 % of the prescriptions were associated with pathologies eligible for funded HEN. In the study by Ferrer et al., this percentage was 44 %, and, after implementing the program for compliance with the NHS rules, this percentage increased to 98.5 % ($p < 0.001$). The implementation of a similar program in our population might save costs.

Regarding the expenditure for patients, it is essential to take into account the considerable cost associated with traveling from the different municipalities to the hospital to collect HEN in the autonomous community under study, unlike most communities where patients collect it in pharmacy offices in the cities or towns where they live. In addition, the health area analyzed covers an extensive geographical region, which involves patients traveling longer distances compared to other health areas.

As regards the limitations of our study, the first lies its design. To obtain more consistent data, a multi-hospital study should be carried out. Another is that we based the calculation of caloric requirements on the average requirements of the EFSA, which estimates the energy expenditure considering age, sex, and AF. Since we did not have our patients' AF, we considered the recommendations for the sedentary group, which may have underestimated the number of patients that did not reach the kcal objective. Another important limitation of this study is the use of an average calculation of daily calorie requirements based on the age and sex of the patients, without taking into account the body weight of each patient. In clinical practice, the calculation of kcal to be provided by the HEN is based on the weight of the patient. In addition, for patients over 80 years of age, as they are not included in the recommendations of the AESAN, the requirements were estimated considering that the energy needs in this group of patients decrease by about 5 % per decade (24).

Furthermore, it would be interesting to calculate the total cost associated with the administration of HEN, since our study only includes the cost of the formulas. The cost of equipment, indirect costs, and costs of the professionals involved in dispensing are not included. Regarding the cost associated with travel to the hospital, this was approximate, since the municipality of origin of the patients was taken into account instead of their specific address. The overcost involved in the prescriptions of specific HEN not adapted to the clinical situation of the patient was also not taken into account, since we did not individually assess whether or not they met the funding criteria for standard HEN, and if so, which would be appropriate.

Finally, our study did not assess patients' satisfaction with the way the HEN are dispensed. It is likely that their perspective would improve if we could bring the HEN closer to their homes. One possible option in our autonomous community, where the NED is dispensed from hospital pharmacy services, could be the implementation of a telepharmacy system and home delivery of the HEN.

CONCLUSION

Due to the advances in the field of nutrition and the importance of managing patients at home, the use of HEN has grown exponentially in recent years. The results of this study show a divergence in the use of HEN compared to the conditions established by the NHS for the funding of this treatment. One of these conditions is the caloric threshold, which justifies the funding of HEN only in patients who do not reach 50 % of their daily caloric requirements from ordinary food. However, current scientific evidence supports the use of HEN in certain patients even when their caloric intake from ordinary food is between 60 % and 75 % of their daily requirement. Although our study focused exclusively on assessing compliance with the funding criteria, it is important to note that the evidence suggests that these may be too restrictive. Given the low compliance rates observed and the current scientific evidence, it may be necessary to re-evaluate the funding criteria to make them more representative of clinical evidence and actual practice.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Pediatría

Percepción materna de las señales de hambre-saciedad y su impacto en la alimentación y el estado nutricional de los lactantes en México

Maternal perception of hunger-satiety signals and their impact on feeding and nutritional status of infants in Mexico

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Resumen

Introducción: la nutrición durante los primeros dos años de vida es crucial para el desarrollo físico, cognitivo y emocional de los niños. Este estudio tuvo como objetivos: 1) asociar la percepción materna de las señales de hambre y saciedad con el tipo de alimentación; 2) asociar la percepción materna de las señales de hambre y saciedad con el estado de peso del lactante; y 3) determinar la influencia del tipo de alimentación sobre el IMC/edad del lactante.

Material y métodos: se realizó un estudio transversal descriptivo correlacional con 424 diadas madre-lactante en Sinaloa, México, usando un muestreo aleatorio sistemático. Las madres completaron cuestionarios sobre prácticas de alimentación y percepción de señales de hambre y saciedad. Se midieron los datos antropométricos del lactante y se analizó la influencia del tipo de alimentación sobre el zIMC/edad del lactante mediante una regresión lineal múltiple.

Resultados: el 45,8 % de las madres reportaron una baja percepción de las señales de hambre y saciedad. El 30,2 % de los lactantes presentaron exceso de peso. Las madres con alta percepción de señales reportaron una menor proporción de lactantes con exceso de peso. La alimentación mixta y la introducción temprana de alimentos complementarios influyen significativamente en el aumento del puntaje zIMC/edad del lactante.

Conclusiones: la percepción materna de las señales de hambre y saciedad influye en el estado ponderal del lactante. La alimentación mixta y la introducción temprana de alimentos complementarios aumentan el riesgo de exceso de peso en los lactantes. Es crucial fomentar la percepción adecuada de estas señales para prevenir problemas nutricionales en la infancia temprana.

Palabras clave:

Nutrición infantil. Lactancia materna. Obesidad infantil. Madre. Prácticas de alimentación. Percepción.

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Abstract

Introduction: nutrition during the first two years of life is crucial for the physical, cognitive, and emotional development of children. This study aimed to: 1) associate maternal perception of hunger and satiety signals with the type of feeding; 2) associate maternal perception of hunger and satiety signals with the infant's weight status; and 3) determine the influence of feeding type on the infant's BMI-for-age.

Methods: a descriptive correlational cross-sectional study was conducted with 424 mother-infant dyads in Sinaloa, Mexico, using systematic random sampling. Mothers completed questionnaires on feeding practices and perception of hunger and satiety signals. Anthropometric data of the infant were measured, and the influence of feeding type on the infant's BMI-for-age z-score was analyzed using multiple linear regression.

Results: 45.8 % of mothers reported a low perception of hunger and satiety signals. 30.2 % of infants were overweight. Mothers with a high perception of signals reported a lower proportion of overweight infants. Mixed feeding and early introduction of complementary foods significantly influence the increase in infant zIMC/age score.

Conclusions: maternal perception of hunger and satiety signals influences the infant's weight status. Mixed feeding and early introduction of complementary foods increase the risk of overweight in infants. It is crucial to promote adequate perception of these signals to prevent nutritional problems in early childhood.

Keywords:

Infant nutrition. Breast feeding. Pediatric obesity. Mothers. Feeding behavior. Perception.

INTRODUCCIÓN

La nutrición durante los primeros dos años de vida es crucial para el desarrollo físico, cognitivo y emocional óptimo de los niños (1). Durante este periodo, los lactantes experimentan un rápido crecimiento y desarrollo, lo que requiere un suministro adecuado de nutrientes para apoyar sus necesidades en constante evolución (2). Las consecuencias de una nutrición inadecuada pueden ser graves y duraderas. La desnutrición en esta etapa puede llevar a un crecimiento deficiente, retraso en el desarrollo físico y cognitivo, debilidad del sistema inmunológico, mayor riesgo de enfermedades infecciosas y mayor mortalidad infantil. Por otro lado, el exceso de nutrientes, como el consumo excesivo de alimentos ricos en calorías y bajos en nutrientes, puede contribuir al desarrollo de enfermedades crónicas como la obesidad, la diabetes de tipo 2 y las enfermedades cardiovasculares a corto y largo plazo (3). Esto implica una significativa carga económica en términos de la familia y de atención médica.

Un peso saludable se considera uno de los pilares fundamentales de la promoción de la salud infantil, según la Organización Mundial de la Salud (OMS). No obstante, las estadísticas globales actuales revelan una preocupante realidad: se estima que 149 millones de niños menores de 5 años a nivel mundial podrían enfrentar retraso en el crecimiento, mientras que 45 millones presentan emaciación y 37 millones estarían en riesgo de sobrepeso u obesidad (2). Es ampliamente reconocido que la prevención de las enfermedades nutricionales se debe iniciar en la primera infancia, ya que las dimensiones conductuales de la alimentación, que comprenden qué, cuándo, cuánto y cómo se alimentan los niños, están fuertemente correlacionadas con su estado ponderal (4). Por ende, los esfuerzos dirigidos a la prevención de los problemas nutricionales infantiles deberían incluir un enfoque centrado en dichas dimensiones.

La mayoría de los estudios actuales en los lactantes tienden a focalizarse principalmente en el qué y cuánto de la dieta, dejando de lado otros aspectos relevantes relacionados al cómo se alimenta (5). Las madres juegan un papel crucial en la mejora de la nutrición durante los primeros dos años de vida de sus hijos, ya que son las principales cuidadoras y proveedores de alimentos en esta etapa temprana, y tienen una influencia significativa en los hábitos alimenticios y las preferencias de alimentos de sus hijos (6).

La relación entre las prácticas de alimentación de los padres y el peso de los niños ha impulsado el interés por una alimentación perceptiva para prevenir los problemas de nutrición infantil (7). La alimentación perceptiva consiste en estar en sintonía con las señales de hambre y saciedad del bebé y responder adecuadamente a estas señales según sus necesidades (8,9). Un componente clave de la alimentación perceptiva es alimentar al bebé solo cuando expresa signos de hambre y suspender la alimentación cuando muestra signos de saciedad, lo que puede conducir a un aumento de peso más saludable durante la infancia (10).

Las señales de hambre y saciedad que emite el niño varían según la edad. Los recién nacidos comunican su disposición a comer chupándose las manos o llorando de hambre, e indican saciedad a través de un amplio repertorio de señales que van desde expresiones faciales sutiles hasta cambios en los gestos y movimientos corporales. En los lactantes mayores de 6 meses, los gustos y aversiones se señalan a través de expresiones faciales francas y balbuceos (11). Un desafío temprano para llevar a cabo la alimentación perceptiva es la capacidad de los cuidadores para percibir e interpretar con precisión estas señales, la cual varía considerablemente. Comúnmente, las señales de hambre se identifican mejor que las de saciedad (12).

La evidencia muestra estudios limitados sobre la identificación de las señales de hambre y saciedad en los lactantes, y los pocos que existen se han realizado principalmente sobre todo en países de altos ingresos. Estos estudios indican que la capacidad de respuesta de las madres para interpretar las señales del bebé está influenciada por las características maternas (edad, escolaridad, nivel socioeconómico), las características del hijo (sexo, peso al nacer, temperamento) y el tipo de alimentación con biberón o desde el seno materno (6,12,13).

La lactancia materna facilita la comunicación al mejorar la capacidad de respuesta materna y aumentar la intensidad de las señales de hambre y saciedad del bebé; es decir, las madres son más sensibles a las señales del bebé durante la lactancia materna al seno que cuando se proporciona alimentación con biberón (14). Sin embargo, es importante considerar que existe un bajo porcentaje de apego a las recomendaciones de lactancia materna a nivel mundial (15).

Se ha identificado una prioridad de investigación para mejorar la comprensión de cómo implementar las recomendaciones

relacionadas con la alimentación perceptiva en los hogares con diferentes niveles de ingresos (16). Este trabajo es fundamental, dado que las barreras y los facilitadores de la práctica de alimentación perceptiva probablemente difieran entre las familias de bajos ingresos en comparación con las de altos ingresos, afectando el éxito potencial de la alimentación perceptiva (13).

México es un país de medianos ingresos y está impulsando políticas y estrategias de atención en la primera infancia para prevenir los problemas de malnutrición (17), especialmente para la prevención del sobrepeso y la obesidad en los lactantes, un problema que ya está presente en los mismos (18). Hasta el momento, la investigación de los factores de riesgo de sobrepeso y obesidad en los lactantes en este país es escasa y se ha limitado a describir el tipo de prácticas de alimentación relacionadas con el qué y el cuánto (19). Comprender cómo practican la alimentación perceptiva las madres de los lactantes podría ayudar a explicar este problema de salud.

El presente estudio tuvo como objetivos: 1) asociar la percepción materna de las señales de hambre y saciedad con el tipo de alimentación; 2) asociar la percepción materna de las señales de hambre y saciedad con el estado de peso del lactante; y 3) determinar la influencia del tipo de alimentación sobre el IMC/edad del lactante.

MATERIAL Y MÉTODOS

DISEÑO

Se realizó un estudio transversal descriptivo y correlacional entre septiembre de 2021 y julio de 2022.

PARTICIPANTES

Se incluyeron en este estudio díadas (madres mayores de 18 años con un hijo lactante menor de seis meses de edad) que acudieron a la consulta preventiva del control del niño sano en dos instituciones públicas de salud del estado de Sinaloa ubicados en el noroeste de México. Se excluyeron las madres que no sabían leer ni escribir en español y los lactantes que presentaban alguna enfermedad que pudiera influir en su peso al momento de la realización del estudio. El muestreo fue aleatorio y sistemático, seleccionando una de cada cinco madres que asistían a la consulta. La muestra se calculó mediante el paquete estadístico nQuery Advisor para un modelo de regresión lineal múltiple con 4 variables predictivas por variable criterio. El nivel de significación se estipuló en 0,05 y el nivel de potencia en el 90 %. El tamaño de la muestra final fue de 424 diadas madre-lactante.

INSTRUMENTOS

Se utilizó una cédula de datos sociodemográficas y clínicos de la madre, se indagaron datos como edad en años, escolaridad, estado civil, ocupación y estado nutricio, entre otras. Del lactante se indagaron la edad en meses y el sexo.

Para evaluar la variable "prácticas maternas de alimentación" se entrevistó a las madres y se les preguntó: a) tipo de alimentación con la pregunta: ¿Qué alimento consumió su hijo en las últimas 24 horas?, con tres opciones de respuesta: 1) lactancia materna exclusiva, 2) leche de fórmula y 3) alimentación mixta (leche materna, leche de fórmula y/o alimentos complementarios); b) inicio temprano de la lactancia materna con las preguntas: ¿Cuánto tiempo en minutos transcurrió para dar inicio a la lactancia materna al nacer su hijo?, y se clasificó en: 1) dentro de la primera hora de vida del lactante, 2) después de la primera hora de vida del lactante y 3) no se proporcionó lactancia materna; finalmente, c) introducción temprana de alimentos complementarios: ¿Cuándo inició (edad del hijo) a dar alimentos diferentes a la leche materna a su hijo? Las respuestas fueron evaluadas de acuerdo con las recomendaciones de la OMS (20).

Para evaluar la Percepción materna de señales de hambre y saciedad de lactantes se utilizó la Escala de Percepción de Señales de Hambre y Saciedad en Lactantes (EPSHSL) menores de 6 meses (21), la cual evalúa cómo las madres perciben las señales de hambre y saciedad que emite su hijo durante la alimentación. La escala incluye dos preguntas: ¿Si su hijo(a) tiene hambre? Seguida de las 10 señales de hambre, y ¿Si su hijo(a) está saciado o lleno? seguida de las 8 señales de saciedad. Las respuestas se miden en cada señal en una escala de respuesta tipo Likert de 5 opciones (1 = nunca, 2 = algunas veces, 3 = regularmente, 4 = casi siempre, 5 = siempre). La puntuación total de la escala se obtiene sumando las respuestas de las señales de hambre/saciedad y posteriormente se clasifican en tres categorías: baja (18-45), moderada (46-66) y alta (67-90) percepción de identificación de señales de hambre y saciedad. La escala ha reportado un alfa de Cronbach de 0,95 en los lactantes mexicanos. Para este estudio se obtuvo un alfa de Cronbach de 0,94.

Se obtuvieron de los lactantes datos antropométricos actuales de peso (kg) y talla (cm) del registro de la cartilla nacional de vacunación del hijo. Con la información de estas mediciones se calcularon los indicadores de puntuación zIMC, mediante el programa WHO Anthro, y finalmente se clasificaron como: bajo peso con una puntuación (< -2), peso normal de (-1 a +1) y exceso de peso (SP +1 a +2 y OB > +2) (22). A la madre se le midió el peso (kg) con una báscula seca modelo 813 y la talla (cm) con un estadímetro portátil seca 213. Posteriormente, con estos datos se calculó el IMC y se clasificó como: insuficiencia ponderal (< 18,5), peso normal (18,5 a 24,9), sobrepeso (SP ≥ 25 a 29,9) y obesidad (OB ≥ 30) (23).

PROCEDIMIENTO

El presente estudio fue aprobado por el Comité de Investigación de la Facultad de Enfermería Mochis de la Universidad Autónoma de Sinaloa y se apegó a las Normas Éticas de la Declaración de Helsinki de 1973. Se solicitó la autorización de las instituciones públicas de salud. Con previa autorización de los directivos

y a partir del listado de citas de los participantes, fueron reclutados en la sala de espera de las instituciones mientras esperaban la consulta para monitoreo del hijo. A las madres se les explicaron los objetivos del estudio, se les invitó a participar voluntariamente y firmar el consentimiento informado en caso de aceptación. La recolección de datos fue realizada por profesionales de enfermería previamente capacitados, en un espacio asignado por los directivos de las instituciones, cuidando la privacidad e integridad de las participantes.

ESTRATEGIA DE ANÁLISIS DE DATOS

Para examinar los datos se utilizó el programa estadístico SPSS (versión 25.0; IBM SPSS, Inc., Chicago, IL, EE. UU.). Para los resultados descriptivos se calcularon las medias, la desviación estándar y las frecuencias relativas de las variables. Se utilizó la prueba V de Cramer (tamaño del efecto: 0,1 pequeño, 0,3 mediano y 0,5 grande (24) para el objetivo 1 y 2. Para determinar la influencia de las prácticas maternas de alimentación sobre el IMC para la edad del lactante se aplicó la regresión lineal múltiple utilizando el método introducir: como variable criterio el zIMC/edad del lactante y como variables predictoras: tipo de alimentación (variable *dummy*-referencia "LME"), inicio temprano de lactancia materna (variable *dummy*-referencia "primera hora del nacimiento") e introducción temprana de alimentos complementarios. Como variables confusoras, edad materna en años, escolaridad materna en años y estado civil *dummy*-codificada: 1 = con pareja y 2 = sin pareja.

RESULTADOS

Participaron 424 díadas (madres-lactantes). En relación con las madres, la media de edad fue de 25,31 (DE = 5,61), el 89,40 % (*n* = 379) tenían pareja y el promedio de años de escolaridad fue de 11,64 (DE = 3,57). Además, el 70,30 % (*n* = 298) se dedicaban al hogar. En relación con los hijos, la media de edad fue de 3,94 meses (DE = 1,59) con un rango de 1-6 meses, y el 53,10 % (*n* = 225) eran del sexo femenino. Referente a las prácticas de alimentación, el 61,30 % de los hijos recibieron leche materna después de la primera hora desede el nacimiento. Actualmente, el 48,80 % de las madres realizan una práctica de alimentación mixta y el 25 % ya habían iniciado alimentación complementaria antes de los 6 meses de sus hijos. Con respecto a la percepción de señales de hambre y saciedad, el 45,80 % de las madres reportaron baja percepción de estas señales. De acuerdo con los datos antropométricos, el 65,10 % (*n* = 276) de las madres y el 30,20 % (*n* = 128) de los lactantes presentaron exceso de peso. En la tabla I se presenta información detallada.

Al asociar la percepción materna de las señales de hambre y saciedad con las prácticas maternas de alimentación, se encontraron diferencias significativas ($X^2 = 12,72$, gl = 4, $p = 0,013$) con tamaño de efecto pequeño (V de Cramer = 0,216). Se evidencio que el 71 % (*n* = 37) de las madres que proporcionaron lactancia materna exclusiva reportaron una percepción más alta de las señales de hambre y saciedad en comparación con las madres que proporcionan leche de fórmula (2 %, *n* = 1) (Tabla II).

De acuerdo con el objetivo de asociar la percepción materna de las señales de hambre y saciedad con el estado de peso del lactante, se reportó una asociación significativa ($X^2 = 15,29$, gl = 4, $p = 0,001$) con un efecto moderado (V de Cramer = 0,413). Se observó que, entre las madres con baja percepción de señales de hambre y saciedad, sus hijos reportaban tener mayor proporción de exceso de peso (42,70 %; *n* = 83) en comparación con las madres que reportaron una alta percepción (15,4 %; *n* = 8). Los detalles se presentan en la tabla III.

Tabla I. Análisis descriptivo de prácticas maternas de alimentación y percepción de señales de hambre y saciedad de los lactantes y estado nutricio de la diada madre-lactante

Prácticas maternas de alimentación	Media (DE)	*n* (%)
Tipo de alimentación		
LME	-	146 (34,50)
Leche de fórmula	-	71 (16,70)
Alimentación mixta	-	207 (48,80)
Inicio temprano de la lactancia materna		
< 1 hora	-	158 (37,30)
> 1 hora	-	260 (61,30)
Nunca	-	6 (1,40)
Introducción temprana de la AC	3,12 (± 2,06)	-
AC no iniciada	-	318 (75,00)
AC iniciada antes de 17 semanas (4 meses)	-	51 (12,00)
AC iniciada antes de 24 semanas (6 meses)	-	55 (13,00)
PMSHS		
Alta	-	52 (12,30)
Moderada	-	178 (41,90)
Baja	-	194 (45,80)
Estado nutricio de la madre		
Insuficiencia ponderal	-	7 (1,70)
Peso normal	-	141 (33,30)
Sobrepeso	-	168 (39,90)
Obesidad	-	108 (25,80)
Estado nutricio del lactante, zIMC		
Bajo peso	-	37 (8,80)
Peso normal	-	259 (61,00)
Exceso de peso	-	128 (30,20)

n = 424; DE: desviación estándar; %: porcentaje; PMSHS: percepción materna de señales de hambre y saciedad; PA: percepción alta; PM: percepción moderada; PB: percepción baja; LME: lactancia materna exclusiva; AC: alimentación complementaria.

Finalmente, para determinar la influencia de las prácticas maternas de alimentación sobre el zIMC/edad del lactante se aplicó la prueba de la regresión lineal múltiple. El modelo resultó significativo (F = 12,74, gl = 8, p = 0,001) y explicó el 20,1 % de la varianza. Las variables que contribuyeron al modelo fueron la alimentación mixta (β = 0,383, p = 0,001) y la introducción temprana de alimentos complementarios (β = -0,536, p = 0,004). Es decir, los lactantes que reciben alimentación mixta tienen mayor probabilidad de presentar exceso de peso en comparación con los lactantes que reciben lactancia materna exclusiva. Además, introducir alimentos complementarios a menor edad incrementa el peso de los lactantes (Tabla IV).

Tabla II. Percepción de las señales de hambre y saciedad asociadas al tipo de alimentación

Tipo de alimentación	PMSHS, *n* (%)			V de Cramer	Valor *p*
	Alta	Moderada	Baja		
LME	37 (71,00)	76 (42,60)	33 (17,00)	0,216	< 0,013
Leche de fórmula	1 (2,00)	29 (16,40)	41 (21,20)		
Alimentación mixta	14 (26,0)	73 (41,00)	120 (61,80)		

n: 424; PMSHS: percepción materna de señales de hambre y saciedad; LME: lactancia materna exclusiva; AC: alimentación complementaria.

Tabla III. Percepción de las señales de hambre y saciedad asociadas al estado de peso del lactante

	Estado de peso del lactante, *n* (%)			V de Cramer	Valor *p*
PMSHS	Bajo peso	Peso normal	Exceso de peso		
Baja	20 (10,30)	91 (47,00)	83 (42,70)	0,413	0,001
Moderada	14 (7,90)	127 (71,30)	37 (20,80)		
Alta	3 (5,80)	41 (78,80)	8 (15,40)		

n: 424; PMSHS: percepción materna de las señales de hambre y saciedad.

Tabla IV. Prácticas de alimentación predictoras del peso del lactante

Variables predictoras	*β*	SE	t	IC 95 %		*p*
Edad materna	0,005	0,013	0,387	-0,021	0,032	0,699
Escolaridad materna	-0,001	0,021	-0,041	-0,042	0,040	0,967
Estado civil	-0,206	0,234	-0,881	-0,665	0,254	0,379
Tipo de alimentación (LME *ref)*						
Leche de fórmula	0,294	0,210	1,396	-0,120	0,707	0,163
Alimentación mixta	0,383	0,042	9,194	0,301	0,465	*0,001*
Inicio temprano de lactancia materna, *< 1 hora (ref)*	0,099	0,146	0,679	-0,188	0,387	0,497
> 1 hora	0,098	0,153	0,645	-0,202	0,399	0,520
Nunca	-0,379	0,623	-0,607	-1,604	0,847	0,544
Introducción temprana de alimentos complementarios	-0,536	0,183	-2,928	-0,896	-0,176	*0,004*

n: 424. El estado civil se codificó con una dummy: *1 = con pareja, 2 = sin pareja. б: coeficiente de regresión no estandarizado; SE: error estándar; t: estadístico de prueba; IC: intervalo de confianza; p: significación.*

DISCUSIÓN

Este estudio aporta una perspectiva novedosa sobre la alimentación perceptiva, un área poco explorada en la investigación sobre nutrición infantil en México. Al asociar la percepción materna de las señales de hambre y saciedad con las prácticas de alimentación y el estado de peso de los lactantes, se proporciona una comprensión más profunda de cómo estas percepciones influyen en las decisiones de alimentación materna y, por ende, en el desarrollo del peso de los lactantes.

Los resultados de este estudio revelan una alta prevalencia de exceso de peso tanto de la madre como en los lactantes evaluados en el norte de México. Específicamente el 65 % de las madres y el 30 % de los lactantes presentaron exceso de peso. Estos altos porcentajes son consistentes con estudios previos que han documentado tendencias similares en otras regiones de México y países con contextos socioeconómicos comparables (18,25). En el caso de los lactantes, el exceso de peso es preocupante, ya que la obesidad temprana se ha asociado con un mayor riesgo de obesidad en la niñez y la adolescencia, así como con la aparición de enfermedades crónicas en la edad adulta (26). Esta información es crucial para la salud pública, ya que resalta la necesidad urgente de intervenir y diseñar estrategias específicas para reducir estas altas tasas de obesidad en la primera infancia, tanto en el corto como en el largo plazo.

Los resultados de este estudio identificaron prácticas de alimentación alejadas a las recomendaciones de la OMS (15,16). Un alto porcentaje de lactantes no recibieron leche materna por primera vez dentro de la primera hora de vida, solo el 30 % recibe lactancia materna exclusiva y un 25 % de las madres introdujeron alimentación complementaría antes de los 6 meses de edad. Estos hallazgos sugieren una posible falta de apoyo o información de las madres sobre prácticas de alimentación recomendadas que pudieran estar contribuyendo a las tasas elevadas de sobrepeso y obesidad observadas en los lactantes. Es necesario seguir fortaleciendo los programas de educación a las madres sobre la importancia de la lactancia materna inmediata después del nacimiento y abordar cualquier barrera que pueda impedir este proceso. Además, se deben apoyar las políticas que promuevan un entorno laboral, social para la lactancia materna y el cuidado infantil, para que madres, padres y cuidadores puedan adoptar prácticas de lactancia y alimentación complementaria adecuadas (27).

Alrededor del 50 % de las madres no perciben adecuadamente las señales de hambre y saciedad de sus hijos. Este dato es significativo, ya que las señales emitidas por los lactantes son clave para que las madres respondan adecuadamente a sus necesidades alimentarias. A través de estas interacciones de madre e hijo se establecen los patrones de alimentación del lactante (12,28,29). Esto sugiere una posible falta de conciencia sobre las necesidades nutricionales y las señales de saciedad de los lactantes por parte de las madres. Mejorar la educación y el apoyo a las madres en la interpretación de estas señales podría ser beneficioso para promover hábitos alimenticios saludables y prevenir consecuencias derivadas de la alimentación insuficiente o excesiva.

Los resultados de este estudio indican una asociación significativa entre la percepción materna de las señales de hambre y saciedad y las prácticas de alimentación. Fue relevante observar que más de tres cuartos de las madres que practican la lactancia materna exclusiva reportaron una percepción alta de las señales de hambre y saciedad de sus hijos. Este resultado sugiere que la lactancia materna exclusiva podría estar asociada con una mayor sensibilidad y capacidad de las madres para reconocer y responder a las necesidades alimentarias de sus hijos. Las madres que alimentan exclusivamente con leche materna pueden estar más en sintonía con las señales de sus bebés, posiblemente debido a la mayor frecuencia y proximidad del contacto durante la lactancia, lo que puede facilitar una mejor interpretación de las señales de hambre y saciedad. Estos resultados coinciden con estudios previos en mujeres que proceden de países de altos ingresos (12,29,30).

El análisis reveló una asociación significativa y moderada entre la percepción materna de las señales de hambre y saciedad y el estado de peso del lactante. Estos resultados son consistentes con la literatura previa que sugiere que la percepción materna de las señales de hambre y saciedad de la madre desempeña un papel crucial en el desarrollo del peso del lactante (6,10,16,31). La alta proporción de madres con percepción baja en el grupo de lactantes con exceso de peso indica una posible contribución de esta percepción deficiente a la sobrealimentación y al desarrollo del sobrepeso en los bebés. Esto sugiere que las madres con una baja percepción de estas señales pueden enfrentar más dificultades para regular la alimentación de sus hijos, contribuyendo así al desarrollo de un estado ponderal excesivo en los lactantes (32-34). Por lo tanto, se recomienda proporcionar educación y apoyo a las madres para mejorar su comprensión de estas señales y promover hábitos alimenticios saludables desde una edad temprana (15,16).

Los resultados de nuestro estudio indican que las prácticas maternas de alimentación, específicamente el tipo de alimentación mixta y la introducción temprana de alimentos complementarios, están influenciadas significativamente con el índice de masa corporal (zIMC) por edad de los lactantes. Estos hallazgos están en línea con la literatura existente que sugiere una relación entre las prácticas de alimentación infantil y el estado ponderal de los bebés (16,35). Estos resultados resaltan la importancia de realizar intervenciones específicas con los padres, donde se considere aumentar el conocimiento y la autoeficacia sobre las prácticas de alimentación (lactancia materna y alimentación complementaria), de alimentación perceptiva con el fin de prevenir el desarrollo del exceso de peso en los lactantes (30).

LIMITACIONES Y FUTURAS DIRECCIONES

Este estudio es el primero en explorar las percepciones maternas sobre las señales de hambre infantil bajo diferentes métodos de alimentación en una población mexicana; sin embargo, todavía existen algunas limitaciones potenciales. Es importante señalar que éste estudio es de diseño transversal, lo que no permite establecer relaciones causales definitivas entre las prácticas de

alimentación y el estado ponderal de los lactantes. Este estudio utilizó datos autoinformados de la madre que pueden verse afectadas por informes selectivos o sesgos de recuerdo. Se necesitan estudios longitudinales y ensayos controlados aleatorios en la población mexicana para confirmar estas asociaciones y explorar más a fondo los mecanismos subyacentes. Además, sería valioso investigar otros posibles factores de confusión, como la actividad física del lactante y la composición dietética de los alimentos complementarios.

CONCLUSIÓN

Las madres que utilizan diferentes métodos de alimentación en México también muestran diferentes niveles de percepción hacia las señales de hambre y saciedad de los bebés. Las madres que amamantan exclusivamente tienen más probabilidades de percibir señales de hambre infantil que las madres que utilizan la alimentación en fórmula. Los resultados de este estudio resaltan la influencia significativa de las prácticas maternas de alimentación en el zIMC por edad del lactante. La alimentación mixta y la introducción temprana de alimentos complementarios están asociadas con un mayor riesgo de exceso de peso en lactantes. Estos hallazgos subrayan la importancia de promover la lactancia materna exclusiva y de seguir las pautas recomendadas para la introducción de alimentos complementarios para prevenir problemas de peso en la infancia. Este estudio contribuye al entendimiento de la alimentación perceptiva y destaca la necesidad de desarrollar intervenciones educativas y cambios de comportamientos de apoyo para las madres, así como estudios cualitativos que exploren las interacciones entre factores socioculturales, prácticas alimentarias y estado nutricional en madres con hijos pequeños.

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ARÁN

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Trabajo Original

Pediatría

Diseño y validación de un instrumento para medir los hábitos saludables y el estado emocional en adolescentes

Design and validation of an instrument to measure healthy habits and emotional state in adolescents

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Resumen

Introducción: la obesidad es un padecimiento que incrementa el riesgo de presentar otras enfermedades no transmisibles, reduciendo la esperanza y la calidad de vida en los individuos. En su desarrollo participa una interacción compleja de varios factores, siendo los principales la ingesta inadecuada de alimentos y la falta de actividad física.

Objetivo: diseñar y validar una herramienta que permita identificar los hábitos alimenticios, la actividad física y el estado emocional en adolescentes.

Métodos: se realizó un estudio observacional en 2 instancias, diseño y validación, utilizando el método Delphi y tomando como base para su diseño las 7 etapas propuestas por Sampieri. El diseño, apoyado en una revisión sistemática de la literatura, fue propuesto por el grupo coordinador. La validación se realizó en 2 fases: la primera mediante el criterio de jueces con la participación de 17 expertos que evaluaron la redacción y pertinencia de cada ítem, y la segunda a través del análisis estadístico, estimando el coeficiente V de Aiken, pruebas binomiales, el coeficiente alfa de Cronbach y el omega de McDonald. Se aplicó a una muestra de 673 adolescentes de la zona sur del estado de Tamaulipas, México.

Resultados: se obtuvo un instrumento compuesto por 46 ítems en 3 dimensiones. En la validación se estimaron las pruebas binomiales, presentando una significancia de 0,000, lo que indica que las preguntas se encuentran correlacionadas. Asimismo se estimó el coeficiente V de Aiken para todos los ítems, los cuales obtuvieron un valor > 0,7, estableciendo una adecuada validez del contenido para cada uno de ellos. Por último, las pruebas de fiabilidad estimadas mediante el alfa de Cronbach y el omega de McDonald obtuvieron un valor global de 0,777, lo que nos indica que el instrumento es reproducible y consistente.

Conclusiones: la herramienta generada presentó validez y fiabilidad, indicando que es apta para su aplicación en la evaluación del riesgo en los hábitos saludables de los adolescentes (alimentación y actividad física) y en la de la alteración de su estado emocional.

Palabras clave:

Método Delphi. Hábitos alimenticios. Actividad física. Estado emocional. Adolescentes.

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Abstract

Introduction: obesity is a condition that increases the risk of presenting other non-communicable diseases, reducing life expectancy and quality of life in individuals. Its development involves a complex interaction of several factors, the main ones being inadequate food intake and lack of physical activity.

Objective: to design and validate a tool to identify eating habits, physical activity and emotional state in adolescents.

Methods: an observational study was carried out in 2 instances design and validation, using the Delphi method, taking as a basis for its design the 7 stages proposed by Sampieri. The design, based on the systematic review of the literature, was proposed by the coordinating group. Validation was carried out in 2 phases: the first by means of the criteria of judges, with the participation of 17 experts who evaluated the wording and relevance of each item, and the second by means of statistical analysis estimating the Aiken V coefficient, binomial tests, Cronbach's Alpha and McDonald's Omega. It was applied to a sample of 673 adolescents from the southern area of the state of Tamaulipas, Mexico.

Results: an instrument composed of 46 items in 3 dimensions was obtained. In the validation, binomial tests were estimated, showing a significance of 0.000, which indicates that the questions are correlated. Likewise, the Aiken V coefficient was estimated for all the items, which presented a value > 0.7, establishing adequate content validity for each one of them. Finally, the reliability tests estimated by means of Cronbach's Alpha and McDonald's Omega obtained an overall value of 0.777, which indicates that the instrument is reproducible and consistent.

Conclusions: the tool generated presented validity and reliability indicating that it is suitable for its application in the assessment of risk in healthy habits of adolescents (diet and physical activity) and of alteration in their emotional state.

Keywords:

Delphi method. Eating habits. Physical activity. Emotional state. Adolescents.

INTRODUCCIÓN

De acuerdo con los criterios de la Organización Mundial de la Salud (OMS) (1) la adolescencia es una etapa de la vida que acontece entre los 10 a 19 años, en la cual ocurren cambios fisiológicos, biopsicosociales y culturales. A nivel mundial, en esta etapa se concentra más del 18 % de la población (1).

A diferencia de la OMS, la Sociedad Americana de Salud y Medicina de la Adolescencia (SAHM) ubica esta etapa entre los 10 y 21 años, dividiéndola en tres etapas: de 10 a 14 años la denominada como adolescencia inicial; de 15 a 17 años, la adolescencia media; y de 18 a 21 años la adolescencia tardía (2). La adolescencia media se identifica como la etapa de mayor probabilidad para el desarrollo de conductas de riesgo, que incluyen toxicomanías, conductas sexuales, embarazos no deseados, violencia, problemas en el núcleo familiar, problemas escolares y trastornos mentales, resaltando que todas estas conductas son modificables y que afectan su calidad de vida en la adultez (2-4).

Los adolescentes son parte de un grupo poblacional muy valioso ya que en esta etapa de la vida se adquieren múltiples hábitos que perdurarán hasta la adultez. En la adolescencia da inicio el pensamiento abstracto, lógico y científico, lo cual tiene efecto en el desarrollo de las habilidades para comunicarse, para tomar decisiones y para la negociación. Además, en esta etapa es donde de manera orgánica se obtienen masa ósea, grasa y músculos, y se llega a la talla adulta (2). Por lo tanto, la OMS (1) determina que esta edad es un momento clave para que los adolescentes desarrollen hábitos saludables y de autocuidado.

En México podemos ubicar datos actualizados sobre los estilos de vida de los adolescentes en los resultados de la Encuesta Nacional de Salud y Nutrición (ENSANUT) de 2021 (5). Dicha información se generó en el año de la pandemia y en ellos se establece, en el área de alimentación, que un 73,2 % de la población adolescente no presentó cambios en su consumo, en comparación con el presentado antes de la pandemia, es decir, de acuerdo con el reporte de ENSANUT 2020 (6). Se identificó que la ingesta de alimentos recomendables, considerados como saludables en los adolescentes, fue en la siguiente proporción: lácteos 37 %, frutas 35,2 %, leguminosas 37 %, carnes 50 %, huevos 28,9 % y verduras 24,9%. En lo que respecta a los alimentos no recomendados o poco saludables, la proporción fue: bebidas no lácteas endulzadas 85 %; botanas, dulces y postres 53,7 %, cereales dulces 35,2 %, bebidas lácteas endulzadas 10,9 %, carnes procesadas 10,2 % y comida rápida y antojitos mexicanos en un 22,9 %, identificando en las regiones Pacífico-Norte, Centro, Ciudad de México y Estado de México una mayor proporción de consumos de este tipo de alimentos.

En lo que corresponde a la actividad física durante la pandemia, el estrato de edad del grupo de adolescentes que se manifestó como más activo fue el de 15 a 19 años con un 34,8 %, con mayor prevalencia en el género masculino (59,1 %). Entre los 10 y 14 años se reportó actividad física en un 33,4 %. Se identificó el tiempo frente a pantallas de mayor prevalencia entre los 10 y 14 años con un 52,9 % y de los 15 a 19 años con 43,7 %. Se encontró una mayor prevalencia en el género femenino (54,3 %) y la zona con mayor incremento en el tiempo frente a pantallas fue la frontera, en donde podemos ubicar el estado de Tamaulipas.

Referente al estado emocional durante la pandemia, en México se registró que el 71,6 % de los adolescentes manifestaron presentar sentimientos de tristeza la mayoría del tiempo (5).

En el área de la salud es muy frecuente utilizar escalas para identificar variables como alimentación, actividad física y estado emocional, para las cuales se validan de manera formal implementando instrumentos en donde el propósito de estos es medir la variable de la forma más objetiva posible. Para llevar a cabo la recopilación de datos es importante verificar la existencia de 2 atributos en el instrumento: validez y confiabilidad de los resultados; la primera está relacionada con garantizar que los indicadores de un cuestionario representen los elementos básicos de un tema en específico; la segunda se refiere a la precisión con la que los indicadores dan resultados similares calculándose de diferentes maneras (7,8). Por lo anterior, el objetivo del presente trabajo fue diseñar y validar una herramienta que permitiese medir los hábitos saludables (conducta alimenticia y actividad física) y el estado emocional en adolescentes de la zona sur del estado de Tamaulipas, México.

MATERIAL Y MÉTODOS

Se diseñó y validó un instrumento autoadministrado, con respuestas de escala tipo Likert, que permitieron evaluar la actitud (9) referente a los hábitos alimenticios, actividad física y aspectos emocionales en adolescentes. La metodología se desarrolló siguiendo las etapas descritas por Hernández Sampieri y cols. (9) y el diseño del estudio se representa en la figura 1.

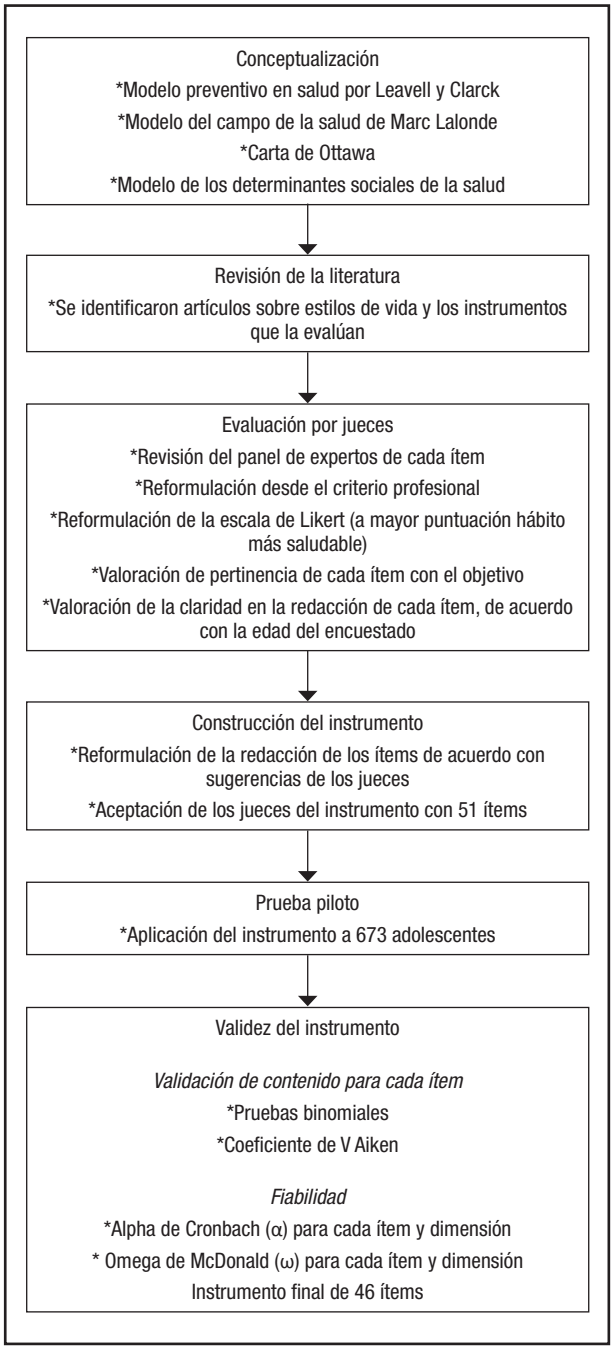

Figura 1.

Etapas implementadas para la validación de un instrumento según Hernández Sampieri y cols. (9) (diagrama de flujo). Fuente: elaboración propia.

CONCEPTUALIZACIÓN DE DEFINICIONES FUNDAMENTALES

Se revisaron las teorías que identifican los estilos de vida saludables y su promoción en etapas tempranas de vida (Fig. 1), incluyendo el modelo preventivo en salud por Leavell y Clarck (10), el modelo del campo de la salud de Marc Lalonde (11,12), la Carta de Ottawa (11-13) y el modelo de los determinantes sociales de la salud (14), relacionados con la relevancia de los estilos de vida en el área de la salud.

REVISIÓN DE LA LITERATURA ENFOCADA

Se revisaron las bases de datos electrónicas de acceso libre Scielo, EBSCO, MEDLINE (PubMed), Dialnet, LILACS, Dimensions, Google académico y Medigraphic, para identificar los fundamentos teóricos que describieran las características de los instrumentos que han sido empleados para medir el concepto de estilo de vida en el área de la salud llevando a cabo la selección de ítems.

CARACTERÍSTICAS DE LOS DOMINIOS Y VARIABLES SELECCIONADOS

La estructuración del instrumento se conformó por las dimensiones: 1) alimentación (líquidos y lácteos, productos con alto contenido calórico, características de las comidas, verduras y frutas, leguminosas y alimentos de origen animal, cereales); 2) actividad física (frecuencia, duración, actividad física en la escuela, en el trayecto, actividades recreativas y ocio); y 3) estado emocional (ansiedad y depresión).

TOMA DE DECISIONES CLAVE

El cuestionario de 46 ítems se elaboró implementando respuestas de tipo Likert y se sometió a la validación por expertos, mediante el método Delphi (15). Este debe cumplir con 4 características (16,17): 1) proceso iterativo, en el que los expertos emitieron sus opiniones; 2) anonimato, en donde los expertos no se conocen entre sí, evitando influencias de otros miembros; 3) retroalimentación, en donde el grupo coordinador controla y permite el flujo de información entre los expertos; y 4) respuesta estadística del grupo, mediante una estimación numérica de las respuestas individuales de los expertos, las cuales en este estudio se midieron por respuestas dicotómicas para evaluar el criterio de pertinencia con el objetivo y la claridad en la redacción acorde con la edad de los encuestados; por último, estimando pruebas binomiales y el coeficiente V de Aiken para su validación de contenido.

En el presente estudio participaron 17 jueces con experiencia en atención y promoción de hábitos saludables en la adolescencia en su práctica diaria, 14 eran profesionales en el ámbito

de la salud de primer y segundo nivel de atención médica pública y privada, los 3 restantes laboran en escuelas acreditadas por la Secretaría de Educación Pública de México (Tabla I).

Se les presentó a cada uno de los expertos una ficha con una estructura en orden de objetivos, contenido y fundamentación teórica del instrumento, así como el instrumento con las respuestas con escala de tipo Likert y la bibliografía.

Se les solicitó revisar detalladamente cada uno de los ítems y evaluar la pertinencia con el objetivo y la claridad de redacción de cada uno de los ítems de acuerdo con los criterios y calificaciones (18) indicadas en la tabla II. El plazo máximo otorgado para responder fue de 2 semanas.

CONSTRUCCIÓN DEL INSTRUMENTO

Los jueces recomendaron agregar 5 ítems, para un total de 51, distribuidos en 3 dimensiones: hábitos alimenticios, actividad física y estado emocional. Todas las respuestas tuvieron cinco opciones en la escala de tipo Likert, lo que permitía una puntuación de hasta 1 para la opción menos saludable y 5 para la más saludable. Un mayor puntaje global indicaba un adolescente con hábitos más saludables. El proceso general de evaluación por criterio de expertos se llevó a cabo de enero a febrero 2024.

VALIDEZ DE CONTENIDO

Se realizó por el método de juicios con prueba binomial (19), el cual consiste en medir el grado en que cada uno de los ítems representa el contenido de lo que trata evaluar en el instrumento (20).

La prueba binomial se realizó a partir de frecuencias de respuestas dicotómicas con puntuación de 0 y 1 (Tabla II), lo cual permite identificar la probabilidad de correlación y validez de contenido de cada ítem; un valor de significancia de $p < 0,05$ es significativo para establecer la correlación (21,22).

Tabla I. Perfil de los expertos en la evaluación del instrumento

Tipo de experto	Organización en que labora	Función del experto	Participantes
Sector salud	Instituto Mexicano del Seguro Social	Atención hospitalaria y consulta de cardiopediatría	1
		Atención hospitalaria y consulta de pediatría	1
		Consulta en segundo nivel de atención de psiquiatría	1
		Consulta de primer nivel de atención	3
		Atención de medicina preventiva, primer nivel de atención	1
		Encargada de programas para promoción de la salud	2
		Coordinador del área de preparación en alimentos hospitalarios	1
		Consulta de primer nivel de atención de nutrición	2
		Consulta en el centro de atención al paciente diabético IMSS	1
Sector salud público y privado	Instituto Mexicano del Seguro Social Consulta privada	Consulta privada y pública de psicología	1
Sector educativo	Secretaría de Educación Pública	Atención de alumnos de escuelas primaria y secundaria	1
		Maestro de la asignatura de educación física	2

Fuente: elaboración propia.

Tabla II. Modelo cuantitativo para operacionalizar cada ítem y dictaminar la validez de contenido por un juez

Criterio	Calificación	Indicador
Pertinencia El ítem tiene relación lógica con objetivo y es congruente con la dimensión que está midiendo.	0	El ítem no tiene relación lógica con la dimensión y el objetivo
	1	El ítem tiene congruencia y está relacionado con la dimensión y el objetivo
Claridad El ítem es congruente en redacción, tiene sintaxis y semántica adecuadas para la edad de los participantes	0	El ítem requiere modificación extensa de palabras de acuerdo con su significado y acorde a la edad que se implemente
	1	El ítem es claro, tiene semántica y sintaxis adecuadas

Fuente: adaptado de Escobar y Cuervo (2008) (16).

Se analizó también validez de contenido con el coeficiente V de Aiken, con la fórmula propuesta por Aiken en 1985 (20). La validez de los ítems se considera como adecuada según Escurra (1988) (23) con valores iguales o mayores de 0,75, en tanto que Torres y cols. (15) consideran como válido los ítems con valores a partir de 0,70 (24).

PRUEBA PILOTO

El instrumento se aplicó a 673 alumnos matriculados en escuelas secundarias de la zona sur del estado de Tamaulipas, México, bajo el consentimiento de los padres o tutores y el asentimiento de los adolescentes. La aplicación de la encuesta se realizó en aulas privadas, sin acceso o presencia de personal externo al de las instituciones, con el apoyo de 2 adultos, con previa capacitación para el conocimiento de los objetivos del presente estudio. El tiempo promedio por participante fue de 20 minutos (rango de 15 a 25 minutos).

VERSIÓN FINAL

Se realizó la revisión y adecuación de las palabras o frases claves en donde, por consenso, se determinó nombrar al instrumento como: Estilos de vida saludable en Alimentación, Actividad Física y Estado Emocional en Adolescentes (AAFEEA).

ANÁLISIS ESTADÍSTICO

Los análisis se realizaron con un nivel de confianza del 95 %, un margen de error 5 % y un valor $p < 0,05$. Se estimó la fiabilidad (alfa de Cronbach y omega de McDonald) utilizando el software SPSS 27 y el Jamovi 2.3.28.

RESULTADOS

DISEÑO DEL INSTRUMENTO

Se localizaron 943 artículos relacionados con el tema de los hábitos de vida saludable, entre los que había 37 instrumentos descritos completamente. Entre ellos se incluían 16 dimensiones que acumulaban 946 ítems. Las tres dimensiones más frecuentemente consideradas fueron: alimentación, actividad física y estado emocional, las cuales se seleccionaron para el presente estudio, conformando un instrumento de 46 ítems (Fig. 2). Estas dimensiones se encontraron presentes en el último reporte ENSANUT (2021) (5), en el que se consideran que se ven afectadas negativamente, con riesgo de permear la calidad de vida a corto y mediano plazo de los adolescentes.

VALIDACIÓN DE EXPERTOS

El grupo de expertos emitió recomendaciones para 17 (36 %) de los 46 ítems de la primera versión del instrumento. Se realizaron los cambios sugeridos, modificando la redacción de las preguntas, y se agregaron los 5 ítems recomendados (Fig. 2).

El análisis del coeficiente V de Aiken arrojó valores superiores a 0,7 en todos los ítems, tanto en la pertinencia con el objetivo como en la claridad de la redacción, en tanto que, en la prueba binomial, todos los ítems presentaron una significancia de 0,000 (Tabla III).

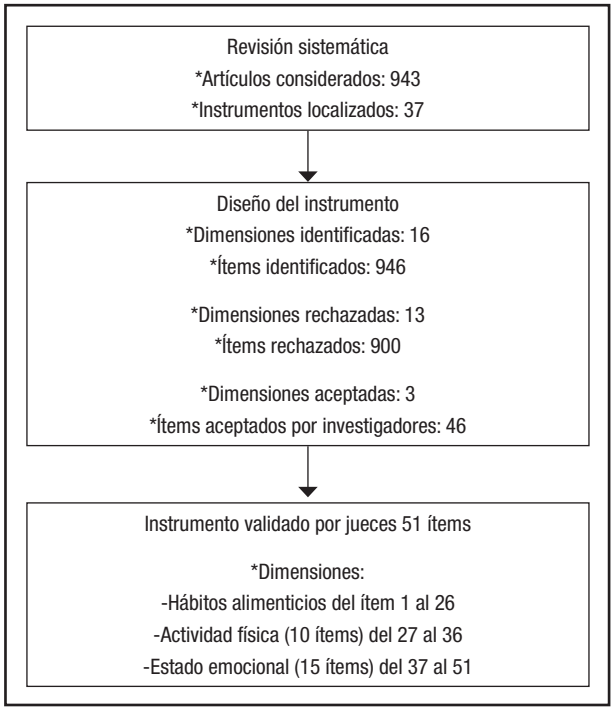

Figura 2.
Selección de ítems. Fuente: elaboración propia.

FIABILIDAD

Se refiere a la consistencia interna, en donde se consideraron aquellos valores con punto de corte para el alfa de Cronbach (α) mayor o igual a 0,6 como aceptable, y con buena consistencia un valor mayor o igual a $\alpha = 0,725$. Además se confirmó la fiabilidad mediante el coeficiente omega de McDonald (ω), considerándole aceptable (26) a partir de 0,65. El instrumento con los 51 ítems aceptados por los expertos presentó un alfa de Cronbach (α) y un coeficiente omega de McDonald (ω) de 0,762, lo que indicó una buena fiabilidad, para los 3 dominios: 1) para hábitos alimenticios fue de $\alpha = 0,612$ y $\omega = 0,623$; 2) para actividad física, $\alpha = 0,640$ y $\omega = 0,673$; por último, 3) para estado emocional, $\alpha = 0,811$ y $\omega = 0,832$.

Aunque la fiabilidad del instrumento global fue buena, las dimensiones de hábitos alimenticios y actividad física presentaron valores cuestionables, por lo que se descartaron los elementos con menor correlación con otros ítems, mejorando estadísticamente el alfa de Cronbach (α) y el coeficiente omega

Tabla III. Resultados de validez de contenido, Coeficiente V de Aiken

Ítems	Pertinencia con el objetivo				Claridad en redacción				*p*
	Media	DE	V de Aiken	Interpretación de la V	Media	DE	V de Aiken	Interpretación de la V	
1	0,8	0,44	0,8	Válido	1	0	1	Válido	0,00
2	0,8	0,44	0,8	Válido	1	0	1	Válido	0,00
3 a 4	1	0	1	Válido	1	0	1	Válido	0,00
5	0,8	0,44	0,8	Válido	0,94	0,24	0,94	Válido	0,00
6	1	0	1	Válido	1	0	1	Válido	0,00
7	1	0	1	Válido	0,94	0,24	0,94	Válido	0,00
8 a 19	1	0	1	Válido	1	0	1	Válido	0,00
20	1	0	1	Válido	0,94	0,24	0,94	Válido	0,00
21	0,8	0,44	0,8	Válido	0,94	0,24	0,94	Válido	0,00
22 a 32	1	0	1	Válido	1	0	1	Válido	0,00
33	1	0	1	Válido	0,88	0,33	0,88	Válido	0,00
34	1	0	1	Válido	0,82	0,39	0,82	Válido	0,00
35	0,8	0,44	0,8	Válido	0,94	0,24	0,94	Válido	0,00
36 a 39	1	0	1	Válido	0,94	0,24	0,94	Válido	0,00
40	1	0	1	Válido	1	0	1	Válido	0,00
41	1	0	1	Válido	0,88	0,33	0,88	Válido	0,00
42	1	0	1	Válido	0,82	0,39	0,82	Válido	0,00
43 a 44	1	0	1	Válido	1	0	1	Válido	0,00
45 a 46	1	0	1	Válido	0,94	0,24	0,94	Válido	0,00
47 a 51	1	0	1	Válido	1	0	1	Válido	0,00

Fuente: elaboración propia.

de McDonald (ω). En la dimensión de hábitos alimenticios se eliminaron 3 ítems que hacían referencia a: 1) con qué frecuencia tomas leche saborizadas: chocolate, fresa, vainilla, etc.; 2) con qué frecuencia ingieres alimentos entre comidas; y 3) con qué frecuencia comes elote. En la dimensión de actividad física se eliminaron 2 ítems: 1) durante el recreo realizas algún deporte o actividad como correr, caminar o saltar; y 2) realizas alguna actividad recreativa como tocar la guitarra o algún otro instrumento musical, asistir al teatro, al cine, a danza, etc., mejorando en ambas dimensiones la fiabilidad y siendo esta mayor de 0,65 para ambos coeficientes, α y ω. En la tabla IV se muestra la estructura general del instrumento final con 46 ítems, la puntuación para cada una de las dimensiones y su interpretación.

En esta etapa inicial, el instrumento permite establecer que más del 60 % de los adolescentes presentan hábitos poco saludables en lo que respecta a la alimentación y la actividad física; en el estado emocional, la ansiedad es el trastorno que presentó mayor riesgo de desarrollarse, como podemos observar en la tabla V.

DISCUSIÓN

La revisión de la literatura permitió desarrollar un instrumento de 46 ítems que permitiera evaluar la existencia de un estilo de vida saludable en población adolescente, considerando tres dimensiones que actualmente se encuentran afectadas de acuerdo con la encuesta ENSANUT (2021) (5): hábitos alimenticios, actividad física y estado emocional.

El método Delphi, utilizado para la validación de criterios y contenidos, permitió obtener información mediante una consulta estructurada a expertos del área, utilizando el análisis y la reflexión del problema en estudio (27).

Andrés y cols. (27) mencionan que utilizar el método Delphi modificado, es decir, sin un número de rondas prolongado, facilita el proceso y disminuye la deserción de los jueces, contemplando un tiempo óptimo de 2 meses para llegar al cuestionario definitivo. Por otro lado, Varela y cols. (17) proponen como tiempo ideal 45 días para que el proceso concluya, lo cual coincide con el tiempo invertido en la validación por criterio de expertos del instrumento realizado en este estudio.

[Nutr Hosp 2025;42(2):219-231]

Tabla IV. Instrumento para evaluar estilo de vida en adolescentes; estadística de fiabilidad descartando un ítem por dimensión; interpretación

Preguntas	Respuestas					Alfa de Cronbach si se descarta el elemento	Omega de McDonald si se descarta el elemento
	1 punto	2 puntos	3 puntos	4 puntos	5 puntos		
Dimensión de hábitos alimenticios (alfa de Cronbach = 0,655) / (omega de McDonald = 0,653)							
1. ¿Con qué frecuencia tomas refrescos o jugos saborizados embotellados?	Todos los días	3 a 6 veces a la semana	1 a 2 veces a la semana	1 a 3 veces al mes	Nunca	0,647	0,646
2. ¿Con qué frecuencia tomas bebidas energizantes como Red Bull, Monster o bebidas que contengan alcohol?	Todos los días	3 a 6 veces a la semana	1 a 2 veces a la semana	1 a 3 veces al mes	Nunca	0,650	0,649
3. ¿Con qué frecuencia consumes queso?	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,644	0,641
4. ¿Con qué frecuencia consumes yogurt?	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,657	0,656
5. ¿Con qué frecuencia consumes leche?	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,643	0,643
6. ¿Con qué frecuencia bebes 6 o más vasos diarios de agua natural?	Nunca. Siempre tomo menos de 6 vasos de agua	1 a 2 veces por semana	3 a 4 veces a la semana	5 a 6 veces a la semana	Todos los días tomo 6 o más vasos de agua	0,645	0,643
7. ¿Con qué frecuencia comes alimentos con bajo aporte nutricional (frituras, galletas, dulces, papas fritas, etc.)?	Todos los días	3 a 6 veces a la semana	1 a 2 veces a la semana	1 a 3 veces al mes	Nunca	0,655	0,654
8. ¿Con qué frecuencia comes pizzas preparadas fuera de casa?	Todos los días	3 a 6 veces a la semana	1 a 2 veces a la semana	1 a 3 veces al mes	Nunca	0,651	0,649
9. ¿Con qué frecuencia comes hamburguesas preparadas fuera de casa?	Todos los días	3 a 6 veces a la semana	1 a 2 veces a la semana	1 a 3 veces al mes	Nunca	0,655	0,653
10. ¿Con qué frecuencia comes *hot dogs* preparados fuera de casa?	Todos los días	3 a 6 veces a la semana	1 a 2 veces a la semana	1 a 3 veces al mes	Nunca	0,656	0,653
11. ¿Con qué frecuencia desayunas antes de salir de tu casa?	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,628	0,633
12. ¿Con qué frecuencia llevas el almuerzo a la escuela preparado de casa?	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,637	0,638
13. ¿Con qué frecuencia acostumbras a comer fuera de casa?	Todos los días	3 a 6 veces a la semana	1 a 2 veces a la semana	1 a 3 veces al mes	Nunca	0,654	0,651
14. ¿Con qué frecuencia das las 3 comidas al día (desayuno, comida y cena)?	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,631	0,632

(Continúa en página siguiente)

Tabla IV (cont.). Instrumento para evaluar estilo de vida en adolescentes; estadística de fiabilidad descartando un ítem por dimensión; interpretación

Preguntas	Respuestas					Alfa de Cronbach si se descarta el elemento	Omega de McDonald si se descarta el elemento
	1 punto	2 puntos	3 puntos	4 puntos	5 puntos		
Dimensión de hábitos alimenticios (alfa de Cronbach = 0,655) / (omega de McDonald = 0,653)							
15. ¿Con que frecuencia comes 2 o más porciones de frutas?	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,636	0,634
16. ¿Con qué frecuencia comes 2 o más porciones de verduras?	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,628	0,627
17. ¿Con qué frecuencia comes frijoles, habas, lentejas o garbanzos?	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,640	0,637
18. ¿Con qué frecuencia comes carne de pollo, res, cerdo o pescado?	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,646	0,644
19. ¿Con qué frecuencia comes huevo?	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,643	0,639
20. ¿Con qué frecuencia comes arroz?	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,637	0,633
21. ¿Con qué frecuencia comes tortillas de maíz?	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,650	0,647
22. ¿Con qué frecuencia comes pan de caja, bolillo o galletas integrales?	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,645	0,642
23. ¿Con qué frecuencia comes papa o camote?	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,641	0,639
Dimensión actividad física (alfa de Cronbach = 0,678) / (omega de McDonald = 0,710)							
24. Si realizas algún deporte, ¿con qué frecuencia lo practicas?	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,688	0,724
25. ¿Cuántas horas al día, aproximadamente lo practicas?	Menos de 30 minutos	De 30 a 50 minutos	Más de 50 minutos a 90 minutos	De 91 a 120 minutos	Más de 120 minutos	0,696	0,729
26. Participas de manera activa en tu clase de educación física	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,687	0,726
27. De casa a la escuela sueles caminar o ir en bicicleta	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,593	0,636

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[Nutr Hosp 2025;42(2):219-231]

Tabla IV (cont.). Instrumento para evaluar estilo de vida en adolescentes; estadística de fiabilidad descartando un ítem por dimensión; interpretación

Preguntas	Respuestas					Alfa de Cronbach si se descarta el elemento	Omega de McDonald si se descarta el elemento
	1 punto	2 puntos	3 puntos	4 puntos	5 puntos		
Dimensión actividad física (alfa de Cronbach = 0,678) / (omega de McDonald = 0,710)							
28. De escuela a la casa sueles caminar o ir en bicicleta	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,586	0,628
29. Te trasladas de la casa a la escuela en vehículo motorizado (carro, motocicleta, autobús)	5 días a la semana	4 días a la semana	3 días a la semana	2 días a la semana	Un día a la semana o nunca	0,590	0,635
30. Te trasladas de la escuela a la casa en vehículo motorizado (carro, motocicleta, autobús)	5 días a la semana	4 días a la semana	3 días a la semana	2 días a la semana	Un día a la semana o nunca	0,591	0,635
31. ¿Cuánto tiempo pasa sentado frente a pantallas como televisión, videojuegos, computadora, tabletas o celular?	Más de 120 minutos	De 91 a 120 minutos	De 50 minutos a 90 minutos	De 30 a 50 minutos	Menos de 30 minutos	0,698	0,734
Dimensión estado emocional (alfa de Cronbach = 0,811) / (omega de McDonald = 0,832)							
32. Te sientes ansioso, nervioso o preocupado en tu casa	Todos los días	3 a 6 veces a la semana	1 a 2 veces a la semana	1 a 3 veces al mes	Nunca	0,788	0,812
33. Te sientes ansioso, nervioso o preocupado en tu escuela	Todos los días	3 a 6 veces a la semana	1 a 2 veces a la semana	1 a 3 veces al mes	Nunca	0,785	0,810
34. Sientes dificultad para concentrarte debido a las preocupaciones	Todos los días	3 a 6 veces a la semana	1 a 2 veces a la semana	1 a 3 veces al mes	Nunca	0,782	0,807
35. Sientes miedo constante a que suceda algo terrible	Todos los días	3 a 6 veces a la semana	1 a 2 veces a la semana	1 a 3 veces al mes	Nunca	0,789	0,814
36. Te molestas fácilmente en tu casa	Todos los días	3 a 6 veces a la semana	1 a 2 veces a la semana	1 a 3 veces al mes	Nunca	0,794	0,818
37. Te molestas fácilmente en tu escuela	Todos los días	3 a 6 veces a la semana	1 a 2 veces a la semana	1 a 3 veces al mes	Nunca	0,801	0,824
38. Sientes que tienes una buena relación con las personas que te rodean en tu casa	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,803	0,826
39. Sientes que tienes una buena relación con las personas que te rodean en tu escuela	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,808	0,831
40. Tienes poco interés por hacer cosas en la escuela	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,838	0,850
41. Tienes poco interés por hacer cosas en tu casa	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,837	0,850

(Continúa en página siguiente)

Tabla IV (cont.). Instrumento para evaluar estilo de vida en adolescentes; estadística de fiabilidad descartando un ítem por dimensión; interpretación

Preguntas	Respuestas					Alfa de Cronbach si se descarta el elemento	Omega de McDonald si se descarta el elemento
	1 punto	2 puntos	3 puntos	4 puntos	5 puntos		
Dimensión estado emocional (alfa de Cronbach = 0,811) / (omega de McDonald = 0,832)							
42. Te sientes incapaz de realizar alguna actividad	Todos los días	3 a 6 veces a la semana	1 a 2 veces a la semana	1 a 3 veces al mes	Nunca	0,799	0,823
43. Tienes sentimientos de tristeza, estás decaído o deprimido en tu casa	Todos los días	3 a 6 veces a la semana	1 a 2 veces a la semana	1 a 3 veces al mes	Nunca	0,784	0,807
44. Tienes sentimientos de tristeza, estás decaído o deprimido en la escuela	Todos los días	3 a 6 veces a la semana	1 a 2 veces a la semana	1 a 3 veces al mes	Nunca	0,783	0,806
45. Te sientes bien o satisfecho en las actividades que desempeñas en la escuela	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,800	0,824
46. Te sientes bien o satisfecho en las actividades que desempeñas en tu casa	Nunca	1 a 3 veces al mes	1 a 2 veces a la semana	3 a 6 veces a la semana	Todos los días	0,801	0,824
Instrumento global (alfa de Cronbach = 0,777) / (omega de McDonald = 0,777)							

Ítems	Puntaje mínimo/máximo	Interpretación
Hábitos alimenticios (23 ítems)		
1 al 23	23/115	• < 81 hábitos deficientes • 81 a 92 hábitos suficientes • > 92 hábitos saludables
Actividad física (8 ítems)		
24 al 31	8/40	• 32 a 40 estilo de vida activo • 24 a 31 semiactivo • < 24 sedentario
Estado emocional (15 ítems)		
32 al 46	15/75	a) Subescala de ansiedad Interpretación: • Sumatoria de los ítems del 32 al 39 • Rango de puntuación 8 a 40 • Una puntuación igual o menor de 20 se considera sugestiva de presentar trastorno de ansiedad b) Subescala de depresión Interpretación: • Sumatoria de los ítems del 40 a 46 • Rango de puntuación de 7 a 35 Una puntuación igual o menor de 15 se considera sugestiva de presentar trastorno de depresión

Fuente: elaboración propia.

Tabla V. Caracterización de la muestra

Característica	Frecuencia	Porcentaje
Sexo		
Mujer	358	53,2
Hombre	315	46,8
Grado de secundaria		
1º año	237	35,2
2º año	202	30,0
3º año	234	34,8
Tipo de escuela		
Escuela pública	518	77,0
Escuela privada	155	23,0
Hábitos alimenticios		
Saludables	45	6,7
Suficientes	209	31,1
Deficientes	419	62,3
Actividad física		
Activo	79	11,7
Semiactivo	185	27,5
Sedentario	409	60,8
Estado emocional		
Depresión		
Sin riego de presentar depresión	635	94,4
Con riesgo de presentar depresión	38	5,6
Ansiedad		
Sin riesgo de presentar ansiedad	547	81,3
Con riesgo de presentar ansiedad	126	18,7

Fuente: elaboración propia.

La validez está definida como el grado en que una teoría respalda la interpretación de un instrumento para su uso, es decir, que mide lo que dice que está midiendo. En el caso del instrumento desarrollado, los jueces establecieron que el cuestionario estaba integrado por los elementos básicos o representativos de lo que pretendía medir (17), por lo que fue posible asumir la validez de contenido. El número de expertos que participaron (17) fue acorde con lo identificado en la literatura, en la que se recomienda (17) que no deben ser menos de 7 ni más de 30. Otros autores (28) afirman que 6 son una cantidad aceptable, pero concuerdan que contemplar un número grande de participantes como jueces puede generar confusión en las recomendaciones, ya que estas pueden ser muy variadas o incluso contradictorias.

En lo que respecta a la fiabilidad, la cual se refiere a la certeza de la validación de la estructura interna del cuestionario al realizar mediciones consistentes (17), los coeficientes alfa de Cronbach y omega de McDonald permitieron establecer el resultado global como bueno (25) con un valor de 0,777; en la dimensión de alimentación presenta un $\alpha = 0,655$ y un $\omega = 0,653$, considerándolos aceptables de acuerdo con la literatura, ya que algunos autores (29) señalan como aceptable un valor de α a partir de 0,6 en las primeras etapas de una investigación; la de actividad física, con un $\alpha = 0.678$ y un $\omega = 0,710$, mostró una buena consistencia interna, y el estado emocional presenta en ambos coeficientes (α y ω) un valor mayor de 0,8. Por otro lado, el omega de McDonald es un coeficiente que se utiliza como alternativa para medir la fiabilidad; el valor a partir de 0,65 se establece como aceptable y se considera una prueba más precisa al no verse afectado por el número de ítems, permitiendo someter datos multidimensionales, considerando que tiene mayor estabilidad por determinarse a partir de las cargas factoriales, convirtiéndolo así una herramienta útil en el área de la salud (25,26).

En la estructura de las dimensiones, la primera trata sobre los hábitos alimenticios, en donde se incluyeron preguntas para identificar hábitos saludables y no saludables en el área de nutrición mediante la frecuencia del consumo de productos con alto contenido calórico, con bajo aporte nutricional (30,31) y de alimentos que son considerados como saludables, abarcando los tres grupos alimenticios de acuerdo con el plato del bien comer, así como la jarra del bien beber (30).

Dentro del grupo de verduras y frutas, la OMS reconoce que el bajo consumo de estas es un factor de riesgo de muerte temprana (31). Por otro lado, Ahmadi y cols. (32), en su estudio para identificar el patrón de estilo de vida en los consumidores de fruta y verduras, afirma que existe evidencia de que la edad afecta a este patrón, siendo las etapas tempranas de la vida las que menos las consumen.

La medición de los hábitos alimenticios suele ser compleja debido a que implica patrones de consumo que van desde la elección, compra y preparación del producto o alimento hasta la acción de comerlo. Y en el caso de las familias, este proceso suele quedar en manos de los cuidadores, quienes impactan de manera significativa en el estado nutricional de sus integrantes (33).

De acuerdo con Martínez y cols. (34), un mal estado nutricional está asociado a malos hábitos o a un mal estilo de vida. Estos autores, en un estudio sobre adolescentes de la Ciudad de México, identificaron que la mayoría de los participantes tenían hábitos poco saludables con respecto alimentación y hábitos inadecuados de actividad física, presentando un estado nutricional deficiente, reflejado en bajo peso, sobrepeso y obesidad.

La medición de la actividad física se puede evaluar con enfoques objetivo y subjetivo. El primero, emplea dispositivos electrónicos costosos y algunos de compleja implementación, el segundo, hace referencia al uso de cuestionarios. Aunque el primero es más exacto, el segundo es más fácil de aplicar y permite describir, con cierta reserva, los patrones de comportamiento en este rubro.

La segunda dimensión, correspondiente a la actividad física, en donde los ítems seleccionados se diseñaron para valorar la promoción hacia un mundo activo como un buen modelo de salud, de acuerdo con las directrices ofertadas por la OMS (35) en la etapa de la adolescencia, así como identificar los diferentes

espacios en donde se puede realizar actividad física de acuerdo con la Organización para la Cooperación y el Desarrollo Económico (OCDE), como son en casa, durante el traslado y de forma ocupacional, la cual sería el equivalente a la actividad física en la escuela y el ocio, haciendo énfasis en actividades frente a los dispositivos electrónicos compuestos por pantallas (3), tratando así de establecer de manera subjetiva la actitud presentada sobre la actividad física y cubriendo indicadores como la frecuencia y la duración (36-38).

Betancourt y cols. (39) presentaron un estudio en una población de adolescentes mexicanos con edades entre 13 a 18 años, encontrando que solo una quinta parte de la población cumple con las recomendaciones de la OMS para realizar actividad física, lo cual resalta la importancia de evaluar estas dimensiones, ya que el problema se presenta de manera representativa desde etapas tempranas de la vida.

La tercera dimensión medida abarca el estado emocional, identificando el riesgo de presentar un trastorno de ansiedad y depresión en un entorno (familia, escuela o ambos) ya que, de acuerdo con Ayala y cols. (40), el contexto es un factor importante para influenciar el comportamiento de los adolescentes, haciendo énfasis en que el núcleo familiar influye sobre el apego a programas para cambios de estilo de vida.

En esta fase exploratoria de diseño y validación, el instrumento identificó en la muestra estudiada que más de la mitad de la población adolescente de la sur de Tamaulipas presenta hábitos deficientes, tanto alimenticios como en actividad física, algo muy similar a lo reportado en la ENSANUT de 2021. En lo que respecta a los trastornos emocionales, predominó la ansiedad, siendo la depresión la presentada en menor proporción (5,6 %), contrastando ampliamente con lo reportado en el periodo de lapandemia en México (71,6 %) (5).

CONCLUSIONES

El instrumento desarrollado, consistente en 46 ítems distribuidos en 3 dimensiones, demostró tener validez (criterio y contenido) y fiabilidad. La herramienta propuesta y generada puede ser utilizada en la caracterización de una población adolescente en la que se pretenda determinar la actitud con respecto a los hábitos alimenticios y la práctica de actividad física, sirviendo también como indicador para identificar el riesgo de desarrollar una alteración del estado emocional (depresión y ansiedad).

El fundamento teórico para el diseño del cuestionario, validado en este estudio por juicio de expertos, está en la evaluación e identificación de las conductas, ya que los estilos de vida han evolucionado gracias a la globalización y urbanización del mundo así como al confinamiento que se vivió durante la pandemia de COVID-19, reduciéndose así los hábitos saludables, favoreciéndose la mala alimentación y empobreciéndose con ello la calidad de vida de los individuos. Se debe hacer hincapié en la necesidad de crear estrategias como los cuestionarios de autoinforme, que no requieren un presupuesto alto, para identificar los problemas y así poder generar estrategias desde etapas tempranas de la vida para el desarrollo de estilos de vida saludables, favoreciendo con ello el estado de salud de las personas a corto y mediano plazo.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Nutrición en el anciano

The effect of supplementation with prebiotic fiber on the gut microbiota of a group of older people with Parkinson's disease from the city of Santiago de Chile. A pilot study

Efecto de la suplementación con fibra prebiótica sobre la microbiota intestinal de un grupo de personas mayores con enfermedad de Parkinson de la ciudad de Santiago de Chile. Un estudio piloto

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Abstract

Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide. It has been demonstrated that there is a correlation between the increase in bacterial abundance and the severity of certain symptoms associated with PD.

Aim: the aim of this pilot study was to analyze the effect of supplementation with prebiotic fiber on the gut microbiota (GM) and nutritional status of elderly volunteers with Parkinson's disease.

Methodology: this is a pilot study of pre and post intervention with prebiotic fiber. All subjects involved were volunteers with PD, who were given nutritional counseling and gut microbiota measured on time cero and after 30 days of prebiotic fiber intervention.

Results: a statistically significant difference was found in calf circumference (p 0.0422) after the intervention with prebiotic fiber. GM analyses show an initial difference in gut bacterial abundance of older people with PD and people without PD. Furthermore, our results showed a difference in bacterial families and genera after the supplementation with prebiotic fiber. in addition, we found a statistically significant difference in the value of circumference calf and a trend in the improvement of body weight, Body mass index (BMI), neck circumference, arm circumference, brachial area, and Diet Quality Questionnaire (DQQ) for older adults.

Conclusion: supplementation with 20 g of prebiotic fiber for 30 days could modify the intestinal microbiota, reducing bacterial genera and phylum that are abundant in Parkinson's disease, such as *Verrucomicrobia*. Therefore, the use of prebiotic fiber could represent an alternative to improve intestinal health and nutritional status of people with Parkinson's disease.

Keywords:

Dietary fiber. Inulin. Gastrointestinal microbiome. Parkinson's disease.

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Authors' contributions: P. G.: main idea, planning, implementation, analysis, nutritional assessment, and manuscript's writing; M. M.: biostatistical analysis, results; W. D.: director of the FONDECYT Project, funding acquisition, manuscript's review; G. N.: doc-toral thesis director, planning study, manuscript's review; C. T.: microbiota analysis.

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Resumen

Introducción: la enfermedad de Parkinson (EP) es el segundo trastorno neurodegenerativo más común a nivel mundial. Se ha demostrado que existe una correlación entre el aumento de la abundancia bacteriana y la gravedad de determinados síntomas asociados a la EP.

Objetivo: el objetivo de este estudio piloto fue analizar el efecto de la suplementación con fibra prebiótica sobre la microbiota intestinal (MI) y el estado nutricional de voluntarios ancianos con enfermedad de Parkinson.

Metodología: este es un estudio piloto de pre y post intervención con fibra prebiótica. Todos los sujetos involucrados fueron voluntarios con EP, a quienes se les brindó asesoramiento nutricional y se midió la microbiota intestinal en el tiempo cero y después de 30 días de intervención con fibra prebiótica.

Resultados: se encontró diferencia estadísticamente significativa en la circunferencia de la pantorrilla (p 0,0422) después de la intervención con fibra prebiótica. Los análisis de transgénicos muestran una diferencia inicial en la abundancia de bacterias intestinales entre personas mayores con EP y personas sin EP. Además, nuestros resultados mostraron una diferencia en las familias y géneros bacterianos después de la suplementación con fibra prebiótica. además, encontramos una diferencia estadísticamente significativa en el valor de la circunferencia de la pantorrilla y una tendencia en la mejora del peso corporal, índice de masa corporal (IMC), circunferencia del cuello, circunferencia del brazo, área braquial y el Cuestionario de Calidad de la Dieta (DQQ) para adultos mayores.

Conclusión: la suplementación con 20 g de fibra prebiótica durante 30 días podría modificar la microbiota intestinal, reduciendo géneros y filos bacterianos abundantes en la enfermedad de Parkinson, como la *Verrucomicrobia,* por lo que el uso de fibra prebiótica podría representar una alternativa para mejorar la fibra prebiótica. Estado de salud y nutrición de las personas con enfermedad de Parkinson.

Palabras clave:

Fibra dietética. Inulina. Microbioma gastrointestinal. Enfermedad de Parkinson.

INTRODUCTION

Gut microbiota (GM) is an assemblage of microorganisms present in the intestine and constitutes the largest population of microorganisms inhabiting the human body, including more than 1,000 bacterial species, with *Firmicutes* and *Bacteroidetes* being the predominant phyla in the human gastrointestinal tract and representing 90 % of the microbial population (1); these phyla are mainly associated with the metabolism of carbohydrates and amino acids, respectively.

GM is regulated by several factors throughout a person's life, such as delivery mode, gestational age, exposure to antibiotics and metals, and diet (2), this latter factor directly and significantly influences gut microbial communities, even in short periods of time; GM may be positively or negatively modulated when it comes to the subject's health, and can ultimately accelerate the progression of chronic diseases such as chronic kidney disease or Parkinson's disease (PD) (3).

PD is the second most common neurodegenerative disorder worldwide, after Alzheimer's disease and is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta due to the build-up of Lewy bodies in these cells, causing oxidative stress and the consequent neuronal death (4). These events lead to diverse motor symptoms, with the most classic being gait difficulty, postural instability and involuntary tremor, and non-motor complications such as chronic constipation, deterioration of nutritional status, sarcopenia, and cognitive impairment (5).

Studies conducted in mice have demonstrated that there is a correlation between the increase in bacterial abundance present in GM and the severity of certain symptoms associated with the disease (6), even the relationship that GM has in the synthesis of dopamine given the intrinsic enzymatic activity that is highly involved in dopamine metabolism (7). Researchers have studied GM of people who suffer from this disease and have identified an alteration in the biodiversity and abundance of resident bacteria, confirming a bidirectional relationship between gut microbiota (GM) and the central nervous system, establishing the existence of the microbiota-gut-brain axis (8), which is thought to be a potential trigger for brain diseases. According to recent studies, the alteration of GM is related to motor disorders, chronic constipation, muscle mass loss; moreover, it has been hypothesized that intestinal dysbiosis would be an indicator to determine the stages of cognitive impairment (9).

Vegetable dietary fibers are food-sourced carbohydrates that are not digested or absorbed by human enzymes, passing intact into the intestine where bacteria (10), mainly *Firmicutes* such as *Bifidobacteria* and *Lactobacillus*, ferment them, producing components that provide benefits to human health (11). Studies have shown that the intake of this type of fibers leads to an increase in phylum level and in the production of short-chain fatty acids such as butyric acid (12). For this reason, the objective of this pilot study was to analyze the effect of supplementation with prebiotic fiber on the GM and nutritional status of elderly volunteers with Parkinson's disease.

MATERIALS AND METHODS

This is a pilot study of pre- and post-intervention with prebiotic fiber. Nine people were recruited, of whom five completed the treatment. The median age was 71 years, with a minimum age of 62 years and a maximum age of 75 years. All subjects involved were volunteers with Parkinson's disease (Parkinson group), who received nutritional counseling at the Clinical Neurological Center CENPAR, Chile. They are individuals over 60 years old, with Parkinson's disease, who donated their samples to be analyzed and compared in their basal state (without prebiotic fiber intervention) with a group of 4 people over 60 years old, volunteers in an ongoing study at the molecular microbiology and food research laboratory, who did not have serious illnesses, did not suffer from Parkinson's disease (PD), and were self-sufficient. This group of people without PD served as the control group for the microbiota analysis in fecal samples "at time zero" (without intervention). The control group for fecal samples did not receive intervention or evaluation of nutritional status, as the samples had been vol-

untarily donated to the laboratory months earlier for an ongoing study in which their baseline gut microbiota had already been analyzed.

This pilot study aims to identify issues and errors in the protocol to improve the design for the final intervention study, which intends to analyze 40 fecal samples from volunteers with PD (non-probabilistic sample based on published studies).

NUTRITIONAL ASSESSMENT

The Parkinson group underwent a nutritional status assessment (NSA) that included measurements of weight, height, body mass index (BMI) for this, a professional SECA® brand scale and stadiometer was used, according to the protocol declared in the Krause diet therapy book (13). Dynamometry, a CAMRY® hand dynamometer is used, based on the protocol described by Paz TDSR et al 2022 (14). Calf circumference, brachial circumference, tricipital skinfold thickness, neck circumference was measured with a SECA brand medical tape according to the measurement protocol of Raymond & Morrow, 2021.

It was also measured the application of the SARC-F screening sarcopenia tool (SARC-F) (15), Mini Nutritional Assessment (MNA) (16), and Diet Quality Questionnaire (DQQ) for older adults (17).

The nutritional evaluation method was applied before the intervention and at the end of the study, using the same instruments and protocols declared.

The collection of anthropometric data was carried out in the nutritional office especially implemented for the study, with a maximum duration of 1 hour to prevent older people to get tired.

INTERVENTION WITH PREBIOTIC FIBER

The nutritional intervention consisted of the supplementation of 20 grams of inulin or oligofructose per day in the form of prebiotics derived from polysaccharides, for a period of 30 days, without modifying the diet.

The fiber (inulin/oligofructose) was randomly selected using software (26), without mentioning the type of fiber the volunteers were consuming. According to this distribution, 3 people were supplemented with inulin and 2 with oligofructose (Fructooligosaccharides).

Participants were instructed to consume 20 g of a prebiotic with a glass of water in the mornings, avoiding simultaneous dairy intake due to its possible chelating effect.

The determination of the dose and intervention time is based on previous studies (18) and subsequent modification according to own test carried out in the Molecular Microbiology and Food Research laboratory, San Sebastian University.

INCLUSION AND EXCLUSION CRITERIA

Exclusion criteria were defined as follows: use of medication such as antibiotics and laxatives; history of serious or severe pathology, immunodeficiency, digestive and intestinal disease, or malabsorption; chemotherapy or radiotherapy treatment; history of alcohol and drug abuse; morbid obesity, defined with a BMI over 40 kg/m^2; completely immobile, hospitalized, or institutionalized patients. Additionally, if there was a modification in diet or exercise, or a change in medical treatment during the intervention, or probiotic consumption, the participation in the study was over.

Any person over 60 years of age with Parkinson's disease who was willing to participate and voluntarily signed the informed consent was included.

ANALYSIS OF THE GUT MICROBIOTA

Measurement of GM was performed for 3 times: at the beginning or time zero (without intervention), after one week (7 days), and when the 30 days of supplementation were completed. The determination of GM was conducted using a qPCR-based GUt Low Density Array (GULDA), high-throughput real-time quantitative PCR-based analysis platform.

DNA EXTRACTION

DNA was extracted from stool samples with high fiber content, according to the standardized method of the Molecular Microbiology and Food Research laboratory.

Samples were thawed at 4 °C and placed in aliquots of 200 mg of sample containing 200 mg of beads for mechanical disruption. TE buffer was added for resuspension, vortexed at 2500 rpm for 10 min, then the sample was centrifuged for 1 min at maximum speed and transferred to a clean tube. Proteinase K was added to a final concentration of 1 mg/ml and incubated at 50 °C for 10 min. Subsequent steps were performed according to the manufacturer's instructions (Qiagen Power Fecal Kit protocol) and finally, the eluted DNA was stored at -20 °C until use (19).

Subsequently, the integrity of the genetic material obtained was visualized through the method of 1 % agarose gel electrophoresis, and quantified using TECAN methods, establishing an adequate presence of the genetic matter in a value higher than 50 ng/µl. To identify the different groups of existing bacteria, the real-time PCR-based GUt Low-Density Array (GULDA) was used. This technique was validated by Bergström et al. (2012). was designed for simultaneous analysis of the change in the abundance of 31 different microbial 16S rRNA gene targets in fecal samples obtained from individuals at various points in time (20), to screen human stool samples from the volunteers.

The sequencing of the V4 region of the 16S rRNA gene was performed by synthesis sequencing with a Miseq illumina equipment, using 50 ng of bacterial genomic DNA from each sample provided by our laboratory. The primers that will be used were those indicated by the Argonne laboratory: 515F (5′-GTGCCAGCMGCCGCGGTAA-3′) y 806R (5′-GGACTACHVGGGTWTCTAAT-3′) (21).

In order to determine the richness and abundance of bacterial genera present in stool samples of each subject, evaluating the

increase or decrease of such genera, we did use the DESeq2 package was used (R version 4.1.2, DESeq2 version 3.14).

To determine significant changes in the genera found in each sample, the SILVA database (version 138.1) was employed to assign the taxonomy to operational taxonomic units, so that it is possible to characterize the alpha diversity of each genus found, by means of the Microbiome package (version 3.14). The alpha indexes used were Shannon and Simpson.

SAMPLE COLLECTION

Nutritional status assessment was conducted in the first appointment, and it was explained how the stool sample must be obtained, providing the subject with an informative leaflet along with a sampling kit that consisted of: gloves; a tongue depressor or wooden spatula; a sterile vial; labels to indicate name, date, and hour; a toilet hat.

Regarding the delivery of the stool sample, this must be handed under specific conditions, such as: handing it at room temperature immediately after having been collected or within a maximum of 1 hour, or it could be delivered frozen in case of handing it days after the sample collection; in the latter case, participants were informed about the cold storage and transportation conditions before delivering the sample in our laboratory.

Supplementation with fiber was introduced in the second appointment; subjects were required to provide a stool sample 1 week after initiating the supplementation, in order to observe if there were short-term changes in GM.

Telephone follow-up was conducted during the study, and a final nutritional appointment was scheduled to perform the initial assessment again; a stool sample was required at the end of the intervention, with prebiotic fiber being discontinued after the collection of the stool sample.

ETHICS COMMITTEE

All the participants of the intervention were handed an informative leaflet about the study; all the topics related to the intervention were reinforced in an in-person explanatory interview, with the aim of complying with the standards on ethics and dissemination of information, before signing the informed consent form.

The preparation of the ethical report, as well as the development of the intervention, were based on the declaration of Helsinki, and the CIOMS Guidelines were consulted for conducting the research with human beings.

This study was approved by the ethics committee of the University of Murcia, Spain ID 2202/2018.

SAMPLING AND DATA COLLECTION

A non-probabilistic convenience sample was conducted, incorporating all individuals who met inclusion or exclusion criteria and agreed to participate and signed the informed consent form; a deadline and a minimum number of volunteers were established, conditions that were disrupted by reasons not related to the study, that was closed with 9 patients, of whom only 5 completed the intervention. We consider that nutritional studies in Parkinson's disease usually have small samples (between 8 and 30 people) (22).

STATISTICAL ANALYSIS

Statistical analyses were conducted by means of a non-parametric test to compare the middle range of two related Wilcoxon samples for NSA and GM Analysis data between intervention periods (pre and post). For that we used Statistical software for data science (STATA).

RESULTS

In this study, 5 of 9 subjects complete the intervention, of the 5 participants with PD, 1 was female (20 %) and 4 were male (80 %).

The reasons why not all participants completed the study include: use of antibiotics due to an infectious condition, discontinuation of treatment with the prebiotic fiber (non-adherence), failure to attend the final evaluation, and failure to submit the final fecal sample for analysis within the required timeframe.

According to the descriptive analysis of the nutritional status assessment (NSA), the average body mass index (BMI) was 25 kg/m^2, which corresponds to a normal nutritional status which is in line with the national criteria established and mentioned by the Spanish Society of Geriatrics and Gerontology (SEGG, for its acronym in Spanish) and the Spanish Society of Clinical Nutrition and Metabolism (SENPE, for its acronym in Spanish) (23), with no presence of sarcopenia or alterations in muscle composition, based on the assessment of: calf circumference, brachial circumference or arm circumference, brachial perimeter, brachial area, dynamometry, and the SARC-F screening questionnaire (Table I).

According to the data, we can mention a statistically significant increase in calf circumference (p 0.0422) after the intervention with prebiotic fiber, and a trend in neck circumference (p 0.0568) which presented a decrease of 2.8 in their medians, as did the Diet Quality Questionnaire (DQQ) for older adults, which increased in comparison after the intervention (p 0.0796) (Table I).

Also, after the treatment with prebiotic fiber, the subjects reported a slight improvement in the consistency of their depositions, indicated in the quality of their stools according to the Bristol Stool Form scale (Table II).

MICROBIOTA BASELINE ANALYSIS

Microbiota analysis was performed at time zero (without intervention) on the 5 volunteers suffering from Parkinson's disease and compared with fecal samples from 4 volunteers without Parkinson's disease.

Table I. Descriptive analysis of the nutritional status assessment pre- and post-intervention. Values expressed in median (p25-p75) (*n* = 5)

Variable	PRE			Post			*p* value
	Median	(p25	p75)	Median	(p25	p75)	
Weight (kg)	68.2	65.1	73.9	68	66.6	75.5	0.0796
Height (mts)	1.66	1.65	1.67	1.66	1.65	1.67	1.0000
BMI (kg/mt^2)	25	23.6	27.8	24.9	24.1	28.4	0.0796
Calf circ. (cm)	35	34	37	36	36	39.8	0.0422
Neck circ. (cm)	39.2	37.5	40	42	37.5	43.3	0.0568
Arm circ. (cm)	30	28	30	30	28.5	31	0.0568
Tricipital skinfold thickness (mm)	12	11	15	14	10	16	0.1736
BMA	5092.2	4797.0	5478.6	5248.0	5219.5	5372.2	0.2249
BMP	252.9	245.5	262.3	256.7	256.0	259.8	0.2249
Brachial area	7165.6	6242.0	7165.6	7165.6	6467.0	7651.3	0.0568
BFA	1687.0	1445.0	2068.1	1946.1	1771.5	2279.0	0.1380
Dynamometry (kg)	32.6	26	33.2	28	28	32.9	0.5002
SARC-F (points)	2	0	2	2	0	2	0.3173
MNA (points)	26	25.5	27.5	28	26.5	28.5	0.2228
DQQ (points)	81	80	87	86	85	87	0.0796

BMA: brachial muscle area; BMP: brachial muscle perimeter; BFA: brachial fat area; circ: circumference; MNA: Mini nutritional assessment; DQQ: Diet Quality Questionnaire for older adults; *BMI: body mass index. Sarc-f: screening sarcopenia tool.*

Table II. Self-registration of the volunteers involved in the evaluation of constipation according to the Bristol stool form scale

Subject	Initial assessment (without intervention)		Final assessment (after the intervention)	
	Frequency of depositions declared	Bristol Scale declared	Frequency of depositions declared	Bristol Scale declared
PDS1	7/7	2	7/7	4
PDS2	2/7	3	3/7	4
PDS3	7/7	3	7/7	4
PDS4	2/7	2	2-3/7	4
PDS5	5/7	2	5/7	4

Subject: PDS corresponds to the coding of the intervened volunteers in accordance with data protection and confidentiality regulations.

By performing of Observed (A), Shannon (B) and Simpson (C) alpha diversity analysis, we observed a trend showing a difference in alpha diversity between people suffering from PD and older people without the disease (healthy controls) (Fig. 1).

Time-zero analyses of bacterial phyla abundance showed significant differences between the subjects with PD and the controls, the main differences are related to the phyla *Bacteroidetes, Proteobacteria* and *Verrucomicrobia*, which are present in greater abundance in people of the Parkinson group. The most abundant phylum, both in the Parkinson group and in the control group, is *Firmicutes*, with slightly higher numbers in the controls. Another abundant phylum corresponds to *Verrucomicrobia,* with significantly greater numbers in people living with the disease (Fig. 2).

The relative abundance analysis of the bacterial genera identified in stool samples of the study subjects shows a significant difference in *Bacteroidetes, Akkermansia, Escherichia, Shigella, Agathobacter*, being highly predominant in the Parkinson group. In addition, a greater presence of *Streptococcus* and *Catenibacterium* can be noted in the controls (Fig. 3).

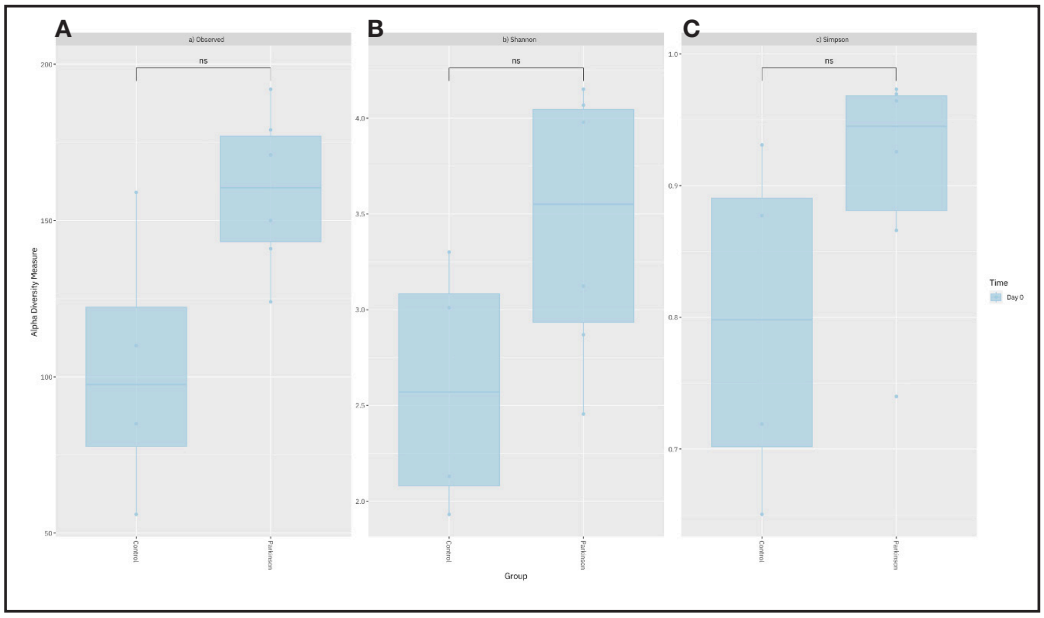

Figure 1.

Comparison analysis of the alpha diversity of the microbiota without inter-vention (time zero) between volunteers with Parkinson's disease and volunteers with-out Parkinson's disease. The graph shows the mean values of each group evaluated for time zero (without intervention), evaluated in the indices observed (A), Shannon (B), and Simpson (C). ns: not significant for the Wilcoxon statistical test.

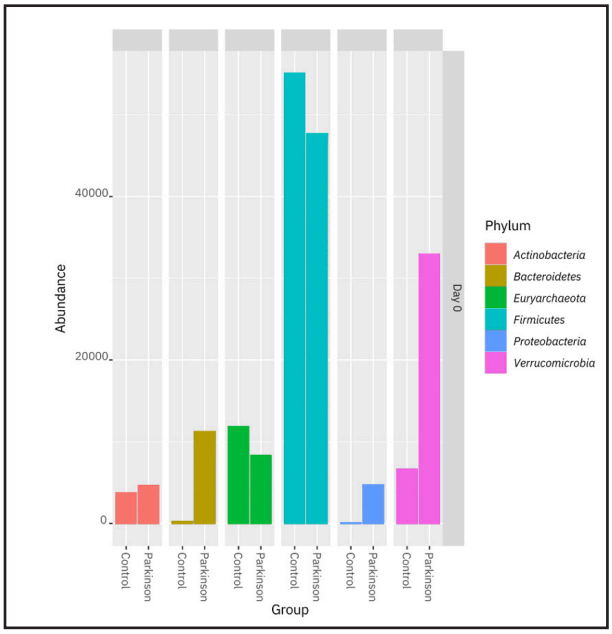

Figure 2.

Analysis of microbiota phylum abundance without intervention (time zero) between volunteers with Parkinson's disease and volunteers without Parkinson's disease. The graph shows an observation of the total abundance of phylum. Analysis of total abundance, the bacterial phylum is shown in colors, according to the volunteers; Control: Volunteers without Parkinson's disease; Parkinson's: Volunteers with Par-kin-son's disease. In colors you can see the bacterial phylum.

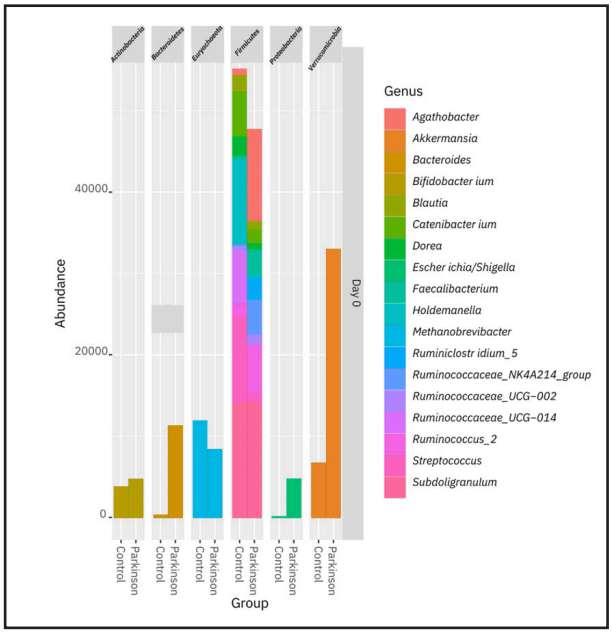

Figure 3.

Analysis of microbiota genus abundance without intervention (time zero) between volunteers with Parkinson's disease and volunteers without Parkinson's disease. The graph shows an observation of the total abundance of bacterial genus. Analysis of total abundance, bacterial genera are shown in colors, according to the volunteers; Control: Volunteers without Parkinson's disease; Parkinson's: Volunteers with Parkinson's disease. In colors you can see the bacterial genera organized into phyla.

MICROBIOTA ANALYSIS ACCORDING TO THE INTERVENTION PERFORMED

In graph 4 you can see the analysis of alpha diversity expressed in the means of each of the groups and intervention time.

In the analysis of Observed (A), Shannon (B) and Simpson (C), a trend towards increasing alpha diversity is observed in the group that underwent inulin intervention after 30 days of intervention, which is observed as a separation in their values from the average between both groups (Fig. 4).

GENUS ABUNDANCE ACCORDING TO TIME AND TYPE OF INTERVENTION

It was possible to observe that the intervention with oligofructose caused a modulation of genera in the intervened patients, both at 7 days of consumption and at the end of the 30 days of intervention. According to the figure 5, genera related to dysbiosis in subjects with PD, such as *Enterorhabdus, Bacteroidetes, Euryarchaeota, Proteobacteria* and *Verrucomicrobia* showed a decrease in the presence of oligofructose, along with a proliferation of *Firmicutes* in each one of the samples of the subjects treated with this prebiotic. Similarly, GM in patients who received Inulin was evaluated; it is observed a decrease in *Bifidobacterium, Verrucomicrobia*, Agathobacter (Fig. 5).

A similar effect was found in the phyla, where the intervention with oligofructose resulted in a decline in the abundance of *Bacteroidetes, Euryarchaeota*, *Proteobacteria* and *Verrucomicrobia* at the end of the treatment period, nevertheless, it was noted a slight increase in *Firmicutes* after 30 days.

With respect to the intervention with Inulin, it is observed a decline in *Verrucomicrobia* and a slight decrease in *Firmicutes* (Fig. 6).

A Wilcoxon statistical analysis was applied to the GM at baseline in the Parkinson's disease volunteers, comparing it with the group of volunteers without the disease. The results show statistically significant differences in 10 bacterial genera, which are detailed in table III.

The genera *Alistipes* followed by *Ruminiclostridium 50* are present in 4 and 5 of the evaluated volunteers, respectively, compared to 0.5 in the volunteers without the disease. It is important to note that *P50* refers to a value located in the middle range in relation to the other evaluated species.

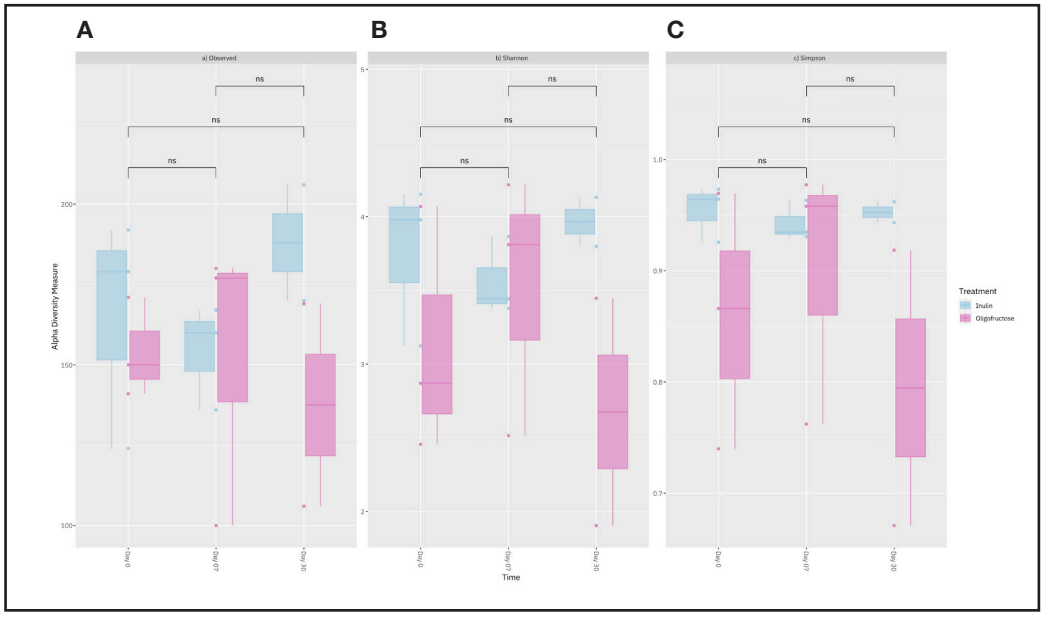

Figure 4.

Analysis of the alpha diversity of the microbiota according to intervention time, in volunteers operated on with prebiotic fiber (inulin and oligofructose). The graph shows the standard deviation of the abundance measured in the Shannon and Simpson indices. Alpha diversity analysis according to intervention time in volunteers with Parkinson's disease receiving prebiotic fiber. It is evaluated according to the indices observed (A), Shannon (B), and Simpson (C). In light blue, volunteers operated on with inulin and in pink, volunteers operated on with oligofructose. ns: not significant after Wilcoxon test.

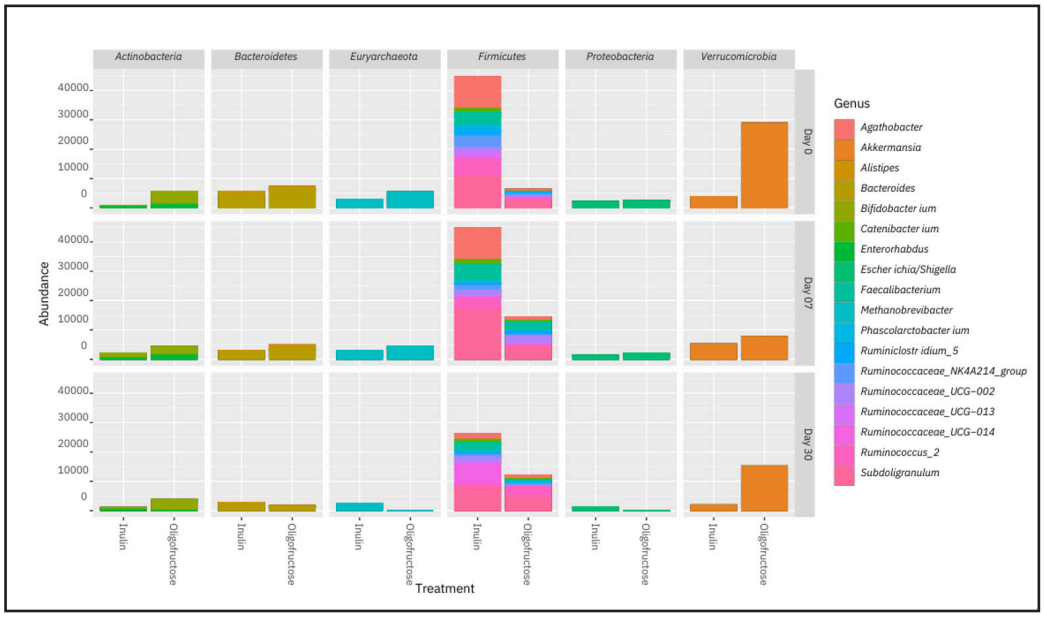

Figure 5.

Analysis of the abundance of genera according to intervention time and type of prebiotic fiber. The graph shows the total sum of abundance of bacterial genera. Analysis of the abundance of bacterial genera according to the type of prebiotic fiber used and intervention time. In colors the bacterial genus is observed.

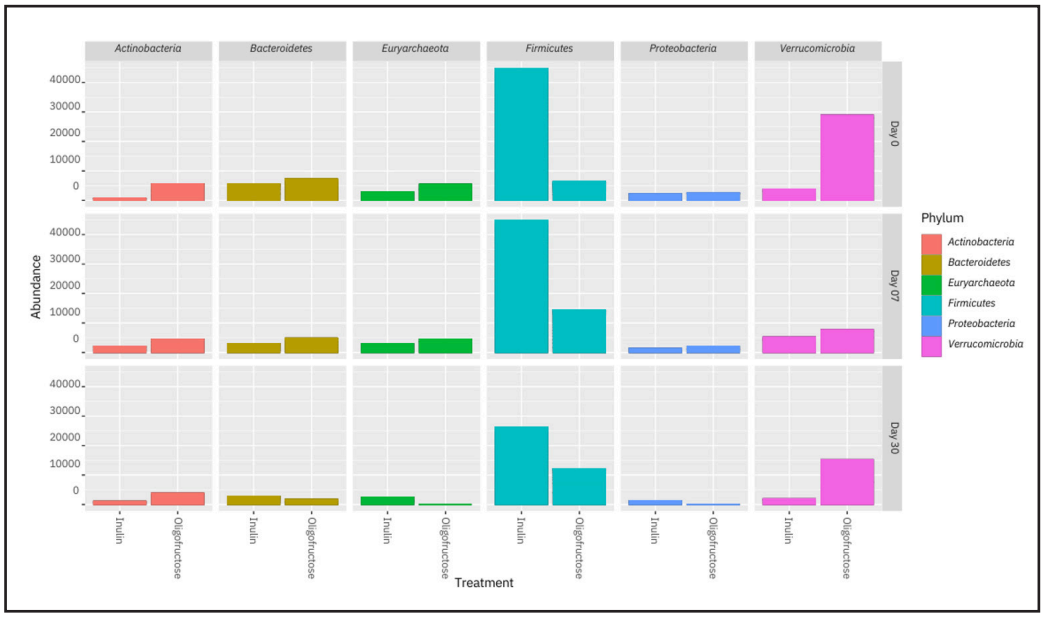

Figure 6.

Analysis of the abundance of phylums according to intervention time and type of prebiotic fiber. The graph shows the sum of the abundance of bacterial phyla. Analysis of the abundance of bacterial phyla according to the type of prebiotic fiber and intervention time. A particular color is assigned to each genus found among the 25 most abundant genera in the samples.

Table III. Comparison of the microbiota at time zero between volunteers with Parkinson's disease and volunteers without Parkinson's disease (*n* = 5)

Variable	Volunteers with Parkinson's disease			Volunteers without Parkinson's disease			*p* value
	n	p50	(p25-p75)	*n*	p50	(p25-p75)	
Alistipes	5	5	(4-5)	4	0.5	(0-1)	0.0131
Butyricimonas	5	1	(1-1)	4	0	(0-0)	0.0237
Catenibacterium	5	0	(0-1)	4	1	(1-1)	0.0736
Desulfovibrio	5	1	(0-1)	4	0	(0-0)	0.0736
Flavonifractor	5	1	(1-1)	4	0	(0-0)	0.0285
Hungatella	5	1	(0-1)	4	0	(0-0)	0.0736
Intestinimonas	5	1	(1-1)	4	0	(0-0)	0.0237
Lachnospiraceae	5	0	(0-0)	4	0	(0-0)	0.079
Negativibacillus	5	1	(0-1)	4	0	(0-0)	0.0736
Odoribacter	5	1	(1-1)	4	0	(0-0)	0.0237
Oscillibacter	5	1	(1 -1)	4	0	(0-0)	0.0285
Parabacteroides	5	2	(2 -3)	4	0.5	(0-1.5)	0.0282
Paraprevotella	5	1	(0 -1)	4	0	(0-0)	0.0736
Parasutterella	5	1	(1 -1)	4	0	(0-0)	0.0237
Phascolarctobacterium	5	1	(1-1)	4	0	(0-0.5)	0.0253
Prevotella	5	1	(0-1)	4	0	(0-0)	0.079
Prevotella 90	5	0	(0-0)	4	1.5	(1-2.5)	0.0528
Ruminiclostridium 50	5	4	(3-6)	4	0.5	(0-1.5)	0.0131

The table shows the data in percentile values.

DISCUSSION

Nutritional status is fundamental for older people suffering from PD; it has been noted that the severity and duration of the disease, as well as its symptoms and L-Dopa intake are closely correlated with nutritional status (24). It is important to mention thar levodopa or L-Dopa (3,4-dihydroxyphenylalanine), it is a chiral amino acid generated via biosynthesis from l-tyrosine in plants and some animals (25). Dopamine (DA) supplementation therapy by L-dopa for Parkinson's disease (PD) was established around 1970 and has since become the gold standard medical therapy (26).

The importance of Levodopa in nutrition lies in the high pharmaco-nutrient interaction between the drug and the amino acids in the diet (27); In addition to the association that has been found between the use of L-dopa and malnutrition in people suffering from the disease. According to a study that evaluated nutritional status through mini nutritional assessment (MNA) and compared it with the use of dopaminergic drugs, it concluded that otal levodopa (L-dopa) equivalent daily dose was associated with worse MNA (B = -0.14, 95 % CI = -0.26--0.02; $p = 0.019$). Presenting a worse nutritional status and risk of malnutrition (28).

Recent studies have highlighted the role of GM in PD, indicating that intestinal dysbiosis could promote the development and progression of the disease (29) and intervene in the absorption of levodopa (30). There is a connection between gut bacteria and PD (31) that might be the key in the treatment of the disease. Moreover, according to recent studies, there are bacterial species present in gut microbiota, such as *Clostridium sporogenes* (10), *Enterococcus faecalis* (11) that have the ability to metabolize L-DOPA, reducing the effectiveness of this treatment in subjects with PD.

In the first instance, constipation of the participants was assessed after completion of the treatment. In a double-blind randomized controlled trial conducted with PD patients, it was found that the consumption of fermented milk along with prebiotic fiber was superior to placebo in improving constipation. On the other hand, animal studies have showed an increase in fecal water content in mice treated with Lotus seed oligosaccharides (LSO), along with an enhancement in the concentration of short-chain fatty acids (SCFAs), concluding that LSO or the combination with resistant starch has a better effect on relieving constipation (32). Similar results were obtained in a rat model with Diphenoxylate-induced constipation. The rats were treated with inulin and isomalto-oligosaccharide (IMO), showing an increase in SCFAs and an improvement in the number, weight, and water content of fecal pellets (33).

In our study, after the treatment with prebiotic fiber, the subjects reported a slight improvement in the consistency of their depositions, indicated in the quality of their stools according to the Bristol Stool Form scale (34), with similar results being observed with inulin versus oligofructose; however, the frequency or number of depositions did not increase (Table II).

When establishing the relative abundance of each one of the phyla present in the samples of subjects with PD and controls in time zero, we were able to determine that there is a significant difference in the abundance of *Bacteroidetes, Proteobacteria* and *Verrucomicrobia*; this last phylum stands out for its richness, since GM of Chilean subjects generally contains a higher percentage of *Verrucomicrobia* due to the high consumption of wheat-based baked products, such as bread. These results are similar to those found in a study on the characterization of GM in the Chilean population, which showed that the most prevalent phylum was *Firmicutes*, followed by *Bacteroidetes*, *Verrucomicrobia*, *Proteobacteria*, *Actinobacteria* and *Euryarchaeota*, with *Verrucomicrobia* being one of the most abundant phyla in subjects with PD, thus representing a window of opportunity to examine if this prevalence of *Verrucomicrobia* in GM of Chileans is related to the prevalence of Parkinson's disease in Chile (35).

GM population profiles of individuals with PD are correlated with those presented by a meta-analysis that analyzed the 16S ribosomal RNA gene sequencing analysis in samples obtained from 223 patients with PD and 137 controls; it was found that genera *Akkermansia* and *Catabacter*, as well as families *Akkermansiaceae* were increased, whereas genera *Roseburia*, *Faecalibacterium,* and *Lachnospiraceae* were decreased in people with PD (36). This supports the view that subjects with PD present a characteristic intestinal dysbiosis. This has an impact on the health of people with PD, since these genera are producers of short-chain fatty acids (37), on the other hand, it has been found that an increase in *Akkermansiaceae* might degrade the intestinal mucin layer and may be involved in the pathophysiological processes of PD (38). In our study, when performing the treatment with the selected prebiotics, it could be noted a decrease in *Akkermansiaceae*, *Bacteroidetes*, *Verrucomicrobia*, and *Actinobacteria* in the treated subjects, both when employing inulin and oligofructose, modulating GM profile so that it was similar to that of the control subjects.

A group of researchers analyzed GM of people with PD, comparing them with a control group, finding significant differences. When analyzing baseline GM, it was found a greater abundance of *Alistipes*, *Rikenellaceae_RC9_gut_group*, *Bifidobacterium*, *Parabacteroides*, with a decline in *Faecalibacterium*. These results greatly differ from those observed in our intervention group, with the only similarity found being *Bifidobacterium* (39).

Furthermore, it was found that PD, constipation, sex, age, and the intake of catechol-O-methyltransferase (COMT) inhibitors affected the overall composition of GM (37).

In our study, it was observed a significant difference between time zero and post-intervention time in the parameter of calf circumference, and a trend in the parameters of weight, BMI, neck circumference, calf circumference, brachial area.

These results are similar to those found in a longitudinal study where it was observed a decrease in BMI, overall body fat percentage, visceral fat, and subcutaneous fat in comparison to controls, concluding that the severity of motor impairment is associated with a decrease in total body fat (40). On the other hand, BMI is significantly correlated with the global scores of parts I, II and III of the Unified Parkinson's Disease Rating Scale (UPDRS).

It is certainly interesting to examine what the real impact of prebiotic fiber supplementation is with respect to parameters of mus-

cle composition and nutritional status of older people with PD, and how is microbiota involved in these potentially favorable changes.

Most studies related to the consumption and benefits of dietary fiber are oriented towards a gastrointestinal system and health benefits perspective, particularly targeting GM, cardiovascular health, and some types of cancer. Nevertheless, our view is that there is a knowledge gap when we want to examine the relationship between dietary fiber and nutritional status, specifically the effect on body composition parameters.

LIMITATIONS OF THE STUDY

It is important to mention that the main limitation of the study was the number of samples and, subsequently, those who were able to complete the intervention. On the other hand, using two types of fiber in a sample of only five individuals does not allow for robust observations.

In the future, we will include a larger sample size with a control group, to which all evaluations and interventions will be performed, assigning participants according to the laws of randomization for this type of study.

Finally, we would like to mention that this pilot study has allowed us to analyze and improve the protocols and quality of the intervention, which in the future may help guide decision-making and be applied in the final intervention study, thus reducing potential biases and complications that may arise.

CONCLUSION

The consumption of 20 g of prebiotic fiber for 30 days could favorably modify the intestinal microbiota in people with Parkinson's disease. Bacterial populations such as *Verrucomicrobia*, which are found in a higher percentage in the Chilean population than in the rest of the world, and which increase abundance in subjects with PD, are reduced when consuming prebiotic fiber.

Many studies support the benefits of consuming prebiotic fiber for the health and microbiota of those who consume it. Moreover, our results allow us to state that the incorporation of fiber into the diet could be a treatment alternative to improve the intestinal microbiota and the health of older people with Parkinson's disease.

It is necessary to deepen how these changes could be affecting the symptoms of the disease, however, diet and in this case the use of prebiotic fiber may represent an alternative to improve the intestinal health of people with Parkinson's disease.

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ARÁN

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Trabajo Original

Obesidad y síndrome metabólico

Association between Dietary Inflammatory Index and IL-17A level in a Mexican cross-sectional study

Asociación entre el Índice Inflamatorio de la Dieta y los niveles de IL-17A: estudio transversal en México

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Abstract

Introduction: the Dietary Inflammatory Index (DII) provides a quantitative means for assessing the role of diet in relation to health outcomes.

Objetive: this study aimed to assess the association between the inflammatory potential of diet, as measured by the DII and IL-17A levels in young adults.

Methods: a cross-sectional study was conducted on 69 adults between 18-30 years of age in San Luis Potosi, Mexico. Fasting blood samples were collected to analyze lipid profile, glucose homeostasis, and IL-17A. Dietary intake was assessed using a 24-hour recall. DII scores were calculated from 19 available food parameters. Univariate linear regression models were estimated to evaluate the possible dependence of IL-17A levels (dependent variables) on some potential explicative variables such as anthropometric, clinical, biochemical, and dietary variables.

Results: there was a high inflammatory potential, with a mean DII score of +1.04 (range: -2.19 to +2.78). The DII was not associated with BMI, IL-17A levels or cardiometabolic risk factors.

Conclusion: the study shows that the diets of healthy college-aged Mexican adults had a high inflammatory potential.

Keywords:

Dietary Inflammatory Index. Dietary intake. Serum IL-17A. Overweight/obesity. Young adults.

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Resumen

Introducción: el Índice Inflamatorio de la Dieta (DII) proporciona un medio cuantitativo para evaluar el papel de la dieta en relación con los resultados de salud.

Objetivo: este estudio tuvo como objetivo evaluar la asociación entre el potencial inflamatorio de la dieta, medido por DII y los niveles de IL-17A en adultos jóvenes.

Métodos: se realizó un estudio transversal en 69 adultos entre 18 y 30 años de edad en San Luis Potosí, México. Se recogieron muestras de sangre en ayunas para analizar el perfil lipídico, glucosa y la IL-17A. La ingesta dietética se evaluó mediante un recordatorio de 24 horas. Las puntuaciones DII se calcularon a partir de 19 parámetros alimentarios disponibles. Se estimaron modelos de regresión lineal univariante para evaluar la posible dependencia de los niveles de IL-17A (variables dependientes) de algunas variables explicativas potenciales, como variables antropométricas, clínicas, bioquímicas y dietéticas.

Resultados: con una puntuación DII media de +1,04 (rango: -2,19 a +2,78), se determinó un alto potencial inflamatorio. El DII no se asoció con el IMC, los niveles de IL-17A ni con los factores de riesgo cardiometabólico en esta población.

Conclusión: el estudio muestra que las dietas de adultos mexicanos sanos en edad universitaria muestran un alto potencial inflamatorio.

Palabras clave:

Índice inflamatorio de la dieta. Ingesta dietética. IL-17A. Sobrepeso/Obesidad. Adultos jóvenes.

INTRODUCTION

Obesity is a serious medical condition associated with various non-communicable diseases (NCDs), reaching epidemic rates worldwide (1). Obesity is defined as the excessive accumulation of adipose tissue (AT) that presents a potential health risk (2). In Mexico, Obesity has become a public health concern as its rates have been steadily increasing for the past 30 years (3). In 2021, 72.4 % of Mexican adults (> 20 years) were classified as having overweight (35.7) or obesity (36.7) (4). Individuals affected by obesity can present an increased risk of developing NCDs such as cardiovascular disease, type 2 diabetes *mellitus,* and obesity-related cancers.

Obesity is identified as a low-grade chronic inflammation state and is characterised by a raised expression of inflammatory markers into adipose tissue (AT). AT in obesity is characterized by increased lipid storage, which leads to its dysfunction, cellular lipid toxicity, inflammation, and oxidative stress, triggering the release of acute phase proteins, and pro-inflammatory adipokines including interleukin (IL)-6 (5). Furthermore, IL-6 is required for the differentiation of *naïve* CD4 T cells into the T helper 17 (Th17) subpopulation (6). The involvement of traditional inflammatory mediators, such as tumor necrosis factor α (TNF-α) and C-reactive protein (CRP), has been thoroughly examined in the context of obesity (7). Recent investigations have suggested the potential role of the Th17 T cell sub-lineage in metabolic disorders. Th17 cells participate in obesity-dependent inflammation and an increased frequency of these cells in individuals with obesity as well levels of IL-17A have been observed (8).

IL-17 family of cytokines consists of six ligands from IL-17A to IL-17F. IL-17A is the effector and the classic cytokine of Th17 cells. IL-17 plays a protective role in the host's defense against pathogens, response to injury, and physiological stress. However, excessive production of IL-17A is one of the potential mechanisms underlying chronic inflammatory conditions (9) IL-17A is involved in the induction of adipogenesis role in several inflammatory diseases (10). Obesity promotes expansion of IL-17-producing T cells in AT and periphery (11,12). Subjects with obesity had a higher level of IL-17 cytokines and a correlation was found between the level of these cytokines and the content of adipose tissue. In addition, the intake of potassium, iron, vitamins B6 and C, and folic acid has been associated with decreased concentrations of IL-17 isoforms (13).

Diet is a crucial modifiable factor for reducing the risk of chronic diseases (14). Specific compounds found in nutrient-dense foods, such as omega-3 fatty acids, fiber, and polyphenols, exhibit anti-inflammatory properties. Conversely, reduced intake of fruits and vegetables and high consumption of calorie-dense ultra-processed food correlate with increased levels of inflammatory markers (14). Researchers have linked unhealthy diets, characterized by high sugar consumption, high saturated fat intake, and low fiber, vitamins, minerals, and other plant-derived molecules such as antioxidants, to an increased risk of NCDs. It is also thought that these diets cause dysbiosis, oxidative stress, the NF-B pathway, and higher levels of TNF- and IL-6, all of which lead to low-grade systemic inflammation (15,16).

The Dietary Inflammatory Index (DII) is a literature-derived population-based dietary score intended to assess the inflammatory potential of an individual's overall diet based on the balance of pro- and anti-inflammatory properties of its components, including macronutrients, vitamins, minerals, flavonoids, and specific food items (17). A positive DII score has been associated with a higher BMI (18), and several studies have confirmed that a higher DII score was associated with an increased risk of obesity (19-21). According to Sakhaei et al., participants in the top tertile of the healthy diet score had lower concentrations of serum IL-17A compared to those in the lowest tertile (22). However, the association between dietary inflammatory potential and IL-17A levels remains unclear. We aimed to investigate the association of the Dietary Inflammatory Index (DII) with L-17A levels in healthy adults and adults who are overweight or obese. We also want to find out if these cytokine levels are linked to clinical and dietary parameters in a cross-sectional sample of 62 adults in San Luis Potosí, Mexico.

MATERIALS AND METHODS

This was a cross-sectional study conducted in San Luis Potosí, Mexico. The study population included adults aged 18 years to 30 years, recruited from the surrounding community via public signage and flyers. All participants provided written informed

consent, and all study procedures were approved by the University of Illinois Institutional Review Board (Protocol #15503) and conformed to standards for the use of human participants in research as outlined in the seventh revision of the Declaration of Helsinki. Subjects were compensated with US$ 15 for their participation in this study. Inclusion criteria included no previous history of physician-diagnosed gastrointestinal or metabolic disease. Adults were excluded if they had previously been diagnosed with cardiovascular, hepatic, renal, or oncological conditions, or if they were pregnant or lactating. Participants were eliminated if they did not completed the evaluation.

ANTHROPOMETRICS AND BIOLOGICAL MEASURES

Anthropometric parameters such as weight, height, and waist circumference (WC) were measured in duplicates and the average of the two numbers were documented. Body mass index (BMI) was calculated by dividing weight (kg) by the squared value of height in meters. The reference interval of BMI was defined as 18.5-24.9 kg/m^2. Over-weight and obesity were considered with a BMI of ≥ 25 or 30 kg/m^2, respectively. Height was measured using a mobile stadiometer (Seca 213), weight was collected on a calibrated electronic weighing scale TANITA UM-081, and waist circumference was measured at the midpoint between the last floating rib and the iliac crest using a LUFKIN Executive Thin line 2 m, W606PM metal tape.

Blood pressure was measured in a seated position using an automatic blood pressure monitor (Omron Healthcare Co.). Venous blood was collected from the antecubital vein following a 10-h overnight fast. These parameters were measured by trained research staff as previously described (23).

BLOOD ANALYSIS

Fasting blood samples were collected in vacutainer tubes, which were cooled to 4 °C and centrifuged 15 min to obtain serum and subsequently stored at -70 °C. Serum samples were used to measure the concentrations of total cholesterol, HDL-c, triglycerides, and fasting glucose were assessed on the automated analytical platform BS300 (Mindray®, Nanshan, Shenzhen, China) following the internal test protocols and the use of commercially available reagent kits. IL-17A was measured using ELISA kit (Bio Legend, San Diego, CA, US). The assays were carried out following the manufacturer's instructions.

DIETARY ASSESSMENT

Before participants were interviewed, they attended a brief session where registered dietitians (RD) demonstrated how to appropriately estimate food intake using household utensils. Participants were asked to write down the type and amount of food eaten, using scales or household measures to gauge portion sizes where possible. Dietitians interviewed each participant and recorded the estimate of food and drinks consumed. The information included in the 24-hour recall was the date of record, mealtime, and amount of food consumed. Information from one 24-hours dietary recall was coded by a trained RD using the Nutrikcal computer program (Nutrikcal VO®, Mexico), which is based on the Mexican System of Food and Equivalents. Macro and micronutrient intakes were compared with sex and age-specific nutrient requirements defined by the Food and Nutrition Board of the National Academy of Science (24). VC, vitamin A (VA), vitamin E (VE), VD, thiamin (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), folate (B9), cobalamin (B12), calcium (Ca), potassium (K), magnesium (Mg), sodium (Na), phosphate (P), selenium (Se), iron (Fe), and Zn.

DIETARY INFLAMMATORY INDEX (DII)

Dietary information data of participants were compared with the global standard dietary intake database, which provide a reliable estimation of the median and interquel range and the Z-score of each nutrient or food was calculated, i. e.:

$$Z = (\text{actual dietary intake amount} - \text{standard global median}) / \text{standard deviation})$$

Subsequently, to minimize the effect of "right-skewing", the Z-value was converted into percentiles, while each percentile was multiplied by 2 and finally subtracted by 1. Then the resulting value was multiplied by the corresponding food parameter effect score to obtain the food parameter-specific DII score for an individual (18). Finally, all dietary parameter-specific DII scores were added together to calculate the overall DII score. The higher the DII score, the stronger the proinflammatory effect. In the present study, a total of 19 dietary intake parameters were obtained by the 24 h recall, and used to compute DII (namely: protein, total fat, carbohydrates, cholesterol, dietary fiber, vitamin A, thiamine, riboflavin, niacin, vitamin C, vitamin E, folic acid, vitamin B6, magnesium, iron, zinc, and selenium).

STATISTICAL ANALYSIS

Data are shown as the mean ± the standard deviation (SD) or the median ± interquartile range. The distribution of each one of the variables was assessed by the Shapiro-Wilk normality test. Groups were compared using the Mann-Whitney U test or t-test according to the distribution of the data. Spearman correlation was employed to assess the correlation between different parameters. Differences were considered significant at $p < 0.05$. Univariate and multivariate linear regression models were estimated to assess the possible dependence of IL-17A on some explicative variables. A multivariate model (by stepwise procedure) was estimated considering the following independent vari-

ables: overall DII score and specific DII score for the 19 dietary intake parameters. Statistical analyzes were conducted using the statistical packages SPSS (version 20.0), and InStat GraphPad software (InStat GraphPad Inc.,San Diego, CA, USA), version 5.0.

RESULTS

A total of 69 individuals (56.4 % females) were included in the cross-sectional analysis. Participant characteristics according to BMI are presented in table I. The prevalence of overweight and obesity in the sample was 48.3 %. In comparison with the healthy group, the overweight and obesity group showed increased values for body mass index, triglycerides, waist circumference, systolic and diastolic pressure, TC/HDL, triglyceride-glucose index (TyG), and visceral adiposity index (VAI) score. Adults impacted by overweight or obesity were significantly older than those with a BMI < 25 kg/m^2. The mean DII was 1.04 (SD = 1.12) and ranged from -2.18 (most anti-inflammatory) to 2.77 (highly pro-inflammatory). Finally, no differences in IL-17A levels were detected. The usual intakes of macro and micronutrients from foods according to BMI are shown in table II. Among 18-35-year-old individuals, the intakes of the following macro and micronutrients were significantly different across the two groups: Kcal/kg weight, protein (g/kg weight), carbohydrate (g/kg weight), lipids (g/kg weight), B2, and Mg. The percentage of macronutrients in relation to the total energy value (TEV) was within the values recommended by the acceptable macronutrient distribution ranges (AMDR). There was no significant difference observed in usual dietary intakes according to sex except for Se intake which was lower in women.

Individuals with obesity had higher level of IL-17A (p = 0.02) than overweight groups (data not shown). When classifying the subjects according to the parameter of abdominal obesity, a tendency towards an increase in the levels of IL-17A can be observed (p =0.07). No differences on IL-17A levels between Normal weight and individuals with BMI ≥ 25 was detected (Fig. 1).

A correlation analysis to assess the possible associations between IL-17A, anthropometric parameters, traits of metabolic syndrome, macronutrient, and micronutrient intake was carried out. Glucose had a weak, but positive association when these variables were analyzed with respect to serum IL-17A in all participants (p = 0.02) (Fig. 2).

Table I. Sample characterization in all subjects and according to BMI status

Variables	All *n* = 69	Healthy *n* = 34	Overweight and obesity *n* = 35	*p*[1]
Age, years	21 (18-30)	20 (18-28)	23 (19-30)	*0.03*
Sex	M 43 % F 57 %	M 44 % F 56 %	M 42 % F 58 %	
BMI (kg/m^2)	25.1 ± 3.8	22.06 ± 1.9	28.28 ± 2.3	*< 0.0001*
IL-17A (pg/mL)	2.4 (0.04-6.6)	2.5 (0.12-6.6)	2.6 (0.04-4.8)	0.99
TC (mg/dL)	124 (100-215)	123 (100-203)	124 (100-215)	0.26
LDL-C (mg/dL)	70.2 ± 21.3	64.8 ± 20.4	75.4 ± 21.2	0.07
Glucose (mg/dL)	84.6 ± 6.7	84.6 ± 5.5	84.6 ± 7.9	0.49
HDL-C (mg/dL)	45.5 ± 11.7	46.7 ± 10.6	44.2 ± 12.7	0.10
TG (mg/dL)	110 (46.9-316.7)	102.5 (46.9-250.8)	123.1 (60.7-316.7)	*0.01*
WC (cm)	86 ± 11	77.7 ± 6.5	94.3 ± 8.1	*< 0.001*
DBP (mmHg)	117 (96-147)	112.8 (96-142)	119 (99-147)	*0.02*
SBP (mmHg)	69 (51-132)	66 (51-80)	73 (57-132)	*< 0.01*
TC/HDL	2.9 ± 0.6	2.7 ± 0.6	3.1 ± 0.6	*0.02*
TyG index	4.5 ± 0.2	4.5 ± 0.2	4.6 ± 0.2	*0.01*
VAI score	1.7 (0.5-5)	1.6 (0.5-3.6)	1.9 (0.8-5)	*< 0.01*
Overall DII score	1.04 ± 1.12	0.88 ± 1.08	1.2 ± 1.1	*0.09*

BMI: body mass index; WC: waist circumference; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC/HDL: total cholesterol/high-density lipoprotein cholesterol ratio; TyG index: triglyceride-glucose index; VAI: visceral adiposity index; DII: Dietary Inflammatory Index. p[1] Healthy vs overweight and obesity.

Table II. Description of the energy values, macronutrients, micronutrients, fiber and references in all subjects and according to BMI status

Nutrient intake	All *n* = 69	Healthy *n* = 34	Overweight and obesity *n* = 35	*p*[1]
Energy (kcal) kcal/kg weight	1948 ± 636.4 29 ± 10.5	2043 ± 710 34.2 ± 11.2	1847 ± 540.6 23.54 ± 6.3	0.07 *< 0.0001*
Protein g/kg weight %TEV	1.1 ± 0.4 17.15 ± 6.6	1.4 ± 0.5 16.8 ± 4.6	0.95 ± 0.3 17.50 ± 8.3	*< 0.0001* 0.39
Protein g per 1000 kcal	42.7 ± 16.4	41.85 ± 11.6	43.74 ± 20.7	0.87
Carbohydrate g/kg weight %TEV	3.7 ± 1.7 52.1 ± 12.5	4.4 ± 1.8 53.1	3.0 ± 1.1 50.97 ± 11.4	*0.0003* *0.75*
CHO g per 1000 kcal	130.4 ± 31.2	133.2 ± 33.6	127.4 ± 28.7	*0.23*
Fiber g/kg weight g/day	0.25 ± 0.1 17.3 ± 10.5	0.25 ± 0.1 17.1 ± 9.6	0.22 ± 0.1 17.6 ± 11.4	0.40 0.47
Fiber g per 1000 kcal	9.6 ± 6.9	8.8 ± 5.6	10.5 ± 8.1	0.33
Lipids g/kg weight %TEV	1.0 ± 0.5 33.0 ± 11.8	1.2 ± 0.6 31.7 ± 12.0	0.9 ± 0.4 34.5 ± 11.6	*0.01* 0.19
Lipids g per 1000 kcal	36.67 ± 13.1	35.1 ± 13.4	38.2 ± 12.8	0.18
% saturated fat	8 (2-21)	9 (4-20)	8 (2-21)	0.40
% monounsaturated	9 (2-29)	9.5 (2-28)	9 (3-29)	0.49
% polyunsaturated	4 (1-17)	3.5 (1-15)	5 (1-17)	0.10
Saturated fat (g)	17.4 (3.2-60)	19.1 (3.9-57)	17 (3.2-60.9)	0.20
Monounsaturated (g)	17.9 (2-69)	19.3 (2.1-69)	17.8 /3.5-66)	0.20
Polyunsaturated (g)	9.1 (1.5-35)	9.3 (1.5-35)	8.9 (2.9-34.3)	0.35
Cholesterol (mg)	340 ± 262.8	303.5 ± 267	379.8 ± 256.9	0.06
Sugar (g)	32 (0-140)	43 (5.4-140)	22.9 (0-119.2)	0.09
Liquids (ml)	1752 ± 1002	1718 ± 975	1788 ± 1044	0.43
Vitamin A retinol (mcg)	999.1 ± 1407	852.3 ± 1200	1156 ± 1604	0.20
Vitamin B1 thiamin (mg)	1.4 ± 0.9	1.6 ± 1.1	1.22 ± 0.5	0.05
Vitamin B2 riboflavin (mg)	1.7 ± 1.1	2.0 ± 1.4	1.4 ± 24.4	*0.01*
Vitamin B6 piridoxin (mg)	3.5 ± 17.0	1.6 ± 1.6	5.6 ± 1.9	0.17
Vitamin B12 cobolamin (mg)	3.1 ± 2.1	3.21 ± 2.2	2.9 ± 119.2	0.27
Vitamin C ascorbic acid (mg)	118.4 ± 123.6	128.4 ± 128.7	107.7 ± 382.7	0.25
Folic acid (mg)	290 ± 352.1	308.2 ± 325.9	270.6 ± 1.8	0.33
Pantothenic acid (mg)	2.9 ± 1.7	2.9 ± 1.605	2.8 ± 1.8	0.33
Niacin (mg)	18.0 ± 13.7	20.4 ± 16.2	15.4 ± 10.2	0.07
Vitamin E (mg)	4.4 ± 4.5	4.1 ± 4.9	4.7 ± 4.6	0.30
Calcium (mg)	1083 ± 623.1	1175 ± 672.5	984.7 ± 560.2	0.11
Iron (mg)	16.2 ± 18.1	19.0 ± 24.8	13.3 ± 4.4	0.10
Potassium (mg)	2353 ± 1130	2417 ± 903.7	2284 ± 1343	0.32
Magnesium (mg)	319.8 ± 266.2	388.6 ± 326.4	246.4 ± 156.1	*0.01*
Sodium (mg)	2200 ± 1493	2471 ± 1575	1911 ± 1366	0.07
Phosphorus (mg)	907.2 ± 474.2	981.8 ± 483.9	827.6 ± 458.2	0.10
Selenium	62.45 ± 32.9	68.59 ± 36.2	55.9 ± 28.08	0.06
Zinc (mg)	7.0 ± 3.7	7.6 ± 3.9	6.4 ± 3.4	0.08

Total energy value percent (%TEV). p[1] *Healthy vs overweight and obesity.*

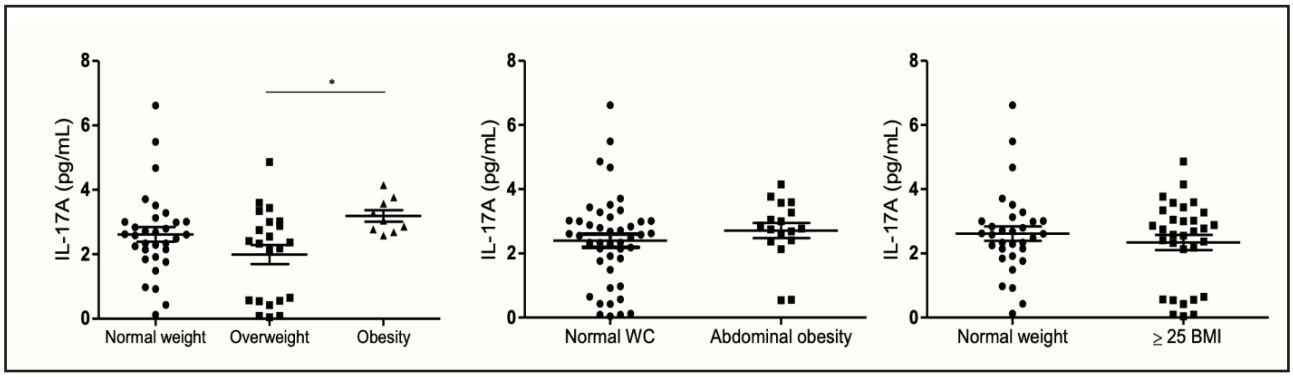

Figure 1.

IL-17A levels according to body mass index.

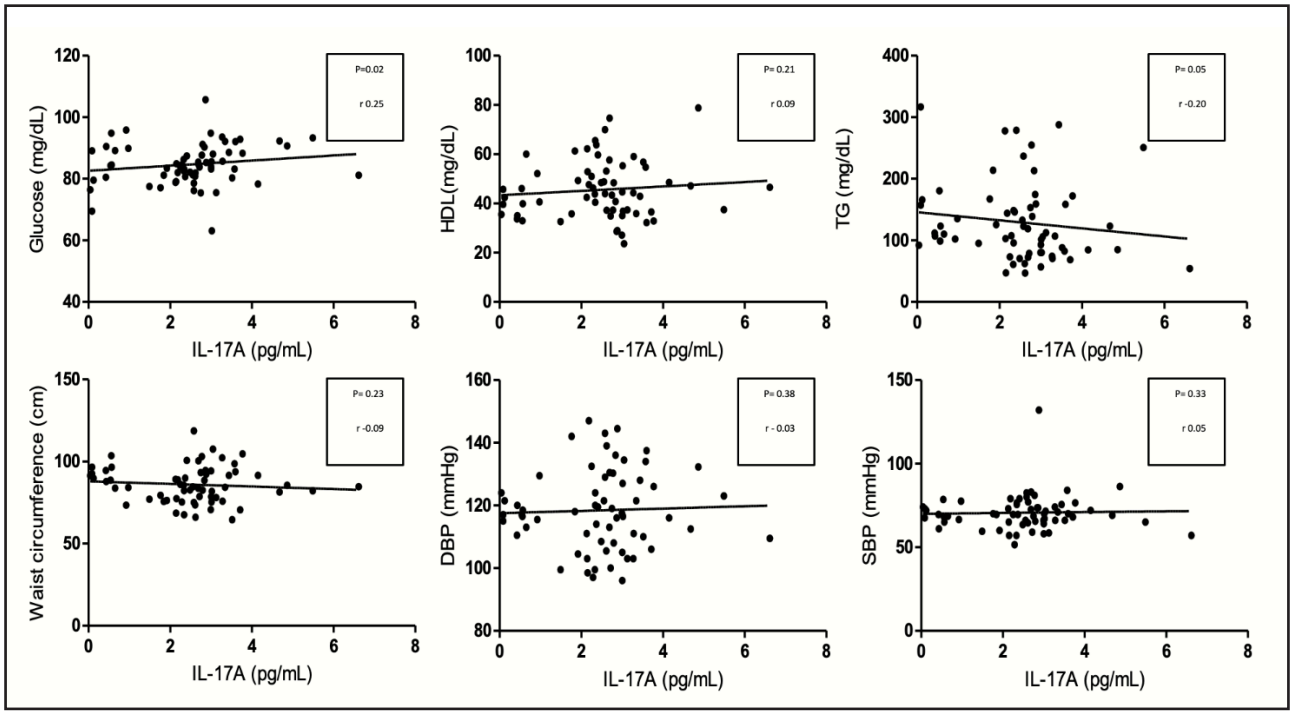

Figure 2.

Associations between IL-17A levels and anthropometric parameters, traits of metabolic syndrome, and dietary intake.

In females, IL-17A levels were negatively associated with triglycerides ($p = 0.02$, r -0.34), and TyG index ($p = 0.02$, r -0.33). A positive correlation with cholesterol intake ($p = 0.03$, r 0.30) was found. In males, a significant positive correlation with glucose was observed ($p = 0.03$, r 0.357, and carbohydrates percentage from diet ($p = 0.04$, r 0.338).

We analyzed the levels of IL-17A according to the adequacy in the intake and found that individuals with an adequate intake of sodium, and those with inadequate intake of B3 present higher levels of IL-17A. The categorization of the individuals according to the adequacy of the intake of the other micronutrients evaluated, did not show differences in the levels of IL-17A (Fig. 3).

Neither components of metabolic syndrome nor adiposity index predicted IL17-A levels. Furthermore, we investigated the independent effect of several macro and micronutrients dietetic intake. B1 was the strongest predictor of IL-17A levels in both males and females, following by Niacin (Table III). Each unit increase in B1 was associated with 1.08-fold increased odd of IL-17A levels, suggesting that B1 intake is useful in predicting IL-17A levels in young adults.

The mean DII was 1.04 (SD = 1.12), ranging from -2.18 (most anti-inflammatory) to 2.77 (highly pro-inflammatory). No association between overall or specific DII and IL-17A levels was found. Also, no statistical association was observed between DII and other biochemical indices (data do not show). We further investigated the independent effect of specific DII. The β coefficients of correlation between specific DII and IL-17A are shown in table IV. Moreover, the specific DII score for niacin was positively associated with the IL-17 in the unadjusted model 1 (β = 0.275, $p < 0.001$). In addition, there was a negative relationship between IL-17 and specific DII score for Vit B1 in model 2 (β = -0.376, $p = 0.02$).

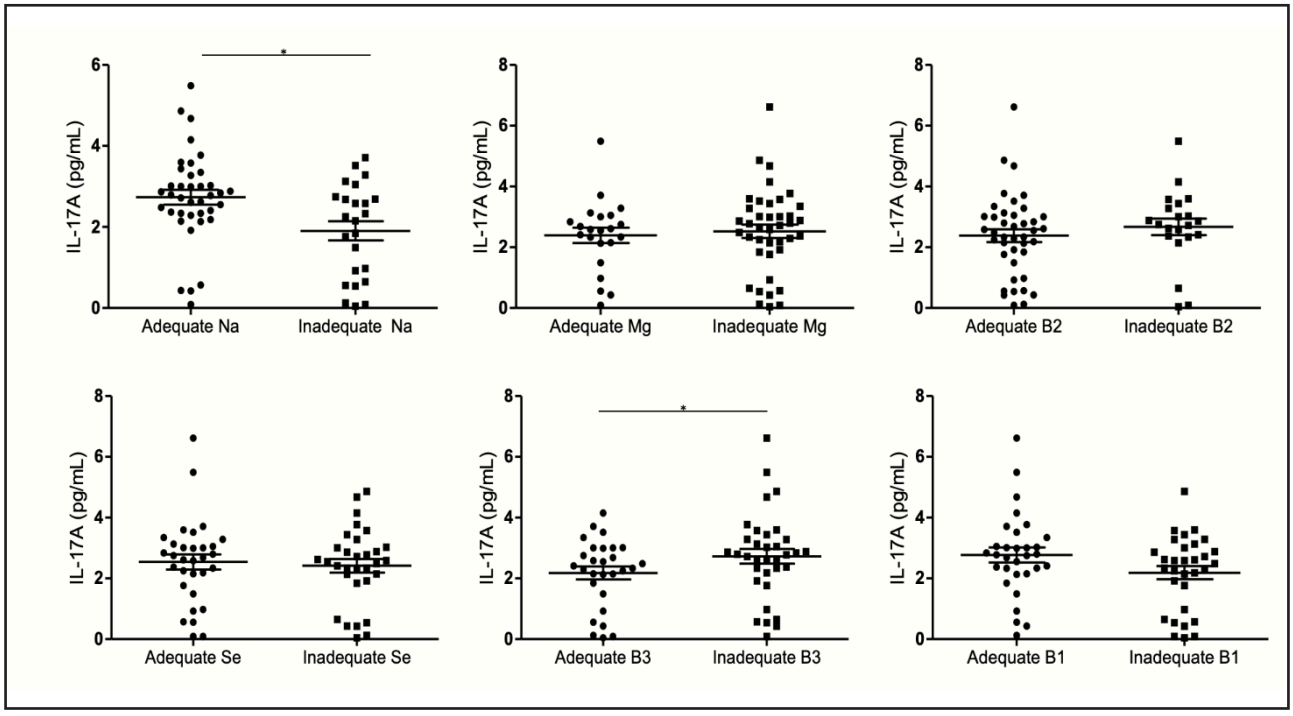

Figure 3.
IL-17A levels according to the adequacy of intake of micronutrients.

Table III. Multivariate linear regression analysis that evaluates the association between IL-17A

Model 1				
		β	p	r^2
IL-17A	TC/HDL	-0.009	0.949	0.031
	TyG	-0.277	0.200	
	VAI	0.152	0.557	
	BMI	-0.009	0.949	
Model 2				
		β	p	r^2
IL-17A	TG	-0.140	0..329	0.068
	HDL	0.108	0.442	
	Glucose	0.174	0.193	
	SBP	0.015	0.935	
	DBP	0.098	0.593	
	WC	-0.077	0.614	

(Continues on next page)

Table III (cont.). Multivariate linear regression analysis that evaluates the association between IL-17A

Model 3				
		β	p	r^2
IL-17A	% fat	-1.006	0.205	0.083
	% sat fat	.902	0.223	
	%MUFA	0.396	0.467	
	%PUFA	0.323	0.653	
	g sat fat	0.003	0.275	
	cholesterol	-0.224	0.226	
Model 4				
		β	p	r^2
IL-17A	Zinc	0.065	0.776	0.275
	Selenium	-0.071	0.690	
	Fosfote	0.100	0.680	
	Sodium	-0.119	0.594	
	Magnesium	-0.193	0.329	
	Potassium	0.286	0.349	
	Iron	0.175	0.755	
	Calcium	-0.127	0.528	
	Vit E	-0.044	0.768	
	Niacin	-0.793	0.021	
	Pantothenic acid	0.120	0.530	
	Folic acid	-0.566	0.051	
	C	-0.200	0.403	
	B12	-0.140	0.541	
	B6	0.013	0.928	
	B2	-0.196	0.658	
	B1	1.087	0.043	
	A	0.138	0.403	

Table IV. Multivariate linear regression analysis that evaluates the association between IL-17A with specific DII

Model 1				
		β	p	r^2
IL-17A	DII niacin	0.275	0.031	0.075
Model 2				
		β	p	r^2
IL-17A	DII niacin	0.537	0.002	0.148
	DII B1	-0.376	0.029	
Model 3				
		β	p	r^2
IL-17A	DII niacin	0.415	0.021	0.204
	DII B1	-0.617	0.004	
	DII iron	-0.413	0.048	

DISCUSSION

Adipose tissue (AT) in obesity presents a progressive infiltration of pro-inflammatory immune cells, which together with increased inflammatory adipokine secretion including IL-17 and other cytokines, to promote chronic inflammation-associated metabolic syndrome and insulin resistance (25). The current study was designed to examine the DII and dietary intake in association with IL-17A (a systemic proinflammatory marker) and cardiometabolic risk factors among young adults. We hypothesized that DII might be positively associated with IL-17A levels. However, in this cross-sectional study of Mexican adults, we found no association with DII, neither with macro nor micronutrient-specific intakes.

Obesity and obesity-related diseases are closely connected to the serum levels of IL-17A (26). We did not find differences on IL-17A levels according to BMI status. Polak-Szczybył et al., reported that IL-17F, IL-17E but not IL-17A levels were positively correlated BMI (27). Nevertheless, the participant's BMI ranged from 30.0 to 58.1 kg/m^2, with a mean of 36.65 ± 5.27 kg/m^2, and in our study the mean BMI was 25.1 ± 3.8 kg/m^2. The above, may explain why in the overweight/ obese group IL-17A levels did not differed from healthy individuals. However, we initially included 85 participants in our study, 13 of whom had IL-17A levels below the detection threshold, leading to their exclusion from the overall analysis. Additionally, we employed the graphpad outlier calculator, and the Grubbs' test successfully identified three significant outliers.

Healthy dietary pattern is inversely related with inflammatory markers (28). Thus, diet is a key modifiable factor since DII score for a more pro-inflammatory diet, were associated with a higher risk of obesity (29). Our study, using the DII score calculation, indicated that participants' diets were more pro-inflammatory. Nevertheless, DII did not show a correlation with IL-17A levels or any cardiometabolic risk factor. The analysis, stratified by BMI and sex, produced similar findings. The above suggests that our population does not show significant systemic markers of inflammation levels, despite a pro-inflammatory diet.

We calculated the DII score computed from 19 food parameters, ranged from -2.19 to + 2.78 with a mean of 1.04, which indicates a proinflammatory diet. These results contrast with a prior study conducted in Mexico (30), where an anti-inflammatory diet had a mean score of –0.68 in adults. These conflicting results may be partly due to the differences in sample size and region representation. On the other hand, it is important to note that our study population is younger and might be less interested in a healthy diet, but this is just a speculation. However, one study reports that the diet of young adults showed a high inflammatory potential, with a mean DII score of +1.10 (range: -4.69 to +5.28). Also, DII was not associated with Metabolic syndrome components in the study population (31).

DII consistently reflects the levels of six inflammatory markers: interleukin (IL)-1β, IL-4, IL-6, IL-10, tumoral necrosis factor-α and C-reactive protein (17). However, we could not find any correlation between IL-17A and overall DII. We analyzed the specific DII for dietary macro and micronutrients and found that niacin and B1 specific DII can predict IL-17A levels. Nevertheless, it is important to mention that a specific micro or macronutrient DII has not been reported or discussed in any previous publication. Regarding nutrient intake, we observed that subjects with the most pro-inflammatory diet (overweight and obesity) had lower intakes of riboflavin and magnesium. In addition, dietary intake of riboflavin and niacin are predictors of IL-17A levels in Model 4.

The strength of our study is that we use a validated DII score specially constructed to assess the inflammatory potential of any diet. Then, DII provides results that can be compared to those from studies based on diverse populations. Some potential weaknesses of our study need to be highlighted. Because of its cross-sectional design, this study cannot infer causality. The sample size in this study was relatively small, which may have contributed to less precise estimates. Finally, we recognize the limitation of using a single measurement of 24-hour recall to evaluate the dietary factors to calculate the DII, as it is subject to random error that would tend to underestimate the true association between DII and the tested variables.

Our data suggest that the Mexican population follows a pro-inflammatory diet, with a mean DII of 1.10. However, this study did not contribute to the hypothesis that a higher BMI, higher DII, we did not find an association of overall DII with IL-17A levels. However, specific DII for niacin and B1 are predictors of IL-17A levels which are in accordance with the dietary intake of the same nutrients. In a population of young adults with a proinflammatory diet, IL-17A levels, and overall DII do not show changes between study groups. Nevertheless, it is important to monitor populations that follow a proinflammatory diet that, if perpetuated over time without intervention, could be related to the increase in inflammatory markers, as demonstrated by scientific evidence. Finally, the DII may be a good tool to characterize the diet of the Mexican population and further explore associations with non-communicable diseases. Our results may contribute to improved dietary recommendations. They could increase public awareness of adhering to a healthy and anti-inflammatory diet.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Obesidad y síndrome metabólico

Effects of probiotic supplementation on blood lipids in hypercholesterolemic obese patients: a randomized, double-blind, placebo-controlled pilot trial

Efectos de la suplementación con probióticos sobre los lípidos sanguíneos en pacientes obesos hipercolesterolémicos: un ensayo piloto aleatorizado, doble ciego y controlado con placebo

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Abstract

Objective: this trial aimed to determine the effects of probiotic supplementation on weight loss and lipid profiles in hypercholesterolemic obese patients.

Methods: in this pilot randomized, double-blind, placebo-controlled trial, hypercholesterolemic obese patients (BMI = 30.0-35.0 kg/m^2) were randomly divided into 2 groups to receive either probiotic capsules ($n = 12$) or a matching placebo ($n = 12$) groups. The patients in the probiotic group took capsules 2 times a day that contained *Enterococcus faecium, Lactobacillus plantarum, Streptococcus thermophiles, Bifidobacterium lactis, Lactobacillus acidophilus, Bifidobacterium longum* (1.5×10^9 CFU/g) for 8 weeks. All patients adhered to a medical nutrition therapy that aimed for a weight loss of 0.5 to 1 kg per week. Anthropometric measurements and body composition were taken at baseline and were monitored every week throughout the study. Blood lipids were assessed at baseline and after the 8-week intervention.

Results: after the 8-week dietary intervention, both probiotic and placebo groups showed significant decreased in total cholesterol (-36.50 ± 19.27 vs -25.91 ± 19.25, mg/dl), LDL-C (-(31.75 ± 18.11 vs -31.91 ± 31.00 mg/dl) and TG (-31.83 ± 67.37 vs -28.25 ± 59.09), respectively ($p < 0.05$). Body weight, BMI, body fat ratio, and waist circumference also significantly decreased after the dietary intervention in both groups ($p < 0.05$). Overall, no significant difference was found neither in the reductions of total cholesterol, LDL-C, TG concentrations nor the anthropometric indices between the probiotic and placebo groups ($p > 0.05$).

Conclusions: the results of our study demonstrated that the administration of probiotic supplements for 8 weeks in obese subjects with hypercholesterolemia had favorable effects on lipid profiles, although there was no beneficial effect compared to the control group. These results indicate that anthropometric indices significantly decreased in response to adherence to the low-calorie diet recommended by dietitians in both the groups. However, conducting more trails with large sample size and longer follow-up time is necessary.

Keywords:

Probiotics. Obesity. Hypercholesterolemic. Blood lipids.

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Resumen

Objetivo: este ensayo tuvo como objetivo determinar los efectos de la suplementación con probióticos en la pérdida de peso y los perfiles lipídicos en pacientes obesos con hipercolesterolemia.

Métodos: en este ensayo piloto aleatorizado, doble ciego, controlado con placebo, los pacientes obesos con hipercolesterolemia (IMC = 30,0-35,0 kg/m^2) se dividieron aleatoriamente en 2 grupos para recibir cápsulas probióticas ($n = 12$) o un grupo placebo equivalente ($n = 12$). Los pacientes del grupo probiótico tomaron cápsulas 2 veces al día que contenían *Enterococcus faecium, Lactobacillus plantarum, Streptococcus thermophiles, Bifidobacterium lactis, Lactobacillus acidophilus, Bifidobacterium longum* ($1,5 \times 10^9$ UFC/g) durante 8 semanas. Todos los pacientes adhirieron a una terapia nutricional médica que tenía como objetivo una pérdida de peso de 0,5 a 1 kg por semana. Se tomaron medidas antropométricas y de composición corporal al inicio del estudio y se controlaron todas las semanas durante todo el estudio. Se evaluaron los lípidos en sangre al inicio y después de la intervención de 8 semanas.

Resultados: después de la intervención dietética de 8 semanas, tanto el grupo probiótico como el grupo placebo mostraron una disminución significativa en el colesterol total (-36,50 ± 19,27 frente a -25,91 ± 19,25 mg/dl), LDL-C (-31,75 ± 18,11 frente a -31,91 ± 31,00 mg/dl) y TG (-31,83 ± 67,37 frente a -28,25 ± 59,09), respectivamente ($p < 0,05$). El peso corporal, el IMC, el índice de grasa corporal y la circunferencia de la cintura también disminuyeron significativamente después de la intervención dietética en ambos grupos ($p < 0,05$). En general, no se encontraron diferencias significativas ni en las reducciones de colesterol total, LDL-C, concentraciones de TG ni en los índices antropométricos entre los grupos probiótico y placebo ($p > 0,05$).

Conclusiones: los resultados de nuestro estudio demostraron que la administración de suplementos probióticos durante 8 semanas en pacientes obesos con hipercolesterolemia tuvo un efecto favorable en el perfil lipídico, aunque no hubo ninguna diferencia en comparación con el grupo control. Estos resultados indican que los índices antropométricos disminuyeron significativamente en respuesta a la adherencia a la dieta baja en calorías recomendada por los dietistas en ambos grupos. Sin embargo, es necesario realizar más estudios con un tamaño de muestra grande y un tiempo de seguimiento prolongado.

Palabras clave:

Probióticos. Obesidad. Hipercolesterolemia. Lípidos en sangre.

INTRODUCTION

Obesity is a pathological condition characterized by excessive body mass accumulation, particularly in the abdominal region resulting from an imbalance between energy intake and expenditure. Importantly, obesity is a risk factor for many fatal diseases, especially diabetes, cardiovascular diseases, non-alcoholic fatty liver disease, and several cancer types. Obesity is associated with abnormal blood lipid levels (total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG)) which are the major risk factors for cardiovascular diseases (1).

A recent meta-analysis observed a linear association between serum cholesterol levels and cardiovascular disease (CVD) mortality. One of the effective population-based strategies of cardiovascular disease prevention is associated with decreased cholesterol levels by improving the nutritional status of the population (2). Although dietary recommendations and exercise are the primary treatment for hypercholesterolemic patients, these methods can only modestly improve high blood cholesterol levels among patients (3). Owing to the known side effects of statin-like drugs that reduce serum cholesterol levels, there is a growing interest in non-drug therapies to improve the blood cholesterol profile. Probiotics, safe for human consumption and available as functional foods and nutritional supplements, have been shown to reduce serum cholesterol levels, offering a potential non-drug therapy for improving human blood cholesterol levels (4,5).

At present, the most widely accepted scientific definition of probiotic determined by WHO (World Health Organization) and FAO (Food and Agriculture Organization of the United Nations) is "*live microorganisms that support health conditions in the host when given in appropriate amounts*" (6). Several genera are used as probiotics, including *Lactobacillus, Bifidobacterium, Bacillus, Pediococcus*, and several yeasts (7). Probiotics are available in various forms, including food and dietary supplements in capsules, tablets, liquids, and powders. Many probiotic supplements contain 1-10 billion CFU per dose, in addition both specific strains and mixtures of specific strains in effective doses are important to make the connection between clinical benefits. Besides these live, active microorganisms can be found in fermented dairy products such as kefir, yoghurt, and cheese (5).

Different types of probiotics have different functions so that human health benefits have mainly been demonstrated for specific probiotic strains (7,8). The health benefits of fermented functional foods are expressed either directly through the interactions of ingested live microorganisms with the host (probiotic effect) or indirectly by ingesting microbial metabolites synthesized during fermentation (biogenic effect) (9,10). Among them, dairy products (particularly fermented milk and yogurt) are by far the most efficient and widely used (11,12). The content and activity of a bioactive compound in dairy-fermented foodstuffs result from the type of food matrix, the individual bacterial strain properties, the processing conditions, and storage time. In this regard, it should be noted that the high bioactive biosynthetic rates observed in culture media might not always be extrapolated to dairy products. Therefore, factors such as optimal temperature for microbial growth and viability, food composition or bioactive stability, and shelf-life in the final foodstuff are paramount to reaching the final product's maximum concentration and activity of probiotics (9).

Probiotics have been shown to modulate intestinal flora, prevent the colonization of harmful bacteria in the intestine, strengthen the immune system, reduce and prevent symptoms related to diarrhea and constipation, and have beneficial effects on cancer and inflammatory bowel diseases. Thus, consuming probiotics is useful for maintaining health against pathogenic bacteria in the gut microbiota, and maintaining the normal balance of gut microbiota helps to improve digestive health as well as the immune system. Accordingly, the main evidence-based positive effects of probiotics have been shown to include antimicrobial and antimutagenic activities, also anticarcinogenic properties. The advantages of probiotics are associated with the increase

in bioavailability of macro and micronutrients, mitigation of nutritional intolerances, beneficial effects on intestinal diseases and Crohn's disease, alleviation of allergic incidences and decrease of LDL and total cholesterol levels (7,8).

Supplementation with probiotics significantly reduced TC, LDL-C, and TGs and increased HDL-C in hypercholesteremic patients. Also, probiotic supplementation improved the anthropometric measurements (11,13). Meta-analysis of randomized clinical trials revealed that probiotic supplementation could be useful in the primary prevention of hypercholesterolemia and may lead to reductions in risk factors for cardiovascular disease (14,15). Similarly, a systematic review study suggests that probiotic supplementation should be indicated as adjunctive treatment for dyslipidemias (11).

Probiotics have been suggested to lowering plasma cholesterol levels through various mechanisms (5,16). Possible mechanisms than can be attributed to the hypocholesterolemic effect of probiotics *in vitro* and *in vivo* studies include; assimilation of dietary cholesterol into the cell surface, binding of cholesterol to the cellular surface, inhibition of *de-novo* synthesis of cholesterol, disruption of cholesterol micelles, and deconjugation of bile salt and bile salt hydrolase (BSH) activity (17-19).

The genera most often administered to groups treated with probiotics were *Lactobacillus* and *Bifidobacterium*. Less frequently than these other genera used were *Saccharomyces, Streptococcus,* and *Enterococcus* (11). Probiotic strains, particularly *Lactobacillus*, play a significant role in lowering cholesterol levels (4). In a randomized, double-blind placebo-controlled study results showed that both single *(Lactobacillus rhamnosus)* and combined strains *(Lactobacillus acidophilus* and *Bifidobacterium animalis)* of probiotics, which are used regularly for 8 weeks, could be effective in hypercholesterolemic patients to reducing serum lipids (20). No significant differences were observed for any probiotics for serum lipids in a 18-week, randomised, double-blind crossover study with healthy obese adults (21). Available evidence indicates that probiotics supplements can significantly reduce serum TC. Furthermore, higher baseline TC, longer intervention time, and probiotics in capsules form might contribute to a better curative effect. The present study was conducted to evaluate the effects of combined strains probiotic supplementation on weight loss and lipid profiles in obese hypercholesterolemic patients. This randomized, double-blind, placebo-controlled pilot trial were designed to evaluate the effects of probiotics on the lipid profile with *Enterococcus faecium, Lactobacillus plantarum, Streptococcus thermophiles, Bifidobacterium lactis, Lactobacillus acidophilus, Bifidobacterium longum* strains.

MATERIAL AND METHODS

STUDY DESIGN

This 2-arm parallel randomized, double-blind, placebo-controlled trial was conducted in Nutrition and Diet Polyclinic in Özel Konya Hospital lasting 12 weeks, individuals with a total cholesterol level of > 240 mg/dl and a BMI value of 30.0-35.0 kg/m^2 who applied to the diet polyclinic for weight loss were included.

This study protocol was approved by the Ethics Committee of Eastern Mediterranean University (approval date: 21.06.2016, approval no: 2016/28-14). The present study was performed according to the principals of the Declaration of Helsinki. Written consent was obtained from each participant prior to the study. All the patients were considered for possible enrollment into the study, and they were screened by an expert cardiologist for eligibility.

STUDY POPULATION

The inclusion criteria for this study were: a) being hypercholesterolemic obese patient with total cholesterol > 240 mg/dl, and having a body mass index (BMI) 30.0-35.0 kg/m^2; b) men and women aged between 25 and 55 years; c) having no infections and no any other metabolic diseases (diabetes, hypertension, coronary heart disease, renal or liver failure, thyroid disease, severe gastrointestinal disease); d) not using of any regular medications; and e) not using omega-3, antioxidants, multivitamin, or polyphenols supplements for the last 3 months prior to the study. Individuals were excluded if they: a) taking statin-type drugs, bile acid sequestrants, cholesterol absorption inhibitors, or nicotinic acid and drug combination therapy due to hyperlipidemia; b) using alcohol or smoking cigarette; c) taking weight loss drugs or applying recent weight reduction program; and d) being pregnancy, and lactation.

RANDOMIZATION

Each participant was randomly assigned into intervention or placebo group, according to 1:1 equal proportion rule. Randomization assignment was performed using computer-generated random numbers. The randomized allocation sequence, enrolling and allocating participants to interventions were conducted by an independent investigator not involved in the assessment of the participants or in the data collection and analysis. All participants were blinded to treatment allocation (Fig. 1).

DIETARY INTERVENTION

In this randomized, double-blind, placebo-controlled trial, hypercholesterolemic obese patients were randomly divided into 2 groups to receive either probiotic capsules ($n = 13$) or a matching placebo ($n = 15$) groups. The patients in the probiotic group took capsules 2 times a day (morning and evening after meals) (8) that contained *Enterococcus faecium, Lactobacillus plantarum, Streptococcus thermophiles, Bifidobacterium lactis, Lactobacillus acidophilus, Bifidobacterium longum* (1.5×10^9 cfu/g) for 8 weeks. Participants in the placebo group received a capsule that contained starch but no bacteria. The appearance of the placebo was indistinguishable in colour, shape, size and pack-

aging, smell and taste from the probiotic capsule. All capsules were produced by NOBEL Company (Turkey), that was approved by Food and Drug Administration. The products were delivered to the dietitian by the company and were given to individuals by the dietitian according to their 2-week usage amounts.

All patients adhered to a medical nutrition therapy that aimed for a weight loss of 0.5 to 1 kg per week, checked weekly during the visits, by a dietitian. The subjects included in the probiotic and control groups adhered to a medical nutrition therapy (MNT) for 8 weeks. Each individual in the research group consisting of obese individuals was given a low-fat, low-cholesterol weight loss diet by a dietitian from the beginning of the study. All obese individuals continued a MNT including all food groups. Also, weekly 0.5-1 kg body weight loss was targeted in the applied MNT. Accordingly, the energy content of the applied diet was calculated to be 500 kcal/day less than the total energy requirements of the individuals. The content of the diet applied was consist of 50-55 % carbohydrate, 12-15 % protein, and 25-30 % fat. Macronutrients, micronutrients, the fiber content of the diet were calculated to be similar between groups, and also both groups take a low cholesterol diet. They were advised not to modify their physical activity habits.

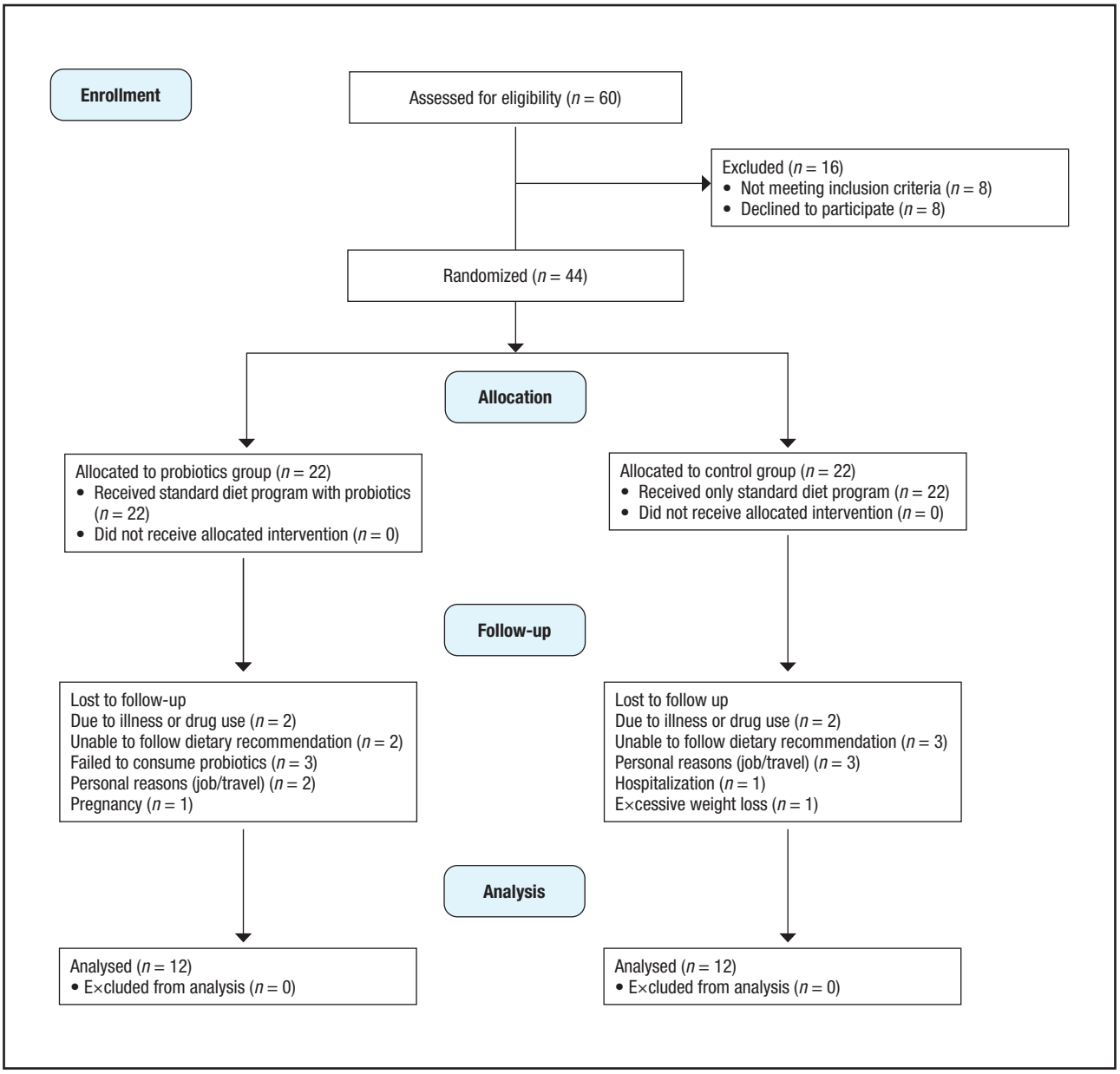

Figure 1.

Flow diagram of the study.

DATA COLLECTION

Dietary intake

At baseline, demographic data and general nutritional habits were obtained with a form. To control the confounding effects of dietary intake, 24-h food consumption records (1 regular day) were collected from all individuals, and data were analyzed by a dietitian to obtained macronutrients and micronutrients intake, with Nutrition Data Base Software (version 7.2, Mavi Elma Group, Turkey).

Anthropometric measurements

Anthropometric measurements of the subjects were obtained at the beginning of the study and were monitored every week throughout the study. Body weight and body composition were measured by standard protocols in a fasting status and, without shoes and heavy clothing to the nearest 0.1 kg by using Tanita BF-350 body composition analyzer. Height measurement was conducted without shoes to the nearest 0.5 cm with a stadiometer (Medicaplus) in the Frankfort plane position. BMI was calculated by dividing the weight in kilograms by the square of the height in meters.

Biochemical analysis

Blood samples (10 ml) were taken in 12-h overnight fasting state at the beginning and after 8 weeks of intervention. After separation of serum, blood parameters were measured. The levels of triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL-C) and high-density lipoprotein (HDL-C) cholesterol were determined using a Dimension Xpand Plus integrated clinical chemistry autoanalyzer (Siemens Healthcare Diagnostics, Deerfield, IL, USA) in Özel Konya Hospital biochemistry laboratory.

STATISTICAL ANALYSIS

Statistical analyses were performed using the software package of SPSS Statistics for Windows (version 20.0, Statistical Package for the Social Sciences). Non-parametric hypothesis tests were used in the study. Quantitative variables were compared between groups at baseline and at the end of the study using a Mann-Whitney U test. Quantitative variables before and after treatment within each group were compared using Wilcoxon test**.** All analyses were performed on participants who completed the study duration (15 in probiotics and 15 in the placebo group). All values are reported based on mean ± SD, p value < 0.05 was considered as the statistical significance level.

RESULTS

Daily dietary intakes of the participants are presented in table I. There were no significant differences in daily total energy and intakes between the probiotics and placebo groups at the beginning of the intervention ($p > 0.05$). There was no difference in the average energy amount recommended from the dietitian between the groups during intervention ($p > 0.05$). Also, comparisons showed no significant differences in age, marital status, physical activity level and education status between the two groups at baseline ($p > 0.05$) (data not shown).

Table I. Age, daily dietary intakes and recommended energy of the participants at the beginning of the intervention

Dietary intakes, mean ± SD	Probiotics (n = 12)	p*	
Women			
Age (year)	43,88 ± 12,75	43,77 ± 9,39	
Energy (kcal)	1906,88 ± 308,10	1982,18 ± 315,07	
Protein (%)	15,49 ± 4,64	15,33 ± 4,74	
Fat (%)	35,50 ± 7,72	37,88 ± 6,67	
Carbohydrate (%)	49,01 ± 7,69	46,79 ± 7,14	
Cholesterol (mg)	246,04 ± 131,09	232,05 ± 144,99	
Fiber (g)	27,80 ± 6,77	28,96 ± 6,29	
RE	1777.77 ± 156.66	1733.33 ± 141.42	< 0.05
Men			
Age (year)	44,66 ± 12,01	44,00 ± 10,60	
Energy (kcal)	2229,70 ± 339,02	2191,33 ± 319,20	
Protein (%)	14,44 ± 6,02	14,96 ± 4,04	
Fat (%)	38,23 ± 8,21	36,75 ± 6,94	
Carbohydrate (%)	47,33 ± 7,21	48,295 ± 2,62	
Cholesterol (mg)	279.23 ± 143.10	262.83 ± 148.06	
Fiber (g)	30.40 ± 7.00	29.20 ± 6.95	
RE	2113.33 ± 135.50	2133.33 ± 157.73	

*Values are expressed as mean ± (SD). *Mann-Whitney test was used to calculate the p value. RE: recommended daily energy intake from dietitian during intervention.*

Table II shows the effect of probiotic supplementation on lipid profiles of the participants after 8 weeks of intervention. There were no significant differences in lipid profiles between the probiotics and placebo groups at the beginning of the intervention ($p > 0.05$). After 8 weeks of probiotics or placebo supplementation, changes in total cholesterol and LDL-C were found to be significant within both groups, notedly in women. No significant change in other parameters (HDL-C, and TG) were observed within groups. Overall, a non-significant decrease in serum TC (-36.50 ± 19.27 vs -25.91 ± 19.25, mg/dl, p = 0.193), LDL-C concentrations (-31.75 ± 18.11 vs -31.91 ± 31.00 mg/dl, p = 0.908), TG (-31.83 ± 67.37 vs -28.25 ± 59.09, p = 0.932) were detected following the supplementation with probiotic, compared to the placebo. Thus, taking probiotics resulted in a non-significant decrease in lipid profiles in comparison with the placebo (Table II).

As shown in table III, BMI, weight, FM, and FM % decreased significantly by the end of study in both probiotics and placebo groups, although no statistically significant difference was observed between the groups at baseline and after intervention ($p > 0.05$). Within-group analyses indicated that anthropometric indices significantly decreased in response to adherence to low-calorie diet recommended by dietitian in both groups.

Table II. Effect of probiotics supplementation on lipid profile of the participants after 8 weeks of intervention

Variable	Probiotic group (*n* = 12)	Placebo group (*n* = 12)	*p* value**
TC (mg/dL)			
Men (n = 3)			
Before	266.33 ± 8.50	276.33 ± 20.79	0.513
After	210.66 ± 13.31	245.66 ± 44.09	0.275
MD, *p* value*	-55.66 ± 7.63, 0.109	-30.66 ± 28.00, 0.109	0.275
Women (n = 9)			
Before	266.22 ± 20.14	271.44 ± 27.12	0.860
After	236.11 ± 30.09	247.11 ± 25.23	0.539
MD, *p* value*	-30.11 ± 17.68, *0.008*	-24.33 ± 17.39, *0.008*	0.691
Total (n = 12)			
Before	266.25 ± 17.55	272.66 ± 24.86	0.665
After	229.75 ± 28.69	246.75 ± 28.58	0.184
MD, *p* value*	-36.50 ± 19.27, *0.002*	-25.91 ± 19.25, *0.002*	0.193
TG (mg/dL)			
Men (n = 3)			
Before	213.66 ± 77.39	269.66 ± 220.61	0.827
After	141.33 ± 15.50	278.00 ± 220.46	0.827
MD, *p* value*	-72.33 ± 64.50, 0.109	-91.66 ± 85.80, 0.109	0.513
Women (n = 9)			
Before	197.88 ± 93.3	165.55 ± 45.40	0.596
After	168.44 ± 61.42	158.44 ± 37.03	0.269
MD, *p* value*	-18.33 ± 66.19, 1.00	-7.11 ± 30.83, 0.779	0.965
Total (n = 12)			
Before	201.83 ± 86.49	216.58 ± 117.09	0.453
After	170.00 ± 56.69	188.33 ± 112.95	0.371
MD, *p* value*	-31.83 ± 67.37, 0.224	-28.25 ± 59.09, 0.130	0.932
LDL (mg/dL)			
Men (n = 3)			
Before	176.00 ± 4.00	174.00 ± 41.94	0.513
After	139.33 ± 8.08	144.66 ± 58.51	0.827
MD, *p* value*	-36.66 ± 10.26, 0.109	-29.33 ± 57.07, 0.593	0.513
Women (n = 9)			
Before	183.88 ± 18.38	190.66 ± 27.36	0.331
After	153.77 ± 21.91	157.88 ± 21.60	0.566
MD, *p* value*	-30.11 ± 20.31, *0.008*	-32.77 ± 22.45, *0.008*	0.791
Total (n = 12)			
Before	181.91 ± 16.17	186.50 ± 30.35	0.272
After	150.16 ± 20.09	154.58 ± 31.58	0.435
MD, *p* value*	-31.75 ± 18.11, *0.002*	-31.91 ± 31.00, *0.008*	0.908

(Continues on next page)

Table II (cont.). Effect of probiotics supplementation on lipid profile of the participants after 8 weeks of intervention

Variable	Probiotic group (*n* = 12)	Placebo group (*n* = 12)	*p* value**
HDL			
Men (n = 3)			
Before	45.00 ± 8.54	38.00 ± 18.68	0.513
After	51.66 ± 4.50	38.66 ± 15.50	0.127
MD, *p* value*	6.66 ± 4.16, 0.109	0.66 ± 9.01, 0.655	0.376
Women (n = 9)			
Before	51.88 ± 17.50	55.44 ± 11.19	0.424
After	49.94 ± 12.00	53.65 ± 14.36	0.965
MD, *p* value*	-1.94 ± 8.33, 0.677	-1.78 ± 9.81, 0.635	0.825
Total (n = 12)			
Before	50.16 ± 15.67	50.15 ± 15.67	0.506
After	50.37 ± 10.44	49.90 ± 15.48	0.686
MD, *p* value*	0.20 ± 8.29, 0.271	-1.17 ± 9.28, 0.689	0.590

*MD: mean difference; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglyceride; TC: total cholesterol. Values are expressed as mean ± (SD). *Wilcoxon test. **Mann-Whitney test.*

Table III. Effect of probiotic supplementation on anthropometric indices after 8 weeks of intervention

Variable	Probiotic group (*n* = 12)	Placebo group (*n* = 12)	*p* value**
BMI (kg/m²)			
Man (n = 3)			
Before	31.33 ± 1.71	30.40 ± 0.36	0.376
After	30.43 ± 1.32	28.83 ± 1.04	0.127
MD, *p* value*	-0.09 ± 0.65, 0.109	-1.56 ± 1.36, 0.180	0.513
Women (n = 9)			
Before	32.70 ± 2.36	32.50 ± 2.97	0.479
After	31.57 ± 3.21	31.32 ± 3.52	0.627
MD, *p* value*	-1.12 ± 1.28, *0.008*	-1.17 ± 1.13, *0.011*	0.625
Total (n = 12)			
Before	32.35 ± 2.16	31.97 ± 2.71	0.347
After	31.29 ± 2.84	30.70 ± 3.23	0.319
MD, *p* value*	-1.06 ± 1.13, *0.002*	-1.27 ± 1.14, *0.004*	0.630
BW (kg)			
Man (n = 3)			
Before	93.43 ± 11.47	95.66 ± 5.25	0.827
After	90.66 ± 11.15	90.20 ± 2.02	0.513
MD, *p* value*	-2.76 ± 2.00, 0.109	-5.46 ± 3.91, 0.109	0.275
Women (n = 9)			
Before	79.16 ± 5.00	86.73 ± 15.08	0.354
After	76.41 ± 7.00	83.06 ± 15.85	0.596
MD, *p* value*	-2.75 ± 2.88, *0.008*	-3.66 ± 2.56, *0.008*	0.340

(Continues on next page)

Table III (cont.). Effect of probiotic supplementation on anthropometric indices after 8 weeks of intervention

Variable	Probiotic group (*n* = 12)	Placebo group (*n* = 12)	*p* value**
BW (kg)			
Total (n = 12)			
Before	82.73 ± 9.15	88.96 ± 13.66	0.242
After	80.05 ± 9.98	84.85 ± 13.92	0.478
MD, *p* value*	-2.75 ± 2.60, *0.002*	-4.11 ± 2.87, *0.002*	0.266
FM (%)			
Man (n = 3)			
Before	31.13 ± 2.83	27.46 ± 0.55	0.052
After	28.56 ± 2.50	26.16 ± 2.15	0.275
MD, *p* value*	-2.56 ± 1.53, 0.109	-1.30 ± 2.17, 0.285	0.513
Women (n = 9)			
Before	40.01 ± 2.65	42.04 ± 5.44	0.331
After	38.22 ± 3.85	40.38 ± 4.75	0.566
MD, *p* value*	-1.78 ± 1.70, *0.008*	-1.65 ± 2.33, 0.068	0.691
Total (n = 12)			
Before	37.79 ± 4.76	38.40 ± 8.06	0.832
After	35.80 ± 5.56	36.83 ± 7.65	0.630
MD, *p* value*	-1.98 ± 1.63, *0.002*	-1.56 ± 2.20, *0.029*	0.443
FM (kg)			
Man (n = 3)			
Before	28.83 ± 1.61	26.20 ± 2.13	0.127
After	25.80 ± 1.65	23.60 ± 2.22	0.127
MD, *p* value*	-3.03 ± 2.30, 0.109	-5.46 ± 3.91, 0.285	0.827
Women (n = 9)			
Before	31.56 ± 3.25	36.91 ± 10.88	0.566
After	29.85 ± 5.21	34.18 ± 10.58	0.691
MD, *p* value*	-1.71 ± 2.32, *0.021*	-3.66 ± 2.56, *0.011*	0.170
Total (n = 12)			
Before	30.88 ± 3.11	34.23 ± 10.51	0.977
After	28.84 ± 4.85	31.54 ± 10.26	1.000
MD, *p* value*	-2.04 ± 2.29, *0.006*	-2.69 ± 2.34, *0.005*	0.347
FFM (kg)			
Man (n = 3)			
Before	65.50 ± 11.59	69.13 ± 3.69	0.827
After	65.10 ± 10.07	66.80 ± 1.85	0.513
MD, *p* value*	-0.40 ± 2.35, 1.00	-2.33 ± 2.01, 0.109	0.275
Women (n = 9)			
Before	47.41 ± 3.10	49.48 ± 4.88	0.200
After	46.97 ± 3.35	48.87 ± 5.50	0.965
MD, *p* value*	-0.43 ± 1.93, 0.407	-0.61 ± 2.70, 0.110	0.566
Total (n = 12)			
Before	51.93 ± 9.91	54.40 ± 9.94	0.378
After	51.50 ± 9.68	53.35 ± 9.40	0.954
MD, *p* value*	-0.42 ± 1.93, 0.455	-1.04 ± 2.58, *0.034*	0.266

*MD: mean difference; BMI: body mass index; BW: boyd weight; FM: fat-mass; FFM: fat-free mass. Values are expressed as mean ± (SD). *Wilcoxon test. **Mann-Whitney test.*

DISCUSSION

In the present study receiving 1.5×10^9 CFU/g combined strains probiotic capsules for 8 weeks along with individualized dietary intervention in hypercholesterolemic obese patients showed significant decreased in total cholesterol, LDL-C and TG concentrations. However, no intergroup statistical differences were determined in the reductions of total cholesterol, LDL-C, TG concentrations between the probiotic and placebo groups.

Daily dietary intakes of the participants are presented in table I. There were no significant differences in daily total energy and intakes between the probiotics and placebo groups at the beginning of the intervention ($p > 0.05$). There was no difference in the average energy amount recommended from the dietitian between the groups during intervention ($p > 0.05$). In this study, when the anthropometric values of male individuals in the probiotics and control groups were examined before and after the study, no significant statistical difference was found between the values at the beginning and end of the study within the groups ($p < 0.05$). However, when the pre and post-study values of the female participants in this study were examined, the values were found to be 79.16 ± 5.00 kg and 76.41 ± 7.00 kg, respectively, in the group receiving probiotics 86.73 ± 15.08 kg and 83.06 ± 15.85 kg, respectively, in the group receiving placebo. In addition, a significant decrease was observed between the pre and post-study values within the groups in some of the anthropometric measurements ($p < 0.05$) (Table III). This was attributed to the fact that there was no significant difference because the number of male individuals was lower than the number of female individuals, while the significant decrease in body weight in women revealed the effectiveness of the low-fat, low-cholesterol weight loss diet given by the dietitian. Regularly monitoring the groups depending on the nutritional treatment by the dietitian led to weight loss in both the probiotics and control groups. The most crucial step in the treatment of obesity is medical nutrition therapy, and the treatment aims to reduce obesity, and all kinds of complications related to obesity (22). Meckling et al. examined 31 overweight and obese individuals to evaluate the effectiveness of a low-fat diet; the mean weight loss at the end of 10 weeks was 6.8 kg, and the mean decrease in BMI was 2.2 kg/m^2 (23). Hu et al. examined the effect of two different diet programs containing low carbohydrate (< 40 g/day) and low fat (< 30 % kcal/day and 7 % saturated fat) for 12 months. The mean weight loss in the low-carbohydrate diet group was 5.3 kg, whereas it was 1.5 kg in the low-fat diet group (24). In this study, weight loss in both the study and control groups due to the nutritional treatment created by the dietitian led to improved lipid levels. One of the reasons there was no significant difference in lipid levels between the group receiving probiotics and the group receiving placebo in both men and women was attributed to the improvement in lipid levels caused by the weight loss in the placebo group due to the diet recommended by the dietitian.

In this study, the mean weight loss in male participants was 2.46 kg in the probiotics group and 5.46 kg in the control group. The mean decrease in BMI was 0.90 kg/m^2 in the probiotics group and 1.56 kg/m^2 in the control group. Statistically, there was no significant difference between this weight loss and the decrease in BMI values ($p > 0.05$). Similarly, the mean weight loss in female participants was 2.75 kg in the probiotics group and 3.66 kg in the control group. The mean decrease in BMI was 1.12 kg/m^2 in the probiotics group and 1.17 kg/m^2 in the control group. Statistically, there was no significant difference between this weight loss and the decrease in BMI values ($p > 0.05$) (Table III). No statistically significant group differences were found in the anthropometric measurements taken at the beginning and end of the study, which was attributed to factors such as the fact that the study was conducted on obese individuals, the study period was limited (8 weeks), and the small sample size.

One meta-analysis has highlighted the effects of consuming fermented foods and positive impacts on weight maintenance, while separate studies have demonstrated that consumption of fermented yogurts and dairy foods can attenuate the likelihood of developing CVD and type 2 diabetes *mellitus* (26). Milk hydrolysis generates peptides with satiety or anti-obesity effects. Consumption of fermented milk enriched with probiotics positively affects body weight reduction and serum lipids. In a study of 14 healthy individuals, it was observed that consumption of probiotic yoghurt (*Lactobacillus acidophilus* and *Bifidobacterium lacti*) caused a significant decrease in serum total cholesterol levels compared with normal yoghurt ($p < 0.05$) (12). In a study conducted by Larsen et al., 70 obese participants (20 men and 50 women) aged between 18 and 55 years were randomly assigned to five groups over an 8-week period. One group consumed the experimental yoghurt Gaio®, while the second and third groups were given two newly developed yoghurts fermented with different bacterial cultures. The yoghurt provided to one of these groups was fermented with two strains of *S. thermophilus* and two strains of *L. acidophilus*, while the yoghurt given to the other group was fermented with two strains of *S. thermophilus* and one strain of *L. rhamnosus*. The fourth group received a placebo yoghurt, and the final group was given two daily placebo tablets. When all five treatment groups were compared after adjusting for small changes in body weight, a significant reduction in LDL cholesterol levels (8.4 %, $p < 0.05$) was observed after 8 weeks in the group consuming only Gaio® product (27). However, in fermented milk or yogurt consumption, it is more difficult to achieve standardization due to factors such as optimum temperature for microbial growth and viability, food composition, or bioactive stability (9). In this trial, we considered these standardization difficulties as a limitation and preferred to use probiotic strains. Standardization of used products affects quality in research. However, it is thought that planning and conducting this study with a fermented milk product may support similar positive results in obese individuals. We also preferred to use supplement forms to highlight the effects of probiotics on blood lipids in obese individuals. In addition to this, dietary supplements can differ in quality, purity, and consistency, leading to inconsistencies in dosing. To avoid this, all products are supplied from the same company in this research.

In this study, when the pre- and post-study values of male and female individuals in the probiotics group were compared, it was observed that total cholesterol and LDL cholesterol levels decreased significantly at the end of the study ($p < 0.05$) (Table II). In addition to this, when HDL levels and triglyceride levels of male and female individuals in the probiotics and control groups were compared before and after the study, no significant statistical difference was found ($p > 0.05$) (Table II). While no significant change was observed in HDL levels in 9 of the 11 meta-analyzed studies ($p = 0.59$), no significant change was observed in triglyceride levels in 8 ($p = 0.89$) (15). In the study conducted by Fuentes et al., no statistically significant differences were found in total cholesterol, triglycerides, LDL, and HDL cholesterol levels between individuals with cholesterol levels > 250 mg/dL who received either a placebo or *L. plantarum* at baseline and after 6 weeks. However, a significant decrease in LDL cholesterol and total cholesterol levels was observed after 12 weeks (4). In a meta-analysis of 11 randomized clinical trials that conducted to evaluate the effects of probiotics on blood lipids, a significant decrease in total cholesterol and LDL values was found ($p = 0.001$) (14). One of the reasons for these inconsistent results was that the study period was limited to 8 weeks, and another reason was that there was an insufficient number of people during randomization. Again, the same meta-analyse study demonstrated the duration of probiotic supplementation was positively associated with the LDL-C lowering effects of probiotics, also high-dose probiotics more effectively reduced LDL-C levels than low-dose probiotics (14). Based on these studies, it was thought that a significant decrease in blood lipid levels could be seen when the study period was increased above 8 weeks. Also, the effectiveness of each probiotic strain depended on the dosage.

In this study a non-significant decrease in serum TC, TG, and LDL-C concentrations were detected following the supplementation with probiotic, compared to the placebo. Thus, taking probiotics resulted in a non-significant decrease in lipid profiles in comparison with the placebo (Table II). If we discuss this information by emphasizing important studies in the literature; in a study conducted by Jones et al. on hypercholesterolemic adults by giving yoghurt containing BSH-active *Lactobacillus reuteri* NCIMB 30242, no statistically significant difference was observed when total cholesterol, LDL, HDL and triglyceride levels were compared between the two groups receiving placebo yoghurt and yoghurt containing *L. reuteri* after 3 weeks ($p > 0.05$). When the differences of the same values were compared after 6 weeks, significant decreases were observed in total cholesterol ($p = 0.031$) and LDL cholesterol ($p = 0.016$) levels, whereas no statistically significant difference was observed in HDL ($p = 0.808$) and triglyceride ($p = 0.230$) levels (28). In another study conducted by Jones et al. using a capsule containing *Lactobacillus reuteri* NCIMB 30242, when total cholesterol, LDL, HDL and triglyceride levels were compared after 9 weeks, significant decreases were observed in total cholesterol and LDL cholesterol levels ($p < 0.001$), while no statistically significant difference was observed in HDL and triglyceride levels (29). While several clinical trials have shown that probiotics have cholesterol-lowering activity (27,30), some studies have shown the opposite result (31). These negative results may be related to poor bacterial strain selection, the study method or the clinical design of the trial, and these studies did not specify BSH activity as a characteristic of the strain administered. In contrast, a BSH-active strain (*L. plantarum* and *L. reuteri)* has been shown to significantly reduce total cholesterol and LDL cholesterol when administered as a synbiotic in humans (32). Probiotics with BSH activity have often been found to have cholesterol-lowering effects *in vivo* studies (33,34). In a meta-analysis, it was determined that when yoghurt containing two strains of *S. thermophilus* and *E. faecium* was given, these strains showed a cholesterol-lowering effect (35). These results suggest that the use of probiotics may improve lipid metabolism by decreasing total and LDL cholesterol concentrations. However, both the efficacy of probiotics for cholesterol lowering and safety should be investigated further in well-designed clinical trials. The findings of recent meta-analysis suggest that probiotics can enhance SCFA content in the body, improve oxidative stress and inflammation, and effectively alleviate hyperlipidemia. The primary lipid-lowering mechanisms of probiotics encompass: a) the production of BSH, which enhances cholesterol excretion; b) the promotion of cholesterol catabolism and the inhibition of cholesterol synthesis in the body via key intestinal metabolites, specifically SCFAs; and c) the modulation of immune regulation and the intestinal barrier through signaling molecules (36). In a recent study results demonstrated that regular and strain-specific use of probiotics (probiotics containing *Lactobacillus* or *Bifidobacterium*) could be effective to reducing plasma lipid level in hypercholesterolemic patients (20). In this study, a probiotic product supplement containing 1.5×10^9 CFU active probiotic microorganisms (*Lactobacillus acidophilus, Enterococcus faecium, Lactobacillus plantarum, Streptococcus thermophillus, Bifidohacterium lactis, Bifidobacteriurn longum*) was used. Also the other reason for inconsistent results may attributed to the different type of strains that have been used (11). Finally, the confusing and interconnected reasons for this study's results between groups may be attributed to the different types of probiotic strains used, doses of probiotics, delivery matrix, study duration, and study population. However, not all probiotic interventions are effective against dyslipidemia. The results are controversial and depend on several factors such as probiotic strain, dose, duration of the treatment, lifestyle changes, etc. Additional studies are highly recommended on the cholesterol-lowering property of probiotics, which could help to reduce the risk of CVD and other dyslipidemia-associated health issues.

CONCLUSION

In this randomized controlled clinical trial, dietary supplementation of probiotics for 8 weeks had no prominent favorable effect on serum total cholesterol, LDL-C, TG levels, and body weight loss in obese subjects with hyperlipidemia. However, further well-designed large sample size randomized controlled trials, with longer supplementation durations are needed for a stronger

assessment of the lipid-modulating properties of probiotics on obese subjects. Thus, more specific data regarding the duration and dosage of probiotic use in obese individuals may reveal significant beneficial effects on health.

LIMITATIONS

Some limitations might explain the contradictory findings of the present trial. Firstly, the reduced number of patients is one of the major limitations of this study, this is probably the reason why there are no differences in most of the parameters evaluated. Secondly, the short follow-up time is another limitation of the study. Moreover, doses of probiotics and type of strains that have been used may attributed to the inadequate results. Additionally, it was emphasized that the efficacy of probiotics would be strengthened by increasing the treatment period to ≥ 8 weeks. Also, during the regulation of nutritional intake, the individual declaration is taken into consideration so that, unbalanced and higher consumption amounts may also affect the results.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Desnutrición hospitalaria en Argentina: prevalencia y predicción de riesgo nutricional en adultos hospitalizados según seis herramientas de tamizaje nutricional (Estudio AANEP-2)

Hospital malnutrition in Argentina: prevalence and nutritional risk prediction in hospitalized adults according to six nutritional screening tools (AANEP-2 Study)

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Resumen

Introducción: el tamizaje nutricional (TN) es crucial para detectar desnutrición (DN) y predecir "riesgo nutricional".

Objetivos: establecer prevalencia de DN hospitalaria por Evaluación Global Subjetiva (EGS) y evaluar la concordancia de herramientas de TN y su capacidad predictiva de mortalidad (M), complicaciones infecciosas (CI) y no infecciosas y estancia prolongada (> 11 días).

Métodos: estudio multicéntrico, prospectivo, observacional. El estado nutricional se determinó con EGS y, se midieron herramientas de TN como: *Malnutrition Screening Tool* (MST), *Short Nutritional Assessment Questionnaire* (SNAQ), *Malnutrition Universal Screening Tool* (MUST), *Nutrition Risk Screening* (NRS-2002) y *Mini Nutritional Assessment Short Form* (MNA-SF). Estas herramientas se clasificaron en tres categorías para equivalencia con EGS. Se utilizó *kappa* para la concordancia y regresión logística, sensibilidad, especificidad y área bajo la curva ROC para la capacidad predictiva.

Resultados: se incluyeron 1546 pacientes de 64 hospitales de Argentina, 52,6 % varones, edad mediana 58 años. La prevalencia de DN hospitalaria según EGS fue 48,06 % (IC95 % 45,57; 50,55) con 37 % moderadamente desnutrido (B) y 11 % severamente desnutrido (C). La mejor concordancia con EGS la mostró MST (*k* 0,41) y, entre métodos, MST con SNAQ (*k* 0.52). Los eventos de mala evolución se asociaron a DN por cualquiera de los métodos. EGS, MNA-SF y NRS-2002 mostraron mejor capacidad predictiva (área ROC 0,74-0,72 para M). Las CI fueron las más difíciles de predecir (máxima área ROC 0,62). Las sensibilidades oscilaron entre 60 y 96 %, y las especificidades para DN por EGS fueron superiores al 90 %.

Conclusiones: las variaciones de capacidad predictiva entre métodos de TN no afectan su aplicabilidad clínica.

Palabras clave:

Desnutrición hospitalaria. Tamizaje nutricional. Riesgo nutricional. Evaluación Global Subjetiva.

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Conflicto de intereses: los autores declaran no tener conflicto de interés.

Inteligencia artificial: los autores declaran no haber usado inteligencia artificial (IA) ni ninguna herramienta que use IA para la redacción del artículo.

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Abstract

Introduction: nutritional screening (NS) is crucial for early detection of malnutrition (MN) and prediction of "nutritional risk".

Objectives: to establish the prevalence of hospital malnutrition by Subjective Global Assessment (SGA) and evaluate the agreement of NS tools and their ability to predict mortality (M), infectious (IC) and non-infectious complications, and prolonged stay (> 11 days).

Methods: a multicenter, prospective, observational study was conducted. Nutritional status was assessed with SGA and simultaneously measured with Malnutrition Screening Tool (MST), Short Nutritional Assessment Questionnaire (SNAQ), Malnutrition Universal Screening Tool (MUST), Nutrition Risk Screening (NRS-2002), and Mini Nutritional Assessment Short Form (MNA-SF). All methods were classified into three categories for equivalence with SGA. Kappa was used to assess agreement and logistic regression, sensitivity, specificity, and area under the ROC curve for predictive ability.

Results: a total of 1546 patients from 64 hospitals in Argentina were included, 52.6 % male, median age 58 years. According to SGA, hospital malnutrition prevalence was 48.06 % (95 % CI 45.57; 50.55), with 37 % moderately malnourished (B) and 11 % severely malnourished (C). MST showed the best agreement with SGA (k 0.41), and among methods, MST with SNAQ (k 0.52). Adverse outcomes were associated with MN by any method. SGA, MNA-SF, and NRS-2002 had the best predictive ability (ROC area 0.74 to 0.72 for M). IC were the hardest to predict (maximum ROC area 0.62). Sensitivities ranged from 60 to 96 %, and specificities were above 90 % for MN by SGA.

Conclusions: variations in predictive ability among NS methods do not affect their clinical applicability.

Keywords:

Hospital malnutrition. Nutritional screening. Nutritional risk. Subjective Global Assessment.

INTRODUCCIÓN

El tamizaje nutricional (TN) para identificar individuos desnutridos o en riesgo de desnutrición al ingreso hospitalario ha sido recomendado por organizaciones científicas y exigido por agencias de acreditación de calidad de atención médica en diversos países (1-4). El TN identifica a quienes requieren una evaluación completa del estado nutricional y/o un abordaje nutricional precoz para mejorar la evolución y el pronóstico de la hospitalización. Varios estudios han reportado la capacidad de distintas herramientas de TN para predecir el *riesgo nutricional*, es decir la asociación entre algún grado de alteración del estado nutricional y una peor evolución y pronóstico durante la hospitalización: mayor mortalidad, incidencia de complicaciones y tiempo de estancia hospitalaria (5-7).

Existen métodos de TN "exhaustivos/largos" o "sencillos/cortos", pero no existe pleno consenso respecto a cuál es la herramienta más eficiente para responder distintas preguntas en pacientes hospitalizados a ser realizadas por diferentes profesionales de la salud (8-17). Se ha publicado la validez y confiabilidad de varios métodos de TN (9-29) con resultados algo variables, probablemente debido a diferencias en la metodología, en las poblaciones y en el método de referencia o "gold standard" utilizado.

El método de Evaluación Global Subjetiva (EGS) (30,31) del estado nutricional es ampliamente aceptado para el diagnóstico y el tamizaje nutricional y ha sido utilizado como método patrón para validar algunas herramientas de TN (9,15-20,22,26,32).

El estudio AANEP´99 (realizado por la Asociación Argentina de Nutrición Enteral y Parenteral – AANEP) mostró que la desnutrición hospitalaria en Argentina, categorizada por el método EGS, no solo fue prevalente, sino que tuvo asociación con el aumento de la mortalidad, la incidencia de complicaciones infecciosas y no infecciosas y con el tiempo de estancia hospitalaria, incluso luego de ajustar por varios factores y comorbilidades (33,34). El presente estudio fue implementado por AANEP para actualizar la prevalencia de desnutrición hospitalaria con el riesgo nutricional asociado a la misma y para evaluar la concordancia, al compararlos con la EGS como método patrón, de algunos métodos validados de TN: MST (9); SNAQ (10); MUST (11); NRS-2002 (12) y MNA-SF (13).

Los objetivos del estudio fueron: establecer la prevalencia de desnutrición en hospitales generales de Argentina utilizando EGS y varios métodos de TN y, evaluar la concordancia y capacidad de estas herramientas para predecir la evolución clínica de los pacientes hospitalizados, incluyendo mortalidad, complicaciones infecciosas, complicaciones no infecciosas, y estancia prolongada (> 11 días).

MATERIALES Y MÉTODOS

Estudio multicéntrico, observacional, de cohorte prospectiva con seguimiento desde la evaluación nutricional hasta el alta hospitalaria en 64 instituciones generales de agudos, públicas y privadas, localizadas en 42 ciudades de 14 provincias de la República Argentina que aceptaron la invitación de AANEP para participar. Se tomó una muestra aleatoria de las camas informadas por los evaluadores de cada institución. La selección aleatoria se realizó en forma centralizada y computarizada en forma estratificada por centro y proporcional a la población de camas disponibles. Los pacientes que se encontraban en la cama seleccionada eran potencialmente elegibles para ingresar al estudio. Se informó al paciente y/o su familia las características del estudio y se les solicitó la firma de un consentimiento informado (CI). El protocolo y el CI fueron aprobados por el comité de ética de AANEP (Acta AANEP 253/2012) y las autoridades pertinentes de las instituciones participantes.

Se incluyeron pacientes mayores de 18 años, de ambos sexos, hospitalizados por patologías médicas o quirúrgicas (electivas o de urgencia), en sala, terapias intermedias y terapias intensivas, durante el año 2014. Se excluyeron mujeres embarazadas o puérperas de hasta 72 horas; pacientes de cirugías o procedimientos invasivos ambulatorios; enfermos en coma o alteraciones del estado de conciencia o con enfermedades psiquiátricas en quienes no se pudiera completar la evaluación prevista e individuos en aislamiento por cualquier causa.

EVALUACIÓN/TAMIZAJE NUTRICIONAL

Todos los pacientes fueron clasificados acorde a las categorías de la EGS (30) en A (bien nutrido), B (desnutrición leve/moderada

o en riesgo de desnutrición) y C (desnutrición severa). Para los métodos de TN, se utilizaron los puntajes propuestos por los autores y alguna adaptación para expresarlos en tres categorías a los fines de comparación con la EGS.

El MST considera el puntaje 0-1 como "sin riesgo" y el ≥ 2 indica "riesgo nutricional". Para este estudio se consideró un puntaje de 2 como equivalente a la categoría "B" de la EGS y el puntaje ≥ 3 como categoría "C". En el SNAQ se consideró 0-1 como "sin riesgo", 2 como equivalente a categoría B y el puntaje ≥ 3 como equivalente a categoría "C". Para el MUST se consideró 0 como bien nutrido, 1 como equivalente a en riesgo de desnutrición y el puntaje ≥ 2 como equivalente a la categoría "C". Con el método NRS-2002 se consideró bien nutrido al puntaje "0", "al 1-2" como en riesgo de desnutrición y un puntaje ≥ 3 como desnutrido equivalente a la categoría "C". El MNA-SF se clasificó como bien nutrido a puntajes entre 12 a 14, "en riesgo" a puntajes de 8 a 11 y desnutrición severa a puntajes de 0 a 7 puntos. Los equivalentes a las categorías "B" y "C" pueden asumir en adelante las distintas denominaciones planteadas y se resumen con los números 2 y 3 en tablas de resultados V y VI.

RECOLECCIÓN DE LOS DATOS

Inicialmente se registraron, además de la evaluación nutricional, datos de las patologías de ingreso y de comorbilidades para calcular la puntuación de Charlson (35). Los datos de evolución de los pacientes hasta el alta hospitalaria incluyeron eventos y tratamientos durante la hospitalización. Al momento del egreso hospitalario, se registró condición de vivo o muerto, diagnósticos de egreso, tiempo de internación, complicaciones infecciosas y no infecciosas ocurridas en la hospitalización.

La EGS, los métodos de TN y el registro de los eventos de la hospitalización fueron realizados por profesionales médicos y/o licenciados en nutrición pertenecientes a cada institución, acorde a instructivos estandarizados de cada herramienta (9-14).

ASPECTOS ESTADÍSTICOS

Se calculó que se requerían 1062 pacientes para una prevalencia de desnutrición hospitalaria según EGS de 47,3 % (estudio AANEP99: 33-34), para un nivel de confianza del 95 % y semiamplitud del intervalo de 2,49 %. Para la selección aleatoria de camas, al número calculado se le agregó un 30 % por posibilidad de cama vacía o de tener criterios de exclusión y un 20 % por posibles pérdidas de seguimiento. Por lo tanto, se seleccionaron aleatoriamente 1592 camas.

Los resultados se presentan como medianas y rango intercuartílico (RIQ) para variables numéricas y porcentajes para las categóricas. Se calcularon intervalos de confianza (IC) para el 95 %. Para comparar variables numéricas con distribuciones no normales en tres o más grupos se utilizó test de Kruskal Wallis y para las proporciones, la prueba de chi cuadrado (Chi^2). La concordancia entre las distintas herramientas se calculó con el índice *kappa (κ),* considerando una concordancia $\kappa < 0,4$ como mala, 0,4 a 0,6 regular, > 0,6-0,8 buena y > 0,8 óptima.

Para evaluar la capacidad predictiva de las distintas herramientas de TN se calcularon los "odds ratios" (OR) crudos y ajustados, mediante regresión logística múltiple, por edad (< 60; 60-79 y ≥ 80 años), infecciones, cáncer, cirugía, índice de masa corporal (IMC) y score de comorbilidades de Charlson. Las variables dependientes fueron: mortalidad global, complicaciones infecciosas, complicaciones no infecciosas y estancia hospitalaria prolongada definida como mayor a 11 días (mediana de la muestra). En todos los casos se testeó a dos colas con $\alpha = 0,05$.

También se evaluó la capacidad predictiva de cada método clasificatorio para los eventos de riesgo (muerte, complicaciones y estadía prolongada) mediante sensibilidad (S), e*specificidad (E),* áreas bajo la curva ROC y las razones de verosimilitud positivas (LR+) y negativas (LR-) de cada uno de los métodos, tanto en las categorías B y C y sus equivalentes, como en ambas colapsadas, lo cual se denominó "algún grado de deterioro nutricional" (B + C). Se consideró un valor de área bajo la curva ROC < 0,6 como malo, 0,6 a 0,7 aceptable, > 0,7 a 0,8 bueno y > 0,8 muy bueno.

RESULTADOS

Se analizaron los datos de 1546 individuos hospitalizados en 64 instituciones generales de agudos, públicas y privadas, de 42 ciudades de 14 provincias de la República Argentina, en quienes se realizó la EGS, 52,6 % hombres y 47,4 % mujeres, con rango de edad entre 18 y 99 años. El 52,85 % se encontró por debajo de los 60 años y el 13,97 % por encima de los 80 años. Acorde al motivo de ingreso los pacientes fueron catalogados como quirúrgicos electivos (26,5 %) o de urgencia (10,8 %) y con patologías médicas (62,7 %). Según el diagnóstico de ingreso las patologías estuvieron relacionadas con el aparato digestivo (24,4 %), aparato respiratorio (15,1 %), causas ortopédicas y traumatológicas (12,2 %), enfermedades del corazón (10,6 %), sistema nefrourológico (9,3 %), sistema nervioso central (8,4 %) y patologías varias (20,0 %).

La mediana de días en los cuales se realizaron las evaluaciones nutricionales fue de 4 días del ingreso (Pc 25-75: 2-9 días). El 38,49 % del total de pacientes fueron valorados dentro de los dos primeros días de internación y, quienes no fueron evaluados tempranamente (61,51 %), mostraron una amplia dispersión de tiempos. La prevalencia de desnutrición hospitalaria, que incluye a todos los pacientes con algún grado de deterioro nutricional (categorías B + C) fue de 48,06 % (IC95 % 45,57-50,55) el cual no mostró diferencia con el 47,3 % hallado en el estudio AANEP99 (33) (*p: 0,76; test Z proporciones).*

De acuerdo a la EGS, el 51,94 % del total de pacientes fueron clasificados como bien nutridos (A), el 36,87 % como moderadamente desnutridos o en riesgo de desnutrición (B) y el 11,19 % como severamente desnutridos (C). En la tabla I se describe la muestra y se comparan grupos según EGS. La prevalencia de desnutrición fue superior en los pacientes mayores de 80 años (62,5 %) e inferior entre los menores de 60 años (43,21 %) *(Chi^2 p < 0,001).*

Tabla I. Descripción de la muestra y comparación de grupos según EGS

Características	Total	EGS A	EGS B	EGS C	Valor de *p*
	(*n* = 1546)	(*n* = 804)	(*n* = 569)	(*n* = 173)	
Edad en años	58	56	60	63	< 0,0001
Mediana (RIQ)	(41-71)	(38-67)	(44-74)	(51-74)	
Sexo masculino n (%)	813 (52,59)	420 (52,30)	294 (51,58)	99 (57,23)	0,417
Índice de masa corporal	25,25	27,13	24,07 (24,50-28,00)	19,92	< 0,0001
Mediana (RIQ)	(22,25-29,30)	(24,09-30,44)		(17,52-22,80)	
Motivo de ingreso, n (%)					
Patologías médicas	969 (62,68)	459 (47,37)	369 (38,08)	141 (14,55)	< 0,0001
Patologías quirúrgicas	577 (37,32)	345 (59,79)	200 (34,66)	32 (5,55)	< 0,0001

No se encontraron diferencias significativas en la incidencia de desnutrición moderada o severa de acuerdo al sexo. En el grupo total de pacientes, la mediana del IMC fue 25,3 y estas fueron significativamente inferiores en las categorías con deterioro nutricional.

De los 1546 individuos con datos de EGS completos, el 96 % pudieron ser categorizados con las otras cinco herramientas de TN. En la tabla II se observan los porcentajes de pacientes en cada categoría nutricional junto con la puntuación utilizada para las equivalencias en cada método. Los porcentajes de desnutridos severos clasificados por todos los métodos de TN superaron ampliamente los referidos por el gold standard considerado en el estudio. MST y MNA-SF duplicaron la prevalencia de la referencia mientras que SNAQ, MUST y NRS-2002 llegaron a triplicarlos. La prevalencia de desnutrición hospitalaria (equivalentes B+C) fue muy superior cuando se utilizó el NRS-2002 y MNA-SF.

En la tabla III se presenta la concordancia entre los diferentes métodos de TN. La mejor concordancia entre métodos de TN fue entre MST y SNAQ, con un *k* regular (0,52) y la peor entre NRS-2002 y el standard EGS (*k* 0,28). MST fue el más concordante al *standard*.

En el total de la muestra, la mortalidad fue del 7,05 % (RIQ 5,77-8,32), el 19,60 % (RIQ 17,62-21,57) presentó complicaciones infecciosas y el 17,40 % (RIQ 15,51-19,28) complicaciones no infecciosas. Las CI más frecuentes fueron: neumonías 10,54 %, sepsis sistémica 5,82 %, infección urinaria 6,27 % e infecciones de herida quirúrgica 2,3 %. Las no infecciosas más prevalentes fueron: escaras 7 %, fístulas 3,17 %, hemorragia digestiva 3,10 %, dehiscencia de sutura 3,04 %, tromboflebitis 2,85 %, atelectasia 2,72. La mediana del tiempo de estancia hospitalaria fue 11 (RIQ 6-22) días. La tabla IV resume los porcentajes de mortalidad, de complicaciones, de internación prolongada y de los días de estancia hospitalaria en cada una de las categorías equivalentes de los métodos de TN.

Todos los eventos de peor evolución incrementaron su incidencia de modo progresivo y significativo desde los estados de normalidad hacia los grados crecientes de deterioro nutricional por todos los métodos de TN, siendo más notable el impacto de la desnutrición severa en la mortalidad principalmente y luego en las complicaciones infecciosas. MNA-SF fue el método con mayor riesgo asociado a la categoría desnutridos severos entre todos los métodos de TN, y el único que se acercó al *gold standard* EGS en su incidencia de complicaciones de cualquier tipo y estancia prolongada.

La desnutrición en grados crecientes se asoció también con un aumento estadísticamente significativo de días de internación con prolongación de 2 a 6 días en las medianas entre los clasificados como desnutridos moderados y los severos. Los valores fueron muy similares entre categorías equivalentes independientemente del método de TN (Tabla IV).

En la tabla V se presentan los OR correspondientes a las categorías equivalentes B (2) y C (3) de todos los métodos de TN como medidas de asociación a los eventos de peor evolución/pronóstico ajustadas por edad, infecciones, cáncer, cirugía, IMC y puntaje de comorbilidades de Charlson.

Los OR ajustados mostraron diferente y significativa fuerza de asociación con mortalidad. El único OR ajustado no significativo para predecir mortalidad fue el correspondiente a pacientes en riesgo de desnutrición del MUST. Los mayores valores de OR fueron para MNA-SF, y NRS-2002; los OR de menor valor y sobre todo menos diferenciados entre las 2 categorías fueron los de MST.

Los pacientes clasificados como *desnutridos severos* predijeron de modo independiente el riesgo de estancia prolongada, complicaciones infecciosas y no infecciosas cualquiera sea el método de TN utilizado. En cambio, los pacientes en *riesgo de desnutrición*, no siempre lograron hacerlo.

Los factores que además de justar la relación, se comportaron como predictores estadísticamente significativos de alguno/s de los eventos de riesgo fueron: la edad > 80 años (rango OR 1,60-2,95) predictor de todos los eventos menos estancia hospitalaria; el score de Charlson (rango OR 1,01-1,04) predictor de todos los eventos menos complicaciones infecciosas; infecciones predictor de complicaciones infecciosas (rango OR 2,22-2,4) y mortalidad (rango OR 1,86-1,96); cáncer (rango OR 1,81-2,03) solamente predictor de mortalidad y cirugía que fue predictor de

estancia prolongada (rango OR 1,40-1,60) y de complicaciones no infecciosas (rango OR 1,42-1,47) pero solo cuando los individuos se valoraron por EGS, MNA-SF y SNAQ.

En la tabla VI se presentan los datos de validez predictiva de los diferentes métodos.

Los mejores valores de área ROC se obtuvieron en los modelos de predicción de mortalidad y con las herramientas MNA-SF y NRS-2002. Luego, los valores de área ROC fueron aceptables al predecir complicaciones no infecciosas y estancia prolongada, y se redujeron al pronosticar las complicaciones infecciosas. La sensibilidad de los dos métodos destacados fue muy buena tanto discriminando en equivalentes 2 y 3 como colapsando las dos categorías de deterioro nutricional, que es cuando alcanzó la más alta tasa de verdaderos positivos para mortalidad y también para los otros eventos de riesgo, aunque en valores porcentuales sensiblemente menores. SNAQ alcanzó una sensibilidad cercana a los anteriores cuando predijo la mortalidad con sus 2 categorías colapsadas.

Tabla II. Porcentaje de pacientes en cada categoría de la EGS (bien nutridos, desnutrición moderada/riesgo de desnutrición y desnutrición severa) y de las equivalencias asumidas en cada uno de los diferentes métodos de TN

Diagnóstico nutricional	EGS (*n* = 1546)*	MST (*n* = 1529)*	SNAQ (*n* = 1488)*	MUST (*n* = 1505)*	NRS-2002 (*n* = 1458)*	MNA-SF (*n* = 1492)*
Bien nutrido	51,94 % Categoría "A"	52,58 % (0-1 puntos)**	44,83 % (0-1 puntos)**	52,76 % (0 punto)**	28,67 % (0 punto)**	35,39% (12 a 14 puntos)**
Riesgo de desnutrición /desnutrición moderada	36,87 % Categoría "B"	19,42 % (2 puntos)**	21,77 % (2 puntos)**	10,30 % (1 punto)**	34,22 % (1-2 puntos)**	35,32 % (8 a 11 puntos)**
Desnutrición severa	11,19 % Categoría "C"	27,99 % (≥ 3 puntos)**	33,40 % (≥ 3 puntos)**	36,94 % (≥ 2 puntos)**	37,11 % (≥ 3 puntos)**	29,29 % (0-7 puntos)**
Algún grado de desnutrición B + C	48,06 %	47,41 %	55,17 %	47,24	71,33 %	64,61 %

**Total de pacientes evaluados con cada método; **Puntaje utilizado para definir cada una de las categorías de los métodos de TN.*

Tabla III. Grado de concordancia (Índice *kappa* y error estándar) entre la EGS y cada una de las herramientas de TN y entre ellas entre sí

	EGS	MST	SNAQ	MUST	NRS-2002	MNA SF
	I. *kappa* (ES)	I. *kappa* (ES)	I. *kappa* (ES)	I. *kappa* (ES)	I. *kappa* (ES)	I. *kappa* (ES)
MST	0,41 (0,02)*	-------	0,52 (0,02) **	0,45 (0,02)*	0,34 (0,02)*	0,39 (0,02)*
SNAQ	0,36 (0,02)*	0,52 (0,02)**	--------	0,49 (0,02)*	0,42 (0,02)*	0,44 (0,02)*
MUST	0,39 (0,02)*	0,45 (0,02) *	0,49 (0,02)*	--------	0,40 (0,02)*	0,40 (0,02)*
NRS	0,28 (0,02)*	0,34 (0,02) *	0,42 (0,02)*	0,40 (0,02)*	--------	0,43 (0,02)*
MNA-SF	0,38 (0,02)*	0,39 (0,02) *	0,44 (0,02)*	0,40 (0,02)*	0,43 (0,02)*	--------

**p < 0,001; ** p < 0,0001.*

Tabla IV. Porcentajes de mortalidad, complicaciones infecciosas, complicaciones no infecciosas, internación prolongada y medianas de internación en c/u de las 3 categorías de la EGS y en sus equivalentes acorde al puntaje de los métodos de tamizaje nutricional

	EGS* (*n* = 1546)	MST* (*n* = 1529)	SNAQ* (*n* = 1488)	MUST* (*n* = 1505)	NRS-2002* (*n* = 1458)	MNA-SF* (*n* = 1492)
Mortalidad %						
Bien nutrido	2,12	3,36	2,4	2,77	0,96	1,14
Riesgo desnutrición	8,77	9,76	6,79	6,45	4,61	5,50
Desnutridos	24,28	12,78	13,68	13,49	14,42	16,48
Complicaciones infecciosas %						
Bien nutrido	13,82	16,29	14,69	15,11	11,00	12,88
Riesgo desnutrición	24,21	19,19	20,99	16,77	18,24	17,27
Desnutridos	31,21	26,40	25,35	26,62	28,28	30,66

(Continúa en página siguiente)

Tabla IV (cont.). Porcentajes de mortalidad, complicaciones infecciosas, complicaciones no infecciosas, internación prolongada y medianas de internación en c/u de las 3 categorías de la EGS y en sus equivalentes acorde al puntaje de los métodos de tamizaje nutricional

	EGS* (*n* = 1546)	MST* (*n* = 1529)	SNAQ* (*n* = 1488)	MUST* (*n* = 1505)	NRS-2002* (*n* = 1458)	MNA-SF* (*n* = 1492)
Complicaciones no infecciosas %						
Bien nutrido	10,34	11,82	10,94	11,71	8,13	8,33
Riesgo desnutrición	24,04	21,21	18,21	17,42	15,03	17,08
Desnutridos	28,32	25,23	25,96	25,54	26,99	28,38
Internación prolongada > 11 días %						
Bien nutrido	37,11	41,17	37,18	40,68	36,60	33,33
Riesgo desnutrición	60,18	54,88	57,41	49,68	45,49	48,95
Desnutridos	73,41	60,98	61,37	62,23	65,62	70,02
Días de internación. Mediana (RIQ)						
Bien nutrido	9 (5-15)	9 (5-17)	8 (5-15)	9 (5-17)	8 (4-14)	8 (4-14)
Riesgo desnutrición	14 (8-28)	12 (7-23)	13 (8-26)	11 (7-20)	10 (6-19)	11 (7-20)
Desnutridos	19 (10-39)	15 (8-29)	15 (8-31)	15 (8-31)	16 (9-33)	17 (9-34)

En todos los casos, p < 0,0001 (k wallis - chi²). (RIQ: rango intercuartílico).

Tabla V. *Odds ratios* ajustados de las categorías en riesgo de desnutrición y desnutridos de cada una de las herramientas para: mortalidad, complicaciones infecciosas, no infecciosas y estancia hospitalaria prolongada

Herramientas		Mortalidad	Complicaciones infecciosas	Complicaciones no infecciosas	Estancia > 11 días
EGS	B	3,31	1,88	2,8	2,53
		(1,84-5,95)	(1,36-2,58)	(1,99-3,93)	(1,97-3,26)
		p: 0,0001	*p*: 0,0001	*p*: 0,0001	*p*: 0,001
	C	9,21	2,86	3,89	4,49
		(4,56-18,59)	(1,79-4,58)	(2,38-6,36)	(2,91-6,93)
		p: 0,0001	*p*: 0,0001	*p*: 0,0001	*p*: 0,001
MST	2	2,25	1,04	1,94	1,62
		(1,27-3,98)	(0,71-1,54)	(1,32-2,85)	(1,98-2,18)
		p: 0,006	(*) NS	*p*: 0,001	*p*: 0,001
	3	2,36	1,61	2,3	2,14
		(1,40-4,00)	(1,16-2,24)	(1,63-3,26)	(1,63-2,82)
		p: 0,001	*p*: 0,005	*p*: 0,0001	*p*: 0,001
SNAQ	2	2,38	1,22	1,73	2,36
		(1,20-4,71)	(0,83-1,80)	(1,15-2,61)	(1,74-3,18)
		p: 0,012	(*) NS	*p*: 0,007	*p*: 0,001
	3	3,79	1,66	2,6	2,54
		(2,07-6,93)	(1,18-2,35)	(1,81-3,74)	(1,64-2,76)
		p: 0,0001	*p*: 0,004	*p*: 0,0001	*p*: 0,001
MUST	2	1,8	1,11	1,38	1,36
		(0,85-4,00)	(0,67-1,85)	(0,83-2,31)	(0,93-1,98)
		(*) NS	(*) NS	(*) NS	(*) NS
	3	4	1,99	2,42	2,12
		(2,32-6,90)	(1,44-2,76)	(1,73-3,38)	(1,64-2,76)
		p: 0,0001	*p*: 0,0001	*p*: 0,0001	*p*: 0,001

(Continúa en página siguiente)

Tabla V (cont.). *Odds ratios* ajustados de las categorías en riesgo de desnutrición y desnutridos de cada una de las herramientas para: mortalidad, complicaciones infecciosas, no infecciosas y estancia hospitalaria prolongada

Herramientas		Mortalidad	Complicaciones infecciosas	Complicaciones no infecciosas	Estancia > 11 días
NRS-2002	2	3,83	1,74	2,14	1,31
		(1,28-11,53)	(1,14-2,67)	(1,32-3,47)	(0,98-1,78)
		p: 0,017	*p*: 0,01	*p*: 0,002	(*) NS
	3	8,59	2,63	3,91	2,85
		(2,96-24,98)	(1,70-4,07)	(2,41-6,34)	(2,06-3,96)
		p: 0,0001	*p*: 0,0001	*p*: 0,0001	*p*: 0,001
MNA-SF	2	4,05	1,35	2,31	1,91
		(1,62-10,09)	(0,93-1,98)	(1,51-3,55)	(1,44-2,52)
		p: 0,003	(*) NS	*p*: 0,0001	*p*: 0,001
	3	10,35	2,6	4,31	4,52
		(4,21-25,45)	(1,75-3,87)	(2,77-6,71)	(3,27-6,27)
		p: 0,0001	*p*: 0,0001	*p*: 0001	*p*: 0,001

**p no significativa.*

Tabla VI. Sensibilidad y especificidad (S/E) de categorías nutricionales discriminadas y agrupadas de los métodos TN, área ROC e IC al 95 % de los modelos de predicción para mortalidad, complicaciones infecciosas, complicaciones no infecciosas y estancia prolongada

Herramientas		Mortalidad		Complicaciones infecciosas		Complicaciones no infecciosas		Estancia prolongada > 11 días	
		S/E %	Área ROC (IC95 %)	S/E %	Área ROC (IC95 %)	S/E %	Área ROC (IC95 %)	S/E %	Área ROC (IC95 %)
EGS	B	74,6/ 60,1		44,6/ 61,6		62,3/ 62,4		53,5/ 69	
	C	38,5/ 90,9	0,746	17,8/ 90,4	0,604	18,2/ 90,3	0,634	16,5/ 94,1	0,642
	B + C	84,6/ 54,5	(0,71-0,78)	63,4/ 55,7	(0,57-0,64)	69,1/ 56,4	(0,60-0,67)	61,2/ 64,9	(0,62-0,67)
MST	2	51,8/ 74,4		30,3/ 73,7		40,9/ 75,2		32,9/ 77,9	
	3	48,6/ 75,6	0,661	37,5/ 74,4	0,569	40,6/ 74,7	0,61	34,6/ 78,4	0,593
	2 + 3	75,6/ 54,8	(0,61-0,71)	56,2/ 54,8	(0,53-0,60)	64,3/ 56,1	(0,57-0,64)	56,2/ 61,1	(0,57-0,62)
SNAQ	2	57,9/ 68,3		41,0/ 68,9		44,7/ 69,2		42,8/ 75,2	
	3	64,2/ 69,0	0,698	43,2/ 69,0	0,58	49,4/ 70,0	0,622	41,3/ 74,4	0,618
	2 + 3	84,9/ 47,1	(0,65-0,74)	66,4/ 47,6	(0,55-0,61)	72,0/ 48,4	(0,59-0,66)	66,4/ 55,9	(0,59-0,64)
MUST	2	31,3/ 84,2		17,8/ 83,9		22,5/ 84,6		19,3/ 85,8	
	3	70,1/ 65,6	0,694	50,3/ 66,3	0,586	54,2/ 66,7	0,615	46,4/ 72,3	0,603
	2 + 3	79,4/ 55,2	(0,65-0,74)	59,9/ 55,7	(0,55-0,62)	72,0/ 78,4	(0,58-0,65)	56,7/ 62,1	(0,58-0,63)
NRS-2002	2	85,2/ 46,5		66,4/ 47,7		68,8/ 47,5		59,7/ 49,3	
	3	74,3/ 65,8	0,727	52,8/ 66,8	0,62	57,3/ 67,2	0,646	48,3/ 74,3	0,63
	2 + 3	96,1/ 30,6	(0,69-0,76)	84,1/ 31,9	(0,59-0,65)	86,7/ 39,2	(0,61-0,68)	79,2/ 36,7	(0,60-0,66)
MNA-SF	2	82,9/ 51,2		57,2/ 51,3		67,2/ 52,6		59,5/ 56,7	
	3	67,3/ 73,7	0,746	45,7/ 74,7	0,62	48,1/ 74,6	0,652	41,4/ 82,6	0,659
	2 + 3	94,4/ 37,7	(0,71-0,78)	76,8/ 38,4	(0,59-0,65)	86,7/ 39,2	(0,62-0,68)	76,2/ 46,8	(0,63-0,68)

DISCUSIÓN

La prevalencia de desnutrición hospitalaria en Argentina acorde a la EGS sigue siendo alta y similar a la reportada en el estudio AANEP99 (32). En esta oportunidad el tamaño de la muestra fue mayor, con representatividad de todo el país, siendo una de las fortalezas de este estudio. Esta prevalencia se encuentra dentro del rango de 40-60 % de desnutrición hospitalaria reportada en Latinoamérica (36,37).

Las herramientas de TN que discriminaron mayor cantidad de pacientes con algún grado de desnutrición fueron NRS-2002 y MNA-SF, mientras que MST y MUST mostraron porcentajes similares.

MST fue el método más concordante con EGS con el porcentaje más cercano de bien nutridos y desnutridos severos entre todas las herramientas de TN. La menor concordancia con EGS se observó con NRS-2002, y esto podría deberse al sistema de categorización que se utilizó, lo cual llevó a magnificar los diagnósticos de desnutrición más que ningún otro método de TN. Por ejemplo, en un estudio reciente, donde se utilizó solo dos categorías, la precisión de NRS-2002 en diagnosticar desnutrición en pacientes quirúrgicos fue aceptable con una sensibilidad del 93 %, especificidad del 60 % y área ROC de 0.76 comparado con EGS (38).

Las concordancias entre métodos fueron regulares a malas, con tendencia a sobreestimar el número de desnutridos severos en relación al standard. Se podría especular que esto ocurre debido a los distintos dominios que priorizan las herramientas. Justamente, la mejor concordancia (κ 0,52) se encontró entre métodos que comparten algunas variables como SNAQ y MST. Otra de las razones podría ser la heterogeneidad de la población, dado que los pacientes correspondieron a áreas de cuidados clínicos, quirúrgicos, intermedios y críticos en donde no todas las herramientas mostraron la misma solidez en la aplicación. Estudios previos con valores superiores a los nuestros han contrastado métodos de TN utilizando solo dos categorías sin distinguir desnutrición moderada y severa al momento de la comparación (17,21,25,26,29). En uno de ellos (17), tanto NRS-2002 como MUST mostraron concordancia con EGS mayores a 0,85. Otras diferencias metodológicas influyentes podrían ser la heterogeneidad de las poblaciones (17,20,27), el patrón de comparación (8,16,28) y la metodología utilizada acorde a los objetivos de cada estudio (16). En otros estudios, la concordancia fue menor a los antes mencionados, pero aun así superiores a los nuestros, con valores de *k* entre EGS-MUST de 0,42 a 0,67 (20-22,25,26), EGS-NRS-2002 de 0,53 a 0,75 (20,21,25) y EGS-MNA-SF de 0,66 (26). Se destaca que herramientas de detección rápidas como MST y SNAQ funcionaron correctamente en varios estudios (8,15), y en el presente su concordancia no difirió con la de las herramientas largas.

La validez predictiva de las herramientas se constató para todos los eventos pronósticos estudiados. Las incidencias de mortalidad, complicaciones infecciosas, no infecciosas y estancia prolongada mostraron una tendencia constante y significativamente superior desde la normalidad hacia los dos grados crecientes de deterioro nutricional establecidos en todos los métodos de TN.

La capacidad predictiva evaluada por área ROC, en todos los modelos analizados fue siempre superior en los dos métodos que estimaron un mayor deterioro nutricional (MNA-SF y NRS-2002). Los OR ajustados, fueron mayores en estos dos métodos y con mayor fuerza de asociación a la mortalidad que a los otros riesgos. Los desnutridos severos identificados por los distintos métodos pudieron predecir de modo independiente los cuatro riesgos, en cambio, los desnutridos moderados fallaron en la predicción de alguno de los eventos pronóstico, siendo complicaciones infecciosas la más difícil de anticipar. El método más débil en este sentido fue MUST que no pudo predecir ningún riesgo con la categoría de desnutrición moderada, por su escasa representatividad en la muestra, en comparación al resto de las herramientas TN.

Asimismo, en otras publicaciones los métodos NRS-2002, MNA-SF y MUST demostraron tener validez predictiva para mortalidad (área ROC 0,6 a 0,8) (16,24). En cuanto a complicaciones, estudios previos evaluaron la capacidad predictiva del TN utilizando en general dos categorías de clasificación nutricional. NRS-2002, MUST y MNA-SF tuvieron valores de área ROC mayor a 0,6 en los estudios comparativos, mientras que en una revisión solo EGS, NRS-2002 y MUST mostraron validez predictiva regular a buena (24,27).

Todos los métodos fueron muy sensibles para predecir todos los riesgos tan solo clasificando a los individuos que se apartaron de la normalidad independientemente del grado de deterioro que mostraran. Todos los métodos al clasificar a sus desnutridos severos exhibieron estimaciones altas de especificidad para todos los riesgos. Si bien ninguno logró igualar la especificidad del método patrón EGS, fue MST, herramienta corta, el que le siguió en orden de mérito predictivo. Sus tasas de verdaderos negativos para "riesgos" siempre superiores a su par SNAQ y similares a las de MNA-SF MUST fue el único método con alta especificidad en su categoría desnutrición moderada.

Los valores medianos de días de estadía hospitalaria fueron significativamente superiores en las categorías con mayor deterioro en cualquiera de los métodos analizados, estableciendo brechas de hasta 10 días de hospitalización entre normonutridos y desnutridos severos. EGS y MNA-SF fueron los que más se destacaron en esta consideración. El valor predictivo de todos los métodos de TN para la estancia hospitalaria ha sido confirmado en otras publicaciones y muestra la relevancia clínica del TN sistemático al ingreso (24,39).

La principal fortaleza de este estudio es la muestra de pacientes, que en número y características es representativa de pacientes hospitalizados en Argentina y que permitió conocer la prevalencia de desnutrición hospitalaria con distintos métodos de TN y evaluar su capacidad predictiva ajustada por covariables, incluyendo sensibilidad y especificidad, además de la concordancia entre ellos para el tamizaje nutricional Las limitaciones del estudio están relacionadas con la metodología utilizada, lo cual no permite comparación directa de los resultados con los de otras publicaciones: evaluaciones realizadas en distintos mo-

mentos de la hospitalización (debido al método de aleatorización de camas utilizado); diferentes puntos de corte utilizados para categorizar a los pacientes en riesgo de desnutrición y desnutrición severa (MST y NRS-2002) a los fines de la comparación con el método patrón; en unos pocos pacientes no se completaron los datos de todos los métodos de TN (aunque ello no afectó un adecuado análisis estadístico).

CONCLUSIONES

- Se ratificó la prevalencia de DN hospitalaria (48,06 %; IC95 % 45,57; 50,55) por EGS, con diferente capacidad discriminativa entre métodos y baja concordancia entre ellos para diagnóstico, considerando tres categorías nutricionales con dos grados crecientes de deterioro nutricional.
- Los "riesgos" registrados dependieron fuertemente de la categorización nutricional basal más que de otros factores habitualmente considerados tales como edad (factor importante en sí mismo), diagnóstico y estado evolutivo de la enfermedad, comorbilidades, presencia de cáncer o infecciones, algunos tratamientos y otros factores.
- La capacidad predictiva (ROC y valor OR) fue siempre superior en los dos métodos que estimaron un mayor deterioro nutricional (MNA-SF y NRS-2002) alcanzando valores de probabilidad para los eventos similares al patrón comparativo EGS.
- Los desnutridos severos (equivalente C) de todos los métodos de TN pudieron predecir de modo independiente los cuatro riesgos, en cambio los desnutridos moderados (equivalentes B) fallaron en la predicción de alguno/s de los "outcomes". En este sentido no pudieron igualar al método patrón.
- Los métodos mostraron sensibilidad buena a muy buena para predecir los riesgos tan solo clasificando a los individuos que se apartaron de la normalidad, independientemente del grado de deterioro que mostraran.
- Los desnutridos severos clasificados por todos los métodos exhibieron alta especificidad especialmente en relación a mortalidad y estancia prolongada.
- Se encontraron variaciones en la capacidad predictiva de los métodos, que no afectan su vasta aplicabilidad clínica. Las comparaciones permitirán que diversas instituciones puedan elegir la herramienta de TN que mejor se adapte a sus objetivos, necesidades y posibilidades.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Healthy nutrition in primary care: instrument on the knowledge, perception, and sugary product consumption in the adult population

Nutrición saludable en atención primaria: instrumento sobre el conocimiento, percepción y consumo de productos azucarados en la población adulta

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Abstract

Introduction: it is necessary to develop an instrument that enables identifying unhealthy eating habits, and to know those erroneous concepts that the adult population may have in relation to sugary products to be able to design and implement appropriate nutritional education strategies for this population sector.

Aim: to perform the content validation of a questionnaire to determine the level of knowledge, perception, and habits of sugary product consumption in the adult population through expert judgement.

Methods: it is a content and psychometric validation study, carried out between September and October of the last year, in which 13 experts participated, who assessed each one of the instrument's items. Fleiss' *kappa* coefficient was used with the aim of measuring the degree of agreement. A pre-test was performed with 237 participants to measure the degree of comprehensibility of the instrument.

Results: the strength of agreement reached for the dimensions of knowledge and opinion regarding sugary product consumption was almost perfect, and substantial for behaviour with respect to said products. The strength of agreement fluctuated between moderate and almost perfect for each pair of experts. The characteristics of sufficiency and relevance obtained the highest scores using Fleiss' κ according to the degree of overall agreement between experts. The new version of the questionnaire achieved a high degree of comprehensibility.

Conclusions: the results suggest that the instrument is valid and can be applied in future studies to evaluate knowledge, perceptions and habits about sugary products in the adult population, thus contributing to the prevention of chronic diseases and the promotion of a better quality of life.

Keywords:

Content validity. Expert judgement. Feeding behaviour. Primary care nursing. Questionnaire. Validation study.

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Resumen

Introducción: es necesario desarrollar un instrumento que permita identificar hábitos alimentarios poco saludables, y conocer aquellos conceptos erróneos que pueda tener la población adulta con relación a los productos azucarados para poder diseñar e implementar estrategias de educación nutricional adecuadas para este sector poblacional.

Objetivo: realizar la validación de contenido de un cuestionario para determinar el nivel de conocimiento, percepción y hábitos de consumo de productos azucarados en la población adulta mediante juicio de expertos.

Métodos: se trata de un estudio de validación de contenido y psicométrica, realizado entre septiembre y octubre del año pasado, en el que participaron 13 expertos, quienes evaluaron cada uno de los ítems del instrumento. Se utilizó el coeficiente *kappa* de Fleiss con el objetivo de medir el grado de acuerdo. Se realizó un pretest con 237 participantes para medir el grado de comprensibilidad del instrumento.

Resultados: la fuerza de acuerdo alcanzada para las dimensiones de conocimiento y opinión sobre el consumo de productos azucarados fue casi perfecta, y sustancial para el comportamiento respecto de dichos productos. El grado de acuerdo fluctuó entre moderado y casi perfecto para cada par de expertos. Las características de suficiencia y relevancia obtuvieron las puntuaciones más altas utilizando la κ de Fleiss según el grado de acuerdo global entre expertos. La nueva versión del cuestionario logró un alto grado de comprensibilidad.

Conclusiones: los resultados sugieren que el instrumento es válido y puede ser aplicado en futuros estudios para la evaluación de conocimientos, percepciones y hábitos sobre productos azucarados en la población adulta, contribuyendo de esta forma a la prevención de enfermedades crónicas y la promoción de una mejor calidad de vida.

Palabras clave:

Validez de contenido. Juicio de expertos. Conducta alimentaria. Enfermería de atención primaria. Cuestionario. Estudio de validación.

INTRODUCTION

It should be highlighted that the ultra-processed food industry has become an important element that negatively influences eating habits leading to an increase in the rate of overweight and obesity, as well as non-communicable diseases (NCDs), among which it is worth highlighting: cardiovascular diseases, type 2 diabetes *mellitus,* frailty in the elderly, cavities and cancer (1,2).

Likewise, the production of ultra-processed foods is ever increasing, being more accessible to both the adult and juvenile population. The selection of products rich in added sugars, saturated fats and salt, in addition to additive substances, is on the rise and currently provides between 25-50 % of the total calorie intake (3). It should, therefore, be indicated that globalization and industrialization are bringing about a change in the eating habits in the majority of countries (4).

This situation leads to a poorer quality of the population's diet which, moving away from the dietary recommendations established by the WHO, presents a greater risk of suffering from any non-communicable disease, such as obesity, cardiovascular pathologies, and diabetes *mellitus,* among others (5). In this regard, according to the World Health Organization (WHO), more than 650 million people over the age of 18 are obese worldwide, which is about 13 % of the global adult population (11 % of men and 15 % of women), figures which have tripled since 1975 (6).

There is an evident need for the political, educational and healthcare institutions to reinforce nutritional education in the population, with the aim of restricting or reducing the consumption of ultra-processed products (7).

In the one hand, primary care has become a key link for the prevention of chronic diseases internationally, the incidence of which continues to increase progressively. This primary prevention represents a great effort for both the health system and patients (8).

In this way, the importance of nurses in primary care becomes evident, who play a key role in the implementation of health interventions, based on health promotion, disease prevention and management of chronic diseases, given their dual role in clinical practice and research (9,10).

Nutrition is one of the main nursing interventions in primary care for the modification of healthy lifestyles. Generally, dietary guidelines to improve nutritional status and/or weight loss have been based on proportional recommendations for macronutrients, promoting the Mediterranean diet and avoiding the consumption of ultra-processed foods. Currently, it is considered that dietary advice should be individually tailored and consider personal, cultural, and socioeconomic factors (11,12).

On the other hand, despite the relevance of this issue, there is no validated instrument that makes it possible to ascertain the knowledge, perception, and habits of sugary product consumption in the adult population and which facilitates the development and implementation of adequate nutritional education strategies (13). Likewise, it is vital to determine those factors that may be negatively affecting the population's diet, since eating is not only a biological fact, but it can also be influenced by social, economic and cultural factors. In this way, it is possible to influence those factors that involve an appropriate choice of food based on its healthiest characteristics (14,15).

It is, hence, necessary to develop an instrument that enables identifying unhealthy eating habits, and to know those erroneous concepts that the adult population may have in relation to sugary products to be able to design and implement appropriate nutritional education strategies for this population sector (16).

Validity and reliability are two basic characteristics that an instrument must fulfil to be able to guarantee its quality and thus be used by researchers in studies. There are different types of validation methods, including content validity, criteria validity and construct validity, the latter being the most complex (17). The validation criteria used in the present study was content validity. Content validity can be defined as "the degree to which the elements of the measuring instrument are integral, relevant and representative of the construct for a particular evaluation purpose" (18).

Although there are different methods to determine content validity, the expert judgement is the most widely used; it is based on the informed opinion of people with experience in the subject matter, who are recognized as qualified experts in it, and who can

give information, evidence, judgements, and assessments. The experts will assess each one of the items that make up the questionnaire, using a numerical scale as part of the procedure (19-21). The researcher will subsequently thoroughly analyze each one of the ratings and will determine what to modify, improve or remove from the instrument to be validated (22).

No published articles were identified that considered how nurses detect errors in patients' dietary habits, in this case, in sugar consumption. This study sought to fill this deficit in knowledge and a tool that allows us to detect bad healthy habits, possible prediabetic patients who can progress to DM2, and provide adequate nutritional education.

It is important to highlight that excessive sugar consumption has been identified as a critical factor in the development of chronic non-communicable diseases. such as obesity, type 2 diabetes and cardiovascular problems. This approach allows for a detailed analysis of the specific knowledge, perceptions and habits related to added sugars, which tend to be less regulated by the population due to sociocultural and marketing factors that normalize their consumption. In this way, a specific questionnaire can offer a better understanding of these beliefs and behaviors, which helps to develop more effective and focused educational interventions.

Thus, while global diet questionnaires such as the Mediterranean diet are valuable tools for a comprehensive view, they tend to dilute the risk factors specifically associated with sugar consumption. By focusing the questionnaire on a single aspect, such as sugary products, specific details and barriers can be identified that might be missed in an overall assessment, thus providing a more accurate perspective for intervention interventions.

Finally, this specific questionnaire can complement other broader instruments by providing data on a particularly relevant and critical dietary aspect in current health, optimizing resources and efforts in nutritional education interventions aimed at reducing sugar consumption.

Therefore, the objective of this study was to present the procedure for the development and content validation of an instrument to determine the degree of knowledge, perception, and habits of sugary product consumption in the adult population through an expert judgement.

METHODS

STUDY DESIGN

Descriptive study, of content validity through expert judgement, performed in the University of Granada (Melilla).

PARTICIPANTS

The sample, selected due to convenience, was formed by 13 professionals from different disciplines and faculties with an experience of between 5 and 20 years in teaching and research, who voluntarily accepted to take part. The exclusion criteria were the failure to complete the informed consent and submit the questionnaire within the deadline set. Table I shows the areas of knowledge and professional experience of each one of the experts.

DATA COLLECTION

The content questions related to knowledge, behaviour and opinion regarding sugary product consumption were selected after a literature review using the Web of Science and Scopus

Table I. Experts, areas of knowledge, education, and professional experience

Expert	Area of knowledge	Years of experience
1	Didactics of Language and Literature	8
2	Didactics of Language and Literature	20
3	Research Methods and Diagnosis in Education	17
4	Research Methods and Diagnosis in Education	9
5	Evolutionary and Educational Psychology	13
6	Health Sciences	18
7	Health Sciences	16
8	Health Sciences	10
9	Health Sciences	8
10	Health Sciences	8
11	Nutrition and Food Science	23
12	Nutrition and Food Science	15
13	Nutrition and Food Science	10

databases. Finally, 22 questions were proposed, grouped in the three indicated dimensions (knowledge, behaviour and opinion) with 10, 4 and 8 items, respectively.

An e-mail was sent to the experts with the information on the study's main objective, the questionnaire to validate and how to respond, as well as the confidentiality guarantee (cover letter). The experts were given one month to assess, score the questionnaire and return the reply electronically to the researchers.

Once the questionnaire was assessed by the experts, and after taking into consideration the qualitative suggestions made to it, the resulting instrument underwent the standard pre-test with potential recipients to have information about the Instrument's behaviour in real life (23).

To this end, a dichotomous yes/no response was encoded in each of the items to measure the degree of interpretation, as well as their applicability/feasibility. The sample (stratified random) that performed the pre-test was made up of 237 Nursing Degree students. The study was carried out between September and October of 2023 and conclusions derived were drawn during the period of November-December 2023.

DATA ANALYSIS

The data collected were statistically processed using the SPSS software, version 26.0 for Windows. The degree of agreement between the experts was determined using Fleiss' *kappa* coefficient as the statistical test to evaluate the agreement between three or more raters that independently judge a series of items using an instrument with a certain number of ordinal categories (24-26). The scale established by Landis and Koch (27) (which qualitatively expresses the strength of agreement between raters) was taken into account for the interpretation of Fleiss' *kappa* coefficient, which takes values between 0 and 1.

For the analysis of the judges' qualitative considerations on the congruence of the items, breadth of content, wording, clarity and relevance, a Likert-type rating scale was used, attributing categories and rating points, poor, acceptable, good, and excellent, according to your consideration. Items that met all the established requirements were classified as "adequate", items that required some changes were classified as "partially adequate", and items that expressed total inconsistency in relation to the expressed criteria were classified as "inadequate". In cases where it was considered inadequate, the reasons were explained, the suggestions described, and the content redone and improved.

Basic statistics (frequencies and percentages) were used for the analysis of the data gathered in the pre-test.

VALIDITY AND RELIABILITY

Validity and reliability were considered carefully in design and implementation of the study. The COPEHPA ("Knowledge, perception and habits of sugary product consumption") was assessed from the rating of each item, using the "Template for assessing content validity through expert judgement" developed by Escobar-Pérez and Cuervo-Martínez (20), which establishes four levels: does not meet the criterion, low level, moderate and high level for the characteristics assessed: sufficiency, clarity, coherence and relevance (Table II). The indicator "one" of the categories was assigned when the item did not conform to the category, up to indicator "four", which was

Table II. Categories of the tool for the validation by the judges and indicators

Categories	Indicators
Sufficiency The items that belong to the same dimension are sufficient to obtain its measurement	The items are not sufficient to measure the dimension The items measure an aspect of the dimension, but they do not correspond to the total dimension Some items must be increased to be able to completely assess the dimension The items are not sufficient
Clarity The item is easily understood, i.e. its syntax and semantics are appropriate	The item is unclear The item requires several modifications or a very large modification in the use of the words according to their meaning or their ordering. It requires a very specific modification of some of the item's terms The item is clear. It has appropriate syntax and semantics
Coherence The item has a logical relationship with the dimension or indicator it is measuring	The item has no logical relationship with the dimension The item has a tangential relationship with the dimension The item has a moderate relationship with the dimension being measured The item is completely related to the dimension being measured
Relevance The item is essential or important, i.e. it must be included	The item can be removed without affecting the measurement of the dimension The item has some relevance, but another item may be including what it measures The item is relatively important The item is highly relevant and must be included

Table III. Strength of agreement between raters for the dimensions of the original instrument

Dimensions	Fleiss' *kappa* coefficient	Strength of agreement (Landis & Koch, 1977)
Knowledge about sugary products	0.894	Almost perfect
Opinion regarding sugary product consumption	0.870	Almost perfect
Behaviour with respect to sugary products	0.780	Substantial

Table IV. Agreement by pairs of experts

Dimensions	Fleiss' *kappa* coefficient - agreement by pairs of experts												
	1-13	2-12	3-11	4-10	5-9	6-8	7-8	9-6	10-5	11-4	12-3	13-2	2-1
Knowledge	0.900	0.834	0.798	0.985	0.817	0.920	1	0.730	0.835	0.785	0.940	0.835	0.819
Opinion	0.991	0.914	0.801	0.770	0.842	0.863	0.911	0.946	0.744	0.734	0.756	0.808	0.849
Behaviour	0.791	0.714	0.831	0.620	0.812	0.763	0.905	0.646	0.716	0.774	0.716	0.632	0.745

assigned when the item fully conformed to the category (only sufficiency was scored by dimension rather than by item). The experts' qualitative observations for each of the 20 items that made up the initial instrument were also considered as reflected in the statistical analysis section.

The percentage of comprehension and the degree of comprehensibility was established as: high comprehensibility (equal to or greater than 85 %), medium comprehensibility (80 to 85 %) and low comprehensibility (less than 80 %).

ETHICAL CONSIDERATIONS

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Provincial Board of Education of Melilla (protocol code 201802658 on 10 April 2018). All participants were informed of the study's objectives, with voluntary participation and signing of the informed consent.

RESULTS

CONTENT VALIDATION THROUGH EXPERT JUDGEMENT

To evaluate the original instrument, the proportion of possible agreements occurring in each dimension was considered in the calculation of Fleiss' *kappa* coefficient. The magnitude in the strength of agreement by the set of experts was estimated to be almost perfect, for 2 dimensions (knowledge and opinion regarding sugary product consumption), and as substantial for the behaviour with respect to said products, as observed in table III.

Likewise, Fleiss' *kappa* coefficient was determined by pairs of experts, finding a greater variability, between moderate and almost perfect, revealing a disagreement especially in the dimension of behaviour with respect to sugary products as observed in table IV.

Furthermore, the characteristics of the instrument were entirely estimated based on the categorical indicators of sufficiency, clarity, cohesion, and relevance, according to the ordinal measurement scale. A strength of agreement between substantial and almost perfect was found, with the sufficiency and relevance characteristics being the highest (0.832 and 0.903, respectively), according to the overall agreement between experts. With respect to the statistical significance of these characteristics, in all cases a behaviour of 95 % confidence with a significance $p < 0.05$ was found. The "sufficiency" and "relevance" characteristics are especially relevant, with p=.001, as observed in table V.

Table V. Fleiss' *kappa* coefficient and statistical significance of the characteristics of the original instrument

Characteristics	Fleiss' *kappa* coefficient	*p*
Sufficiency	0.832	0.001
Clarity	0.792	0.016
Coherence	0.784	0.018
Relevance	0.903	0.001

These results, together with the observations and recommendations issued qualitatively by the experts to the items contained in the four dimensions established, led to the final questionnaire.

MEASUREMENT OF APPLICABILITY: PRE-TEST

To determine the percentage of comprehension of the dimensions and their corresponding items, the validated final instrument was completed by a total of 237 students from the Nursing Degree. They were all valid. The analysis of the data (percentages of yes/no responses given by the participants) made it possible to establish the degree of comprehensibility of the instrument in the highest range with comprehension percentages equal to or greater than 91 % in all the items, as set down in table VI. The overall comprehensibility of the final validated questionnaire was established at 96.2 %.

DISCUSSION

Although there has been much involvement by different institutions, and even the large international companies from the food sector, who have reduced sugar content in their food by approximately 36 %, there are still processed foods with high quantities of sugar that continue to be harmful for health (28).

There are currently no instruments in existence that measure the knowledge, perception, and habits in relation to sugary products in the general population. However, studies do exist which demonstrate the population's lack of knowledge with regard to sugary drinks, and the high consumption of these products (29-31).

The key concept of content validity is that the items of a measuring instrument are relevant and representative (32). As demonstrated by Utkin (33), the information transmitted through expert judgement is usually more useful in those areas where the experimental observations are limited. This statement is particularly true in the health area, where said judgement has become the main strategy to estimate content validity (20).

Although there are other ways to evaluate the diet, such as global questionnaires that evaluate the general quality of the diet, such as the Mediterranean Diet Adherence questionnaire, the questionnaire developed in this study allows a more specific and detailed analysis of product sugar-sweetened product consumption, a key factor in the appearance of the pathologies mentioned above. This specificity responds to the progressive need to evaluate and modify eating behaviors that represent a risk (34).

Table VI. Percentages of comprehensibility of the dimensions and its items in the final version of the validated instrument

Dimension	Item	Percentage of comprehension (%)	
		Yes	No
Degree of knowledge	Natural sugars	96.2	3.8
	Free sugars in a product	94.9	5.1
	0 % sugar	100	
	Light sugar	91.1	8.9
	Recommended amount for free sugar consumption	100	0.0
	Terminology that indicates a lower quantity of sugar	100.0	0.0
	Excess sugars in the body	100.0	0.0
	Tooth decay and sugar	97.0	3.0
	Decrease in strength, resistance and physiological functions in old age and sugar	100.0	0.0
	Benefits of sugar reduction	100.0	0.0
Perception of sugary	Daily sugar	99.2	0.8
	Interpretation of the nutritional labelling of products	98.3	1.7
	Nutritional labelling and choice, purchase and consumption of products	100.0	0.0
	Importance of the choice of food consumption	100.0	0.0
Product consumption	Knowledge and interpretation of the Mediterranean diet nutritional food pyramid	100.0	0.0
	Implementation of the Mediterranean diet nutritional food pyramid	99.2	0.8
	Best strategy to decrease added sugar intake	100.0	0.0
Consumption habits of sugary products	Consumption frequency of fruit, pastries, snacks or biscuits and sugary drinks	100.0	0.0
	Sugary drink consumption	100.0	0.0
	Type of pastries and brand	100.0	0.0
	Addition of sugar to food and drinks	100.0	0.0

Unlike comprehensive dietary assessment tools that provide an overview of diet quality but can dissolve specific risk factors such as sugar consumption, our questionnaire allows primary care nurses, as well as the health professionals involved, identify and understand behavioral patterns specifics related to sugary products. As Warshaw and Edelman (35) state, this approach is particularly useful in consultations where time is limited and a rapid and direct diagnosis of risk habits in the patient's diet is required. Thus, instead of evaluating all aspects of the diet, the questionnaire helps professionals focus their educational and preventive interventions on a priority dietary aspect.

The implementation of this questionnaire in the primary care setting also facilitates the development of personalized nutritional education strategies, adapted to patients´ specific knowledge and perceptions regarding sugar consumption. The identification of erroneous knowledge and beliefs allows health professionals to design interventions aimed at correcting these errors and promoting healthier food choices. This represents a comparison with other general dietary assessment methods, as it provides a more precise basis for addressing sugar consumption in the adult population, allowing for more effective interventions at the first level of care (36).

Greater involvement on the part of health institutions is necessary to achieve optimal and updated strategies adapted to the population. Increasing the number of nurses in public health and more time in consultations with patients could be a first step towards achieving these objectives. However, this questionnaire, within the nursing functions in primary care, allows for early detection of failures in the nutritional habits of the adult population to promote health and prevent chronic diseases. Likewise, for future research it would be necessary to create questionnaires on other macronutrients such as fats or proteins and thus be able to discover in a more detailed way errors in the patient's nutritional habits.

LIMITATIONS

However, there are some limitations inherent to the content validation process, such as definition of the number of people who must form part of the expert judgement, essential for the validation. Thus, although there are different opinions, there is agreement that the number of experts will depend on the level of experience in the area and of the diversity of knowledge. Whilst Hyrkäs et al. (37) declare that 10 experts would offer a reliable estimate of the content validity of an instrument, Voutilainen and Liukkonen (38) state that if 80 % of the experts have been in agreement with the validity of the item, this can be incorporated in the instrument. Likewise, as Koller et al. (39) assert, the quality and diversity of the professionals may be much more significant than their number.

The present study, bearing in mind that the objective was to validate items of a questionnaire on sugary products with the aim of ascertaining the knowledge, perception, and habits with respect to these products, five of the experts were nurses and three were nutritionists. Furthermore, the judges had extensive knowledge in the subject matter, having different forms of experience in the area.

Nevertheless, as stated by Koller et al. (40), in addition to the group of experts, it is effective to include individuals from the reference population, i.e., they are not specialists in the area. In this way, in this work, 237 students from the Nursing Degree of the Faculty of Health Sciences of Melilla of the Universidad de Granada voluntarily took part in the pre-test, obtaining a high degree of comprehensibility of the COPEHPA questionnaire (96.2 %).

CONCLUSIONS

The instrument described in this study aims to cover the need of having a specific, fast, and reliable tool that allows healthcare staff to know the dietary habits as regards sugary foods, knowledge they have about them and their perceptions. Thus, this questionnaire can be applied both to the healthy adult population and to those who are overweight, have obesity, diabetes *mellitus* and/or any other non-communicable disease, with the aim of avoiding complications and improving their quality of life.

In summary, content validity by means of Fleiss' *kappa* statistic is useful for measuring the degree of agreement between experts and whose results obtained reveal the objectivity of the instrument. Likewise, the pre-test procedure described provides the determination of the degree of comprehensibility of the final instrument. Therefore, we believe that the objective of validating a measuring instrument has been fulfilled. In this way, we recommend the use of the COPEHPA questionnaire (Annex 1), which, in addition to being easy and quick to use, will allow, from the first level of healthcare assistance, to quickly deal with determining the degree of knowledge, perception and habits of sugary product consumption among the adult population, considering optimum eating behaviour, and thus improving quality of life.

Annex 1. COPEHPA questionnaire

I. Degree of knowledge

1. From the following foods, indicate which do not contain natural sugars (called intrinsic):
   a. Banana
   b. Carrot
   c. Milk
   d. Honey
   e. Don't know

(Continues on next page)

Annex 1 (cont.). COPEHPA questionnaire

2. From the following statements about the different types of sugar, indicate the correct one: What do you understand by free sugars in a product?
   a. Intrinsic sugars are those present in just fruit and fruit juice.
   b. Free sugars are those added to foods by manufacturers, cooks or the consumers themselves, including the sugars naturally found in honey, syrups, fruit juices and fruit juice concentrates.
   c. Intrinsic sugar consumption fills you up less than free sugars.
   d. Don't know
3. What does it mean that a product has 0 % sugar?
   a. That it has no added sugars
   b. That it has less than 0.5 g of sugar in 100 g
   c. That I can eat or drink all that I want without putting on weight
   d. Don't know
4. What does light sugar mean?
   a. That it contains a 30 % reduction in sugar
   b. That it contains a 50 % reduction in sugar
   c. Don't know
5. According to the World Health Organization (WHO), what do you think is the recommended amount of free sugar consumption?
   a. Less than 10 % of the total calorie intake
   b. More than 10 % of the total calorie intake
   c. There is no recommended amount
   d. Don't know
6. What terminology indicates that the product contains a lower amount of sugar?
   a. Light sugar
   b. Zero sugar
   c. Reduced sugar
   d. No added sugars
   e. Don't know
7. Excess sugar mainly accumulates in the body as:
   a. Energy
   b. Fats
   c. Proteins
   d. Don't know
8. Tooth decay is directly related to excess sugar:
   a. Yes
   b. No
   c. Don't know
9. Is there a relation between sugar consumption and the decrease in strength, resistance and physiological functions in old age?
   a. Yes
   b. No
   c. Don't know
10. Reducing sugar consumption helps to prevent:
    a. Diabetes
    b. Heart attacks
    c. Obesity
    d. All are correct
    e. Don't know

II. Perception of sugary product consumption

1. How much sugar do you think you consume daily?
   a. Less than 10 g daily (equivalent to one teaspoon)
   b. Between 10 and 30 g
   c. From 30 to 50 g
   d. Over 50 g

(Continues on next page)

Annex 1 (cont.). COPEHPA questionnaire

2. Do you consider that you know how to correctly interpret the nutritional labelling of products?
   a. Yes
   b. No
3. Do you think that the interpretation of nutritional labelling helps in the choice, purchase and consumption of products?
   a. Yes
   b. No
4. Do you think that it is important to choose the food you consume?
   a. Always
   b. Sometimes
   c. Never
5. Do you know the Mediterranean diet food pyramid and how to interpret it?
   a. Yes, I know it and know how to interpret it
   b. Yes, I know it, but I don't know how to interpret it
   c. No, I don't know it
6. Do you implement the Mediterranean diet food pyramid?
   a. Yes
   b. No
7. What do you think is the best strategy to decrease added sugar intake?
   a. Consume fresh, local and seasonal products
   b. Avoid buying products with large quantities of sugar
   v. Radically remove sugar from our diet

III. Sugary product consumption habits

1. Check the box that corresponds to your consumption frequency with an (X)

	Average consumption									
	Never	Monthly			Weekly			Daily		
		1-3	2-4	5-6	1	2-4	5-6	2-3	4-5	+5
Fruit: banana, apples, pears, watermelon, etc.										
Pastries, snacks, or biscuits: crisps, chocolates, doughnuts, etc.										
Sugary drinks: soft drinks, juices, etc.										

2. Do you usually drink sugary drinks? Please, specify the brand in any of the options except in "never".
   a. Always
   b. Almost always
   c. Sometimes
   d. Almost never
   e. Never
3. What type of pastries do you usually consume?
   a. Commercial pastries. Specify the brand: _____
   b. Homemade pastries. Specify the type of pastries you usually consume: _____
   c. I don't consume pastries/baking.
4. Do you usually add sugar to food and drinks?
   a. Always
   b. Almost always
   c. Sometimes
   d. Almost never
   e. Never

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Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Predictive values of body mass index, prognostic nutritional index and C-reactive protein to prealbumin ratio for prognosis of patients receiving radical gastrectomy

Valores predictivos del índice de masa corporal, el índice pronóstico nutricional y el cociente proteína C-reactiva/prealbúmina para el pronóstico de los pacientes sometidos a gastrectomía radical

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Abstract

Introduction: we aimed to analyze the predictive values of body mass index (BMI), prognostic nutritional index (PNI) and C-reactive protein to prealbumin ratio (CRP/PA) for the prognosis of patients receiving radical gastrectomy.

Materials and methods: one hundred patients subjected to radical gastrectomy from August 2015 to January 2018 were enrolled. The cut-off values of BMI, PNI and CRP/PA on the receiver operating characteristic (ROC) curves were obtained and applied to establish a low BMI group ($n = 46$) and a high BMI group ($n = 54$), a low PNI group ($n = 48$) and a high PNI group ($n = 52$), as well as a low CRP/PA group ($n = 57$) and a high CRP/PA group ($n = 43$).

Results and conclusion: through comparing the low BMI group with the high BMI group, there were differences in the tumor diameter, invasion depth, clinical stage, and lymph node metastasis status ($p < 0.05$). Differences were found in the invasion depth, tumor diameter, lymph node metastasis status, clinical stage, and postoperative adjuvant therapy in the low CRP/PA group compared with the high CRP/PA group ($p < 0.05$). The survival rate of all patients was 45 % (45/100) during the 5 years of follow-up. According to the Kaplan-Meier survival analysis, the low BMI group, low PNI group and high CRP/PA group had significantly reduced overall survival rates in comparison to those of the high BMI group, high PNI group and low CRP/PA group, respectively ($p < 0.05$). BMI, PNI and CRP/PA have important predictive values for the prognosis of patients undergoing radical gastrectomy.

Keywords:

Body mass index.
C-reactive protein.
Gastrectomy. Prealbumin.
Prognosis.

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Yijie Yang and Jiale Yang contributed equally to this study.

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Resumen

Introducción: nuestro objetivo fue analizar los valores predictivos del índice de masa corporal (IMC), el índice pronóstico nutricional (IPC) y la relación entre proteína C-reactiva y prealbúmina (PCR/PA) para el pronóstico de los pacientes sometidos a gastrectomía radical.

Materiales y métodos: se incluyeron 100 pacientes sometidos a gastrectomía radical de agosto de 2015 a enero de 2018. Se obtuvieron los valores de corte de IMC, PNI y PCR/PA en las curvas ROC para establecer un grupo de IMC bajo ($n = 46$) y un grupo de IMC alto ($n = 54$), un grupo de PNI bajo ($n = 48$) y un grupo de PNI alto ($n = 52$), así como un grupo de PCR/PA bajo ($n = 57$) y un grupo de PCR/PA alto ($n = 43$).

Resultados y conclusión: al comparar el grupo de IMC bajo con el grupo de IMC alto, se observaron diferencias en el diámetro tumoral, la profundidad de invasión, el estadio clínico y el estado de metástasis en los ganglios linfáticos ($p < 0,05$). Se encontraron diferencias en la profundidad de invasión, el diámetro tumoral, el estado de la metástasis en los ganglios linfáticos, el estadio clínico y el tratamiento adyuvante posoperatorio en el grupo de PCR/PA baja en comparación con el grupo de PCR/PA alta ($p < 0,05$). La tasa de supervivencia de todos los pacientes fue del 45 % (45/100) durante los 5 años de seguimiento. Según el análisis de supervivencia de Kaplan-Meier, el grupo de IMC bajo, el grupo de PNI bajo y el grupo de PCR/AP alto presentaron una reducción significativa de las tasas de supervivencia global en comparación con los grupos de IMC alto, PNI alto y PCR/AP bajo, respectivamente ($p < 0,05$). El IMC, el PNI y la PCR/PA tienen valores predictivos importantes para el pronóstico de los pacientes sometidos a gastrectomía radical.

Palabras clave:

Índice de masa corporal. Proteína C-reactiva. Gastrectomía. Prealbúmina. Pronóstico.

INTRODUCTION

Gastric cancer is a common malignancy around the world. In 2020, there were approximately 1.1 million new cases of gastric cancer globally, with about 770,000 deaths. This trend is expected to increase, with projections indicating that by 2040, the global burden of gastric cancer could reach around 1.8 million new cases and 1.3 million deaths annually (1). The burden is especially high in East Asia, where China has the highest incidence and mortality rates. The most recent data shows that gastric cancer continues to be a major health concern in China, accounting for 42.6 % of new cases and 48.6 % of global gastric cancer-related deaths (2). Gastric cancer frequently occurs at the age of 40-60 years, which is closely related to the region, dietary habits, environmental pollution and heredity (3). Due to insidious onset, most patients have been in the advanced stage once diagnosed. Surgical resection is the only possible cure for gastric carcinoma, with an overall survival (OS) rate of less than 50 % in 5 years (4). Therefore, for the purpose of enhancing the long-term efficacy of radical gastrectomy, multiple measures such as minimally invasive/robotic surgery, postoperative enhanced recovery, chemotherapy, and radiotherapy have been explored by clinicians.

The survival rate plus prognosis of gastric cancer sufferers after operation are determined by host-specific factors in addition to tumor-related factors (5,6). Body mass index (BMI) is an indicator that measures the degree of obesity based on an individual's weight and height. Obesity is a pathogenic factor for cancer development, but the influence of BMI on the survival rate remains controversial (7). An increased BMI is associated with higher risks of disease recurrence and death in breast cancer (8). However, the 5-year overall survival rate of patients with non-metastatic gastric cancer, who have high BMI, exceeds that of the cases with low BMI (9). Besides, prognostic nutritional index (PNI) serves as a sign of host immunity and nutritional status, which is calculated from the peripheral lymphocyte count and serum albumin content. PNI has witnessed extensive application over the years in the evaluation of nutritional status in people suffering from gastrointestinal diseases as well as the assessment of prognosis, living quality after operation, and complications of other patients (10). PNI has also been used to predict the gastric cancer patients at increased risk of postoperative morbidity and mortality (11). Moreover, the C-reactive protein to prealbumin ratio (CRP/PA) is a new inflammatory indicator that combines inflammatory responses and nutritional status, often used to evaluate the outcomes of various cancers (12). A high CRP/PA ratio is an independent prognostic factor in gastric cancer patients, with elevated values associated with poorer overall survival (13).

In this study, the significance of BMI, PNI and CRP/PA in assessing the prognosis of patients undergoing radical gastrectomy was systematically explored, aiming to provide more accurate tools for prognostic evaluation.

METHODS

GENERAL DATA

One hundred subjects treated with radical gastrectomy in our hospital by the same team from August 2015 to January 2018 were enrolled. The inclusion criteria involved 1) patients diagnosed with gastric cancer based on the clinical diagnostic criteria (14), and pathologically diagnosed with gastric cancer at the first visit; 2) those without chronic liver/kidney dysfunction, infectious diseases and immune system diseases; 3) those without using anti-infective drugs before operation; 4) those without distant metastasis; 5) those with indications of radical gastrectomy; and 6) those with complete clinical data and follow-up data.

The exclusion criteria included: 1) patients who could not tolerate radical gastrectomy, 2) those presenting distant metastasis and/or extensive peritoneal seeding, 3) those complicated with other serious diseases or distant metastasis, 4) those with severe diabetes, coronary heart disease, or hepatic/renal insufficiency, 5) those with malignant tumors at other sites, or 6) those undergoing combined resection of other organs intraoperatively.

EVALUATION OF OUTCOMES

Height and weight were obtained for the calculation of BMI: weight (kg)/height $(m)^2$. Fasting venous blood was drawn in the morning the next day after admission, and the blood lymphocyte count, serum albumin and serum PA were detected using an automatic biochemical analyzer. Then serum albumin (g/L) + [5 × blood lymphocyte count (× 10^9/L)] was adopted for PNI

calculation. The CRP level was detected via enzyme-linked immunosorbent assay, with CRP/PA calculated.

The cut-off values of BMI, PNI and CRP/PA on the receiver operating characteristic (ROC) curves were obtained, which were utilized for grouping of patients. Then corresponding intergroup comparisons were performed on the clinicopathological features (age, invasion depth, gender, lymph node metastasis, tumor diameter, differentiation degree, clinical stage, and presence or absence of postoperative adjuvant therapy).

Follow-up was performed until January 2023 on the patients' survival status by telephone or outpatient service, and overall survival was recorded.

STATISTICAL ANALYSIS

The SPSS 23.0 software was used for the statistical analysis. Mean ± standard deviation (x ± s) and the *t*-test were employed to express the measured data. Percentage [*n* (%)] together with the χ^2 test were utilized for the count data. Kaplan-Meier survival curves were plotted to explore the associations of BMI, PNI and CRP/PA with the prognosis of patients undergoing radical gastrectomy. A $p < 0.05$ meant a difference of statistical significance.

RESULTS

ROC CURVES

The mean BMI of all patients was (20.25 ± 2.08) kg/m^2. The ROC curve of 5-year BMI was plotted, with an AUC of 0.709 (95 % CI: 0.635-0.783). Under the optimal cut-off value of 20.88 kg/m^2 for BMI, the Youden index was the highest, the sensitivity was 63.39 %, and the specificity reached 72.26 % ($p < 0.001$) (Fig. 1A). Next, low ($n = 46$) and high ($n = 54$) BMI groups were set up for the patients according to the cut-off value of BMI.

The mean PNI of all patients was (43.54 ± 5.74). The ROC curve of 5-year PNI was plotted, and the AUC reached 0.784 (95 % CI: 0.719-0.850). The Youden index was the highest in the case of the optimal cut-off value of PNI at 44.20, with the sensitivity plus specificity of 60.56 % and 83.94 %, respectively ($p < 0.001$) (Fig. 1B). Later, a low PNI group ($n = 48$) and a high PNI group ($n = 52$) were built for patient allocation *as per* the cut-off value of PNI.

The mean CRP/PA of all patients was (283.52 ± 90.33). The ROC curve of CRP/PA was plotted, with the AUC being 0.721 (95 % CI: 0.651-0.791). The highest Youden index was obtained from 305.26 as the optimal cut-off value of CRP/PA, and the sensitivity of 88.73 % and specificity of 46.72 % were acquired ($p < 0.001$) (Fig. 1C). The cut-off value of CRP/PA was applied to assign the patients to a low ($n = 57$) or high ($n = 43$) CRP/PA group.

ASSOCIATIONS BETWEEN DIFFERENT BMI AND CLINICOPATHOLOGICAL FEATURES

Through comparing the low BMI group with the high BMI group, there were differences in the tumor diameter, lymph node metastasis status, clinical stage, and invasion depth ($p < 0.05$) (Table I).

ASSOCIATIONS BETWEEN DIFFERENT PNI AND CLINICOPATHOLOGICAL FEATURES

The tumor diameter, clinical stage and depth of invasion in the low PNI group were different from those in the high PNI group ($p < 0.05$) (Table II).

ASSOCIATIONS BETWEEN DIFFERENT CRP/PA AND CLINICOPATHOLOGICAL FEATURES

Differences were found in the invasion depth, tumor diameter, clinical stage, lymph node metastasis status and postoperative adjuvant therapy in the low CRP/PA group compared with the high CRP/PA group ($p < 0.05$) (Table III).

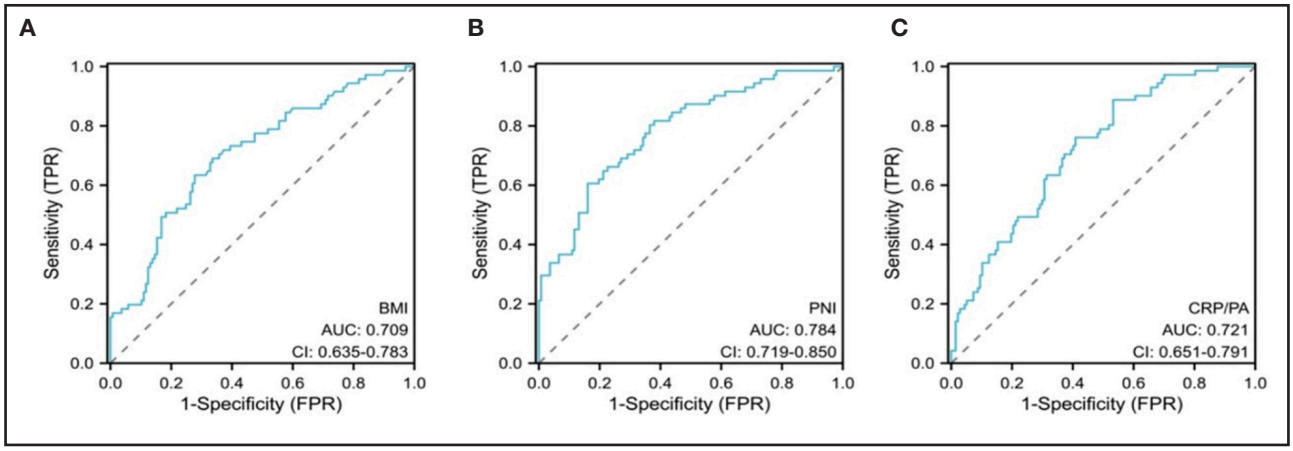

Figure 1.

ROC curves of BMI, PNI and CRP/PA in patients with gastric cancer. A. ROC curve of BMI. B. ROC curve of PNI. C. ROC curve of CRP/PA.

ASSOCIATIONS OF BMI, PNI, AND CRP/PA WITH PROGNOSIS OF GASTRIC CANCER SUBJECTS

The survival rate of all patients was 45.00 % (45/100) during the 5 years of follow-up. According to the Kaplan-Meier survival analysis, the low BMI group, low PNI group and high CRP/PA group had significantly reduced OS rates compared to those of the high BMI group, high PNI group and low CRP/PA group, respectively ($p < 0.05$) (Fig. 2 and Table IV).

Table I. Associations between different BMI and clinicopathological features

Clinicopathological feature		*n*	Low BMI group (*n* = 46)	High BMI group (*n* = 54)	t/χ^2	*p*
Age (year)		100	58.23 ± 11.23	59.36 ± 13.88		
Gender	Male	51	21 (45.65)	30 (55.56)	0.975	0.323
	Female	49	25 (54.35)	24 (44.44)		
Tumor diameter	< 5 cm	83	34 (73.91)	49 (90.74)	4.985	0.026
	≥ 5 cm	17	12 (26.09)	5 (9.26)		
Clinical stage	I-II	35	10 (21.74)	25 (46.30)	6.585	0.010
	III-IV	65	36 (78.26)	29 (53.70)		
Depth of invasion	T1-T2	55	20 (43.48)	35 (64.81)	4.569	0.033
	T3-T4	45	26 (56.52)	19 (35.19)		
Degree of differentiation	Low	29	13 (28.26)	16 (29.63)	0.023	0.880
	Moderate-high	71	33 (71.74)	38 (70.37)		
Postoperative adjuvant therapy	Yes	10	3 (6.52)	7 (12.96)	1.145	0.285
	No	90	43 (93.48)	47 (87.04)		
Lymph node metastasis	Yes	34	22 (47.83)	12 (22.22)	7.257	0.007
	No	66	24 (52.17)	42 (77.78)		

Table II. Associations between different PNI and clinicopathological features

Clinicopathological feature		*n*	Low PNI group (*n* = 48)	High PNI group (*n* = 52)	t/χ^2	*p*
Age (year)		100	58.33 ± 10.65	58.96 ± 12.08		
Gender	Male	51	26 (54.17)	25 (48.08)	0.370	0.543
	Female	49	22 (45.83)	27 (51.92)		
Tumor diameter	< 5 cm	83	35 (72.92)	48 (92.31)	6.652	0.010
	≥ 5 cm	17	13 (27.08)	4 (7.69)		
Clinical stage	I-II	35	24 (50.00)	11 (21.15)	9.129	0.003
	III-IV	65	24 (50.00)	41 (78.85)		
Depth of invasion	T1-T2	55	18 (37.50)	37 (71.15)	11.422	0.001
	T3-T4	45	30 (62.50)	15 (28.85)		
Degree of differentiation	Low	29	12 (25.00)	17 (32.69)	0.717	0.397
	Moderate-high	71	36 (75.00)	35 (67.31)		
Postoperative adjuvant therapy	Yes	10	6 (12.50)	4 (7.69)	0.641	0.423
	No	90	42 (87.50)	48 (92.31)		
Lymph node metastasis	Yes	34	18 (37.50)	16 (30.77)	0.504	0.478
	No	66	30 (62.50)	36 (69.23)		

Table III. Associations between different CRP/PA and clinicopathological features

Clinicopathological feature		*n*	Low CRP/PA group (*n* = 57)	High CRP/PA group (*n* = 43)	t/χ2	*p*
Age (year)		100	60.23 ± 11.48	59.48 ± 10.33		
Gender	Male	51	30 (52.63)	21 (48.84)	0.141	0.707
	Female	49	27 (47.37)	22 (51.16)		
Tumor diameter	< 5 cm	83	54 (94.74)	29 (67.44)	12.941	< 0.001
	≥ 5 cm	17	3 (5.26)	14 (32.56)		
Clinical stage	I-II	35	29 (50.88)	6 (13.95)	14.688	< 0.001
	III-IV	65	28 (49.12)	37 (86.05)		
Depth of invasion	T1-T2	55	40 (70.18)	15 (34.88)	12.334	< 0.001
	T3-T4	45	17 (29.82)	28 (65.12)		
Degree of differentiation	Low	29	15 (26.32)	14 (32.56)	0.464	0.496
	Moderate-high	71	42 (73.68)	29 (67.44)		
Postoperative adjuvant therapy	Yes	10	2 (3.51)	8 (18.60)	6.206	0.013
	No	90	55 (96.49)	35 (81.40)		
Lymph node metastasis	Yes	34	14 (24.56)	20 (46.51)	5.263	0.022
	No	66	43 (75.44)	23 (53.49)		

Table IV. Numbers of survival patients in different groups at each time point *(n)*

Time (month)	Group					
	Low BMI	High BMI	Low PNI	High PNI	Low CRP/PA	High CRP/PA
10	46	54	48	52	57	43
20	43	54	45	50	57	43
30	35	54	34	41	50	30
40	26	50	23	38	39	14
50	13	37	13	38	35	10
60	11	34	9	36	35	10

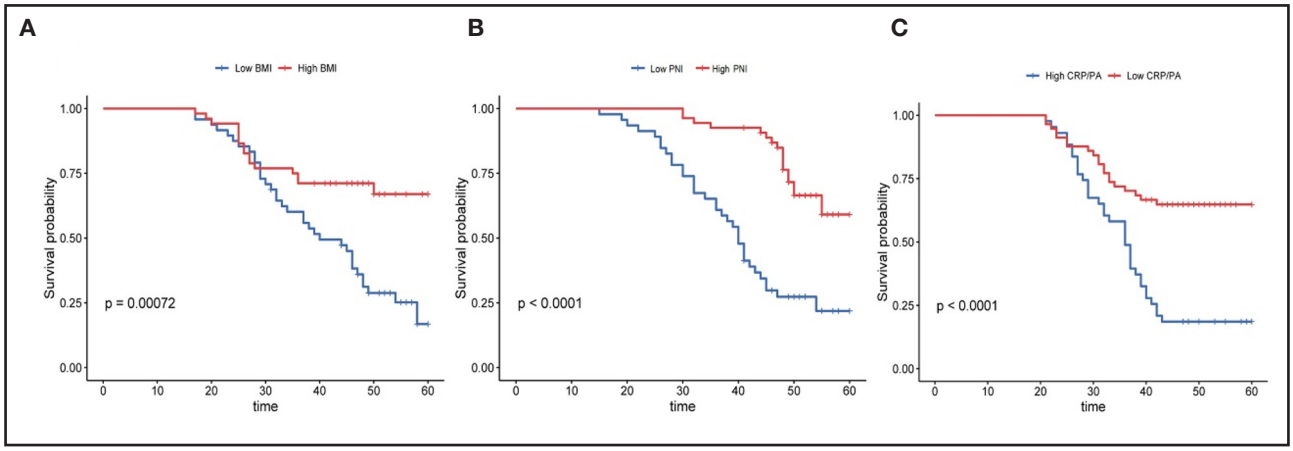

Figure 2.

Associations of BMI, PNI and CRP/PA with gastric cancer patients' outcome investigated by Kaplan-Meier survival analysis.

DISCUSSION

A preoperative abnormal BMI, slightly higher or lower, serves as a risk factor independently affecting the prognosis following operation (including resection of liver cancer, gastrointestinal cancer, and other digestive system tumors) (15). Weight loss not only affects the patients' tolerance and efficacy of treatment, but also increases complications such as infections, resulting in a decline in quality of life and an increase in treatment costs (16). In a recent study exploring the correlation between BMI and prognosis of mantle cell lymphoma (MCL), a low BMI group together with a high BMI group was created to enroll the patients based on the critical value (24 kg/m^2), and they all underwent combined chemotherapy (17). The high BMI group, in comparison to the low BMI group, exhibited a lower death rate and longer OS and progression-free survival, suggesting that high BMI is a protective factor for the prognosis of MCL patients. At present, diversified carcinomas covering gastric cancer (18), renal carcinoma and breast carcinoma have been researched to verify how PNI influences the prognosis (19,20). CRP is an acute phase-reactive protein synthesized by the liver. In the case of inflammatory infection, trauma, stress reaction and fever, CRP generally increases within 2 h, and it enhances the phagocytic function and activates complement during inflammatory responses, which is one of the commonly used inflammatory indicators. Some studies have pointed out that CRP increases to different degrees in patients with malignancies, whose mechanism is related to tumor cell reproduction and division and activation of inflammatory cells and related inflammatory factors. In terms of the underlying mechanism, CRP accelerates angiogenesis by raising interleukin and angiogenic factors in carcinoma sufferers at the circulating level (21). In addition, PA, as a commonly used assessment indicator for nutritional status in clinic, has an intimate relation to the poor outcome of various malignant tumors (22). CRP/PA combines inflammatory responses and nutritional status, and the former is a crucial player in the occurrence and progression of gastric cancer (23).

The cut-off values of BMI, PNI and CRP/PA on the ROC curve were obtained, and the associations of different BMI, PNI and CRP/PA with clinicopathological features of subjects with gastric carcinoma were explored in the present research. It was revealed that BMI was related to the tumor diameter, lymph node metastasis status, invasion depth and clinical stage, PNI was associated with the tumor diameter, clinical stage and invasion depth, and CRP/PA was related to the invasion depth, tumor diameter, lymph node metastasis status, clinical stage, and adjuvant chemotherapy. It can be seen that BMI, PNI and CRP/PA may be involved in gastric carcinoma from the aspect of incidence and progression. BMI reflects the body weight of patients, PNI reflects the nutrition condition in patients, and CRP/PA shows the inflammation severity. The aforementioned three indicators jointly display the physiological conditions of patients, thereby affecting the post-transplant prognosis. In practical clinical work, therefore, the comprehensive evaluation of BMI, PNI and CRP/PA can help improve the accuracy of prognostic prediction for patients undergoing radical gastrectomy. In addition, the OS rate rose prominently in the low BMI group, low PNI group and high CRP/PA group by contrast to that in the high BMI group, high PNI group and low CRP/PA group ($p < 0.05$), according to the Kaplan-Meier survival analysis. BMI may affect the prognosis of patients by affecting their immune function plus nutrition condition, and a higher BMI may indicate better nutritional status, benefitting the prognosis. PNI may affect the immune function of patients, and CRP/PA may reflect the inflammatory responses and immune function of patients, thereby influencing the prognosis.

In conclusion, BMI, PNI and CRP/PA have important predictive value for the prognosis of patients undergoing radical gastrectomy, which can not only provide an effective basis for curing gastric carcinoma in clinic, but also help improve patients' survival rate. These indicators can help clinicians to more accurately assess the prognosis of patients undergoing radical gastrectomy and provide personalized treatment plans for patients. However, it is necessary to further expand the sample size in the future to validate the reliability and practicability of the combined prediction model.

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Trabajo Original

Valoración nutricional

Influence of handgrip strength on postoperative complications and survival in primary liver cancer patients

Influencia de la fuerza de prensión en las complicaciones posoperatorias y la supervivencia en pacientes con cáncer de hígado primario

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Abstract

Objectives: the impact of handgrip strength (HGS) on postoperative complications and long-term survival following hepatectomy in patients with primary liver cancer (PLC) remains unclear. This study aimed to evaluate the influence of HGS on postoperative complications and overall survival in patients with PLC.

Methods: in total, 298 patients with PLC who underwent liver resection were included in the prospective cohort study. Baseline, surgical, and histopathological factors were analyzed using univariate and multivariate analyses to identify risk factors for postoperative complications and mortality.

Results: the incidence of major postoperative complications was 40.3 % and 24.6 % in the low and high HGS groups, respectively. During the median follow-up period of 28.8 months, 57 patients (19.1 %) died. patients with low HGS demonstrated a significantly shorter median overall survival compared to those with high HGS ($p < 0.001$). Short-term analysis revealed that low HGS ($p = 0.022$) and intraoperative blood loss (≥ 200 ml) ($p < 0.001$) were independently associated with postoperative complications. Furthermore, low HGS was identified as an independent predictor of poor overall survival in long-term survival analysis ($p = 0.005$).

Conclusions: preoperative HGS emerged as an independent factor for postoperative complications and a prognostic indicator of poor long-term outcomes in patients with PLC.

Keywords:

Hand grip strength. Primary liver cancer. Nutrition assessment. Postoperative complications. Overall survival. Hepatectomy.

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Resumen

Objetivos: el impacto de la fuerza de prensión (HGS) en las complicaciones posoperatorias y la supervivencia a largo plazo tras la hepatectomía en pacientes con cáncer de hígado primario (PLC) sigue siendo incierto. Este estudio tuvo como objetivo evaluar la influencia de la HGS en las complicaciones posoperatorias y la supervivencia global en pacientes con PLC.

Métodos: un total de 298 pacientes con PLC que se sometieron a resección hepática fueron incluidos en el estudio de cohorte prospectivo. Los factores basales, quirúrgicos e histopatológicos fueron analizados mediante análisis univariados y multivariados para identificar los factores de riesgo de complicaciones posoperatorias y mortalidad.

Resultados: la incidencia de complicaciones posoperatorias mayores fue del 40,3 % y 24,6 % en los grupos de HGS baja y alta, respectivamente. Durante el período de seguimiento mediano de 28,8 meses, 57 pacientes (19,1 %) fallecieron. Los pacientes con HGS baja mostraron una mediana de supervivencia global significativamente más corta en comparación con aquellos con HGS alta ($p < 0,001$). El análisis a corto plazo reveló que la HGS baja ($p = 0,022$) y la pérdida de sangre intraoperatoria (≥ 200 ml) ($p < 0,001$) se asociaron de forma independiente con complicaciones posoperatorias. Además, en el análisis de supervivencia a largo plazo, se identificó la HGS baja como un predictor independiente de una mala supervivencia global ($p = 0,005$).

Conclusiones: la HGS preoperatoria se comportó como un factor independiente para las complicaciones posoperatorias y un indicador pronóstico de malos resultados a largo plazo en pacientes con PLC.

Palabras clave:

Fuerza de prensión. Cáncer de hígado primario. Evaluación nutricional. Complicaciones posoperatorias. Supervivencia global. Hepatectomía.

INTRODUCTION

Primary liver cancer (PLC) ranks sixth in terms of occurrence, while its mortality rate ranks fourth globally, making it one of the most dangerous malignancies. According to Globocan 2018, approximately half of new PLC cases and related death were recorded in China (1). Hepatectomy is the mainstay of treatment for PLC (2). While advancements in surgical techniques, rapid recovery applications, and perioperative management have led to a reduction in recurrence and mortality after liver resection, postoperative complications still occur in 15 %-50 % of cases (3). Although new therapeutic modalities have been introduced for PLC, the overall survival rates remain poor (4).

Handgrip Strength (HGS) offers an invaluable and non-invasive approach to evaluating muscle function (5), predicting nutritional level and overall health status (6,7), as supported by existing research. Additional applications of HGS include the ability to detect early signs of malnutrition through its sensitivity to protein inactivation (8). In cancer *patient*s, the significance of HGS has become evident, as it has been identified as a risk factor for postoperative complications (9,10), longer hospital stays (11) and treatment toxicity (12). Furthermore, the correlation between reduced muscle strength (measured by HGS) and higher mortality rates emphasizes the importance of this metric (13,14). Hence, the HGS is a vital tool for assessing nutritional levels and predicting health outcomes.

Sarcopenia, a loss of skeletal muscle mass, has been the focus of recent PLC research regarding its impact on liver resection prognosis (15-17). Individuals with sarcopenia who undergo hepatic resection experience higher rates of major complications (17) and lower overall and recurrence-free survival compared to those without sarcopenia (15). The European Working Group on Sarcopenia in Older People revised its 2018 guidelines, stating that probable sarcopenia is identified by low muscle strength, with diagnosis confirmed by low muscle quantity or quality (18). The HGS measurement is a simple and cost-effective method that has long been used to objectively quantify muscle strength.

However, the direct correlation between HGS and postoperative outcomes after liver resection remains largely unexplored. Existing research is limited by its focus on the short- or long-term implications of HGS in this specific context. To bridge this knowledge gap, further investigations are required to better understand the extent to which HGS influences the outcomes of liver resection. It remains uncertain whether HGS can serve as a prognostic indicator in these settings; however, it has the potential to be a valuable and straightforward test. This study aimed to evaluate the impact of HGS on short- and long-term outcomes following hepatectomy in *patient*s with PLC. Our hypothesis suggests that low preoperative HGS could serve as a risk factor for poorer prognosis in the postoperative period. However, there is limited research examining this specific relationship in the context of liver resection.

MATERIALS AND METHODS

STUDY DESIGN

We retrospectively evaluated 298 patients with primary liver cancer who underwent hepatectomy at the Tianjin Medical University Cancer Hospital, Tianjin, China, from April 2018 to December 2023. During this time period, HGS was measured in all included populations before surgery. The study inclusion criteria were as follows: age 18-80 years, pathological diagnosis of PLC, well-compensated liver function, no contraindications for surgery, and no obvious hydrothorax or hydroperitoneum. The exclusion criteria were: complication with other malignant tumors and metastatic liver cancer. This study was approved by the Ethics Committee of Tianjin Medical University Cancer Hospital (No. Lx20190814). The current data are part of a registration trial (Clinical Registration No. NCT04218253).

A self-designed questionnaire was used to collect information. The data included baseline demographic data, histopathological variables, nutritional statistics, and surgical data. Based on them, all patients were staged according to tumor lymph nodes metastasis stage (TNM). This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all the participants prior to their inclusion in the study.

MEASUREMENT OF HANDGRIP STRENGTH

The HGS was measured using an electronic hand dynamometer (EH101; CAMRY, Guangdong, China). The dynamometer used in this study had a measurement range of 0 to 99.9 kg, with a precision of 0.1 kg. To enhance the grip, the handle of the dynamometer was customized to fit the size of each individual's palm. During the measurement process, the participants were instructed to maintain an upright stance with their feet shoulder-width apart, while keeping the dynamometer at a distance from their bodies. All patients were measured twice per hand for more than 3 s, and the highest result among the four measurements was used as the hand grip strength value.

To define low Handgrip Strength (HGS), specific thresholds were established based on age and gender. Based on the study by Mauricio SF et al. (19), for individuals aged ≥ 60 years, low HGS was indicated by grip strength ≤ 30 kg for men and ≤ 20 kg for women. For individuals below the age of 60, thresholds were set below 36.7 kg for men and below 20.8 kg for women.

ASSESSMENT OF PATIENT-GENERATED SUBJECTIVE GLOBAL ASSESSMENT (PG-SGA)

Nutritional status was evaluated using the PG-SGA, which is widely used in clinical nutrition assessment (20) and is detailed at PT-Global, consisting of two parts. The first part contains weight history, diet intake, symptoms and functions and needs to be completed by the participant. The second part includes diseases, age, metabolic stress and physical examination and is filled up by the investigator. The PG-SGA (Patient-Generated Subjective Global Assessment) score is divided into three levels: A (0-1) represents good nutrition, B (2-8) indicates suspicious or mild to moderate malnutrition and C (≥ 9) indicates severe malnutrition.

ASSESSMENT OF NUTRITIONAL RISK ASSESSMENT 2002 (NRS-2002)

NRS-2002 (Nutritional Risk Screening 2002) consists of three parts: disease severity score, nutritional status score and age. Given that all the patients underwent liver resection, the disease severity score was 2, ranging from 2 to 6. Remarkably, patients with a minimum NRS-2002 score of 3 were classified as having nutritional risk (21).

OUTCOMES

To determine the impact of the surgery, postoperative complications were assessed using the Clavien-Dindo classification, a recognized system that categorizes complications based on their severity. In this study, grade 2 or higher complications were deemed major complications, indicating their potential to significantly affect patient outcomes (22). The length of hospital stay, another crucial aspect of postoperative recovery, was measured from the day of operation until discharge. Subsequent follow-up appointments were scheduled at intervals of either 3 or 6 months to monitor progress and detect any potential complications or relapses in a timely manner. The last follow-up date was December 25, 2023. Overall survival (OS) was calculated from the date of surgery to the date of death from any cause.

STATISTICAL ANALYSIS

Statistical analysis of the data was performed using SPSS software (version 22). Continuous variables were tested using the Student's t-test or the non-parametric Mann-Whitney U test, and categorical variables were analyzed using Pearson χ^2 or Fisher's exact test. Correlations between variables were analyzed using Spearman's correlation test. Binomial univariate logistic regression analyses were used to identify factors associated with the occurrence of postoperative complications. Factors with a p-value of less than 0.1 were entered into a multiple logistic regression model to identify which factors were significantly correlated with postoperative complications. Cox proportional hazards regression analyses were performed to identify prognostic factors for OS. Multivariate analysis was performed for the factors with $p < 0.1$ in a univariate analysis. To assess survival, we employed the Kaplan-Meier method and compared survival curves using log-rank tests. Statistical significance was set at $p \leq 0.05$.

RESULTS

CHARACTERISTICS OF PARTICIPANTS

In this study, 298 patients were recruited, with males comprising 81.2 % (242) of the sample. Moreover, the participants in this study had a mean age of 58.57 ± 9.44 years. Participants were categorized into groups based on HGS: the low HGS group consisted of 62 patients (20.8 %), whereas the high HGS group included 236 patients (81.2 %). Table I shows the basic population characteristics of the patients divided by HGS.

Comparing the two groups, the low HGS group exhibited significantly lower weight ($p < 0.001$), body mass index (BMI) ($p < 0.001$), albumin (ALB) ($p < 0.001$) levels, hemoglobin (HGB) levels ($p = 0.001$), postoperative 5-day (POD5) ALB levels ($p = 0.011$), POD5 HGB levels ($p = 0.001$), a higher PG-SGA score ($p < 0.001$) and NRS-2002 score ($p = 0.001$), and higher TNM stage ($p = 0.024$), and longer postoperative hospital stay ($p = 0.031$) (Table I) were observed in the study participants. These findings indicate a clear association between HGS and various clinical parameters.

Table I. Sample demographic and clinical characteristics according to handgrip strength

Variables	High HGS *n* = 236	Low HGS *n* = 62	*p*-value
Age (years)[a]	58.18 ± 9.16	60.05 ± 10.38	0.165
SEX (male)	190	52	0.546
Weight (kg)	71.59 ± 12.52	63.65 ± 9.42	< 0.001
BMI (kg/m^2)	24.81 ± 3.42	22.86 ± 3.04	< 0.001
PG-SGA	3.41 ± 2.47	4.79 ± 2.85	< 0.001
NRS-2002	2.42 ± 0.81	2.84 ± 0.98	0.001
ALB (g/L)	42.29 ± 3.92	39.99 ± 4.36	< 0.001
PA (g/L)	0.19 ± 0.05	0.18 ± 0.06	0.199
HGB (g/L)	144.89 ± 16.38	136.94 ± 20.00	0.001
HGS (kg)	38.01 ± 8.79	27.69 ± 6.38	< 0.001
Comorbidity	89	30	0.127
Laparoscope (minimal invasive approach)	59	13	0.509
Intraoperative blood loss (mL) ≥ 200	70	16	0.551
Extent of resection (≥ 3 segments)	71	24	0.195
TNM stage			
I	185	40	0.024
II-IV	51	22	
Operation time (min)	154.51 ± 61.29	151.39 ± 81.30	0.758
Histopathological type			
HCC	198	50	0.209
ICC	33	8	
cHCC-CC	5	4	
POD5 ALB (g/L)	34.91 ± 4.22	33.33 ± 4.56	0.011
POD5 PALB (g/L)	0.11 ± 0.04	0.10 ± 0.04	0.092
POD5 HGB (g/L)	124.15 ± 18.96	114.56 ± 21.36	0.001
Postop69erative hospital stay (day)	8.68 ± 5.60	10.55 ± 7.48	0.031

BMI: body mass index; PG-SGA: Patient-Generated Subjective Global Assessment; NRS-2002: Nutritional Risk Screening 2002; ALB: albumin; PA: prealbumin; HGB: hemoglobin; HGS: handgrip strength; TNM: tumor lymph nodes metastasis stage; HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; cHCC-CC: combined hepatocellular carcinoma and cholangiocarcinoma; POD: postoperative day. [a]Means ± standard deviation or n. *A bold* p*-value indicates statistical significance (*p *< 0.05). Fisher's exact test, Chi-squared test, Student's t-test or Mann-Whitney U test.*

EXPLORING THE NEXUS BETWEEN HANDGRIP STRENGTH AND INDICES EXPLORING NUTRITION

Table II presents the relationship between the HGS and nutrition-related indices. HGS was positively correlated with BMI, ALB, prealbumin (PA), and HGB and negatively correlated with the PG-SGA and NRS-2002 scores. Notably, HGS strongly correlated with HGB levels ($r = 0.416$, $p < 0.001$). When analyzing the data by sex, HGS showed the highest correlation with BMI ($r = 0.344$, $p < 0.001$). However, among the female participants, no statistically significant correlation was observed between HGS and any of the evaluated indices.

LOW HANDGRIP STRENGTH GROUP SHOWS ELEVATED INCIDENCE OF MAJOR COMPLICATIONS

According to the Clavien-Dindo Classification (Table III), of the 83 patients examined, approximately 27.8 % encountered major complications. Notably, a higher occurrence of major complications (grade ≥ 2) was observed in the low HGS group than in the high HGS group. Specifically, 40.3 % of the patients in the low HGS group experienced major complications, while the incidence was lower at 24.6 % in the high HGS group. This discrepancy was statistically significant ($p = 0.014$). The subsequent table provides a breakdown of the complications according to age and sex (Supplementary Tables I and II).

Table II. Correlation between handgrip strength and nutritional assessment methods

	All (*n* = 298)		Male (*n* = 242)		Female (*n* = 56)	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value
PG-SGA	-0.141	0.015	-0.170	0.008	-0.260	0.053
NRS-2002	-0.126	0.029	-0.177	0.006	-0.190	0.160
BMI	0.26	< 0.001	0.344	< 0.001	0.061	0.653
ALB	0.212	< 0.001	0.238	< 0.001	0.143	0.292
PA	0.226	< 0.001	0.176	0.007	0.168	0.216
HGB	0.416	< 0.001	0.226	< 0.001	0.059	0.664

BMI: body mass index; PG-SGA: Patient-Generated Subjective Global Assessment; NRS-2002: Nutritional Risk Screening 2002; ALB: albumin; PA: prealbumin; HGB: hemoglobin.

Table III. Postoperative complications (Clavien-Dindo classification)

Grade	Total (*n*)	High HGS (*n* = 236)	Low HGS (*n* = 62)	*p*-value
Grade 0	100	77 (32.6)	23 (37.1)	
Grade 1	115	101 (42.8)	14 (22.6)	
Grade 2	57	42(17.8)	15 (24.2)	0.004
Grade 3	20	14 (5.9)	6 (9.7)	
Grade 4	6	2 (0.8)	4 (6.5)	
≥ Grade 2	83	58 (24.6)	25 (40.3)	0.014

HGS: handgrip strength. The values given are number (%).

Supplementary Table I. Postoperative complications by gender (Clavien-Dindo classification)

Grade	Total	Male (*n* = 242)	Female (*n* = 56)	*p*-value
Grade 0	100	73	27	
Grade 1	115	101	14	
Grade 2	57	43	14	-
Grade 3	20	19	1	
Grade 4	6	6	0	
≥ Grade 2	83	68	15	0.843

Supplementary Table II. Postoperative complications by age (Clavien-Dindo classification)

Grade	Total	< 65 (*n* = 213)	≥ 65 (*n* = 85)	*p*-value
Grade 0	100	76	24	
Grade 1	115	78	37	
Grade 2	57	39	18	-
Grade 3	20	14	6	
Grade 4	6	6	0	
≥ Grade 2	83	59	24	0.926

FACTORS ASSOCIATED WITH POSTOPERATIVE COMPLICATIONS IN LIVER RESECTION SURGERY

The univariate analysis revealed that several factors were significantly associated with postoperative complications (Table IV). These factors included the extent of resection (≥ 3 segments) ($p = 0.004$), intraoperative blood loss ≥ 200 ml ($p < 0.001$), lower HGS ($p = 0.015$) and higher TNM stage ($p = 0.047$). Additionally, laparotomy showed a trend towards significance with *p*-value below 0.1. Multivariate analysis revealed that blood loss (≥ 200 ml) (odds ratio [OR] = 2.81, 95 % CI: 1.60-4.93, $p < 0.001$) and low HGS (OR = 2.08, 95 % CI: 1.11-3.89, $p = 0.022$) were independently associated with postoperative complications. When grouped by age (Supplementary Tables III and IV), low HGS (OR = 3.10, 95 % CI: 1.40-6.82, $p = 0.005$) and intraoperative blood loss (≥ 200 ml) (OR = 3.02, 95 % CI: 1.53-5.96, $p = 0.001$) were significant risk factors for postoperative complications in the young age group.

Table IV. Logistic regression of risk factors for major complications

Variables	Univariate		Multivariate	
	OR (95 % CI)	*p*-value	OR (95 % CI)	*p*-value
Sex (male/female)	1.07 (0.56,2.06)	0.843		
Age (≥ 65)	1.03 (0.59,1.80)	0.926		
Laparotomy (yes)	1.82 (0.95,3.48)	0.070	1.52 (0.76,3.01)	0.235
Extent of operation Complex (≥ 3 segments)	2.18 (1.29,3.69)	0.004	1.54 (0.87,2.74)	0.141
Intraoperative blood loss (≥ 200 ml)	2.94 (1.72,5.03)	< 0.001	2.81 (1.60,4.93)	< 0.001
HGS (LOW)	2.07 (1.15,3.73)	0.015	2.08 (1.11,3.89)	0.022
Obesity (BMI ≥ 24)	0.79 (0.48,1.32)	0.366		
NRS-2002 ≥ 3	1.43 (0.86,2.37)	0.172		
Comorbidity (yes)	1.06 (0.63,1.78)	0.821		
TNM stage (II-IV)	1.77 (1.01,3.11)	0.047	1.38 (0.75,2.56)	0.298
Pathological type (HCC)	0.63 (0.33,1.20)	0.161		

HGS: handgrip strength; NRS-2002: Nutritional Risk Screening 2002; TNM: tumor lymph nodes metastasis stage; HCC: hepatocellular carcinoma.

Supplementary Table III. Logistic regression of risk factors for major complications in young group (age < 65) ($n = 213$)

Variables	Univariate		Multivariate	
	OR (95 % CI)	*p*-value	OR (95 % CI)	*p*-value
Sex (male/female)	1.04 (0.47, 2.31)	0.920		
Laparotomy (yes)	1.42 (0.69, 2.94)	0.344		
Extent of resection (≥ 3 segments)	2.18 (1.17, 4.06)	0.014	1.52 (0.76, 3.05)	0.238
Intraoperative blood loss (≥ 200 ml)	3.29 (1.74, 6.20)	< 0.001	3.02 (1.53, 5.96)	*0.001*
HGS (LOW)	3.38 (1.63, 6.98)	0.001	3.10 (1.40, 6.82)	*0.005*
Obesity (BMI ≥ 24)	0.66 (0.36, 1.21)	0.183		
NRS-2002 ≥ 3	1.83 (1.00, 3.36)	0.050	1.30 (0.67, 2.55)	0.440
Comorbidity (yes)	1.10 (0.58, 2.08)	0.772		
TNM stage (II-IV)	1.95 (1.02, 3.72)	0.043	1.60 (0.78, 3.25)	0.199
Pathological type (HCC)	0.56 (0.26, 1.21)	0.559		

HGS: handgrip strength; NRS-2002: Nutritional Risk Screening 2002; TNM: tumor lymph nodes metastasis stage; HCC: hepatocellular carcinoma.

Supplementary Table IV. Logistic regression of risk factors for major complications in elderly group (n = 85)

Variables	Univariate	
	OR (95 % CI)	*p*-value
Sex (male/female)	1.13 (0.36, 3.58)	0.833
Laparotomy (yes)	4.25 (0.90, 20.06)	0.068
Extent of resection (≥ 3 segments)	2.19 (0.81, 5.95)	0.124
Intraoperative blood loss (≥ 200 ml)	2.22 (0.79, 6.20)	0.130
HGS (low)	0.80 (0.27, 2.33)	0.678
Obesity (BMI ≥ 24)	1.22 (0.47, 3.15)	0.679
NRS-2002 ≥ 3	0.77 (0.30, 1.99)	0.586
Comorbidity (yes)	0.97 (0.37, 2.54)	0.954
TNM stage (II-IV)	1.34 (0.41, 4.44)	0.630
Pathological type (HCC)	0.84 (0.26, 2.73)	0.766

HGS: handgrip strength; NRS-2002: Nutritional Risk Screening 2002; TNM: tumor lymph nodes metastasis stage; HCC: hepatocellular carcinoma.

FACTORS ASSOCIATED WITH SURVIVAL IN PATIENTS UNDERGOING SURGERY

The median follow-up period was 28.8 months. The low HGS group had 22 deaths (mortality rate 35.48 %), whereas the high HGS group had 35 deaths (mortality rate 14.83 %). OS was significantly worse in the low HGS group than in the high HGS group (hazard ratio (HR) = 2.51, 95 % CI: 1.22-5.16, p = 0.013) (Fig. 1A). The median OS of patients with low HGS was 54.4 months (high HGS group not reached, $p < 0.001$). The survival curves demonstrated that an NRS-2002 score of ≥ 3 ($p = 0.013$), PG-SGA classification ($p = 0.003$) and serum albumin levels ≤ 40 ($p = 0.005$) were also associated with worse overall survival (OS) (Figs. 1 B-D).

Table V presents the results of the analysis of the prognostic factors for OS. In univariate analysis, the following factors were found to be statistically significant: extensive operation (≥ 3 segments) ($p = 0.017$), low HGS ($p < 0.001$), NRS-2002 score of ≥ 3 ($p = 0.014$), and occurrence of major postoperative complications ($p = 0.008$). The pathological type (hepatocellular carcinoma) showed a p value ≤ 0.1. Multivariate analysis concluded that only low HGS (HR = 2.29, 95 % CI: 1.29-4.07, $p = 0.005$) was a significant independent risk factor.

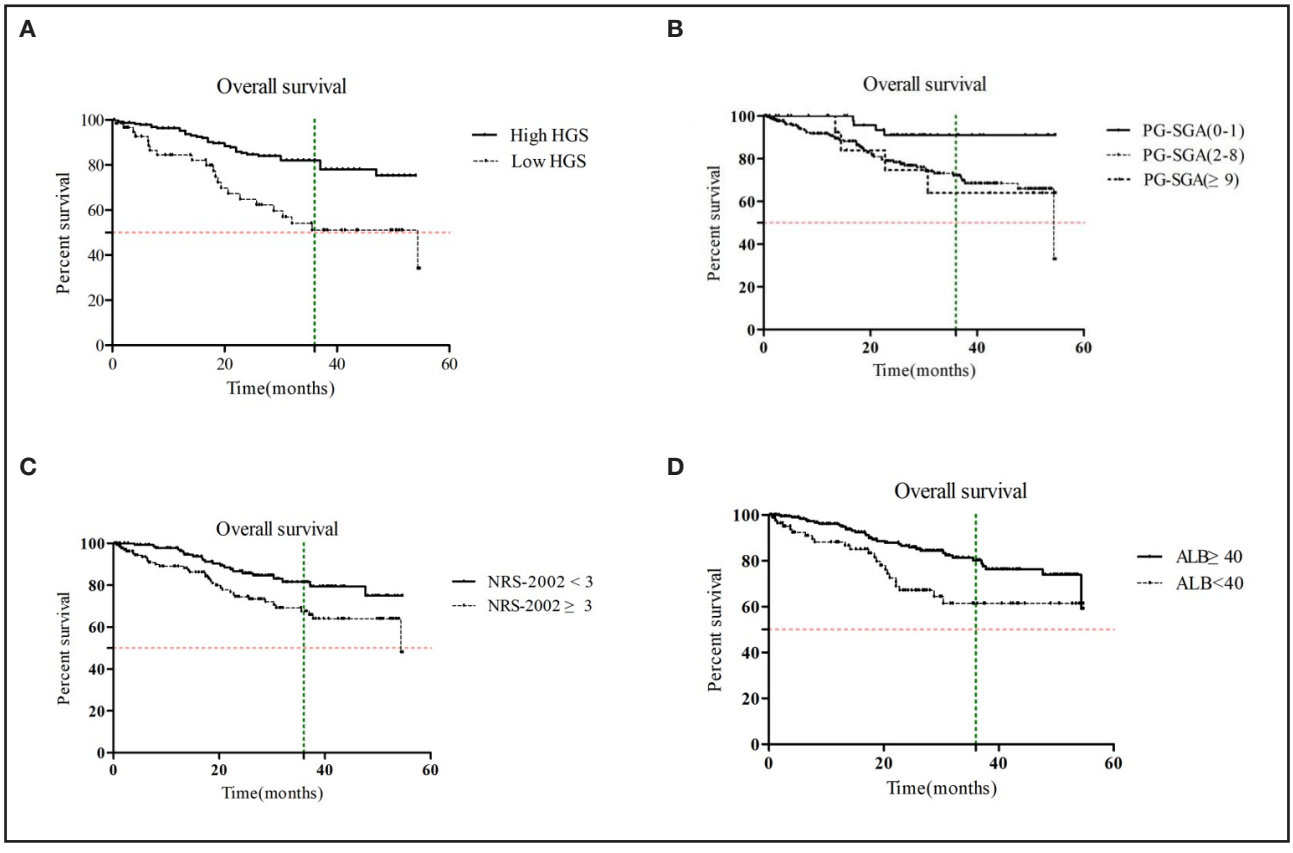

Figure 1.

Kaplan-Meier curve analysis stratified by (A) HGS ($p < 0.001$), (B) PG-SGA ($p = 0.03$), (C) NRS-2002 ($p = 0.013$) and (D) ALB ($p = 0.005$). HGS: handgrip strength; PG-SGA: Patient-Generated Subjective Global Assessment; NRS-2002: Nutritional Risk Screening 2002; ALB: albumin.

Table V. Univariate and multivariate analysis concern overall survival

Variables	Univariate		Multivariate	
	HR (95 % CI)	*p*-value	HR (95 % CI)	*p*-value
Sex (1 = female)	1.30 (0.64, 2.66)	0.470		
Age (≥ 65)	1.08 (0.62, 1.88)	0.790		
Laparotomy (yes)	1.47 (0.74, 2.91)	0.270		
Extent of resection (≥ 3 segments)	1.90 (1.12, 3.22)	0.017	1.54 (0.86, 2.76)	0.144
Intraoperative blood loss (≥ 200 ml)	1.03 (0.58, 1.82)	0.920		
HGS (low)	2.73 (1.60, 4.67)	< 0.001	2.29 (1.29, 4.07)	0.005
Obesity (BMI ≥ 24)	0.74 (0.44, 1.24)	0.250		
NRS-2002 ≥ 3	1.95 (1.14, 3.33)	0.014	1.44 (0.82, 2.54)	0.251
CD ≥ 2	2.06 (1.21, 3.51)	0.008	1.44 (0.80, 2.59)	0.224
Comorbidity (yes)	1.08 (0.64, 1.82)	0.785		
TNM stage (II-IV)	1.06 (0.58, 1.95)	0.843		
Pathological type (HCC)	0.58 (0.31, 1.09)	0.089	0.74 (0.38, 1.43)	0.358

HGS: handgrip strength; NRS-2002: Nutritional Risk Screening 2002; CD: Clavien-Dindo classification; TNM: tumor lymph nodes metastasis stage; HCC: hepatocellular carcinoma.

DISCUSSION

This study aimed to examine the influence of pre-operative Handgrip Strength (HGS) in patients diagnosed with primary liver cancer (PLC) and its impact on postoperative complications and overall survival (OS). Additionally, this study explored the correlation between the HGS and other nutritional assessment tools. Notably, the results indicated that low HGS and substantial intraoperative blood loss increased the risk of postoperative complications in patients with PLC. Furthermore, this study revealed that low HGS was an independent predictor of poor OS in patients with PLC. This investigation is the first to analyze the association between HGS and short- or long-term outcomes following hepatic resection in patients with PLC.

The HGS is an indicator that captures holistic muscle strength and is correlated with physical functionality (6). While the association between preoperative HGS and prognosis has been investigated in various cancer types, such as gastric (23), pancreatic (24), and esophageal cancers (9), limited attention has been given to its impact on Primary Liver Cancer. According to Sato et al. (9), HGS has been identified as a predictive factor for postoperative complications, specifically postoperative pneumonia, in males aged ≥ 70 years. However, this study did not find any significant correlation between HGS and postoperative complications in patients aged ≤ 70 years. Another study in 2022 (4) found that HGS, compared to other nutritional assessment tools, was independently associated with complication-free survival and approached significance for overall survival in patients with multiple liver cancer treatments (25). Thus, HGS has become a popular indicator for clinical assessment.

Furthermore, HGS has been suggested as a marker of aging and shown to influence the outcomes of various diseases (14,26). In this study, other nutritional assessment methods, such as NRS-2002 and BMI, did not predict postoperative complications in the final multivariate analysis. Univariate Cox analysis indicated that factors such as the extent of resection, major postoperative complications, and NRS-2002 scores ≥ 3 were related to shorter OS. Nevertheless, NRS-2002 scores were not significant prognostic factors in multivariate regression analysis. These findings highlight the beneficial use of HGS in identifying physical conditions among patients with PLC. Possible reasons for the superior predictive power of HGS over nutritional assessment tools include the fact that malnutrition and low HGS do not appear simultaneously (27). The HGS reflects the physical condition and illness status more accurately, making it a robust predictor of prognosis. For another, the current nutritional evaluation instruments may not possess the required sensitivity to detect slight variations in liver cancer prior to surgical intervention, while HGS might detect these changes earlier. Additionally, in the present study, an enhanced recovery protocol after surgery was applied, which possibly improve the patients' postoperative condition and eliminate the consequences of malnutrition. However, muscle function responds to early nutritional deprivation and recovery (5).

Baseline analysis showed significant associations between reduced HGS and indicators such as decreased body weight, lowered BMI, diminished albumin levels, elevated NRS-2002 scores, and increased PG-SGA scores. Further analysis revealed a negative relationship between the HGS and nutritional status, particularly in males. However, this relationship was not observed in females, likely attributed to the relatively small number of women in the study. Most studies have reported that individuals exhibiting elevated HGS demonstrate a reduced likelihood of malnutrition and nutritional vulnerability (28). As the liver is responsible

for nutrient metabolism, malnutrition is a significant risk factor for liver cancer. It is important to pay attention to the nutritional status of these patients, as malnutrition can worsen muscle loss and lead to inflammation, thereby affecting their clinical outcomes. Therefore, the nutritional status of patients with liver cancer and low HGS should be closely monitored.

Sarcopenia is defined by the new edition of the European Working Group on Sarcopenia in Older People as a decline in muscle strength and muscle mass (29). Many studies have focused on the association between sarcopenia and short- (15) and long-term prognosis after hepatectomy in patients with liver cancer. Harimoto et al. (15,16) reported that sarcopenia is a prognostic factor for overall and recurrence-free survival in patients following partial hepatectomy. A French study showed that the difference in postoperative mortality and morbidity rates between sarcopenic and nonsarcopenic groups was insignificant (30); however, complications were not analyzed as key outcome variables in this study. Findings from Europe and America reached slightly different conclusions. A study conducted by Valero et al. (31) reported that severe complications (Clavien grade ≥ 3) occurred only in patients with sarcopenia. The differences can be explained by variations in race, heterogeneous cohorts and assessment methods. In summary, sarcopenia predicts a poor outcome after hepatectomy. Unfortunately, several components of sarcopenia such as muscle quantity or gait speed were not included in our study. Despite the potential clinical value of HGS and sarcopenia assessment, the use of sarcopenia is limited factors such as financial limitations and logistical intricacies pose challenges in implementing these findings into routine clinical practice.

In this study, the incidence of grade 2 or higher complications was 27.85 %, which is similar to that reported in a previous study (29 %) (30). To our knowledge, surgical complications are poor prognostic factors after surgery for hepatocellular carcinoma (HCC) (15). Yang et al. (32) showed that short-term postoperative complications of HCC affect the overall postoperative and recurrence-free survival. Medical teams have strived to reduce the incidence of complications. In addition, surgical blood loss (≥ 200 ml) was identified as an independent risk factor for complications. Intraoperative bleeding has been used to predict treatment outcomes (33), mortality and recurrence (34,35). Nevertheless, postoperative complications and intraoperative blood loss remain important concerns for patients undergoing hepatic resection, even though they do not have a significant effect on survival in the final prognostic analysis.

Clinical practice guidelines recommend evaluating patients with liver disease to assess malnutrition and sarcopenia before surgery. Appropriate management of sarcopenia can improve protein status and clinical outcomes (36,37). Early detection and treatment of low HGS using various strategies can enhance the postoperative outcomes in frail patients. Physical exercise has anti-catabolic and anabolic effects on muscles, releasing muscle factors that can positively affect treatment and cachexia (38,39). Additionally, enhancing muscle state through nutritional interventions and regular physical activity has the potential to influence both surgical results (40) and long-term survival (41,42). Pre-rehabilitation studies using resistance training have been shown to reduce postoperative complications in different diseases; however, their effect on poor prognosis resulting from low grip strength has not been studied.

One advantage of this study was that HGS and nutrition were assessed by a trained dietitian, thereby avoiding differences between evaluators. In addition, various preoperative nutritional assessment tools were used to comprehensively assess patients' overall preoperative status. Nevertheless, this study has some limitations. Progression-free survival data were unavailable. In future experimental designs, missing data will be accounted for, and a larger sample size will be used to determine reliable cutoff values for different sex and age groups. The findings from this study are not applicable to patients with advanced liver cancer, as they included only patients who underwent feasible surgical resection. Large observational studies are required to further analyze the association between handgrip strength and far-reaching results. Future studies should also explore whether perioperative muscle strength training can prolong the prognosis.

CONCLUSIONS

Preoperative HGS has been found to have negative effects on the present and future after surgical removal of the liver in individuals diagnosed with PLC. As a straightforward, uncomplicated and cost-effective measure of nutritional profile, HGS should be routinely measured before surgery. The use of HGS as a preoperative indicator can be easily implemented by any healthcare professional following the prescribed procedures. Consequently, it is recommended that HGS measurement becomes a regular practice, as it can provide valuable insights into patients' nutritional status prior to surgery.

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Trabajo Original

Valoración nutricional

Evaluating sarcopenia and nutritional status in outpatients with liver cirrhosis: concordance of diagnostic methods

Evaluación de la sarcopenia y del estado nutricional en pacientes ambulatorios con cirrosis hepática: concordancia de métodos diagnósticos

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Abstract

Introduction and objectives: malnutrition and sarcopenia are prevalent in individuals with cirrhosis, but their diagnosis remains challenging due to limited access to suitable methods across different levels of healthcare. This study aimed to identify the most effective method for diagnosing sarcopenia in outpatients with liver cirrhosis and to evaluate the concordance between subjective and objective diagnostic methods.

Patients and methods: patients aged ≥ 18 years with a diagnosis of cirrhosis (regardless of etiology) under outpatient care were included. Exclusion criteria were: a) neoplasia, b) acute liver failure, c) pregnancy/lactation, d) HIV infection, e) special situations requiring liver transplantation, and f) history of organ failure. Nutritional and sarcopenia assessments used subjective methods, including the Royal Free Hospital-Nutritional Prioritizing Tool (RFH-NPT), SARC-F, SARC-Calf, and RFH-Global Assessment (RFH-GA); and objective methods, including anthropometry, handgrip strength (HGS), the sit-and-stand test (15s), and appendicular skeletal muscle mass index (ASMI) by Dual-Energy X-ray Absorptiometry (DXA). Concordance between ASMI and traditional methods was analyzed. Significance was set at $p < 0.05$.

Results: a total of 45 patients were analyzed, with alcoholic liver disease being the most frequent etiology (44.4 %). The sit-and-stand test (15s) combined with muscle depletion by DXA diagnosed the most cases of sarcopenia (42.2 %). Moderate agreement was found between muscle depletion and isolated calf circumference (CC) ($\kappa = 0.581$; $p < 0.001$).

Conclusions: our study suggests excluding SARC-F and SARC-CalF from sarcopenia screening in outpatients with cirrhosis. While ASMI remains the most reliable diagnostic method, CC may serve as a feasible alternative when DXA is unavailable.

Keywords:

Nutritional status. Liver disease. Malnutrition. Muscular atrophy and liver transplant.

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Institutional Review Board Statement: It was approved by the Ethics Committee no. 5.432.777 on May 26, 2022.

Informed consent statement: All participants in this study signed the Informed Consent Form (ICF).

Data availability statement: This is an unpublished work, not under submission process in any other scientific journal. All data is privately accessible.

Highlights: a) SARC-F tool is inadequate for sarcopenia screening outpatients with liver cirrhosis; b) chair sit-and-stand test proved to be the most effective tool for identifying low muscle strength; c) CC is a viable alternative for muscle mass assessment when DXA or CT are unavailable.

Conflict of interest: The authors declare that they have no conflict of interest.

Artificial intelligence: The authors declare not to have used artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

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Resumen

Introducción y objetivos: la desnutrición y la sarcopenia son prevalentes en individuos con cirrosis, pero su diagnóstico sigue siendo un desafío debido al acceso limitado a métodos adecuados en los diferentes niveles de atención en salud. Este estudio tuvo como objetivo identificar el método más efectivo para diagnosticar sarcopenia en pacientes ambulatorios con cirrosis hepática y evaluar la concordancia entre los métodos de diagnóstico subjetivos y objetivos.

Pacientes y métodos: se incluyeron pacientes de ≥ 18 años con diagnóstico de cirrosis (independientemente de la etiología) en atención ambulatoria. Los criterios de exclusión fueron: a) neoplasia, b) insuficiencia hepática aguda, c) embarazo/lactancia, d) infección por VIH, e) situaciones especiales que requirieran trasplante hepático y f) antecedentes de insuficiencia orgánica. Las evaluaciones de desnutrición y sarcopenia utilizaron métodos subjetivos, como el Royal Free Hospital-Nutritional Prioritizing Tool (RFH-NPT), SARC-F, SARC-Calf y RFH-Global Assessment (RFH-GA); y métodos objetivos como antropometría, fuerza de agarre manual (HGS), prueba de sentarse y levantarse (15s) e índice de masa muscular esquelética apendicular (ASMI) por absorciometría dual de rayos X (DXA). Se analizó la concordancia entre ASMI y los métodos tradicionales. Se estableció significancia en $p < 0.05$.

Resultados: se analizaron un total de 45 pacientes, siendo la enfermedad hepática alcohólica la etiología más frecuente (44.4 %). La prueba de sentarse y levantarse (15s) combinada con la depleción muscular medida por DXA diagnosticó la mayor cantidad de casos de sarcopenia (42.2 %). Se observó una concordancia moderada entre la depleción muscular y la circunferencia de la pantorrilla aislada (CC) ($\kappa = 0.581$; $p < 0.001$).

Conclusiones: nuestros hallazgos sugieren excluir SARC-F y SARC-CalF del cribado de sarcopenia en pacientes ambulatorios con cirrosis. Aunque ASMI sigue siendo el método diagnóstico más confiable, la CC puede servir como alternativa viable cuando DXA no esté disponible.

Palabras clave:

Estado nutricional. Enfermedad hepática. Desnutrición. Atrofia muscular. Trasplante hepático.

INTRODUCTION

The liver is the principal metabolic organ in the human body, responsible for numerous complex biochemical processes involving the metabolism of carbohydrates, proteins, and lipids; storage and activation of vitamins; detoxification and excretion of endogenous and exogenous products, among others. As liver function declines, systemic overload increases, leading to a depletion in nutritional status, which is evident even in the early stages of liver disease (1).

Sarcopenia, recognized as a muscular disease characterized by a reduction in both the quality and quantity of muscle mass, has an estimated prevalence of 37.5 % in patients with cirrhosis. When present, it increases the mortality risk of this population by 2.6 times (2).

Aiming at screening for sarcopenia and identifying the risk of poor functional outcomes, the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) in 2019 suggested an algorithm involving the following steps: (i) screening, using the SARC-F questionnaire which subjectively assesses strength, assistance with walking, getting up from a chair, climbing stairs, and falls; (ii) assessment of muscle strength through methods such as handgrip strength (HGS) and the chair stand test; (iii) evaluation of muscle quantity and quality using body composition methods (3). As an alternative to SARC-F, Barbosa-Silva et al. (2016) proposed the SARC-Calf tool, which adds calf circumference to the subjective criteria of SARC-F (4).

Due to the symptomatic characteristics of patients with cirrhosis, such as ascites and edema, the step of assessing muscle quality and quantity becomes challenging, as it hinders the use of bioelectrical impedance analysis, increasing the reliance on imaging methods such as dual-energy X-ray absorptiometry (DXA) and computed tomography (CT), which are costly and difficult to access in clinical practice (5).

Given the challenges and uncertainties in assessing the presence of sarcopenia in patients with cirrhosis, as well as the impact of its development on the quality of life and survival of these individuals, early identification is essential to establish effective clinical and nutritional treatment. In this context, the objective of this study is to identify the best method for diagnosing sarcopenia in patients with cirrhosis, as well as to evaluate the concordance of subjective and anthropometric methods – classically used in the assessment of these patients – with sarcopenia diagnosed by DXA.

PATIENTS AND METHODS

STUDY DESIGN

This is a cross-sectional study conducted in the Infectious and Parasitic Diseases Department of Professor Alberto Antunes University Hospital, Maceió/Alagoas, Brazil, from October 2022 to November 2023.

STUDY GROUPS

Patients aged ≥ 18 years and less than 70 years, of both sexes, diagnosed with liver cirrhosis, were eligible for participation and divided into two groups. One group had score Model for End-Stage Liver Disease-sodium (MELD-Na) ≥ 15, eligible for Liver Transplant (LT), while the other group had MELD-Na ≤ 14, with portal hypertension. Eligible criteria for portal hypertension were ascites presence, splenomegaly, esophagogastric varices, or the presence of portosystemic collaterals (patent paraumbilical vein, splenorenal collaterals, dilated left gastric veins, and short veins). Exclusion criteria included: (a) neoplasia; (b) acute liver failure; (c) pregnant and lactating women; (d) human immunodeficiency virus infection; (e) patients listed for liver transplantation due to special conditions (intractable pruritus, recurrent cholangitis, refractory ascites, persistent hepatic encephalopathy); (f) history of organ failure affecting nutritional status, such as renal replacement therapy, respiratory, and cardiac failure.

SAMPLE SIZE

This is an exploratory study derived from an original research project aiming to identify the prevalence of sarcopenia among LT candidates. A relative risk of 3 for sarcopenia prevalence was expected, considering a baseline prevalence of 25 % in the control group (patients with liver cirrhosis but without LT indication). Assuming 80 % power and a 5 % alpha level, 19 patients were required in each group (Group 1: MELD-Na ≤ 14; Group 2: MELD-Na ≥ 15).

EVALUATION OF LIVER DISEASE SEVERITY

The severity of liver disease in patients was assessed MELD-Na scores and participants were categorized into two groups: ≤ 14, indicating patients not eligible for LT, and ≥ 15, indicating patients eligible for LT. These scores were determined through a clinical evaluation conducted by a specialized medical professional, combined with laboratory test results obtained at the time of consultation.

SOCIODEMOGRAPHIC DATA AND CLINICAL ASSESSMENT

Personal history, current disease history, presence of signs and symptoms, prior hospitalizations related to hepatic disease decompensation, lifestyle habits, etiology, and time of diagnosis were collected using a standard form.

NUTRITIONAL/FUNCTIONAL ASSESSMENT

Nutritional and functional tests applied to individuals can be visualized in table I.

EQUIPMENT AND TECHNIQUES

Weight and height measurements followed the technique recommended by Lohman (1988), using a Filizola® digital scale and a metal anthropometer (6). Arm circumference (AC) and calf circumference (CC) were measured with a non-extensible tape measure, while triceps skinfold (TSF) was assessed with a Lange® caliper (6). Tetrapolar bioelectrical impedance analysis (BIA) by Sanny® was used to determine the phase angle (PA). Appendicular Skeletal Muscle Mass (ASM) was obtained through Dual-Energy X-ray Absorptiometry (DXA) analysis using the Lunar Prodigy Primo system from GE HealthCare, with a full-body anteroposterior incidence, and the patient lying supine with extended legs, feet together, arms extended alongside the body, without adornments. Muscle strength was identified through the Individual performance in handgrip strength (HGS) using the Jamar® dynamometer, measured three times on the dominant hand by a trained professional.

ETHICAL CONSIDERATIONS

All patients provided written informed consent. The study was conducted following the ethical guidelines of the 1975 Helsinki Declaration. The protocol was approved by the Ethics Committee on May 26, 2022 (Opinion Number 5432777).

STATISTICAL ANALYSIS

We utilized the Statistical Package for Social Science (SPSS®), version 26.0, for all analyses. Descriptive statistics included frequencies, absolute and relative values (*n*/percentage), with continuous variables reported as mean and standard deviation. The kappa concordance test (κ) was used to evaluate the agreement between methods, interpreted as poor (< 0.0), slight (0.01-0.2), fair (0.21-0.4), moderate (0.41-0.6), substantial (0.61-0.8), and almost perfect (0.81-1.00) (15). We initially compared individual diagnostic methods with muscle mass as assessed by DXA. Subsequently, we combined techniques for assessing muscle strength and mass to determine whether any of these combinations showed concordance with the sarcopenia diagnosis obtained via DXA. The alpha value was set at 5 %.

RESULTS

We analyzed 45 patients, with the majority being male (68.9 %), and a mean age of 47.5 ± 14.2 years. Most resided in rural areas (60 %), and 57.8 % reported being married or in a stable relationship.

The most common etiology of liver disease was alcoholic (44.4 %). Among the individuals analyzed, approximately 37.8 % had comorbidities such as systemic arterial hypertension (SAH), diabetes *mellitus* (DM), obesity, dyslipidemia, and hypothyroidism. Additionally, 46.7 % reported episodes of hepatic decompensation in the last 6 months, including upper gastrointestinal bleeding (UGIB), ascites, and hepatic encephalopathy (HE) (Table II). Among these, 28.6 % reported a combination of ascites and HE, and 19 % had UGIB, ascites, and HE in the last 6 months. The presence of ascites and/or edema at the time of data collection is detailed in table II.

The prevalence rates of sarcopenia risk, low muscle strength, and reduced muscle mass are shown in table III. The SARC-Calf identified more patients at risk for sarcopenia compared to the SARC-F, with rates of 20.5 and 13.3, respectively. It is noteworthy that, due to the presence of lower limb edema and the consequent inability to measure CC, the SARC-Calf was applied to fewer patients than the SARC-F (86.7 of those evaluated).

The prevalence of low muscle strength was identified in 91.1 by the chair stand test compared to 15.6 by handgrip strength. Therefore, the chair stand test proved to be a more efficient screening method for sarcopenia than handgrip strength, identifying nearly six times more patients with reduced strength than dynamometry.

Table I. Nutritional and functional tests applied in outpatients with liver cirrhosis

Test	Characteristics	Categories
Appendicular skeletal muscle mass (ASM) and appendicular skeletal muscle mass index (ASMI)	Objective diagnosis of the amount of muscle mass, obtained by densitometry (DXA), summing the muscle masses of the upper and lower limbs. ASMI was calculates using ASM/height²	Depleted: ASM < 20 kg for men and < 15 kg for women, OR ASMI < 7 kg/m² and < 5.5 kg/m² for men and women (3)
Arm circumference (AC) adequacy %	Objective diagnosis of malnutrition	Depleted: AC adequacy < 90 % (7) Not depleted: AC adequacy < 90 %
BMI (kg/m²)	Real weight (kg) - for patients without ascites or edema in lower limbs; Or, Dry weight (kg) - for patients with ascites (deducting 5 %, 10 %, or 15 % of the current weight depending on the ascites classification (mild, moderate, or severe) [8]) or edema in lower limbs (discounting 1 kg, 3 kg, or 6 kg, if edema classified as mild, moderate, or severe, respectively [9]); And Real height (m) – patients aged < 60 years (measure performed in foot); Or, Estimated height - patients aged ≥ 60 years (classified as elderly in Brazil), height was estimated using the Chumlea technique (10)	Malnutrition: BMI < 18.5 kg/m² for adults (11) and BMI < 22.0 kg/m² for the aged (12) Not malnutrition: BMI ≥ 18.5 kg/m²) for adults and BMI ≥ 22.0 kg/m² for the aged
Calf circumference (CC) (cm)	Objective diagnosis of muscle depletion	Depleted: CC < 34 cm for men and < 33 cm for women (4);
Handgrip strength (HGS) (kgf)	Muscle strength/functional capacity screening, using dynamometer	Low strength muscle: HGS < 27 kg for men and < 16 kg for women (4)
Mid-arm muscle circumference (MAMC) adequacy (%)	Objective diagnosis of muscle depletion. Calculated using AC and triceps skinfold	Depleted: TSF adequacy < 90 % (7);
Phase Angle (PA) (°)	Diagnosis of cellular integrity, calculated from the resistance and reactance obtained by BIA	—
Royal Free Hospital Nutritional Prioritizing Tool (RFH-NPT)	Nutritional risk assessment (a combination of the following criteria: alcoholic hepatitis, tube feeding, fluid overload, and dietary intake)	With nutritional risk, RFH-NPT ≥ 1 point (13)
Royal Free Hospital Global Assessment (RFH-GA)	Subjective malnutrition diagnosis (a combination of the following criteria: BMI, MAMC, and dietary intake)	Malnutrition (14); well-noutrished
SARC-F and SARC-Calf	Sarcopenia screening. It uses scores referring to 5 domains that involve strength, difficulty walking, difficulty standing, difficulty climbing stairs and history of falls. For the SARC-CalF, the WC measurement was added	Risk of sarcopenia: SARC-F ≥ 4 (3) points or SARC-CalF ≥ 11 points (4)
Sit-to-stand test	Muscle strength/functional capacity screening	Low strength muscle: sit-to-stand test < 5 in 15 seconds (4)
Sarcopenia	Diagnosed using muscle strength/functional capacity (HGS or sit-to-stand test and appendicular skeletal muscle mass (ASM or ASMI)	Sarcopenia: HGS or sit-to-stand test with low strength muscle, and ASM or ASMI depleted (4)

Table II. Sociodemographic and clinical characteristics in outpatients with liver cirrhosis

Characteristics		*n* (%)
Age group	Adult	37 (82.2)
	Elderly	8 (17.8)
Race	White	11 (24.4)
	Black/brown	34 (75.6)
Schooling	≤ Elementary school incomplete	24 (53.3)
	Other	21 (46.7)
Alcohol consumption	No	14 (31.1)
	Ex-alcohol consumer	31 (68.9)
Etiology of cirrhosis	Alcohol	20 (44.4)
	Autoimmune hepatitis	6 (13.3)
	Cryptogenic hepatitis	6 (13.3)
	Metabolic dysfunction associated fatty liver disease	3 (6.7)
	Alcohol + hepatitis B infection	3 (6.7)
	Other	7 (15.5)
MELD-Na	≤ 14	22 (48.9)
	≥ 15	23 (51.1)
Cirrhosis complications	Upper gastrointestinal bleeding	7 (15.5)
	Hepatic encephalopathy	11 (24.4)
	Ascites	20 (44.4)
	Edema	10 (22.2)

MELD-Na: Model for End-stage Liver Disease-Sodium.

Table III. Prevalence of sarcopenia risk, low strength muscle, and muscle depletion in outpatients with liver cirrhosis

Risk of sarcopenia	Individuals	No (*n* [%])	Yes (*n* [%])
SARC-F	45	39 (86.7)	6 (13.3)
SARC-CalF	39	31 (79.5)	8 (20.5)
SARC-F/SARC-CalF		33 (73.3)	12 (26.7)
Strength muscle		**No (*n* [%])**	**Yes (*n* [%])**
Chair sit-and-stand test (15s)	45	4 (8.9)	41 (91.1)
Hand grip strength (HGS)	48	38 (84.4)	7 (15.6)
Chair sit-and-stand test (15s)/Hand grip strength	45	4 (8.9)	41 (91.1)
Muscle mass (DXA)		**No (*n* [%])**	**Yes (*n* [%])**
ASM	45	27 (60.0)	18 (40.0)
ASMI	45	30 (66.7)	15 (33.3)
ASM or ASMI	45	25 (55.6)	20 (44.4)
Sarcopenia		**No (*n* [%])**	**Yes (*n* [%])**
EWGSOP2 protocol (SARC-F + HGS + ASM/ASMI)	45	42 (93.3)	3 (6.7)
EWGSOP2 protocol (SARC-CalF + HGS + ASM/ASMI)	39	38 (97.4)	1 (2.6)
EWGSOP2 protocol (SARC-F + Chair sit-and-stand test (15s) + ASM/ASMI)	45	40 (88.9)	5 (11.1)
EWGSOP2 protocol (SARC-CalF + Chair sit-and-stand test (15s) + ASM/ASMI)	39	32 (80.0)	8 (20.0)
EWGSOP2 protocol (SARC-F/SARC-CalF + HGS/Chair sit-and-stand test (15s) + ASM/ASMI)	45	34 (75.6)	11 (24.4)
Chair sit-and-stand test (15s) + ASM/ASMI	45	25 (55.6)	20 (44.4)
HGS + ASM/ASMI	45	38 (84.4)	7 (15.6)

ASM: appendicular skeletal muscle; ASMI: appendicular skeletal muscle index; EWGSOP2: European Working Group on Sarcopenia in Older People 2.

Muscle depletion was highly prevalent, observed in 40 % of the evaluated patients. Interestingly, using the sarcopenia diagnostic protocol suggested by EWGSOP2, the prevalence of sarcopenia varied widely depending on the combination of assessment tools used. It ranged from 2.6 % (SARC-Calf + HGS + ASM/ASMI) to 20.0 % (SARC-Calf + Chair sit-and-stand test (15s) + ASM/ASMI), indicating significant variability in the diagnosis of sarcopenia among outpatients with cirrhosis. When positivity in any of the forms (SARC-F or SARC-Calf) and strength tests (HGS or chair sit-and-stand test) was considered, the prevalence increased to 24.4 %.

Notably, the combination of the chair stand test with reduced muscle mass (ASM/ASMI) identified 44.4 % of patients with cirrhosis as having both low strength and low muscle mass, classifying them as sarcopenic. Furthermore, those identified with muscle depletion by DXA were the same individuals classified as sarcopenic, indicating that reduced muscle mass in this group necessarily reflects low strength. This finding aligns with the sarcopenia screening sequence, where decreased strength precedes muscle mass reduction, and underscores the importance of assessing muscle mass in these individuals.

To determine the best method for diagnosing sarcopenia in outpatients with cirrhosis, we compared different muscle and nutritional assessment techniques with muscle depletion diagnosed by DXA. The concordance analysis (Table IV) showed that among anthropometric assessments, CC demonstrated the highest agreement with muscle depletion ($\kappa = 0.581$; $p < 0.001$), successfully identifying 60 % of patients with reduced muscle mass (MMEA/IMMEA). This indicates that CC is the most reliable anthropometric measure for identifying muscle depletion in this population when DXA is unavailable.

Other anthropometric measures, such as AC ($\kappa = 0.341$; $p = 0.019$) and MMAC adequacy ($\kappa = 0.348$; $p = 0.014$), showed fair agreement with DXA being less effective than CC. BMI displayed slight agreement ($\kappa = 0.120$; $p = 0.198$), highlighting its limited utility in detecting sarcopenia in patients with cirrhosis.

Regarding subjective nutritional assessments, the RFH-GA ($\kappa = 0.364$; $p = 0.014$) and RFH-NPT ($\kappa = 0.143$; $p = 0.289$) showed a fair level of agreement with muscle depletion. These findings suggest that while subjective assessments may offer some insights, they cannot replace more objective measures, particularly DXA and CC, in accurately diagnosing sarcopenia.

Therefore, identifying muscle depletion using CC, especially in settings without DXA, appears to be a practical and effective approach for diagnosing sarcopenia in outpatients with cirrhosis.

DISCUSSION

Studies confirm that early identification of nutritional risk, as well as risk of sarcopenia and sarcopenia itself, is crucial for ensuring accurate treatment, potential reversal of the condition, improved prognosis, and quality of life for the affected individual (16-18).

Table IV. Concordance between muscular mass by dual-energy X-ray absorptiometry (DXA) and anthropometrics assessment and subjective instruments used in outpatients with liver cirrhosis

Total		Muscular mass (ASM/ASMI)			Concordance	
		Total	Adequate *n* = 25	Depleted *n* = 20	Kappa	*p*
Anthropometric assessment						
BMI (kg/m²)	Not Malnutrition	41 (91.1)	24 (96.0)	17 (85.0)	0,120	0.198
	Malnutrition	4 (8.9)	1 (4.0)	3 (15.0)		
Arm circumference adequacy	Not Malnutrition	20 (44.4)	15 (60.0)	5 (25.0)	*0.341*	*0.019*
	Malnutrition	25 (55.6)	10 (40.0)	15 (75.0)		
Muscular mass circumference adequacy	Adequate	18 (40.0)	14 (56.0)	4 (20.0)	*0.348*	*0.014*
	Depleted	27 (60.0)	11 (44.0)	16 (80.0)		
Calf circumference	Adequate	25 (64.1)	23 (92.0)	8 (40.0)	*0.581*	*< 0.001*
	Depleted	14 (35.9)	2 (8.0)	12 (60.0)		
Subjective Nutritional Assessment						
RFH-NPT	Without nutritional risk	15 (33.3)	10 (40.0)	5 (25.0)	0.143	0.289
	With nutritional risk	30 (66.7)	15 (60.0)	15 (75.0)		
RFH-GA	Well nourished	27 (60.0)	19 (76.0)	8 (40.0)	*0.364*	*0.014*
	Malnutrition	18 (40.0)	8 (24.0)	11 (60.0)		

ASM: appendicular skeletal muscle mass; ASMI: appendicular skeletal muscle mass index; BMI: body mass index; HGS: handgrip strength; RFH-GA: Royal Free Hospital – Global Assessment; RFH-NPT: Royal Free Hospital - Nutritional Prioritizing Tool.

When proposing to identify nutritional risk or sarcopenia risk, screening instruments are used to maximize true positives within a sample, with subsequent steps aiming to discard false positives (19,20).

Individuals with cirrhosis experience a progressively worsening condition, often leading to episodes of decompensation that frequently require hospitalization, thereby increasing morbidity and mortality rates. Key complications include ascites, UGIB, and HE, which elevate the mortality risk by 5 to 10 times in this population (21). The average survival for patients experiencing these complications is merely 1 to 2 years, while compensated individuals have a survival expectancy of 10 to 12 years (22). Given its impact on global health (as the 11th leading cause of death, accounting for 2 million fatalities) and its substantial cost (with $32.5 million spent in the US alone in 2016) (21), preventing hepatic decompensation through pharmacological or non-pharmacological interventions is crucial to reduce hospitalizations, healthcare expenses, and improve patients' quality of life.

Nutritional status is heavily impacted by cirrhosis progression. Reduced food intake, energy-protein imbalances, altered macronutrient and micronutrient metabolism, diminished absorptive capacity, as well as muscle dysfunction and sarcopenia, are common nutritional complications seen in individuals with cirrhosis (23).

As cirrhosis negatively impacts nutritional status, the presence of nutritional and functional deficits also adversely affects the clinical progression of patients with cirrhosis. This influence extends to quality of life, with increased risks of infection, HE, ascites, and mortality, making it a prognostic factor for individuals with liver cirrhosis (24). However, the identification of nutritional deficits, especially malnutrition and sarcopenia, remains a challenge in cirrhosis due to the frequent occurrence of fluid retention (edema and ascites) in these patients. This retention hampers the use of more affordable and accessible anthropometric and body composition measures, such as weight, CC, and bioimpedance, across various clinical nutrition monitoring settings for these patients.

The EWGSOP2 recommends using the SARC-F tool for sarcopenia risk screening (3). In a study involving patients with cirrhosis, Singla et al. (2024) demonstrated good sensitivity of the SARC-F score for bedside screening in the Indian population (25). However, a meta-analysis by Voelker et al. (2021) suggested applying sarcopenia diagnostic criteria independently of risk screening due to the SARC-F's low sensitivity, which may lead to the detection of only severe cases (26). Our findings support this, as the SARC-F and SARC-Calf showed low efficacy in identifying individuals with low muscle strength and depletion in outpatients with cirrhosis, indicating that these tools should not be solely relied upon for sarcopenia diagnosis in this population.

Our study is pioneering in that it evaluates sarcopenia prevalence using different methods and assesses the agreement between sarcopenia diagnosis, based on decreased strength (sit-to-stand test) and muscle mass (DXA), and various nutritional and functional assessment methods in outpatients with cirrhosis. Following the diagnostic criteria for sarcopenia, decreased strength precedes skeletal muscle depletion, which is why strength tests, such as the sit-to-stand test and HGS, should precede body composition assessment. In our work, we found that relying on HGS could result in a high number of false negatives, potentially depriving many patients with cirrhosis of timely and appropriate interventions involving physical exercise and nutritional adjustments, which are currently the main treatment options, given the lack of effective pharmacological treatments (27).

Although HGS is widely used to measure strength, its limitations are evident, as it primarily assesses hand and forearm muscles, which are not critical for activities that involve supporting body weight. Despite showing moderate correlation with strength in other body compartments (28), HGS might not be as effective as the sit-to-stand test, which is a more comprehensive tool for assessing functional capacity and muscle power (3). Additionally, several mechanisms contribute to muscle strength impairment in patients with cirrhosis, including muscle quality changes, hormonal alterations, electrolyte imbalances, and systemic complications (8,16,29).

DXA, a recommended method for body composition assessment, accurately evaluates muscle mass and is suitable for individuals with cirrhosis, especially since it can bypass ascites interference when using appendicular skeletal muscle mass (ASM/ASMI) (3,16). Our study confirmed the high prevalence of muscle depletion in outpatients with cirrhosis, reinforcing the importance of incorporating muscle mass measurement for sarcopenia diagnosis.

The sit-to-stand test emerged as a highly effective screening tool for probable sarcopenia, as it identified the largest number of individuals with low muscle strength. Its simplicity, requiring only a chair and timer, makes it more accessible than HGS, and it can be employed across different healthcare settings (30). In contrast CC proved to be the most viable alternative for muscle mass assessment when DXA is unavailable, demonstrating the best agreement with ASM/ASMI. Interestingly, while the SARC-Calf incorporates CC as part of its assessment - adding 10 points to the final score –, our findings showed that CC alone presented a stronger correlation with muscle depletion (ASM/ASMI) compared to SARC-Calf. This suggests that isolating CC as an independent measure may enhance its utility in clinical practice, particularly when the broader SARC-Calf framework shows limitations in identifying low muscle strength and quality.

This association between CC and muscle mass was also identified by Kawakami et al. (2020) in their study of Japanese adults, where CC positively correlated with muscle mass measured by bioimpedance or DXA, regardless of the presence of obesity. Therefore, CC can be considered a useful diagnostic marker for sarcopenia (31).

However, it is important to acknowledge the limitations of using CC in patients with lower limb edema, a common condition in cirrhosis. Given this, the chair sit-and-stand test is recommended as an alternative when edema precludes CC measurement, based on the strong agreement observed in our study regarding sarcopenia diagnosis.

LIMITATIONS AND PERSPECTIVES

The data were collected from outpatients with cirrhosis, meaning that in more severe or decompensated cases, alternative criteria might provide more accurate sarcopenia diagnosis. The inclusion criteria for this study aimed to minimize confounding factors, which may have consequently limited the participation of more compromised individuals, such as those with hepatocellular carcinoma, cardiac, renal, and/or pulmonary complications, or hepatic encephalopathy. Therefore, the findings may not fully represent patients with more advanced disease stages. However, by including patients based on MELD-Na scores, an internationally recognized measure of disease severity, our results can be extrapolated to patients who do not present terminal-stage conditions.

Moreover, although DXA was chosen over computed tomography (CT) — the gold standard for muscle assessment in liver disease – due to greater accessibility, this limitation was mitigated by evaluating appendicular skeletal muscle mass (ASM) and its index (ASMI). We acknowledge that CT imaging, particularly in advanced cirrhosis, where it is often performed for hepatic lesion monitoring or pre-transplant evaluation, could provide more precise muscle assessments and should be considered in future studies.

Finally, the etiology of liver disease may significantly influence nutritional status, especially in alcoholic cirrhosis, as alcohol interferes with nutrient absorption, leading to chronic malnutrition and exacerbating nutritional deficits. However, no specific tools currently exist for nutritional risk or status assessment based on disease etiology. Future assessment tools could consider incorporating alcoholic cirrhosis as a criterion, emphasizing its nutritional impact.

CONCLUSION

Our study demonstrates that the EWGSOP2 algorithm tends to underdiagnose sarcopenia in outpatients with cirrhosis, primarily due to the low sensitivity of the SARC-F tool in this population. Therefore, we suggest that the screening step be excluded or that CC measurement be used as an alternative, provided there is no lower limb edema.

The chair sit-and-stand test emerged as the most reliable method for identifying low muscle strength, effectively capturing a greater number of individuals with probable sarcopenia than HGS. Additionally, CC measurement showed moderate concordance with ASM/ASMI and could serve as a practical alternative in the absence of imaging methods, although it may miss a considerable number of patients with muscle depletion. Hence, CC is not sufficient as a standalone diagnostic measure for sarcopenia in this population.

Our findings reinforce the critical need for incorporating imaging techniques such as DXA or CT in the comprehensive care of patients with cirrhosis to ensure accurate identification and appropriate intervention for sarcopenia. Despite the limited availability of DXA in routine clinical settings, its role in accurately assessing muscle mass highlights the necessity for its inclusion, even if performed with reduced frequency.

In alignment with the Delphi consensus from the Global Leadership Initiative in Sarcopenia (GLIS) (32), which emphasizes the practicality and feasibility of sarcopenia assessment components, we propose that combining CC and the chair sit-and-stand test can serve as feasible alternatives for diagnosing and monitoring sarcopenia in cirrhotic patients, particularly in resource-limited settings where imaging methods are not readily accessible.

AUTHORS´ CONTRIBUTION

Conceptualization, data curation and methodology, M. D. R. G., N. B. B., R. M. A. F. W., and F. A. M.; investigation, M. D. R. G., F. L. C. A., A. I. A. N. S., A. J. S. W., and F. A. M.; collection of data and materials, M. D. R. G., A. I. A. N. S., A. J. S. W., and F. A. M.; writing original draft preparation, M. D. R. G., F. L. C. A., N. B. B., J. C. F. S., and F. A. M.; writing, review and editing, M. D.R. G., N. B. B., J. C. F. S., and F. A. M. All authors have read and agreed to the published version of the manuscript.

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ARÁN

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Trabajo Original

Epidemiología y dietética

The empirical pattern of dietary inflammation is unrelated to nutritional status in college students

El patrón empírico de inflamación dietética no está relacionado con el estado nutricional en estudiantes universitarios

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Abstract

Introduction: food contains both inflammatory and anti-inflammatory components. The higher the concentration of inflammatory components, the greater the likelihood of developing obesity and other chronic conditions linked to low-grade chronic inflammation. Consequently, various indices have been developed to quantify dietary inflammation, such as the Empirical Dietary Inflammatory Pattern (EDIP-SP), which has been validated in Brazil. This study aimed to examine the potential association between EDIP-SP and the nutritional status of college students.

Methodology: the study involved 97 undergraduate nutrition students from Fortaleza, Ceará, in Northeast Brazil. Participants completed a food frequency questionnaire to assess their intake of EDIP-SP components, including processed meats, vegetables, fruits, rice, and beans. Anthropometric measurements (weight, height, and waist circumference) were taken to calculate body mass index (BMI) and to categorize nutritional status and abdominal adiposity.

Results: the diet consumed by the participants was primarily anti-inflammatory, with a mean score of -1.57 ± 0.69. Most participants were not classified as overweight (59.79 %) and did not exhibit abdominal adiposity (91.75 %). No significant association was observed between EDIP-SP scores and BMI (r = -0.11; p = 0.297) or waist circumference (r = -0.07; p = 0.489). However, a weak but direct association was found between the inflammatory score of processed meat intake and abdominal adiposity in female participants (r = 0.27; p = 0.019).

Conclusion: the Empirical Dietary Inflammation Pattern (EDIP-SP) does not appear to significantly influence the nutritional status of students. Nevertheless, the inflammatory impact of processed meat intake may contribute to excess abdominal adiposity, particularly among women.

Keywords:

Diet. Inflammation. Nutritional status. Food intake. Health Sciences students.

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Resumen

Introducción: los alimentos poseen componentes con efectos inflamatorios y antiinflamatorios. La prevalencia de elementos inflamatorios en la dieta incrementa el riesgo de obesidad y enfermedades crónicas ligadas a inflamación crónica de bajo grado. Se han desarrollado índices como el "Estándar Dietético Empírico de Inflamación" (EDIP-SP), validado en Brasil, para medir esta variable alimenticia. Los universitarios constituyen un grupo de riesgo tanto para las dietas inflamatorias como para la obesidad.

Objetivo: examinar la asociación entre el EDIP-SP y el estado nutricional de los universitarios.

Metodología: se incluyeron 97 estudiantes de nutrición del noreste de Brasil, quienes completaron cuestionarios de frecuencia alimentaria para evaluar el consumo de componentes del EDIP-SP: carnes procesadas, vegetales, frutas, arroz y frijoles. Se realizaron mediciones antropométricas y se categorizaron el estado nutricional y la adiposidad abdominal.

Resultados: la dieta de los participantes fue antiinflamatoria, con una media de -1,57 ± 0,69. La mayoría no presentó sobrepeso (59,79 %) ni adiposidad abdominal (91,75 %). No se encontró asociación entre EDIP-SP e IMC (r = -0,11; p = 0,297) o circunferencia de la cintura (r = -0,07; p = 0,489). Sin embargo, se observó una relación directa, aunque débil, entre el puntaje inflamatorio de las carnes procesadas y la adiposidad abdominal en las mujeres (r = 0,27; p = 0,019).

Conclusión: el EDIP-SP no parece influir en el estado nutricional de los universitarios. No obstante, el impacto inflamatorio de las carnes procesadas podría contribuir al exceso de adiposidad abdominal en las mujeres.

Palabras clave:

Dieta. Inflamación. Estados nutricionales. Ingesta de alimentos. Estudiantes de Ciencias de la Salud.

INTRODUCTION

Chronic non-communicable diseases (CNCDs) account for most deaths worldwide. According to the World Health Organization (WHO), CNCDs represent 74 % of all global deaths (1). Obesity is recognized as a risk factor for various CNCDs, carrying significant clinical implications. Between 1975 and 2016, the global prevalence of obesity nearly tripled, with 39 % of the adult population classified as overweight and 13 % as obese by 2016 (2). In Brazil, as of 2019, 61.7 % of adults aged 18 and over were overweight, with 25.9 % classified as obese (3).

An analysis of the impact of elevated BMI on global mortality and disability-adjusted life years (DALYs), based on data from the 2021 Global Burden of Disease (GBD) study, estimated that from 1990 to 2021, global deaths and DALYs attributable to high BMI more than doubled for both men and women. However, age-standardized mortality rates remained stable for women while increasing by 15 % for men (4).

Obesity triggers a state of chronic low-grade inflammation. This metabolic inflammatory condition affects adipose tissue and disrupts the function of organs such as the liver, muscles, and pancreas, as well as contributing to cardiovascular dysfunction. In these tissues, a shift in cell population is observed, with increased macrophage infiltration in peripheral tissues. Obesity induces an inflammatory response by activating the toll-like receptor 4 (Toll-4) signaling pathway, which responds to increased exposure to saturated fatty acids (5,6).

Food itself possesses both inflammatory and anti-inflammatory properties, with one or the other prevailing based on the combination of foods consumed. Various strategies have been developed to assess this inflammatory potential, including the recently validated Empirical Dietary Inflammation Pattern (EDIP-SP) in Brazil (7).

Identifying a diet as inflammatory or anti-inflammatory allows for educational interventions that promote anti-inflammatory dietary habits. Such interventions can help modulate the low-grade chronic inflammation associated with certain health conditions such as obesity, and can directly prevent the onset of this type of inflammation (8,9).

In this context, college students, particularly those in health-related fields, may represent a population at risk for poor dietary habits, characterized by inflammatory tendencies and increased obesity risk. This period in life is marked by significant lifestyle changes, including limited free time and restricted access to quality food and adequate physical activity (10,11). Therefore, this study aimed to explore whether there is an association between the empirical pattern of dietary inflammation and the nutritional status of college students.

METHODOLOGY

This cross-sectional study employed a quantitative and analytical approach as part of a Brazilian cohort entitled the "Nutritionist Health Study – NutriHS", conducted between 2019 and 2020 in Fortaleza, Ceará, Brazil. The study involved undergraduate nutrition students and licensed nutritionists, with the primary objective of examining the relationship between diet and cardiovascular risk. All participants were informed about the study's objectives and provided prior consent by signing an informed consent form. The study was approved by the Ethics Committee of Ceará State University under opinion number 3.528.417.

The study population consisted of undergraduate nutrition students. A convenience sample of 97 students from public and private Higher Education Institutions (HEIs) in Fortaleza, Ceará, was included. Eligible participants were college students of both genders, aged 18 or older, and enrolled in any term of the nutrition program. Pregnancy was an exclusion criterion. The data represents a subset collected during the early and pre-pandemic period of COVID-19. The intended sample size was limited by data collection suspension due to social isolation measures that began in Brazil in March 2020.

Demographic, socioeconomic, lifestyle, anthropometric, and dietary intake data were collected from participants. Demographic and socioeconomic data included gender, age, type of HEI attended, monthly family income, and self-reported race/ethnicity. Lifestyle data encompassed smoking status and physical activity, the latter assessed through the short form of the International

Physical Activity Questionnaire (IPAQ), validated for the Brazilian population (12,13).

Anthropometric data, including weight, height, and waist circumference, were collected following the World Health Organization protocol (14). Nutritional status was determined by calculating BMI (weight (kg) / height (m)²) and categorized based on the following cutoffs: ≤ 18.5 kg/m² for underweight, 18.5 to 24.99 kg/m² for normal weight (eutrophy), 25 kg/m² to 29.99 kg/m² for overweight, and ≥ 30 kg/m² for obesity. Waist circumference (WC) (14) was also classified as follows: < 88 cm as adequate and ≥ 88 cm as high for women; < 102 cm as adequate and ≥ 102 cm as high for men.

Dietary intake information was collected using a Food Frequency Questionnaire (FFQ) (15), with quantities reported in household measurements and subsequently converted into daily amounts (grams or milliliters) to estimate each participant's Empirical Dietary Inflammation Pattern (EDIP-SP) score.

The EDIP-SP (7) comprises six dietary components divided into three groups: rice and beans; fruits, vegetables, and greens; and processed meats (e.g., sausage, nuggets, bacon, ham, mortadella, salami, and roast beef). The authors established standard amounts for the calculation: 180 g for rice and beans (in a 5:1 ratio), 90 g for fruits, vegetables, and greens (45 g fruit; 45 g vegetables/greens), and 40 g for processed meats. Processed meats are classified as pro-inflammatory, while the other two groups are anti-inflammatory. For EDIP-SP calculation, weights of -0.27 and -0.12 were assigned to the anti-inflammatory groups of rice and beans, and fruits, vegetables and greens, respectively, whereas a weight of +0.27 was assigned to the pro-inflammatory processed meats group.

For enhanced data analysis, select variables were dichotomized: age (≤ 25 years; > 25 years), nutritional status (not overweight; overweight), physical activity (yes; no), and smoking status (yes; no). Normality of variable distribution was assessed using the Kolmogorov-Smirnov test. Statistical analysis involved calculating means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Spearman's correlation test (r) was used to examine the association between the inflammatory score and nutritional status indicators (BMI and WC). A p-value < 0.05 was considered statistically significant across all inferential tests.

RESULTS

The sample was predominantly female (74 %; 76.29 %). Most participants were enrolled in private HEIs (73 %; 75.26 %) and were under 25 years of age (72 %; 74.23 %). Over half of the participants reported a monthly family income of up to five minimum wages (54 %; 55.67 %) and identified as non-white (57 %; 58.76 %). None of the participants smoked, and more than half engaged in physical activity (51.55 %) (Table I).

Table I. Socioeconomic, demographic and lifestyle categorization of the evaluated college students (n = 97) according to gender. Fortaleza, Ceará, Brazil 2022

Variables	Gender		
	Female	Male	Total
	n (%)	*n* (%)	*n* (%)
Gender	74 (76.29)	23 (23.71)	97 (100)
University			
Public	18 (24.32)	6 (26.09)	24 (24.74)
Private	56 (75.68)	17 (73.91)	73 (75.26)
Age (years)			
≤ 25	54 (72.97)	18 (78.26)	72 (74.23)
> 25	20 (27.03)	5 (21.74)	25 (25.77)
Minimum wage (MW)			
< 1	5 (6.76)	1 (4.35)	6 (6.19)
1-5	40 (54.05)	8 (34.78)	48 (49.48)
6-10	12 (16.22)	2 (8.70)	14 (14.43)
> 10	9 (12.16)	9 (39.13)	18 (18.56)
Don't know	8 (10.81)	3 (13.04)	11 (11.34)
Color (self-reported)			
White	28 (37.84)	12 (52.17)	40 (41.24)
Black	8 (10.81)	2 (8.70)	10 (10.31)
Other	2 (2.70)	1 (4.35)	3 (3.09)

(Continues on next page)

Table I (cont.). Socioeconomic, demographic and lifestyle categorization of the evaluated college students (*n* = 97) according to gender. Fortaleza, Ceará, Brazil 2022

Variables	Gender		
	Female	Male	Total
	n (%)	*n* (%)	*n* (%)
Smoking			
No	74 (100)	23 (100)	97 (100)
Physical activity			
Yes	39 (52.70)	11 (47.83)	50 (51.55)
No	35 (47.40)	12 (52.17)	47 (48.45)

Table II presents the categorization of the students' nutritional status. The majority were not classified as overweight (58 %; 59.79 %) and had adequate waist circumference (89 %; 91.75 %), with no statistically significant differences by gender. However, a notable proportion of participants were classified as overweight (40.21 %).

Table III provides the mean EDIP-SP score of the students, overall and by food group, as well as the mean intake (in grams) of the food groups that constitute the index, disaggregated by gender. The overall EDIP-SP score indicated an anti-inflammatory diet (-1.57). Based on the average intake of the students, the proportions among components of the rice/peas and fruits/vegetables food groups did not align with the standard set for EDIP-SP, as bean intake was higher in the rice/peas mix, and fruit intake was greater in the fruits/vegetables mix.

Regarding the correlation analysis between EDIP-SP score and anthropometric data, table IV displays the results, suggesting no significant correlation between these variables. However, when analyzing the correlation between the EDIP-SP score for processed meats and anthropometric data, a statistically significant, though weak, positive correlation was observed with waist circumference ($p = 0.019$) in females, and with both waist circumference ($p = 0.004$) and BMI ($p = 0.003$) across the entire sample.

DISCUSSION

This study aimed to assess the association between an inflammatory dietary pattern and anthropometric markers in undergraduate nutrition students. Most participants displayed a eutrophic nutritional status with no excess abdominal fat. The group studied is relatively young, with the majority aged up to 25, and around half reported engaging in physical activity. Given these factors, along with their background as nutrition students, a lower proportion of overweight individuals than observed (40.21 %) might be expected.

Data from the Surveillance of Risk and Protective Factors for Chronic Diseases by Telephone Survey, considering the age range of 18 to 24 — the closest range to that of most students assessed in this study — indicates an overweight prevalence of 30.6 %, with 29.2 % among men and 32.3 % among women. These figures are lower than those found in the present study.

The majority of students in the sample were from private institutions. There is only one public Higher Education Institution (HEI) offering a Nutrition program in the capital studied. This distribution may have influenced the findings regarding monthly family income, which is likely higher than that typically observed in this population group across Brazil. Data from the Higher Education Map of Brazil, developed by the Esmes Institute, indicate that most Brazilian university students come from low-income families and reveal that 90 % of young people entering college have a family income of up to three minimum wages (16).

Some findings from studies conducted with college students are presented below to allow for comparison with the group investigated here, particularly regarding nutritional status. A study conducted with undergraduate students across various faculties and class years, aged up to 25, at Hashemite University in Zara, Jordan, found similar results to those in the present study, with a predominance of females (65.9 %) and a majority with no overweight status (63.9 %). However, the Jordanian study reported a higher prevalence of smokers (15.4 %) and a greater proportion of physically active students (89.4 %) (17).

The trend of unhealthy lifestyle choices and eating behaviors is observed globally. In Arab countries, there is a marked shift toward dietary and lifestyle transitions, marked by the replacement of traditional diets (rich in vegetables and whole grains) with a more Westernized pattern. Nevertheless, there is insufficient data on dietary patterns, especially among young women in the Middle East. Factors such as altered eating patterns, meal skipping, a preference for fast food, and reduced intake of fruits and vegetables are increasingly common in the daily lives of this population (17).

In a public university in Recife, northeastern Brazil, a cross-sectional study was conducted based on data from a cohort of Nutrition students of both genders, in which 131 college students aged 18 years or older participated. They also found a predominance of females (83.2 %), 56.5 % of respondents with physical inactivity, 3.1 % smokers, and overweight in 11 % of women and 36.4 % of men. High WC was detected in 7.3 % of women and 13.6 % of men (18).

Table II. Categorization of nutritional status and waist circumference of the college students evaluated (*n* = 97) according to gender. Fortaleza, Ceará, Brazil 2022

Nutritional status	Gender			
	Female *n* (%)	Male *n* (%)	Total *n* (%)	*p*-value
*Overweight**				0.068†
No	48 (64.86)	10 (43.48)	58 (59.79)	
Yes	26 (35.14)	13 (56.52)	37 (40.21)	
Waist circumference				0.676‡
Adequate	67 (90.54)	22 (95.65)	89 (91.75)	
Increased	7 (9.46)	1 (4.35)	8 (8.25)	

**Body mass index (BMI): not overweight (BMI < 25 kg/m²); overweight (BMI ≥ 25 kg/m²), according to World Health Organization (2000). †Chi-square test. ‡Fisher's exact test (p < 0.05 as significant).*

Table III. Mean values, per component and overall, of the Empirical Dietary Pattern of Inflammation (EDIP-SP), and mean consumption of the components by the evaluated college students, according to gender, with standard deviation (SD). Fortaleza, Ceará, Brazil 2022

Food component	EDIP Mean (DP)			Intake (grams) Mean (SD)		
	Female	Male	Total	Female	Male	Total
Processed meat	+0.25 (0.13)	+0.31 (0.16)	+0.26 (0.14)	37.62 (19.13)	46.58 (22.99)	39.57 (20.19)
Rice and beans	-1.40 (0.65)	-1.52 (0.86)	-1.43 (0.70)	101.06/135.40 (52.04/67)	110.90/146.58 (62.03/88.87)	103.38/138.03 (54.39/72.41)
Fruits/Vegetables	-0.40 (0.09)	-0.42 (0.18)	-0.41 (0.12)	123.39/26.77 (30.92/9.49)	130.67/27.60 (58.10/11.96)	125.17/26.97 (38.84/10.07)
Global	-1.55 (0.64)	-1.63 (0.86)	-1.57 (0.69)	---	---	----

Source: Authors, 2022.

Table IV. Correlation between the Empirical Dietary Pattern of Inflammation - EDIP-SP (components and total) and anthropometric data of college students evaluated (*n* = 97) according to gender. Fortaleza, Ceará, Brazil, 2022

Anthropometry	EDIP-SP			
	Processed meat	Rice and beans	Fruits and vegetables	Total
Female				
BMI, kg/m²	0.27 (*p* = 0.056)	- 0.08 (*p* = 0.497)	- 0.03 (*p* = 0.803)	- 0.05 (*p* = 0.651)
WC, cm	*0.27 (p = 0.019)*	- 0,08 (*p* = 0.497)	- 0.01 (*p* = 0.937)	- 0.04 (*p* = 0.757)
Male				
BMI, kg/m²	0.26 (*p* = 0.235)	0.02 (*p* = 0.946)	- 0.13 (*p* = 0.541)	- 0.05 (*p* = 0.823)
WC, cm	0.35 (*p* = 0.102)	- 0.06 (*p* = 0.774)	- 0.24 (*p*=0,267)	- 0.09 (*p* = 0.683)
Total				
BMI, kg/m²	*0.30 (p = 0.003)*	- 0.12 (*p* = 0.246)	- 0.07 (*p* = 0.469)	- 0.11 (*p* = 0.297)
WC, cm	*0.29 (p = 0.004)*	- 0.09 (*p* = 0.372)	- 0.05 (*p* = 0.645)	- 0.07 (*p* = 0.489)

Values expressed as correlation coefficients (r) and p values. BMI = body mass index; WC = waist circumference; p values in italics < 0.05.

Therefore, only regarding excess abdominal adiposity among men, there was a worse nutritional status when compared to the present study, which was also conducted with university students from the northeast of Brazil.

Based on the brief profile presented, it can be observed that the nutritional status of young university students is predominantly marked by the absence of excess weight. It is essential to conduct further comparative and up-to-date studies with robust samples, examining the nutritional status of students in health-related fields and other disciplines, and investigating factors associated with the findings observed. Another aspect evaluated in this study was the empirical pattern of dietary inflammation, which indicated that students maintained an anti-inflammatory dietary pattern. This variable remains understudied in this population, despite other dietary intake assessments being more commonly explored. Some merit further discussion due to their relevance to the dietary components included in the EDIP-SP calculation.

Some studies evaluate the effects of healthy and unhealthy dietary patterns and their outcomes. Adherence to an energy-dense dietary pattern with low nutrient density may contribute to changes in nutritional status and increase the risk of developing chronic diseases (20,21). Studies have reported an association between an inflammatory dietary profile and the etiology of several chronic diseases. Since habitual eating patterns can influence inflammation regulation, Western dietary patterns are linked to higher inflammation levels, while evidence suggests that plant-based diets are associated with lower inflammation levels (19).

In a study conducted at a public institution in southern Brazil, nutritional status and food consumption were assessed (22). The authors observed greater adherence to a traditional Brazilian dietary pattern, characterized by low processed food intake. This consumption pattern was likely influenced by students taking part of their daily meals at the university cafeteria, where fresh and minimally processed foods predominated. Such a pattern fosters a less favorable environment for inflammation (23). Although not assessed in this study, the Dietary Inflammatory Index (DII) is a valuable tool for quantifying the inflammatory potential of different dietary patterns (24).

The traditional Brazilian dietary pattern, as well as the prudent dietary pattern, typically includes beans, with fruits and vegetables also frequent in the prudent pattern (25). Both of these food groups are components in the calculation of EDIP-SP and are considered anti-inflammatory (7). According to the 2017-2018 Household Budget Survey (HBS) (26), foods with the highest average daily per capita consumption in Brazil include beans (142.2 g/day) and rice (131.4 g/day), indicating a diet centered on rice and beans, a combination of good nutritional quality. Participants in this study showed similar consumption averages, as shown in table III (beans 138.03 g/day and rice 103.38 g/day).

Since EDIP-SP validation is recent, there are few published studies evaluating this index in Brazil. Araújo et al. (2022) (27) found no association between an inflammatory diet, according to EDIP-SP, and sleep quality in this same population group. Another study by Cardoso Neto et al. (2023) (28), although involving a different population group of 229 patients with type 2 diabetes *mellitus,* assessed the relationship between EDIP-SP and nutritional status and also found no association between these variables.

Conversely, to allow for some comparisons, it is valuable to examine studies that have evaluated the dietary inflammatory potential using other indices. The Dietary Inflammatory Index (DII) is an important tool to quantify a diet's inflammatory potential, classifying diets as anti-inflammatory or inflammatory based on the intake of foods, nutrients, bioactive compounds, and spices. One study evaluated the association of this index with annual weight changes over a two-year period within a 10-year follow-up, as well as with the incidence of overweight and obesity, in a prospective cohort of graduates from the University of Navarra, Spain (29). The study found that a more inflammatory diet was significantly associated with a greater risk of clinically relevant weight gain (> 3 kg or > 5 kg) and with a higher mean annual weight gain. Additionally, annual weight gain was higher in the group consuming a more inflammatory diet (+264.5 g) compared to those following a more anti-inflammatory diet (+207.2 g). A diet with higher inflammatory potential was associated with an increased risk of overweight or obesity compared to those in the lowest quartile of DII, indicating consumption of an anti-inflammatory diet.

In a cross-sectional study conducted with a Brazilian cohort of alumni (undergraduate and graduate) from universities in Minas Gerais (UMG), with a mean age of 36.3 years (± 9.4), food intake was analyzed to estimate the energy-adjusted Dietary Inflammatory Index (E-DII) and assess its association with overweight and obesity. The study found that the fourth quartile of E-DII was associated with a higher prevalence of overweight and obesity in both men (PR = 1.35; 95 % CI, 1.17-1.65) and women (PR = 1.95; 95 % CI, 1.31-2.90). One conclusion drawn by the authors was that an inflammatory eating pattern, combined with other unhealthy lifestyle habits and an obesogenic diet, represents a risk factor for obesity and chronic diseases (30).

A study conducted with university students in Tehran, which investigated IID and its relationship with obesity, obtained findings like those of this study. The authors identified a predominance of females, with a low percentage of overweight and obesity participants and low prevalence of high WC. However, there was no association between anthropometric markers and DCI (31). Researchers evaluated Iranian female university students and found no significant association between dietary inflammatory index and obesity (32). In the present study, the findings justify the absence of correlation found, since they are eutrophic individuals and all were on a non-inflammatory diet, although with anti-inflammatory values.

It is noteworthy that the proportion of food components used for EDIP-SP in this study differs from that proposed by the authors who validated the instrument. The validation study specifies a proportion of five parts rice to one part beans, totaling 180 g; a 1:1 ratio of fruits to vegetables, totaling 90 g; and 40 g of processed meats. However, no instructions are provided on how to proceed when these proportions and/or amounts are not met (7).

Therefore, the diets assessed may differ in inflammatory content from that suggested by this methodology. As shown in table III, the proportions of rice/peas and fruits/vegetables were not aligned with those used in the EDIP-SP validation. Despite this, the low intake of processed meats, the only inflammatory component of EDIP-SP, may explain the study's findings. Not assessing the specific rice/beans and fruits/vegetables proportions represents a limitation of this study, which future research could address by exploring different consumption proportions.

Although processed meat consumption was low, a weak direct association was observed between this component and waist circumference in women, and with waist circumference and BMI in the overall group. It is possible that studies involving more heterogeneous samples regarding EDIP-SP component intake would yield additional associations. One advantage of using EDIP-SP in Brazilian studies is its validation and adaptation to the Brazilian context. This study also highlights the need for research comparing EDIP-SP data with various dietary patterns to determine whether significant relationships exist between healthy patterns and their anti-inflammatory or inflammatory effects.

Another limitation of this study is the sample size, which is not representative of the population of higher education students in the state where the research was conducted, a constraint influenced by the COVID-19 pandemic, as previously mentioned. A larger sample might have been more heterogeneous in terms of EDIP-SP scores, including a higher proportion of individuals consuming inflammatory diets, which could allow for comparisons between nutritional profiles and inflammatory diet presence.

In conclusion, the sample of undergraduate nutrition students assessed demonstrated an adequate nutritional status and followed an anti-inflammatory diet, according to the EDIP-SP. No correlation was found between nutritional status and the empirical inflammatory pattern of the diet, although processed meat intake showed a weak direct correlation with waist circumference in women, as well as with waist circumference and BMI in the overall group.

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Nutrición Hospitalaria

Trabajo Original

Epidemiología y dietética

Micronutrients adequacy according to six diet quality indices in the "Seguimiento Universidad de Navarra" cohort

Adecuación de micronutrientes según seis índices de calidad de la dieta en la cohorte "Seguimiento Universidad de Navarra"

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Abstract

Objectives: diet quality indices (DQI) tend to relate positively to micronutrient intake. Our aim was to investigate the association between six DQIs and inadequate intake for 19 micronutrients in the SUN ("Seguimiento Universidad de Navarra") cohort.

Methods: we assessed 16,768 participants (59.3 % women, 37.8 years for mean age). Diet quality was evaluated using Dietary Approaches to Stop Hypertension (DASH); Mediterranean Diet Adherence Screener (MEDAS); Alternate Healthy Eating Index (AHEI-2010); Food-Based Global Diet Quality Score (GDQS); Alternative Mediterranean Diet Score (aMED) and Mediterranean Diet Score (MDS). Logistic regression analyses were conducted to estimate the probability of failing to meet Estimate Average Requirement (EAR) for either ≥ 3 or ≥ 6 micronutrients.

Results: overall, the lower and higher prevalence of inadequacy in fifth quintiles was for vitamins A, C, B1, B2, B3, B6, for Fe, P and Cr, and for vitamins E and D, respectively. In the multivariable adjusted model, the OR for failing to meet ≥ 3 DRI for the highest versus the lowest quintiles of DASH, MEDAS, AHEI-2010, GDQS, aMED and MDS were: 0.03 (95 % CI, 0.02 to 0.03), 0.06 (95 % CI, 0.05 to 0.07), 0.10 (95 % CI, 0.09 to 0.12), 0.05 (95 % CI, 0.04 to 0.06), 0.03 (95 % CI, 0.03 to 0.04), and 0.07 (95 % CI, 0.06 to 0.09),respectively.

Conclusions: adherence to six DQIs showed inverse associations with micronutrient inadequacy. Food-based DQIs could be a useful prevention tool. GDQS and MEDAS do not require deriving nutrient intake data, particularly MEDAS, which is even easier and quicker to fill out.

Keywords:

Diet quality indices. Micronutrient adequacy. Adult cohort. Dietary pattern. Mediterranean diet.

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Resumen

Objetivos: los índices de calidad de la dieta (DQI) tienden a relacionarse positivamente con la ingesta de micronutrientes. Nuestro objetivo fue investigar la asociación entre seis DQI y la ingesta inadecuada de 19 micronutrientes en la cohorte SUN ("Seguimiento Universidad de Navarra").

Métodos: se evaluaron 16 768 participantes (59,3 % de mujeres, 37,8 años de edad media). La calidad de la dieta se evaluó mediante la herramienta "Dieta basada en enfoques dietéticos para detener la hipertensión" (DASH), el Cuestionario de Adherencia a la Dieta Mediterránea (MEDAS), el Índice Alternativo de Alimentación Saludable (AHEI-2010), la Puntuación de Calidad de la Dieta Global basada en Alimentos (GDQS); el *score* alternativo de la dieta Mediterránea (aMED) y el score de la dieta Mediterránea (MDS). Se realizaron análisis de regresión logística para estimar la probabilidad de no cumplir con el requerimiento medio estimado (EAR) para ≥ 3 o ≥ 6 micronutrientes.

Resultados: en general, la menor y mayor prevalencia de insuficiencia en el quinto quintil fue para las vitaminas A, C, B1, B2, B3, B6, para Fe, P y Cr, y para las vitaminas E y D, respectivamente. En el modelo ajustado multivariable, las OR para no alcanzar ≥ 3 DRI para los quintiles más altos versus los más bajos de DASH, MEDAS, AHEI-2010, GDQS, aMED y MDS fueron: 0,03 (IC 95 %: 0,02 a 0,03), 0,06 (IC del 95 %: 0,05 a 0,07), 0,10 (IC del 95 %: 0,09 a 0,12), 0,05 (IC del 95 %: 0,04 a 0,06), 0,03 (IC del 95 %: 0,03 a 0,04) y 0,07 (IC del 95 %: 0,06 a 0,09), respectivamente.

Conclusiones: la adherencia a seis DQI mostró asociaciones inversas con la inadecuación de micronutrientes. Los DQI basados en alimentos podrían ser una herramienta de prevención útil. GDQS y MEDAS no requieren obtener datos de ingesta de nutrientes, y en especial, MEDAS, es aún más fácil y rápido de cumplimentar.

Palabras clave:

Índices de calidad de la dieta. Adecuación de micronutrientes. Cohorte de adultos. Patrón dietético. Dieta mediterránea.

INTRODUCTION

Dietary patterns represent the overall combination of foods habitually consumed, which together produce synergistic health effects and constitute an emerging research interest area (1). The concept of diet quality is multidimensional nature and is usually based on: a) adequate intake of nutrients and/or foods that are considered beneficial for health; b) moderation in the intake of certain nutrients and/or foods that increase the risk of chronic disease; c) proportionality of energy sources from macronutrients (proteins, carbohydrates and lipids); and d) dietary diversity or variety in food consumption. In this context, several *a priori* defined diet quality indices (DQIs) have been developed to assess compliance with national nutritional recommendations or dietary guidelines, *a priori* defined healthy dietary patterns, a specific dimension of diet quality (2). Particularly, Alternate Healthy Eating Index-2010 (AHEI-2010), Dietary Approaches to Stop Hypertension (DASH) and different scores appraising the adherence to the traditional Mediterranean diet have been widely used to investigate associations between diet quality and health outcomes or mortality in cohort studies (3,4).

Operationally, DQI may include a broad variety of items: foods, food groups, macronutrients, micronutrients or a combination of them. Regarding the nutrient-based indicators, the ones that are most frequently included in diet quality indices are: fats (cholesterol and fatty acid profile), carbohydrates, sugars, proteins, Ca, Zn, Fe, Na, K, Se, fiber, vitamin C, vitamins A, B1, B3, and folic acid. However, DQI based solely on nutrients are scarce and, compared to food-based indicators, more difficult to manage on a large scale because they require the derivation of nutrient intakes (5).

In general, DQI tend to relate positively to the intake of micronutrients and are considered tools with fair to moderate validity to assess micronutrient intake adequacy (6). In Europe, assessing micronutrient intake and reducing the prevalence of inadequacies is challenging (7). Therefore, the aim of the present study was to investigate the association between 6 *a priori* DQI and micronutrient intake adequacy for 19 micronutrients in the "Seguimiento Universidad de Navarra" (SUN) cohort study.

MATERIAL AND METHODS

STUDY DESIGN AND PARTICIPANTS

The SUN Project (http://proyectosun.es) is a prospective and dynamic Mediterranean cohort study of university graduates conducted in Spain since December 1999. Its recruitment is continually open and the objectives, design and methods have been described in detail elsewhere (8). Baseline assessment and follow-up information every two years from the date of enrolment is gathered via postal or web-based questionnaires. Self-administered questionnaires include information on lifestyle, health conditions and dietary variables.

The SUN project was conducted according to the principles expressed in the Declaration of Helsinki. Informed consent to participate in the cohort is implied when a response to the first questionnaire is received, and participants are informed of their right to refuse to participate or to withdraw their consent to participate at any time. The Institutional Review Board of the University of Navarra approved the study protocol before any data collection (approval code 010830). This cohort is registered at clinicaltrials.gov as NCT02669602.

Up to December 2019, 22,894 subjects had completed the baseline questionnaire. We excluded participants with outside the predefined limits for energy intake, which means that they were above 3500 or 4000 kcal/d or below 500/800 kcal/d (women and men respectively) ($n = 2169$) (9) and for predefined intake values of any micronutrient (≥ 3 standard deviations (SD) from both sides of the mean) ($n = 3957$). Finally, 16,768 participants were included in this analysis (Fig. 1).

DIETARY ASSESSMENT

A semi-quantitative food frequency questionnaire (FFQ, 136 food items) previously validated and repeatedly reevaluated (10-12) was used to assess food consumption and nutrient intakes baseline over the previous year. The food frequency questionnaire (FFQ) is self-administered. Currently, all questionnaires

of the SUN cohort can be filled by paper or mail with a personal code to answer the questionnaire at the SUN website (https://participantes.proyectosun.es/login). This second alternative is available since 2004.

For each food item, the FFQ included a typical portion size. We measured the consumption frequencies in 9 categories, ranging from "never or almost never" to "≥ 6 times/day". Macro and micronutrients intakes were calculated as frequency multiplied by nutrient composition of specified portion size for each food item using an *ad hoc* computer program specifically developed for this aim based on available information in Spanish food composition tables (13,14), which is updated by a dietitian.

Diet quality was evaluated using the following *a priori* DQI: Dietary Approaches to Stop Hypertension (DASH); Mediterranean Diet Adherence Screener (MEDAS); Alternate Healthy Eating Index (AHEI-2010); Food-Based Global Diet Quality Score (GDQS); Alternative Mediterranean Diet Score (aMED) and Mediterranean Diet Score (MDS) (Supplementary Table I).

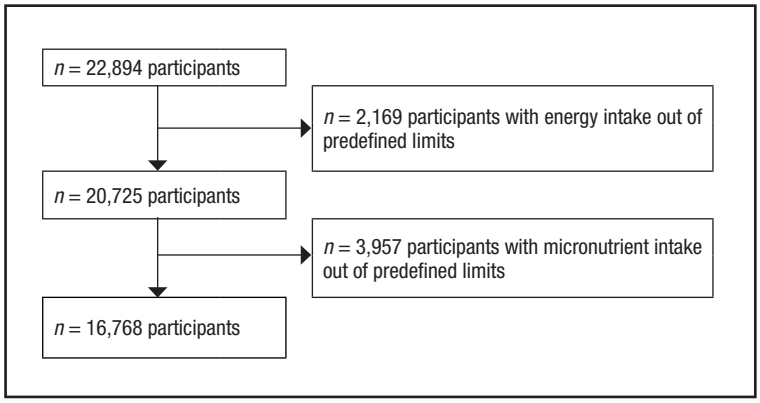

Figure 1.
Flow-chart of participants recruited in the SUN Project, 1999-2019.

Supplementary Table I. Criteria used to calculate diet quality indices

DASH index (16)		
Components, by quintile	**One point scored for each component**	**Scoring criteria**
Fruits	All fruits and fruit juices	Q1 = 1 point Q2 = 2 points Q3 = 3 points Q4 = 4 points Q5 = 5 points
Vegetables	All vegetables except potatoes and legumes	
Nuts and legumes	Nuts and peanut butter, dried beans, peas, tofu	
Whole grains	Brown rice, dark breads, cooked cereal, whole grain cereal, other grains, popcorn, wheat germ, bran	
Low-fat dairy	Skim milk, low-fat yogurt, low-fat cottage cheese	
	Component, by reverse quintile	**Reverse scoring**
Sodium	Sum of sodium content of all foods in FFQ	Q1 = 5 points Q2 = 4 points Q3 = 3 points Q4 = 2 points Q5 = 1 point
Red and processed meats	Beef, pork, lamb, deli meats, organ meats, hot dogs, bacon	
Sweetened beverages	Carbonated and noncarbonated sweetened beverages	
Total index (range)	*8-40*	

14-point Mediterranean Diet Adherence Screener (MEDAS) (17)	
Foods and frequency of consumption	**Criteria for 1 point***
Do you use olive oil as the principal source of fat for cooking?	Yes
How much olive oil do you consume per day (including that used in frying, salads, meals eaten away from home, etc.)?	4 or more tablespoons
How many servings of vegetables do you consume per day? Count garnish and side servings as 1/2 point; a full serving is 200 g.	≥ 2
How many pieces of fruit (including fresh-squeezed juice) do you consume per day?	≥ 3
How many servings of red meat, hamburger, or sausages do you consume per day? A full serving is 100-150 g	< 1
How many servings (12 g) of butter, margarine, or cream do you consume per day?	< 1
How many carbonated and/or sugar-sweetened beverages do you consume per day?	< 1

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Supplementary Table I (cont.). Criteria used to calculate diet quality indices

14-point Mediterranean Diet Adherence Screener (MEDAS) (17)	
Foods and frequency of consumption	**Criteria for 1 point***
Do you drink wine? How much do you consume per week?	≥ 7 glasses
How many servings (150 g) of pulses do you consume per week?	≥ 3
How many servings of fish/seafood do you consume per week? (100-150 g of fish, 4-5 pieces or 200 g of seafood)	≥ 3
How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, or custard?	< 2
How many times do you consume nuts per week? (1 serving = 30 g)	≥ 3
Do you prefer to eat chicken, turkey or rabbit instead of beef, pork, hamburgers, or sausages?	Yes
How many times per week do you consume boiled vegetables, pasta, rice, or other dishes with a sauce of tomato, garlic, onion, or leeks sautéed in olive oil?	≥ 2
**0 points if these criteria are not met.*	

Mediterranean Diet Score (MDS) (18)
The MDS incorporate nine prominent components of the traditional Mediterranean diet. Sample sex-specific median cut-off points for eight items were used.
For beneficial components (vegetables, legumes, fruits and nuts, cereal, fish, and the ratio of monounsaturated lipids to saturated lipids), subjects whose consumption was below the median were assigned a value of 0 and subjects whose consumption was at or above the median were assigned a value of 1.
For components presumed to be detrimental (meat, poultry, and dairy products), subjects whose consumption was below the median were assigned a value of 1 and subjects whose consumption was at or above the median were assigned a value of 0. For ethanol, a value of 1 was assigned to men who consumed between 10 and 50 g/d and to women who consumed between 5 and 25 g/d.
Thus, the total Mediterranean-diet score ranged from 0 (minimal adherence to the traditional Mediterranean diet) to 9 (maximal adherence).

Alternate Mediterranean Diet Score (aMED) (20)		
Components of dietary index	**Foods included**	**Criteria for 1 point**
Vegetables	All vegetables except potatoes	Greater than median intake (servings/d)
Legumes	Tofu, string beans, peas, beans	Greater than median intake (servings/d)
Fruit	All fruit and juices	Greater than median intake (servings/d)
Nuts	Nuts, peanut butter	Greater than median intake (servings/d)
Whole grains	Whole-grain ready-to-eat- cereals, cooked cereals, crackers, dark breads, brown rice, other grains, wheat germen, bran, popcorn	Greater than median intake (servings/d)
Red and processed meats	Hot dogs, deli meat, bacon, hamburger, beef	Less than median intake (servings/d)
Fish	Fish and shrimp, breaded fish	Greater than median intake (servings/d)
Ratio of monounsaturated to saturated fat	-	Greater than median intake
Ethanol	Wine, beer, "light" beer, liquor	5-15 g/d for women 10-25 g/d for men
Total index (range)	*0-9*	

Alternate Healthy Eating Index-2010 (AHEI-2010) (21)		
Components of dietary index	**Criteria for minimum score (0)**	**Criteria for maximum score (10)**
Vegetables, servings/d	0	≥ 5
Fruit, servings/d	0	≥ 4
Whole grains, g/d		
Women		75
Men		90
Sugar-sweetened beverages and fruit juice, servings/d	≥ 1	0
Nuts and legumes, servings/d	0	≥ 1

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Supplementary Table I (cont.). Criteria used to calculate diet quality indices

Alternate Healthy Eating Index-2010 (AHEI-2010) (21)		
Components of dietary index	**Criteria for minimum score (0)**	**Criteria for maximum score (10)**
Red/processed meat, servings/d	≥ 1.5	0
Trans fat, % of energy	≥ 4	≤ 0.5
Long-chain (*n*-3) fats (EPA + DHA), mg/d	0	250
PUFA, % of energy	≤ 2	≥ 10
Sodium, mg/d	Highest decile	Lowest decile
Alcohol, drinks/d		
Women	≥ 2.5	0.5-1.5
Men	≥ 3.5	0.5-2.0
Total index (range)	*0-110*	

Food-based Global Diet Quality Score (GDQS) (22)								
	Categories of consumed amount (g/d)				**Point values**			
	1	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Healthy								
Citrus fruits	< 24	24-69	> 69		0	1	2	
Deep orange fruit	< 25	25-123	> 123		0	1	2	
Other fruits	< 27	27-107	> 107		0	1	2	
Dark Green leafy vegetables	< 13	13-37	> 37		0	2	4	
Cruciferous vegetables	< 13	13-36	> 36		0	0.25	0.5	
Deep orange vegetables	< 9	9-45	> 45		0	0.25	0.5	
Other vegetables	< 23	23-114	> 114		0	0.25	0.5	
Legumes	< 9	9-42	> 42		0	2	4	
Deep orange tubers	< 12	12-63	> 63		0	0.25	0.5	
Nuts and seeds	< 7	7-13	> 13		0	2	4	
Whole grains	< 8	8-13	> 13		0	1	2	
Liquid oils	< 2	2-7.5	> 7.5		0	1	2	
Fish and shellfish	< 14	14-71	> 71		0	1	2	
Poultry and game meat	< 16	16-44	> 44		0	1	2	
Low fat dairy	< 33	33-132	> 132		0	1	2	
Eggs	< 6	6-32	> 32		0	1	2	
Unhealthy in excessive amounts								
High fat dairy (in milk equivalence)	< 35	35-142	142-734	> 734	0	1	2	0
Red meat	< 9	9-46	> 46		0	1	0	
Unhealthy								
Processed meat	< 9	9-30	> 30		2	1	0	
Refined grains and bake goods	< 7	7-33	> 33		2	1	0	
Sweets and ice-cream	< 13	13-37	> 37		2	1	0	
Sugar-sweetened beverages	< 57	57-180	> 180		2	1	0	
Juice	< 36	36-144	> 144		2	1	0	
White roots and tubers	< 27	27-107	> 107		2	1	0	
Purchased deep fried foods	< 9	9-45	> 45		2	1	0	
Total index (range)	*0-25*							

These DQI were originally designed or adapted in the context of the 2015 Dietary Guidelines for Americans and have been extensively cited (3,15). DASH, AHEI-2010 and aMED, previously selected for the Dietary Methods Projects, are considered key indices of particular relevance for dietary guidance and are associated with mortality from cardiovascular disease, cancer, or any cause (4). The DASH diet was defined using the score developed by Fung et al. (2008) (16) which ranges from 8 to 40 points. Adherence to the traditional Mediterranean diet was assessed using 3 dietary DQI. The 14-item MEDAS (17) was built by the PREDIMED team (Schröder et al., 2011) and it is available at www.predimed.es. It is a short food-group based and constitute a validated short screener for rapid assessment of adherence to Mediterranean diet. MDS (18), proposed by Trichopoulou, was the original score to measure adherence to a pre-defined Mediterranean dietary pattern in Greek population. Likewise, is the most extensively used index and actually more than 25 variations have been created for the evaluation of multiple diet–health relationship (19), including the alternate Mediterranean Diet Score (aMED) (20) proposed by Fung in 2005. On the other hand, to build the AHEI-2010 (21), 11 groups of foods or nutrients were considered. Finally, the GDQS (22) is a novel score built from Prime Diet Quality Score and is composed of 25 food groups that are globally important contributors to nutrient intake and/or NCD risk as informed by current nutrition science and epidemiologic literature.

For the statistical analysis of this study, participants were categorized into 5 groups (roughly quintiles) according to their adherence to each DQI described above. Some analyses present only 3 groups (first quintile / second + third + fourth quintiles collapsed/ and fifth quintile).

OUTCOME ASSESSMENT

Micronutrient intake was derived from the previously mentioned validated FFQ. The average intake of micronutrients included both, intake from foods and dietary supplements, considering the consumption frequency over the past year. We assessed micronutrient intake adequacy for the following 19 micronutrients with known public health relevance: vitamins A, E, C, B1, B2, B3, B6, B12, D, folic acid, and Fe, Ca, K, Mg, P, Cr, Se, I and Zn. Inadequate intake for each nutrient was defined when the intake of the nutrient was below the estimated average requirements (EAR) if available, or the adequate intake (AI) levels, if EARs were not available. Both dietary reference intakes have been proposed by the Institute of Medicine (23).

Nutrient intake adequacy for all micronutrients, except for Fe because of its skewed distribution, and Cr and K because they have no EAR values, was also evaluated using the probabilistic approach. This approach calculates the probability of adequacy for a nutrient's usual intake as follows: Z score = (estimated nutrient intake—EAR)/SD of the EAR. The z scores of each nutrient correspond to an estimated probability of inadequacy according to normal distribution. The distribution of iron intake was skewed and it was log transformed.

ASSESSMENT OF OTHER COVARIATES

Information regarding socio-demographic, lifestyles, medical history and family medical history between other variables was obtained from the baseline questionnaire. Self-reported data, such as physical activity, body mass index (BMI) or hypertension, have been previously validated in a subsample of the cohort.

STATISTICAL ANALYSIS

We used inverse probability weighting to adjust the means or proportions of baseline variables for age and sex according to quintiles of adherence to DASH, MEDAS and AHEI-2010. These three DQI are widely used to obtain current and solid scientific evidence on diet and health.

Descriptive results are presented as mean and SD or percentages (%) for quantitative variables and categorical variables respectively by quintile of DASH, MEDAS and AHEI-2010.

We estimated the baseline prevalence of inadequacy for each micronutrient intake. Non-conditional logistic regression models were used to assess the association between DASH, MEDAS, AHEI-2010, GDQS, aMED and MDS and the risk of micronutrient inadequacy using the probabilistic approach. We estimated crude and multivariable-adjusted odds ratio (OR) and its 95 % confidence intervals (CI) estimated for failing to meet EAR for either ≥ 3 or ≥ 6 micronutrients. The multivariable-adjusted model was fitted after controlling for the following potential confounders: age, sex, total energy intake (continuous), BMI (kg/m^2, continuous), physical activity (MET-h/week, continuous), time spent sitting (hours/week, continuous), weight gain in the previous 5 years before entering the cohort (< 3 kg and ≥ 3 kg), following a special diet at baseline (yes/no), educational level (years of higher education, continuous), cumulative smoking habit (packs/year, continuous), alcohol intake (never, < 5 women or < 10 men, g/d; 5-25 women or 10-50 men, g/d; and > 25 women or > 50 men, g/d), snacking (yes/no) and stratified by recruitment period (5 categories) and deciles of age.

To investigate linear trends across quintiles of adherence to each dietary quality index, we assigned the median value to each category and considered the variable as being continuous.

We fitted marginal effects logistic to calculate the mean absolute reduction in the risk of not meeting ≥ 3 micronutrients according to quintiles of adherence to each of the 6 DQI.

Finally, we performed two sensitivity analyses: without adding intakes from dietary supplements to the calculated total intakes, and using a modified Mediterranean Diet Score to assess adherence to the Mediterranean dietary pattern. This modified score was calculated after categorizing participants by tertiles for each score item, rather than by median intake by sex.

Statistical analyses were carried out using STATA version 14 (STATA Corporation). All p values are two-tailed, and statistical significance was established in the conventional cut-off of $p < 0.05$.

RESULTS

A total of 6,826 men and 9,942 women were included in this analysis. Mean age at baseline was 37.8 (SD, 12.2) years. Table I shows the baseline characteristics of participants according to quintiles of adherence to DASH, MEDAS and AHEI-2010 adjusted for sex and age by IPW. Subjects in the fifth quintile of DASH (high adherence, Q5) were more likely to be single, more active, never smokers, have prevalent cancer, diabetes, cardiovascular disease and follow a special diet. On the other hand, participants with higher MEDAS or AHEI-2010 (Q5), compared with participants in the first quintile (Q1), were more likely to be active, former smokers, married, have prevalent hypertension, cancer, diabetes, dyslipemia, cardiovascular disease and follow a special diet.

In table II we present the food consumption, energy and nutrient intake of the 16,768 participants, according to quintiles of each DQI. DASH, MEDAS and AHEI-2010 was directly associated with a higher consumption of low-fat dairy products, vegetables, fruits, fish, nuts, legumes, whole grains and olive oil. The subjects with higher adherence to DASH showed a higher carbohydrate and fiber intake and lower total energy from fat, PUFA, MUFA, SFA, TFA, *n*-6 and *n*-3 fatty acids, cholesterol and alcohol intake. Participants in fifth quintile of MEDAS had less total energy intake from fat, SFA, *n*-6 fatty acids, cholesterol and more from fiber and alcohol. Finally, on average, a higher AHEI-2010 was associated with higher intake of carbohydrates, *n*-3 fatty acids, and fiber.

The prevalence of inadequate intake below the EAR for each nutrient according to DASH, MEDAS and AHEI-2010 is summarized in table III. For these three DQI, most micronutrients had lower prevalence of inadequate intake in highest quintile of adherence, except for B12 in both DASH and MEDAS, and for B3, I and Zn in AHEI-2010. Overall, the lower prevalence of inadequacy in fifth quintiles was for vitamins A, C, B1, B2, B3, B6, for Fe, P and Cr (range from 0 to 1 %) and the higher prevalence was for vitamins E and D (range from 59.6 to 90.1 %).

In tables IV and V we present the estimated probability of not meeting ≥ 3 or ≥ 6 EAR according to quintiles of each dietary quality index using the probabilistic approach to calculate the probability of adequacy for the 17 nutrients with EAR values. In 6 analyses, a higher adherence to each dietary quality index showed a strong inverse association with the risk of unmet EAR values when we compared the highest versus the lowest quintile in the crude and in the multivariable analyses. The estimated probabilities of failing to meet the EAR of ≥ 3 nutrients for the fifth quintile of DASH, MEDAS, AHEI-2010, GDQS, aMED and MDS were 15.1, 15.3, 24.8, 13.7, 12.4 and 12.2, respectively.

In the multivariable adjusted model, the OR for failing to achieve ≥ 3 DRI after adjustment for the main potential confounders, were for fifth quintiles of DASH, MEDAS, AHEI-2010, GDQS, aMED y MDS: 0.03 (95 % CI, 0.02 to 0.03), 0.06 (95 % CI, 0.05 to 0.07), 0.10 (95 % CI, 0.09 to 0.12), 0.05 (95 % CI, 0.04 to 0.06), 0.03 (95 % CI, 0.03 to 0.04), and 0.07 (95 % CI, 0.06 to 0.09), respectively. When we repeated the analyses for failing to meet ≥ 6 DRI, the results did not materially change (Table V).

We fitted marginal-effect logistic regression models to calculate the mean absolute reduction in the risk of not meeting ≥ 3 micronutrients according to quintiles of adherence to each DQI (Fig. 2). In all cases, the adjusted mean absolute risk reduction was higher in participants in the highest quintile as compared to those in the first quintile. This reduction was greater for DASH and aMED.

Finally, when two sensitivity analyses were performed (not adding supplements intakes to calculated total intakes and using a modified MDS to assess adherence to the Mediterranean diet), the main findings did not change (data not shown).

Table I. Baseline characteristics of participants according to adherence to DASH, MEDAS and AHEI-2010: the "Seguimiento Universidad de Navarra" (SUN) cohort: 1999-2019. Adjusted for age and sex by the IPW method

Scores	DASH			MEDAS			AHEI-2010		
	Q1	Q2-Q4	Q5	Q1	Q2-Q4	Q5	Q1	Q2-Q4	Q5
	8-19	20-28	29-40	0-4	5-7	8-12	20-50	51-68	69-99
n	3943	10029	2796	3749	9785	3234	3396	10250	3122
BMI (kg/m^2)	23.5 (3.7)	23.6 (3.6)	23.2 (3.1)	23.3 (3.6)	23.6 (3.6)	23.6 (3.4)	23.4 (3.7)	23.6 (3.5)	23.5 (3.4)
Leisure-time physical activity (METs-h/week)	16.7 (18.7)	21.3 (22.1)	26.9 (27.0)	18.1 (20.0)	20.6 (21.8)	26.2 (26.1)	17.3 (19.6)	21.1 (22.4)	25.5 (24.6)
Sitting hours (hours/week)	5.5 (2.1)	5.3 (2.0)	5.1 (2.0)	5.4 (2.1)	5.3 (2.0)	5.2 (2.0)	5.5 (2.1)	5.3 (2.0)	5.2 (2.0)
Smoking status (%):									
Smokers	28	22.7	16.6	26.2	23.1	18.5	26.5	22.7	19.5
Former smokers	27.6	29.3	29.2	24.4	29.2	33.2	25.4	29.0	32.5
Never smokers	44.4	48.0	54.2	49.4	47.7	48.3	48.1	48.3	48.0
Years of university education	5.1 (1.5)	5.1 (1.5)	5.1 (1.5)	5.1 (1.6)	5.1 (1.6)	5.1 (1.5)	5.0 (1.5)	5.1 (1.5)	5.1 (1.6)

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Table I (cont.). Baseline characteristics of participants according to adherence to DASH, MEDAS and AHEI-2010: the "Seguimiento Universidad de Navarra" (SUN) cohort: 1999-2019. Adjusted for age and sex by the IPW method

Scores	DASH			MEDAS			AHEI-2010		
	Q1	Q2-Q4	Q5	Q1	Q2-Q4	Q5	Q1	Q2-Q4	Q5
	8-19	20-28	29-40	0-4	5-7	8-12	20-50	51-68	69-99
Marital status (%):									
Married	49.7	50.7	47.2	46.7	50.6	51.2	49.6	49.9	50.3
Single	45.3	44.1	46.4	48.1	44.2	42.9	45.2	45.2	43.0
Others	5	5.2	6.4	5.2	5.2	5.9	5.2	5.1	6.7
Hypertension at baseline (%)	11.0	11.0	11.0	8.8	11.3	12.5	9.9	10.8	12.8
Cancer at baseline (%)	2.4	2.4	2.9	2.5	2.2	3.4	1.9	2.5	3.2
Diabetes at baseline (%)	1.1	2.0	2.2	1.1	1.8	2.5	1.3	1.7	2.7
Dyslipemia at baseline (%)	6.3	7.2	6.5	5.6	7.0	8.0	6.2	6.8	7.7
Cardiovascular disease at baseline (%)	4.4	4.3	5.0	3.3	4.6	5.4	4.1	4.2	5.4
Weight gain ≥ 3 kg in previous 5 years (%)	34.0	30.2	22.2	33.6	30.0	24.4	34.2	30.0	23.9
Following special diets (%)	4.6	7.5	11.4	4.1	7.2	12.1	4.6	6.9	12.4
Between-meals snacking (%)	38.9	33.5	26.9	38.5	33.4	29.0	40.2	33.5	26.9
Supplements intake (%)	13.4	16.0	20.3	14.6	16.1	17.9	14.9	15.6	19.1

IPW: inverse probability weighting. Q: quintiles; DASH: Dietary Approaches to Stop Hypertension; MEDAS: Mediterranean Diet Adherence Screener; AHEI: Alternate Healthy Eating Index.

Table II. Food consumption, energy and nutrient intake according to quintiles of adherence to DASH, MEDAS and AHEI-2010 (mean ± SD)

Scores	DASH			MEDAS			AHEI-2010		
	Q1	Q2-Q4	Q5	Q1	Q2-Q4	Q5	Q1	Q2-Q4	Q5
	8-19	20-28	29-40	0-4	5-7	8-12	20-50	51-68	69-99
n	3943	10029	2796	3749	9785	3234	3396	10250	3122
Food consumption									
Low-fat dairy products (g/d)	96 (143)	204 (189)	291 (198)	153 (178)	196 (190)	231 (199)	157 (185)	199 (192)	213 (188)
Whole dairy products (g/d)	260 (194)	176 (170)	113 (123)	230 (186)	183 (175)	137 (150)	257 (203)	191 (168)	120 (134)
Vegetables (g/d)	332 (185)	494 (145)	665 (263)	306 (160)	489 (240)	680 (254)	333 (190)	488 (243)	637 (273)
Fruits (g/d)	177 (143)	318 (225)	479 (259)	196 (138)	305 (222)	468 (275)	193 (164)	312 (227)	441 (258)
Fish (g/d)	79 (44)	93 (49)	107 (53)	67 (40)	93 (48)	118 (49)	75 (46)	93 (48)	107 (63)
Poultry (g/d)	45 (32)	46 (32)	46 (33)	40 (28)	45 (32)	54 (35)	45 (32)	46 (32)	45 (33)
Red and processed meat (g/d)	68 (37)	50 (30)	34 (23)	60 (34)	42 (32)	42 (30)	66 (35)	53 (31)	33 (24)
Eggs (g/d)	26 (18)	23 (14)	21 (15)	24 (17)	23 (15)	22 (14)	25 (16)	23 (16)	21 (14)
Nuts (g/d)	5 (6)	6 (9)	12 (15)	4 (5)	6 (9)	12 (14)	4 (5)	6 (9)	13 (15)
Legumes (g/d)	19 (15)	22 (16)	27 (19)	19 (14)	22 (16)	25 (20)	18 (14)	22 (16)	27 (20)
Grains (g/d)	102 (70)	94 (64)	100 (57)	97 (67)	96 (64)	101 (63)	99 (71)	97 (64)	96 (59)
Whole grains (g/d)	2 (13)	10 (25)	31 (38)	6 (19)	11 (26)	20 (35)	3 (11)	10 (24)	28 (40)
Olive oil (g/d)	17 (15)	18 (15)	19 (15)	13 (11)	18 (14)	24 (17)	16 (14)	18 (14)	20 (16)
Fast-food (g/d)	30 (25)	21 (19)	15 (15)	29 (23)	22 (20)	17 (17)	30 (25)	22 (19)	15 (15)

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Table II (cont.). Food consumption, energy and nutrient intake according to quintiles of adherence to DASH, MEDAS and AHEI-2010 (mean ± SD)

Scores	DASH			MEDAS			AHEI-2010		
	Q1	Q2-Q4	Q5	Q1	Q2-Q4	Q5	Q1	Q2-Q4	Q5
	8-19	20-28	29-40	0-4	5-7	8-12	20-50	51-68	69-99
Intakes									
Energy (kcal/d)	2399 (592)	2232 (592)	2190 (513)	2255 (581)	2250 (592)	2320 (564)	2351 (589)	2271 (589)	2149 (545)
Carbohydrate (% E)	41 (7)	43 (7)	47 (7)	42 (7)	43 (7)	44 (7)	41 (7)	43 (7)	45 (7)
Protein (% E)	18 (3)	18 (3)	18 (3)	18 (3)	18 (3)	18 (3)	18 (3)	18 (3)	18 (3)
Total fat intake (% E)	40 (6)	37 (6)	33 (6)	39 (6)	37 (6)	35 (7)	39 (6)	37 (6)	35 (6)
PUFA (% E)	6 (2)	5 (1)	5 (1)	5 (2)	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)
MUFA (% E)	17 (3)	16 (4)	15 (4)	16 (3)	16 (4)	16 (4)	16 (3)	16 (4)	16 (4)
SFA (% E)	14 (3)	13 (3)	10 (3)	14 (3)	13 (3)	11 (3)	14 (3)	13 (3)	11 (3)
TFA (% E)	1.2 (0.5)	0.9 (0.5)	0.6 (0.4)	1.1 (0.5)	0.9 (0.5)	0.7 (0.4)	1.2 (0.6)	0.9 (0.4)	0.6 (0.4)
n-3 fatty acids (g/d)	3 (1)	3 (1)	3 (1)	2 (1)	3 (1)	3 (1)	2 (1)	3 (1)	3 (1)
n-6 fatty acids (g/d)	21 (14)	17 (11)	14 (8)	20 (13)	17 (11)	15 (11)	19 (13)	17 (11)	15 (11)
Cholesterol (mg/d)	460 (140)	400 (136)	344 (118)	426 (138)	407 (143)	376 (124)	448 (143)	408 (136)	350 (127)
Fiber intake (g/d)	19 (7)	26 (9)	35 (10)	19 (7)	26 (9)	34 (10)	19 (7)	26 (9)	34 (10)
Alcohol intake (g/d)	8 (11)	7 (10)	5 (8)	6 (9)	7 (10)	8 (11)	8 (14)	7 (9)	6 (6)

Q: quintiles; DASH: Dietary Approaches to Stop Hypertension; MEDAS: Mediterranean Diet Adherence Screener; AHEI: Alternate Healthy Eating Index; PUFA: polyunsaturated fatty acids; MUFA: monounsaturated fatty acids; SFA: saturated fatty acids; TFA: trans fatty acids.

Table III. Prevalence of inadequate micronutrient intake: % of participants in the SUN cohort with intakes below EAR according to quintiles of adherence to the DASH, MEDAS and AHEI-2010

	DASH			MEDAS			AHEI-2010		
	Q1	Q2-Q4	Q5	Q1	Q2-Q4	Q5	Q1	Q2-Q4	Q5
Scores	8-19	20- 28	29-40	0-4	5-7	8-12	20-50	51-68	66-99
n	3943	10029	2796	3749	9785	3234	3396	10250	3122
Vit. A (µg/d)	13.4	4.5	0.6	13.2	4.9	0.8	13.3	4.9	1.5
Vit. E (mg/d)	96.1	95.1	90.1	96.7	95.4	89.3	97.9	95.4	88
Vit. C (mg/d)	4.6	1.1	0	4.4	1.3	0.1	4.8	1.2	0.1
Vit. B_1 (mg/d)	5.3	4.1	0.4	5.9	3.9	0.8	5.2	3.8	2.1
Vit. B_2 (mg/d)	2.6	2.1	0.4	2.8	2.1	0.7	1.9	2.1	1.5
Vit. B_3 (mg/d)	0.03	0.1	0	0.1	0.1	0	0.1	0.1	0.1
Vit. B_6 (mg/d)	2.2	1.4	0.1	3.1	1.1	0.1	2.8	1.2	0.4
Vit. B_{12} (mg/d)	0.4	0.8	1.1	0.6	0.9	0.6	1.2	0.7	0.8
Vit. D (µg/d)	84.5	75.1	62.9	89.9	74.8	59.6	85.6	75.6	63.1
Folic acid (µg/d)	64.7	31.6	7.1	66	32.4	8.4	59.1	33.8	14.4
Fe (mg/d)	1.6	1.3	0.1	2.4	1	0.1	2.6	0.9	0.4
Ca (mg/d)	26.2	19.9	12.2	26.5	19.4	14.5	19.4	19.8	21.6
K (mg/d)	22.2	10.8	1.6	23	11	2.1	20.2	11.4	4.8
Mg (mg/d)	32	18.9	4.5	33.3	18.6	6.1	29	19.4	9.9
P (mg/d)	0.1	0.2	0	0.1	0.2	0	0.2	0.1	0.1
Cr (µg/d)	2.5	1.4	0.1	2.6	1.4	0.2	2.8	1.2	0.7
Se (µg/d)	4.3	5.3	2.8	6.8	4.7	1.7	6.2	4.2	4.1
I (µg/d)	11.5	8.6	5.8	10.5	8.8	7.1	8.5	8.5	10.4
Zn (mg/d)	7.1	7	3.2	8.4	6.5	3.5	5.7	6.6	6.3

EAR: estimated average requirement; DASH: Dietary Approaches to Stop Hypertension; MEDAS: Mediterranean Diet Adherence Screener; AHEI: Alternate Healthy Eating Index; Q: quintiles. In the heat mat, colours refer to prevalence of micronutrient inadequacy. Red colour means higher whereas green colour means lower prevalence.

Table IV. Odds ratios (95 % confidence intervals) of not meeting the EAR for ≥ 3 micronutrients according to quintiles of adherence (probabilistic approach)

Not meeting ear for ≥ 3 micronutrients						
DASH	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***p*-trend**
n	3943	3520	3635	2874	2796	
% not meeting ≥ 3 EAR	59.9	45.6	35.8	25.6	15.1	
Crude	1 (Ref.)	0.57 (0.52-0.62)	0.37 (0.34-0.41)	0.23 (0.21-0.26)	0.12 (0.11-0.13)	< 0.001
Multivariable	1 (Ref.)	0.27 (0.24-0.30)	0.13 (0.11-0.15)	0.06 (0.05-0.07)	0.03 (0.02-0.03)	< 0.001
MEDAS	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***p*-trend**
n	3749	3365	3528	2892	3234	
% not meeting ≥ 3 EAR	63.2	48.2	34.5	24.9	15.3	
Crude	1 (Ref.)	0.54 (0.49-0.59)	0.31 (0.28-0.34)	0.19 (0.17-0.21)	0.10 (0.09-0.12)	< 0.001
Multivariable	1 (Ref.)	0.39 (0.35-0.44)	0.19 (0.17-0.22)	0.11 (0.10-0.13)	0.06 (0.05-0.07)	< 0.001
AHEI-2010	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***p*-trend**
n	3396	3390	3711	3149	3122	
% not meeting ≥ 3 EAR	55.7	40.3	37.7	31.8	24.8	
Crude	1 (Ref.)	0.54 (0.49-0.60)	0.49 (0.44-0.53)	0.37 (0.34-0.41)	0.26 (0.24-0.30)	< 0.001
Multivariable	1 (Ref.)	0.39 (0.35-0.44)	0.29 (0.26-0.33)	0.18 (0.16-0.20)	0.10 (0.09-0.12)	< 0.001
GDQS	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***p*-trend**
n	3411	3582	3171	3429	3174	
% not meeting ≥ 3 EAR	71.0	47.4	34.3	23.5	13.1	
Crude	1 (Ref.)	0.37 (0.33-0.41)	0.21 (0.19-0.24)	0.12 (0.11-0.13)	0.06 (0.05-0.07)	< 0.001
Multivariable	1 (Ref.)	0.32 (0.29-0.37)	0.17 (0.15-0.20)	0.09 (0.08-0.11)	0.05 (0.04-0.05)	< 0.001
aMED	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***p*-trend**
n	2949	3163	3766	3471	3399	
% not meeting ≥ 3 EAR	74.1	52.9	35.5	23.3	12.4	
Crude	1 (Ref.)	0.39 (0.35-0.44)	0.19 (0.17-0.21)	0.11 (0.09-0.12)	0.05 (0.04-0.06)	< 0.001
Multivariable	1 (Ref.)	0.33 (0.29-0.38)	0.15 (0.14-0.18)	0.08 (0.07-0.09)	0.03 (0.03-0.04)	< 0.001
MDS	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***p*-trend**
n	5636	3434	3330	2441	1947	
% not meeting ≥ 3 EAR	59.8	39.2	29.7	20.4	12.2	
Crude	1 (Ref.)	0.43 (0.40-0.47)	0.28 (0.26-0.31)	0.17 (0.15-0.19)	0.09 (0.08-0.11)	< 0.001
Multivariable	1 (Ref.)	0.37 (0.33-0.41)	0.23 (0.20-0.25)	0.13 (0.12-0.15)	0.07 (0.06-0.09)	< 0.001

Q: quintiles; EAR: Estimated Average Requirement; DASH: Dietary Approaches to Stop Hypertension; MEDAS: Mediterranean Diet Adherence Screener; AHEI: Alternate Healthy Eating Index; GDQS: Food-Based Global Diet Quality Score; aMED: Alternative Mediterranean Diet; MD: Mediterranean Diet Score. Multivariable: adjusted for age, sex, total energy intake (continuous), BMI (kg/m², continuous), physical activity (MET-h/week, continuous), time spent sitting (hours/week, continuous), weight gain in the previous 5 years before entering the cohort (< 3 kg and ≥ 3 kg), following special diet at baseline (yes/no), educational level (years of higher education, continuous), cumulative smoking habit (packs /year, continuous), alcohol intake (never, < 5 women or < 10 men, g/d; 5-25 women or 10-50 men, g/d; and > 25 women or > 50 men, g/d), snacking (yes/no) and stratified by recruitment period (5 categories) and deciles of age.

Table V. Odds ratios (95 % confidence intervals) of not meeting the EAR for ≥ 6 micronutrients according to quintiles of adherence (probabilistic approach)

Not meeting ear for ≥ 6 micronutrients						
DASH	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***p*-trend**
n	3943	3520	3635	2874	2796	
% not meeting ≥ 6 EAR	11.2	9.8	5.9	3.4	1.1	
Crude	1 (Ref.)	0.86 (0.74-1.00)	0.50 (0.42-0.60)	0.28 (0.23-0.35)	0.09 (0.06-0.13)	< 0.001
Multivariable	1 (Ref.)	0.39 (0.32-0.48)	0.15 (0.12-0.19)	0.07 (0.05-0.10)	0.03 (0.02-0.04)	< 0.001
MEDAS	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***p*-trend**
n	3749	3365	3528	2892	3234	
% not meeting ≥ 6 EAR	12.3	9.2	6.2	3.5	1.3	
Crude	1 (Ref.)	0.72 (0.62-0.84)	0.47 (0.40-0.56)	0.26 (0.21-0.33)	0.10 (0.07-0.13)	< 0.001
Multivariable	1 (Ref.)	0.47 (0.39-0.58)	0.29 (0.23-0.36)	0.16 (0.12-0.21)	0.07 (0.05-0.10)	< 0.001
AHEI-2010	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***p*-trend**
n	3396	3390	3711	3149	3122	
% not meeting ≥ 6 EAR	10.3	7.0	6.7	5.9	3.7	
Crude	1 (Ref.)	0.66 (0.55-0.78)	0.63 (0.53-0.75)	0.55 (0.45-0.66)	0.33 (0.27-0.42)	< 0.001
Multivariable	1 (Ref.)	0.49 (0.39-0.62)	0.37 (0.29-0.46)	0.23 (0.18-0.30)	0.14 (0.10-0.18)	< 0.001
GDQS	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***p*-trend**
n	3411	3583	3171	3429	3174	
% not meeting ≥ 6 EAR	21.1	6.5	6.1	1.8	0.7	
Crude	1 (Ref.)	0.26 (0.22-0.30)	0.12 (0.10-0.15)	0.07 (0.05-0.09)	0.03 (0.02-0.04)	< 0.001
Multivariable	1 (Ref.)	0.23 (0.19-0.29)	0.11 (0.08-0.14)	0.07 (0.05-0.09)	0.03 (0.02-0.05)	< 0.001
aMED	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***p*-trend**
n	2949	3163	3766	3491	3399	
% not meeting ≥ 6 EAR	16.6	10.2	5.2	2.7	1.0	
Crude	1 (Ref.)	0.57 (0.49-0.66)	0.28 (0.23-0.33)	0.14 (0.11-0.17)	0.05 (0.04-0.07)	< 0.001
Multivariable	1 (Ref.)	0.58 (0.47-0.70)	0.32 (0.25-0.39)	0.15 (0.12-0.20)	0.07 (0.04-0.10)	< 0.001
MDS	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***p*-trend**
n	5636	3414	3330	2441	1947	
% not meeting ≥ 3 EAR	12.0	7.2	4.2	2.5	0.6	
Crude	1 (Ref.)	0.57 (0.49-0.67)	0.33 (0.27-0.39)	0.19 (0.14-0.25)	0.05 (0.03-0.08)	< 0.001
Multivariable	1 (Ref.)	0.59 (0.49-0.72)	0.35 (0.28-0.44)	0.19 (0.14-0.27)	0.07 (0.04-0.13)	< 0.001

Q: quintiles; EAR: Estimated Average Requirement; DASH: Dietary Approaches to Stop Hypertension; MEDAS: Mediterranean Diet Adherence Screener; AHEI: Alternate Healthy Eating Index; GDQS: Food-Based Global Diet Quality Score; aMED: Alternative Mediterranean Diet; MD: Mediterranean Diet Score. Multivariable: adjusted for age, sex, total energy intake (continuous), BMI (kg/m2, continuous), physical activity (MET-h/week, continuous), time spent sitting (hours/week, continuous), weight gain in the previous 5 years before entering the cohort (< 3 kg and ≥ 3 kg), following special diet at baseline (yes/no), educational level (years of higher education, continuous), cumulative smoking habit (packs /year, continuous), alcohol intake (never, < 5 women or < 10 men, g/d; 5-25 women or 10-50 men, g/d; and > 25 women or > 50 men, g/d), snacking (yes/no) and stratified by recruitment period (5 categories) and deciles of age.

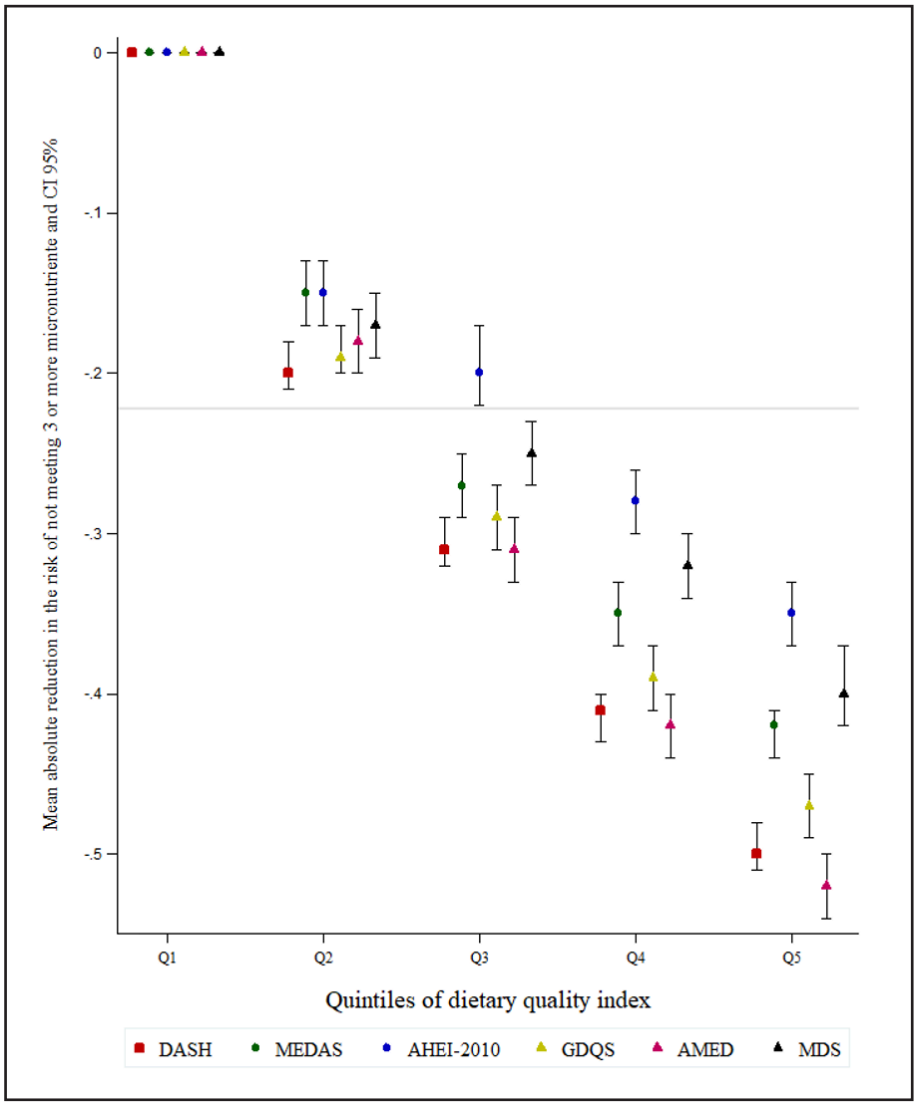

Figure 2.

Adjusted mean absolute reduction in the risk of not meeting (Estimated Average Requirement (EAR) ≥ 3 micronutrients according to quintiles of adherence (mean and 95 % CI) (DASH: Dietary Approaches to Stop Hypertension; MEDAS: Mediterranean Diet Adherence Screener (MEDAS); AHEI: Alternate Healthy Eating Index; GQDS: Food-Based Global Diet Quality Score; aMED: Alternative Mediterranean Diet; MD: Mediterranean Diet Score. Multivariable: adjusted for age, sex, total energy intake (continuous), BMI (kg/m^2, continuous), physical activity (MET-h/week, continuous), time spent sitting (hours/week, continuous), weight gain in the previous 5 years before entering the cohort (< 3 kg and ≥ 3 kg), following special diet at baseline (yes/no), educational level (years of higher education, continuous), cumulative smoking habit (packs/year, continuous), alcohol intake (never, < 5 women or < 10 men, g/d; 5-25 women or 10-50 men, g/d; and > 25 women or > 50 men, g/d), snacking (yes/no) and stratified by recruitment period (5 categories) and deciles of age).

DISCUSSION

In this middle-aged population study, a higher adherence to six *a priori* DQI (mainly food-based) showed a strong inverse association with the risk of micronutrient inadequacy. These results support the use of *a priori* indices of food-based dietary quality indexes as a useful tool for assessing micronutrient adequacy. DQIs capture the essential elements of a healthy dietary pattern and their main advantage is its generalisability and that they can be applied to different populations. Among the six DQI evaluated, GDQS and MEDAS may be suitable for large sample or clinical settings as they do not require the use of a full-length FFQ to be derived, given that they are collected with rapid dietary assessment tools.

Different dietary patterns, including nutrient-dense foods, can meet the micronutrient requirements of individuals and, in general, higher diet-quality scores are usually associated with more favorable nutrient and food intakes (24). According to the Global Nutrient Database, micronutrient availability has increased over the past four decades, although there is wide variation between countries and levels of development (25). Deficiencies of individual micronutrients rarely occur alone, but often coexist. Vitamin A, Fe, I, Zn and folate deficiencies are the most widespread. Micronutrient sufficiency status can be determined using biomarkers, but unfortunately, biomarkers are not available for all micronutrients or are not feasible for widespread assessment or use outside the clinical setting, so dietary intake data or non-specific functional indicators may be used (26).

As expected, participants with higher punctuations on the DASH, MEDAS and AHEI-10 scores had generally healthier food consumptions, as these are all dietary patterns that emphasize the inclusion of nutrient-dense foods and healthy sources of protein. For alcohol, participants in the highest quintile of MEDAS had higher alcohol consumption than participants in AHEI-10. As usually occurs in DQI construction, many differences exist in selected items, depending on the choice of cut-offs and the decisions on the relative contri-

bution of each component to the total score (6). In this context, MEDAS considers that the consumption of a traditional Mediterranean alcohol drinking pattern may have some health benefits for adults over 40 years of age (27). The assumption is that moderate intake means consuming ≤ 7 glasses a week in women and ≤ 14 in men (glass: 100 ml), preferably red wine during meals, together with avoidance of binge drinking (28,29).

Also, as expected, in terms of nutrient intake, participants with the highest DASH, MEDAS and AHEI-10 scores also had higher intakes of fiber and lower percentage of energy intake from total fat, SFA and TFA, because fiber and fat intake or sources of fat had been considered in their construction. In fact, the 3 scores promote a high consumption of fruits, vegetables, whole grains and healthy fats with a low intake of solid fats (15).

In our study, participants in the highest quintile of adherence to DASH, MEDAS and AHEI-10 had a lower prevalence of inadequate intake for most micronutrients. Among all the micronutrients analysed, a higher prevalence of inadequacy was observed for vitamins D and E. The mean absolute reduction in the risk of not meeting ≥ 3 EAR was greater in participants with higher adherence compared with those in the first quintile, particularly for DASH, aMED and MDS. Previous studies in the Spanish population have shown inadequacies in vitamins A, E, C, D, B9, and Ca, Zinc, Fe and Mg (30-34). In a further analysis including the six DQIs, we found a strong inverse association between the highest quintile of each DQI and failure to meet both EAR ≥ 3 or ≥ 6 micronutrients.

Healthy dietary patterns are assumed to be balanced in terms of macro and micronutrients, although these DQI have not often been used specifically to investigate the prevalence of micronutrient inadequacy in adults (35). On the contrary, dietary diversity indices, traditionally used in low- and middle- income countries, have shown the ability to reflect micronutrient adequacy (36,37). Besides, there are available specific nutrient-based diet quality indices that included micronutrients (38) and a review of DQI in children found that the most common vitamins included were A, C, E, B1 and B2, and the most common minerals were Ca, Fe, Zn, and K, while the least common micronutrients were vitamins D, K, pantothenic acid, B6, and Na and P (39).

It is important to highlight that, to date, no single or set of dietary metrics has not been developed or validated to assess the micronutrient quality of the diet in all age groups, although AHEI, MDS and DASH were initially validated for adult populations in high-income countries and were considered appropriate metrics for assessing dietary quality in the whole population in a large study of 185 countries from 1990 to 2018 (40). Previous investigation in the SUN cohort evaluated within-participant longitudinal changes in diet quality using the well-known DQI, in which MEDAS and MDS scores showed the largest improvements (41).

Several strengths of the present study should be noted: the inclusion of a well-known Mediterranean cohort with a large sample size and high retention rate (> 91 % overall), the use of previously validated questionnaires (FFQ validated and subsequently re-evaluated), the adjustment for a wide range of many potential confounders, the selection and comparison of 6 recognized *a priori* DQI to assess diet quality. Besides, we used two different methods to estimate nutrient intake adequacy: the probabilistic approach and the EAR cut-point approach.

However, we must acknowledge certain limitations. First, we used a self-reported FFQ so certain measurement error and misclassification cannot be excluded. However, FFQ is a valid tool to measure the overall dietary intake in epidemiological studies, and although it has been reported that vitamins may be overestimated, most micronutrients estimated by the FFQs are higher than those estimated by 24 hrs (42). Second, our results are based on observed intake data, so we could only asses the likelihood or risk of micronutrient inadequacy, not deficiencies, which should be confirmed by biomarkers. Third, the study population of highly educated adults, which may be considered as a factor that limits the generalizability of our findings, but this homogeneity reduces the likelihood of misclassification and potential confounding by socio-economic status and increase internal validity.

CONCLUSIONS

In conclusion, in this middle-aged population study a higher adherence to six mainly food-based DQI showed a strong inverse association with micronutrient inadequacy, reinforcing the use of *a priori* indices of diet quality as useful tools to assess the adequacy of micronutrient intake. GDQS and MEDAS may be suitable for large sample or clinical settings, as both are food-based indices that are useful for time-relevant assessments of population diet quality, as they can be collected with rapid dietary assessment tools and do not require derivation of nutrient intake data from a full-length FFQ. In particular, the 14-item MEDAS is even easier and quicker to complete (17).

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Trabajo Original

Epidemiología y dietética

Causal effects of vitamin D on leukemia risk: insights from two-sample Mendelian randomization analysis

Efectos causales de la vitamina D sobre el riesgo de leucemia: aportaciones del análisis de aleatorización mendeliana de dos muestras

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Abstract

Background: vitamin D plays a crucial role in immune regulation, anti-inflammatory processes, and tumor suppression, but its relationship with leukemia risk remains unclear. This study aims to evaluate the causal relationship between vitamin D levels and the risk of different types of leukemia through a two-sample Mendelian randomization (MR) analysis.

Methods: data from large-scale genome-wide association studies (GWAS) were used, and genetic variants associated with vitamin D were selected as instrumental variables. The relationship between vitamin D levels and the risk of acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML) was examined. The inverse variance weighted (IVW) method was applied as the primary analytical approach. Heterogeneity was assessed through Cochran's Q test, pleiotropy was evaluated using the MR-Egger intercept, and sensitivity analyses were performed to ensure the robustness of the results.

Results: MR analysis showed a significant inverse association between serum 25-hydroxyvitamin D levels and the risk of CML (OR = 0.44, 95 % CI: 0.25-0.78, $p = 0.005$), suggesting a potential protective effect of vitamin D against CML. No significant causal relationships were found between vitamin D levels and the risks of AML, ALL, or CLL. Sensitivity analyses supported the robustness of these findings, with no evidence of heterogeneity or pleiotropy.

Conclusion: the findings indicate that higher vitamin D levels may reduce the risk of CML, while the effects on other types of leukemia require further investigation. The potential role of vitamin D in leukemia prevention warrants more mechanistic studies and clinical validation.

Keywords:

Vitamin D. Leukemia. Mendelian randomization. CML. Causal relationship. Genome-wide association studies (GWAS).

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Resumen

Antecedentes: la vitamina D juega un papel vital en la inmunomodulación, los procesos antiinflamatorios y la inhibición tumoral, pero su relación con el riesgo de leucemia no está clara. El objetivo de este estudio es evaluar la relación causal entre los niveles de vitamina D y el riesgo de diferentes tipos de leucemia mediante un análisis aleatorizado de Mendel (MR) de dos muestras.

Método: utilizando datos de estudios de asociaciones pangenómicas a gran escala (GWAS) se seleccionaron como variables instrumentales las variaciones genéticas relacionadas con la vitamina D. Se estudió la relación entre los niveles de vitamina D y el riesgo de leucemia mieloide aguda (LMA), leucemia linfoblástica aguda (LLA), leucemia linfoblástica crónica (LLC) y leucemia mieloide crónica. El método de ponderación de variación inversa (IVW) se utiliza como principal método de análisis. La heterogeneidad se evalúa a través de la prueba de la Q de Cochran; la polivalencia se evalúa con la interceptación MR-Egger y se realiza un análisis de sensibilidad para garantizar la solidez de los resultados.

Resultados: el análisis de MR mostró una correlación negativa significativa entre los niveles séricos de 25-hidroxivitamina D y el riesgo de CML (OR = 0,44, IC 95 %: 0,25-0,78, $p = 0,005$), lo que indica que la vitamina D tiene un potencial efecto protector sobre la LMC. No se encontró una relación causal significativa entre los niveles de vitamina D y el riesgo de LMA, LLA o LLC. El análisis de sensibilidad apoya la solidez de estos hallazgos y no hay evidencia de heterogeneidad o polivalencia.

Conclusiones: los resultados del estudio sugieren que los niveles más altos de vitamina D pueden reducir el riesgo de LMC mientras que los efectos en otros tipos de leucemia requieren más estudios. El papel potencial de la vitamina D en la prevención de la leucemia merece más investigación de mecanismos y verificación clínica.

Palabras clave:

Vitamina D. Leucemia. Aleatorización mendeliana. Leucemia mieloide crónica. Relación causal. Estudio de asociación pangenómica (GWAS).

INTRODUCTION

Leukemia is a malignant tumor originating from the hematopoietic system, characterized by the abnormal proliferation of white blood cells in the bone marrow and/or peripheral blood. Based on the degree of cell maturity and the speed of proliferation, leukemia can be classified into two major categories: acute and chronic (1). Acute leukemia includes Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL), which are primarily characterized by the rapid proliferation of immature cells. Chronic leukemia includes Chronic Myeloid Leukemia (CML) and Chronic Lymphocytic Leukemia (CLL), which progress more slowly and involve an increase in mature cells. Leukemia poses a significant threat to global public health. According to the World Health Organization (WHO), hundreds of thousands of new cases are diagnosed each year. Treatment for leukemia is not only costly but also has a severe impact on patients' quality of life (2).

Vitamin D, an essential fat-soluble vitamin, plays a critical role beyond maintaining bone health. It is involved in immune regulation, anti-inflammatory processes, and antitumor activity (3,4). Sunlight exposure is an effective way to increase vitamin D levels in the body, and studies have shown that adequate vitamin D status is associated with a reduced risk of cancer (5). In recent years, increasing attention has been given to the relationship between vitamin D and leukemia, with research suggesting that vitamin D may positively influence survival outcomes in children with leukemia (6-8) . However, findings regarding the association between vitamin D levels and leukemia risk have been inconsistent. Some epidemiological studies have found that higher vitamin D levels appear to be associated with a lower risk of leukemia (9), while clinical evidence has also indicated no significant relationship between vitamin D levels and the prognosis of leukemia patients (10). These conflicting results may be due to limitations in study design, such as inadequate control of confounding factors, small sample sizes, or differences in measurement methods.

Mendelian randomization (MR) is a method that utilizes genetic variants as instrumental variables to assess the causal relationship between exposures and diseases. This approach offers a strategy to reduce the influence of confounding factors and reverse causality. By leveraging the fixed and randomly assigned nature of genetic variants throughout an individual's lifetime, MR provides more reliable causal inferences (11). In this study, we applied Mendelian randomization to investigate the causal relationship between vitamin D levels and the risk of various types of leukemia. Using data from large-scale genome-wide association studies (GWAS), this research aims to resolve the conflicting findings in the existing literature regarding the link between vitamin D and leukemia and to provide evidence-based guidance for leukemia prevention and treatment strategies. The findings from this study may help public health policymakers and clinicians better understand the potential role of vitamin D in leukemia prevention, thereby improving patient management and treatment strategies.

MATERIALS AND METHODS

STUDY DESIGN

As shown in figure 1, this study utilized a Mendelian randomization (MR) design to systematically investigate the association between vitamin D levels and the risk of leukemia. Since this study involved the reanalysis of publicly available genome-wide association study (GWAS) data, no additional ethical approval was required.

DATA SOURCES

In this study we conducted a comprehensive Mendelian randomization (MR) analysis to explore the causal relationship between vitamin D levels and the risk of leukemia. The patients included in this study met the diagnostic criteria defined by the International Classification of Diseases (ICD). The exposure variables in this study were serum 25-hydroxyvitamin D levels (ebi-a-GCST90000616) and overall vitamin D lev-

els (ebi-a-GCST90025967), both sourced from genome-wide association studies (GWAS). Specifically, the dataset for ebi-a-GCST90025967 included 418,691 samples, analyzing 4,225,238 single nucleotide polymorphisms (SNPs) (12), while the dataset for ebi-a-GCST90000616 included 417,580 samples, analyzing 7,234,361 SNPs (13).

The outcome variables included the following four leukemia phenotypes: acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML). AML is characterized by the abnormal proliferation of immature cells in the bone marrow and impaired maturation; ALL primarily affects lymphoid cells, particularly B or T cells; CLL often originates from B lymphocytes and has a slow disease course; and CML is typically associated with the BCR-ABL fusion gene (Philadelphia chromosome), progressing through chronic, accelerated, and blast phases.

The specific data sources for each leukemia subtype are as follows:

- *AML:* data from a 2024 Finnish dataset (finngen_R11_C3_AML_EXALLC), including 321 cases and 345,117 controls, analyzing a total of 20,092,329 SNPs.
- *ALL:* data from a 2024 Finnish dataset (finngen_R11_C3_ALL_EXALLC), including 214 cases and 345,117 controls, analyzing a total of 20,092,328 SNPs.
- *CLL:* data from a 2024 Finnish dataset (finngen_R11_C3_CLL_EXALLC), including 851 cases and 345,110 controls, analyzing a total of 20,092,344 SNPs.
- *CML:* data from a 2024 Finnish dataset (finngen_R11_C3_CML_EXALLC), including 134 cases and 345,117 controls, analyzing a total of 20,092,320 SNPs.

The specific information on exposure and outcome is shown in table I.

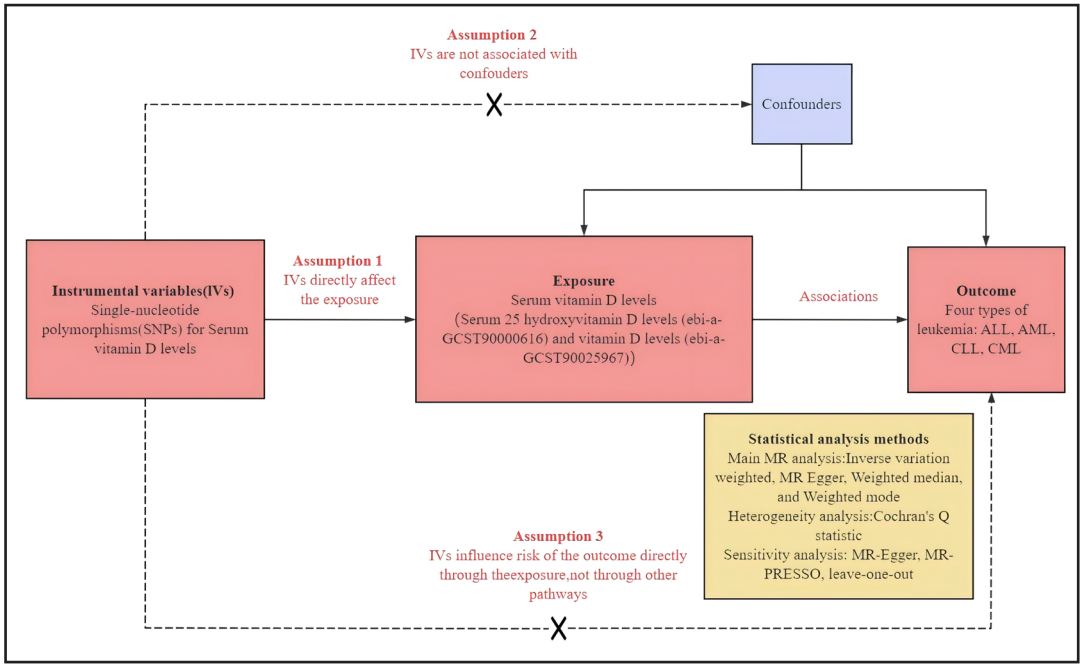

Figure 1.
Mendelian randomization analysis process of serum vitamin D levels and leukemia.

Table I. Basic information on exposures and outcomes

Variable type	Leukemia type	Dataset ID	Sample size	Case count	Control count	SNP count
Exposure	Vitamin D levels	ebi-a-GCST90025967	418,691	-	-	4,225,238
Exposure	Serum 25-hydroxyvitamin D levels	ebi-a-GCST90000616	417,580	-	-	7,234,361
Outcome	Acute myeloid leukemia (AML)	finngen_R11_C3_AML_EXALLC	345,438	321	345,117	20,092,329
Outcome	Acute lymphoblastic leukemia (ALL)	finngen_R11_C3_ALL_EXALLC	345,331	214	345,117	20,092,328
Outcome	Chronic lymphocytic leukemia (CLL)	finngen_R11_C3_CLL_EXALLC	345,961	851	345,110	20,092,344
Outcome	Chronic myeloid leukemia (CML)	finngen_R11_C3_CML_EXALLC	345,251	134	345,117	20,092,320

SELECTION OF INSTRUMENTAL VARIABLES

Mendelian randomization (MR) analysis is based on three fundamental assumptions: 1) the genetic variants must be strongly associated with the exposure factor; 2) the genetic variants must be independent of confounding factors; 3) the genetic variants must not be influenced by the outcome factors (11,14). An initial genome-wide significance threshold of 5×10^{-8} was set to identify single nucleotide polymorphisms (SNPs) significantly associated with lipid metabolism traits (15). To ensure the independence of these SNPs, we applied a linkage disequilibrium (LD) threshold of $r^2 = 0.001$ and required a physical distance of more than 10,000 kb to ensure that no LD occurred between the selected SNPs (16).

Additionally, we calculated the F-statistic for each instrumental variable (IV) to assess the potential for weak instrument bias. The F-statistic was calculated using the formula $F = Beta^2/SE^2$, where Beta represents the effect size of the allele and SE is the standard error of Beta. Only IVs with F-values greater than 10 were retained for further analysis to minimize the risk of bias due to weak instruments (17).

Finally, to further ensure the robustness of our analysis, all selected SNPs were cross-checked using the Phenoscanner database (www.phenoscanner.medschl.cam.ac.uk) on June 10, 2024, to exclude any SNPs potentially associated with confounding phenotypes (18). SNPs that were not associated with confounders were retained for the final analysis, ensuring the validity and reliability of our MR study.

MENDELIAN RANDOMIZATION ANALYSIS

In this study, we employed the inverse variance weighted (IVW) method as the primary approach to estimate causal effects. IVW is regarded as a robust tool for detecting causal relationships in two-sample Mendelian randomization (MR) analysis. To ensure the robustness of our findings, we performed supplementary analyses using MR-Egger regression, weighted median, and weighted mode methods (19).

Additionally, we conducted a series of sensitivity analyses to further validate the results. First, Cochran's Q test was applied to assess heterogeneity, which could influence causal estimates. If the *p*-value was greater than 0.05, heterogeneity was considered negligible, and a fixed-effect model was used. Conversely, if the *p*-value was less than or equal to 0.05, a random-effects model was adopted to account for heterogeneity (20).

To detect horizontal pleiotropy that might bias the MR results, we performed an MR-Egger intercept test. Furthermore, the MR-PRESSO outlier detection method was used to identify and correct for outliers among the SNPs, addressing any potential horizontal pleiotropy (21). Residual sensitivity analyses were also conducted to assess the robustness of the findings. Statistical analyses were performed using R software (version 4.3.1), with the "TwoSampleMR" and "MRPRESSO" packages facilitating the MR analysis, and the "forest plot" package used for visualization. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

INSTRUMENTAL VARIABLES

In this study, we conducted a detailed Mendelian randomization analysis to explore the causal relationship between serum 25-hydroxyvitamin D levels, overall vitamin D levels, and various types of leukemia. SNPs relevant to different types of leukemia were initially selected from large-scale genomic data. For acute lymphoblastic leukemia (ALL), we excluded 5 SNPs from an initial pool of 115, retaining 110 SNPs for the final analysis. The same selection criteria were applied for the analyses of acute myeloid leukemia (AML) and chronic myeloid leukemia (CML). For chronic lymphocytic leukemia (CLL), we excluded 6 SNPs from 115, retaining 109 for further analysis.

In the analysis of overall vitamin D levels, we identified 88 SNPs for ALL, AML, and CML, and excluded 1 SNP in the CLL analysis, retaining 87 SNPs. The selection and exclusion of SNPs were based on the core assumptions of Mendelian randomization to ensure the validity and robustness of the analysis. Detailed information on the selected SNPs and further specifics can be found in supplementary table I (https://www.nutricionhospitalaria.org/files/8598/ADMA1-05541-01.xlsx). These meticulous methodological steps ensured the rigor of our causal inference.

TWO-SAMPLE MENDELIAN RANDOMIZATION ANALYSIS

We employed four methods—inverse variance weighted (IVW), MR-Egger, weighted median, and weighted mode—to assess the causal relationship between vitamin D levels and leukemia. As shown in figure 2, serum 25-hydroxyvitamin D levels did not demonstrate a significant causal relationship with acute lymphoblastic leukemia (ALL) (OR = 0.86, 95 % CI: 0.42-1.74, $p = 0.68$), acute myeloid leukemia (AML) (OR = 0.95, 95 % CI: 0.54-1.68, $p = 0.87$), or chronic lymphocytic leukemia (CLL) (OR = 1.05, 95 % CI: 0.73-1.53, $p = 0.78$). However, a protective relationship was observed with chronic myeloid leukemia (CML) (OR = 0.46, 95 % CI: 0.26-0.81, $p = 0.007$).

Similarly, overall vitamin D levels showed no significant causal relationship with ALL (OR = 0.89, 95 % CI: 0.44-1.79, $p = 0.75$), AML (OR = 1.02, 95 % CI: 0.55-1.88, $p = 0.93$), or CLL (OR = 1.05, 95 % CI: 0.72-1.53, $p = 0.78$). In contrast, a protective relationship was observed with CML (OR = 0.44, 95 % CI: 0.25-0.78, $p = 0.005$).

RELIABILITY EVALUATION

Pleiotropy test

As shown in table II, the MR-Egger intercept results for the analysis of serum 25-hydroxyvitamin D levels and overall vitamin D levels with CML indicated that the Egger intercept

($p > 0.05$) was not significantly different from zero. This suggests that there was no evidence of horizontal pleiotropy in our Mendelian randomization analysis.

Heterogeneity analysis

Table II also shows that the Cochran's Q test for the analysis of serum 25-hydroxyvitamin D levels and vitamin D levels with CML revealed *p*-values greater than 0.05, indicating no heterogeneity in the MR analysis. Furthermore, the MR funnel plots for each group showed a symmetrical distribution of scatter points for the causal association effects, suggesting no potential bias (Fig. 3).

Sensitivity analysis

The leave-one-out test results indicated that excluding individual SNPs one at a time yielded IVW analysis results consistent with those that included all SNPs. In the analysis of serum 25-hydroxyvitamin D levels with CML, SNPs rs1352846 and rs116970203 had a significant influence on the causal association estimates. Similarly, in the analysis of vitamin D levels with CML, SNPs rs4588 and rs117913124 had a significant impact on the causal estimates. Repeating the MR analysis after excluding these influential SNPs showed that the causal effect of serum 25-hydroxyvitamin D levels on CML was not significant (OR = 0.48, 95 % CI: 0.22-1.02, $p = 0.06$). However, vitamin D levels remained a protective factor for CML (OR = 0.44, 95 % CI: 0.19-0.98, $p = 0.04$). These results further confirm the stability of the findings (Fig. 3); "a" represents the funnel plot of causal effects between serum 25-hydroxyvitamin D levels and CML, "b" represents the funnel plot of causal effects between vitamin D levels and CML, "c" represents the sensitivity analysis of the leave one method between serum 25-hydroxyvitamin D levels and CML, and "d" represents the sensitivity analysis of the leave one method between vitamin D levels and CML.

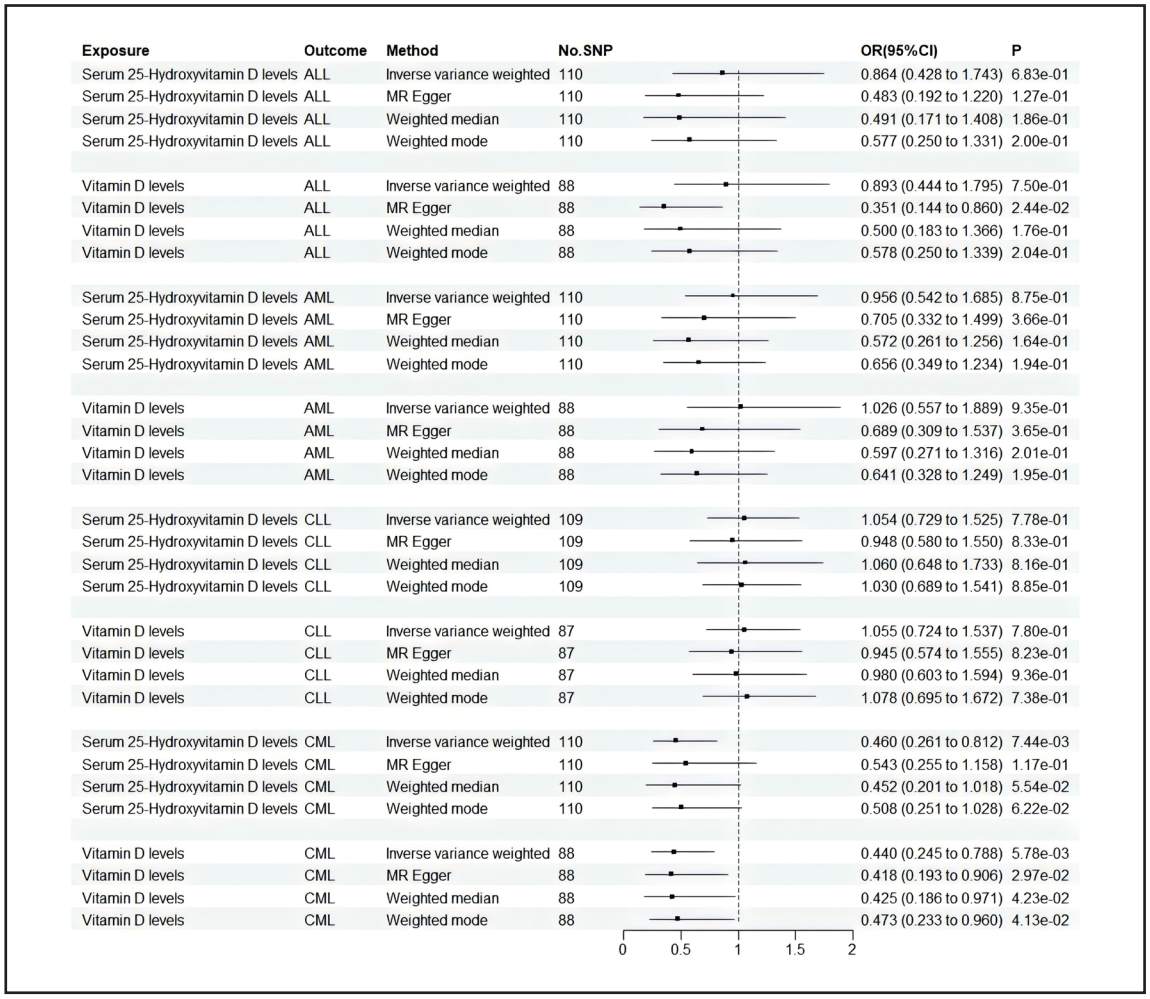

Figure 2.

Forest diagram of causal relationship between vitamin D and leukemia.

Table II. Reliability test of vitamin D and leukemia MR analysis

Expose	Outcome	Cochran Q		MR Egger	
		MR Egger	IVW	Q	*p*
Serum 25-hydroxyvitamin D levels	CML	*p* = 0.69	*p* = 0.70	-0.0008	0.51
Vitamin D level	CML	P = 0.63	*p* = 0.65	0.002	0.84

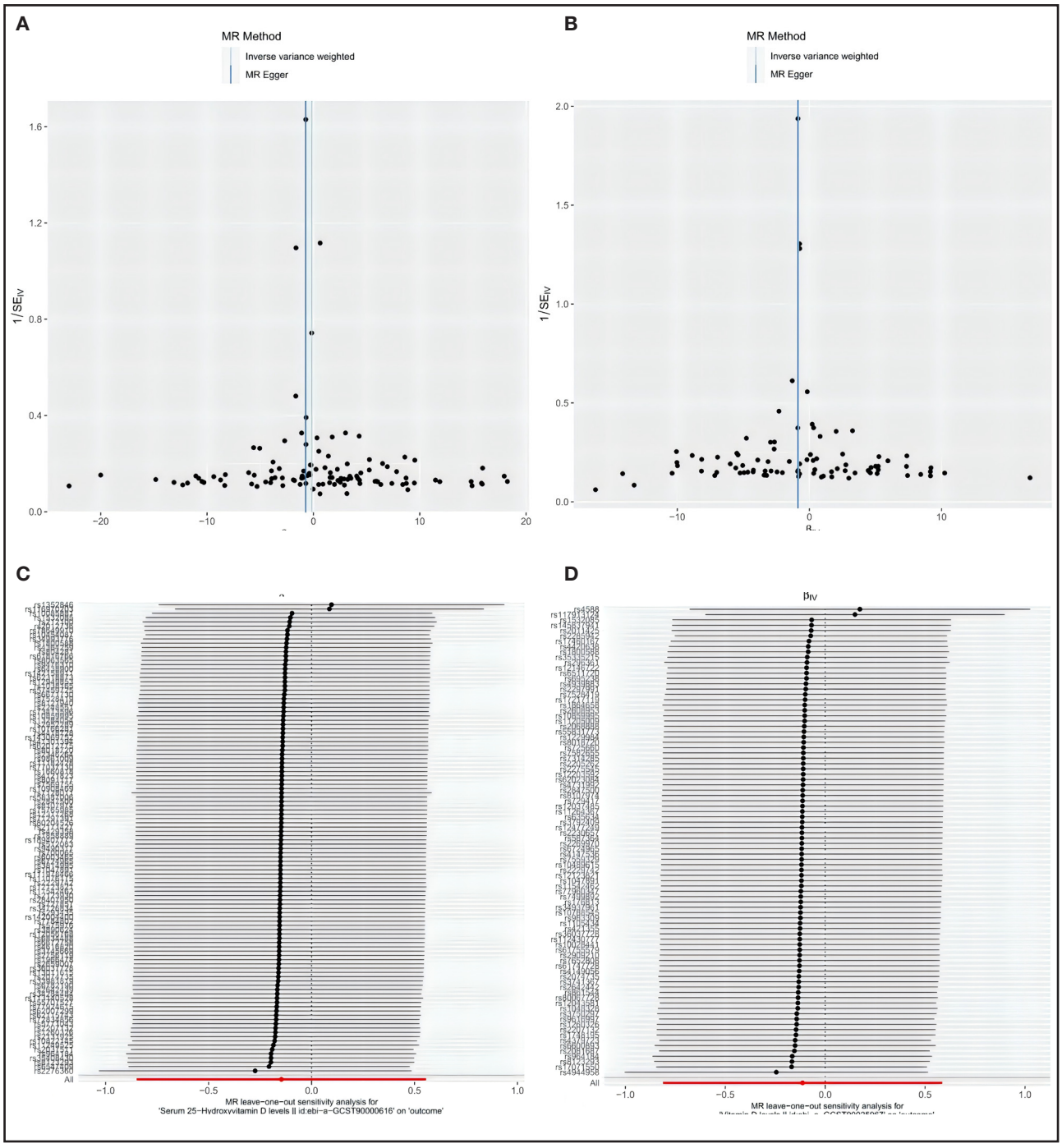

Figure 3.

Funnel plot and sensitivity analysis results of the causal effect of the causal association between vitamin D and leukemia using the leave one method.

DISCUSSION

Vitamin D exerts its antitumor effects through multiple mechanisms, including inhibiting cell proliferation, inducing differentiation and apoptosis, regulating immune responses, and suppressing pro-inflammatory reactions within the tumor microenvironment (22). In this study, we employed various Mendelian randomization (MR) methods to evaluate the relationship between serum 25-hydroxyvitamin D levels and different types of leukemia. The results indicated a significant protective association between serum 25-hydroxyvitamin D levels and chronic myeloid leukemia (CML). Using the inverse variance weighted (IVW) method, we found a significant inverse relationship between serum 25-hydroxyvitamin D levels and the risk of CML (OR = 0.46, 95 % CI: 0.26-0.81, $p = 0.007$). Similarly, overall vitamin D levels also demonstrated a protective effect (OR = 0.44, 95 % CI: 0.25-0.78, $p = 0.005$).

However, for acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic lymphocytic leukemia (CLL), our analysis did not reveal significant associations between vitamin D levels and the risk of these leukemia types. This may suggest that the protective effect of vitamin D varies among different leukemia types or that the limited sample size led to insufficient statistical power to detect smaller effects. For example, the study by Sameer A. Parikh et al. (6) found that vitamin D deficiency may be associated with poor prognosis in CLL patients. Similarly, Yasmeen Jramne-Saleem et al. (7) showed that vitamin D derivatives could enhance the differentiation of AML cells by modulating the Nrf2/ARE pathway and its downstream targets, including glutathione and the AP-1 transcription factor. Furthermore, Eliza Turlej et al. (8) reported that vitamin D analogs (VDAs) could directly inhibit the proliferation of ALL-derived B cells and normal B cells, both of which express vitamin D receptors (VDR).

To validate the robustness of our results, we conducted extensive sensitivity analyses. For instance, MR-Egger regression and leave-one-out sensitivity analyses indicated that although individual SNPs may significantly influence the estimates, the overall results consistently supported the protective effect of vitamin D levels on CML. Kazuki Kanno et al. (23) further emphasized the importance of vitamin D supplementation in specific patient groups through the AMATERASU randomized clinical trial. In this trial, vitamin D supplementation significantly improved the 5-year recurrence-free survival in patients within the p53 immune response subgroup but had no significant impact on patients outside this subgroup, suggesting that p53 may be a key factor in vitamin D's anticancer effects.

Additionally, this study highlights the potential application of serum 25-hydroxyvitamin D as a biomarker for leukemia prevention. Given vitamin D's role in cell proliferation, differentiation, and immune regulation, its potential protective effect against CML and other types of leukemia warrants further mechanistic research and clinical validation. Arkapal Bandyopadhyay et al. (24) conducted a randomized controlled clinical trial that found no significant benefit of vitamin D3 supplementation in early treatment responses in CML patients. However, long-term CML patients treated with imatinib mesylate exhibited significant vitamin D deficiency (25), indicating that vitamin D levels and their interaction with imatinib mesylate could play an important role in CML treatment.

It should be noted that this study was based on publicly available genome-wide association study (GWAS) data, which may be subject to potential selection bias or information bias. For instance, GWAS data often derive from specific populations, which may not fully represent leukemia patients from other ethnic groups or regions. Therefore, the generalizability of our findings may be limited, especially in populations with distinct racial or environmental differences. Additionally, vitamin D levels are influenced by various factors, including sun exposure, dietary intake, and lifestyle habits. While the Mendelian Randomization approach helps reduce confounding factors present in traditional epidemiological studies, it cannot entirely eliminate the influence of non-genetic factors on vitamin D levels. Moreover, this study only explored the causal relationship between vitamin D and leukemia without delving into the specific biological mechanisms or the dynamic interactions between vitamin D and leukemia development.

In summary, these findings support the notion that vitamin D may reduce the risk of certain types of leukemia by modulating tumor-related biological pathways. Our study provides a strong biological basis for the development of future leukemia prevention strategies and supports the potential benefits of vitamin D supplementation in clinical settings. Future research should further investigate the mechanisms by which vitamin D impacts different types of leukemia and evaluate its potential applications in leukemia prevention and treatment. These results provide scientific evidence for the development of vitamin D-based preventive measures, which could positively influence public health policy and clinical practice.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Epidemiología y dietética

NHANES data analysis of the cardiometabolic index in relation to lumbar spine bone mineral density

Análisis de datos del NHANES sobre el índice cardiometabólico en relación con la densidad mineral ósea de la columna lumbar

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Abstract

Objective: to investigate the correlation between cardiometabolic index (CMI) and lumbar spine bone mineral density (LSBMD) in U.S. adults.

Methods: the study selected eligible participants from the National Health and Nutrition Examination Survey (NHANES) database from 2011 to 2018. After adjusting for age, gender, race/ethnicity, body mass index (BMI), liver function markers, kidney function markers, blood routine indicators, metabolic markers, and chronic disease status, a logistic regression model combined with a restricted cubic spline model, smooth curve fitting, and threshold effect analysis was used to examine the association between CMI and LSBMD. Subgroup analysis was performed to verify the robustness of the results.

Results: among the 3,885 participants, for each unit increase in CMI, LSBMD decreased by 0.011 g/cm². Additionally, a turning point was identified at CMI = 0.797. When CMI was below 0.797, LSBMD decreased as CMI increased, showing a strong negative correlation (β = -0.077, 95 % CI: -0.097 to -0.058, $p < 0.001$). However, beyond this threshold, the relationship between CMI and LSBMD was no longer significant. Subgroup analysis revealed that the negative correlation between CMI and BMD was consistent across most subgroups (such as gender, BMI, hypertension, and high cholesterol), but instability was observed in subgroups such as individuals aged 51-59, Mexican Americans, non-Hispanic Blacks, and those with diabetes.

Conclusion: there exists a non-linear inverse correlation with CMI and LSBMD, showing that CMI could be a potential contributing factor for decreased bone mineral density, with a more pronounced effect within a specific range.

Keywords:

Cardiometabolic index (CMI). Lumbar spine bone mineral density (LSBMD). Large sample cross-sectional study. NHANES.

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Ethics approval: Research involving human participants was reviewed and approved by the NCHS Research Ethics Review Board (ERB).

Consent to participate: Written informed consent was not required for this study in accordance with national legislation and institutional requirements.

Data availability statement: Data for this study are available from the NHANES database: https://www.cdc.gov/nchs/nhanes/index.htm.

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Resumen

Objetivo: investigar la correlación entre el índice cardiometabólico (CMI) y la densidad mineral ósea de la columna lumbar (LSBMD) en adultos estadounidenses.

Métodos: el estudio seleccionó participantes elegibles de la base de datos de la Encuesta Nacional del Examen de Salud y Nutrición (NHANES) de 2011 a 2018. Después de ajustar por edad, sexo, raza/etnia, índice de masa corporal (IMC), marcadores de función hepática, marcadores de función renal, indicadores de rutina sanguínea, marcadores metabólicos y estado de enfermedad crónica se utilizó un modelo de regresión logística combinado con un modelo de *spline* cúbico restringido, ajuste de curva suave y análisis de efecto umbral para examinar la asociación entre el IMC y la LSBMD. Se realizaron análisis de subgrupos para verificar la solidez de los resultados.

Resultados: entre los 3885 participantes, por cada unidad de aumento del IMC, la LSBMD disminuyó 0,011 g/cm². Además, se identificó un punto de inflexión en el IMC = 0,797. Cuando el CMI era inferior a 0,797, la LSBMD disminuía a medida que aumentaba el CMI, mostrando una fuerte correlación negativa (β = -0,077; IC del 95 %: -0,097 a -0,058; $p < 0,001$). Sin embargo, por encima de este umbral, la relación entre el IMC y la LSBMD dejó de ser significativa. El análisis por subgrupos reveló que la correlación negativa entre el IMC y la DMO era constante en la mayoría de los subgrupos (como el sexo, el IMC, la hipertensión y el colesterol alto), pero se observó inestabilidad en subgrupos como los individuos de entre 51 y 59 años, los estadounidenses de origen mexicano, los negros no hispanos y los diabéticos.

Conclusiones: existe una correlación inversa no lineal entre el CMI y la LSBMD, lo que demuestra que el CMI podría ser un factor potencial que contribuya a la disminución de la densidad mineral ósea, con un efecto más pronunciado dentro de un rango específico.

Palabras clave:

Índice cardiometabólico (CMI). Densidad mineral ósea de la columna lumbar (LSBMD). Estudio transversal de muestra grande. NHANES.

INTRODUCTION

The cardiometabolic index (CMI) is a newly developed indicator of visceral fat, derived from the ratio of triglycerides to high-density lipoprotein cholesterol (TG/HDL-C) and the waist-to-height ratio (WHtR). It comprehensively reflects an individual's level of visceral fat and cardiometabolic risk. CMI has shown significant advantages in identifying atherosclerosis, diabetes, stroke, renal dysfunction, and metabolic diseases. Due to its simplicity and strong correlation with various cardiovascular risk factors, CMI has recently become an important tool in research on cardiometabolic health. Lumbar spine bone mineral density (LSBMD) serves as a crucial marker for evaluating bone health, where reduced density is often linked to a higher risk of osteoporosis and fractures. Previous research on visceral fat and cardiovascular diseases has consistently focused on imaging studies. Radiomics techniques have achieved notable results in predicting visceral fat texture and its association with heart failure (1), atrial fibrillation (2), and coronary artery calcified plaques (3). However, no reports have explored the relationship between CMI and bone health. Therefore, this study aims to analyze the correlation between CMI and BMD through a large-scale cross-sectional study based on the U.S. National Health and Nutrition Examination Survey (NHANES) database. Thus, this study seeks to examine the correlation between CMI and BMD using data from a large-scale cross-sectional analysis based on the U.S. National Health and Nutrition Examination Survey (NHANES) database. The goal is to provide new insights into how visceral fat affects bone health and offer scientific evidence for the comprehensive management of cardiometabolic risk factors.

MATERIALS AND METHODS

RESEARCH OBJECTS

All data were from the National Health and Nutrition Examination Survey (NHANES, https://wwwn.cdc.gov/nchs/nhanes/Default.aspx). This study analyzed data from 2011 to 2018, initially including 39,156 participants. Exclusion criteria included individuals younger than 18 years and those missing data on lumbar spine BMD, height, waist circumference, triglycerides, high-density lipoprotein cholesterol or weights of subsamples (WTSAF2YR) data. Ultimately, 3885 eligible participants were included. The screening process is shown in figure 1.

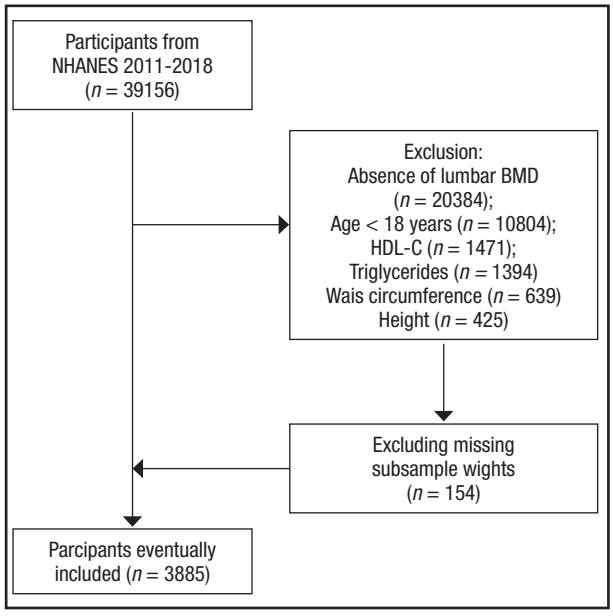

Figure 1.
Study flowchart.

CLINICAL AND LABORATORY DATA

Demographic information, anthropometric measurements, laboratory test results, and self-reported questionnaire data were collected. These included race/ethnicity, age, sex, body mass

index (BMI), liver function-related indicators (aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, gamma-glutamyl transferase, total protein, total cholesterol, total bilirubin,), complete blood count parameters (hemoglobin, serum calcium, serum phosphorus), metabolism-related indicators (25OHD2 + 25OHD3, serum glucose), lumbar spine bone mineral density, albumin-creatinine ratio, and chronic diseases (hypertension, diabetes).

CMI AND BONE MASS ASSESSMENT

The CMI was calculated using the following formula: (TG mmol/L / HDL-C mmol/L) / (waist circumference cm / height cm). DXA scans were performed by a certified radiographer using a Hologic QDR-4500A fan-beam bone densitometer (Hologic, Bedford, Massachusetts, USA), and Lumbar spine BMD (LSBMD) was analyzed and evaluated by a Hologic Discovery A bone densitometer (Hologic, Inc., Bedford, Massachusetts, USA) and its Apex version 3.2 software.

STATISTICAL ANALYSIS

Using R version 4.3.3 and EmpowerStats RCH software for organization and analysis, metric data conforming to normal distribution will be represented by mean ± standard deviation ($\bar{x} \pm s$). To ensure representativeness and accuracy, all estimates were adjusted for sample weights according to NCHS analytical guidelines. Participants' CMI values were divided into quartiles, followed by one-way analysis of variance (ANOVA) and chi-square tests. Weighted multivariate linear regression was used to explore the linear association between CMI and LSBMD, with three different models: Model 1 as the baseline without any variable adjustments; Model 2 adjusted for sex, age, BMI, and race/ethnicity; and Model 3 adjusted for multiple factors, including age, sex, BMI, race/ethnicity, 25OHD2 + 25OHD3, albumin-creatinine ratio, aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, total cholesterol, gamma-glutamyl transferase, serum glucose, serum calcium, serum phosphorus, total bilirubin, total protein, hemoglobin, diabetes, and hypertension. Stability of results was assessed using subgroup analyses. The restricted cubic spline method was used to explore non-linear relationships between CMI and LSBMD. Finally, the nonlinear relationship between the two was further assessed using the smoothed curve fitting technique and threshold effect assessment, respectively.

RESULTS

The final analysis included 3885 participants from 18 to 59 years of age with a mean age of 37.97 ± 12.34 years. Among them, 2,008 were male (51.7 %) and 1,877 were female (48.3 %). The CMI (cardiometabolic index) was divided into quartiles, ranging from 0.027 to 14.90. As can be seen in table I, there were significant differences in the distribution of sex, age, BMI, race, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, 25OHD2+25OHD3, total cholesterol, glutamine transferase, serum glucose, serum phosphorus, total bilirubin, hemoglobin, diabetes *mellitus,* and hypertension among the quartiles ($p < 0.05$). Participants in the highest quartile of CMI were more likely to be older males with higher BMI compared to those in the lowest quartile. Additionally, the proportion of non-Hispanic whites and Mexican Americans was greater, and they exhibited higher levels of ALT, AST, ALP, total cholesterol, GGT, and serum glucose.

Three models of linear regression were used to examine the association between CMI and LSBMD, with results presented in table II. Findings from all three models showed a negative and significant correlation between CMI and LSBMD ($p < 0.05$). After adjusting for relevant covariates, LSBMD decreased by 0.011 g/cm² for each unit increase in CMI, although the statistical significance was slightly lower compared to Model 1 and Model 2. When CMI was grouped by quartiles, the negative correlation remained significant ($p < 0.001$). Moreover, compared to the lowest quartile (Q1), higher CMI quartiles (Q2, Q3, Q4) were all significantly associated with lower LSBMD.

Participants were divided into subgroups based on gender, age, BMI, race, diabetes, hypertension, and total cholesterol. After adjusting for individual factors, the β coefficient for the association between CMI and LSBMD remained consistently negative across all subgroups (all $\beta < 0$), though some subgroups—such as those aged 51-59, Mexican Americans, non-Hispanic Blacks, and individuals with diabetes—exhibited variability in the strength of this negative correlation. Furthermore, gender and age were strongly associated with CMI ($p = 0.006$ and $p < 0.00$), but the interaction of BMI, race, diabetes, hypertension, and high cholesterol with CMI was not significant ($p > 0.05$), as illustrated in figure 2.

After performing the restricted spline regression (RCS) test and fitting it with a smoothed curve, figures 3 and 4 demonstrate a significant the non-linear association and saturation effect between CMI and LSBMD ($p < 0.001$). The results of the two-segment linear regression analysis indicate a notable non-linear characteristic in the association between CMI and LSBMD. In Model 1, CMI shows a negative correlation with LSBMD, while in Model 2, after CMI exceeds the threshold of 0.797, the regression coefficient increases, and the relationship between CMI and LSBMD is no longer significant (Table III).

DISCUSSION

As a composite index incorporating lipid profiles and anthropometric measurements, the CMI is closely associated with metabolic disorders related to obesity. Compared to other traditional anthropometric methods, CMI has demonstrated a superior ability to predict hyperuricemia in general populations (4), asthma (5), cardiovascular diseases (6), and non-alcoholic fatty liver disease (NAFLD) (7).

Table I. Weighted characteristics of the study population according to CMI quartiles

	Q1 (0.027-0.258)	Q2 (0.028 0.448)	Q3 (0.449-0.838)	Q4 (0.839-14.908)	*p*
Age	34.90 ± 12.24	37.62 ± 12.75	39.15 ± 12.08	41.77 ± 10.94	< 0.0001
Gender					< 0.0001
Male	41.94	48.3	53.3	67.8	
Female	58.06	51.7	46.7	32.2	
BMI	24.10 ± 4.50	27.76 ± 5.87	30.09 ± 6.22	32.86 ± 7.02	< 0.0001
Racist					< 0.0001
Mexican American	7.46	9.91	13.56	13.03	
Non-Hispanic White	62.00	68.38	60.33	71.22	
Non-Hispanic Black	18.74	13.51	13.09	6.4	
Other races	11.80	8.21	13.02	9.34	
LSBMD	1.06 ± 0.15	1.03 ± 0.15	1.02 ± 0.14	1.01 ± 0.14	< 0.0001
Albumin-creatinine ratio	18.08 ± 122.71	15.35 ± 116.40	29.83 ± 344.65	26.59 ± 154.52	0.1435
Alanine Aminotransferase	20.17 ± 17.27	23.41 ± 18.81	26.49 ± 17.88	32.58 ± 20.94	< 0.0001
Aspartate Aminotransferase	23.53 ± 16.02	24.17 ± 23.74	24.27 ± 14.57	26.80 ± 21.39	0.0129
Alkaline phosphatase	62.64 ± 22.31	66.37 ± 21.33	70.21 ± 19.84	72.67 ± 24.45	< 0.0001
Serum calcium	9.34 ± 0.33	9.33 ± 0.34	9.31 ± 0.33	9.33 ± 0.33	0.4098
Vitamin D	69.02 ± 27.02	67.42 ± 26.13	64.39 ± 24.92	63.64 ± 23.60	0.0093
Total cholesterol	176.00 ± 33.59	182.35 ± 35.95	194.38 ± 37.17	205.33 ± 43.26	< 0.0001
Gamma-glutamyl tansferase	21.29 ± 32.43	22.48 ± 28.26	28.16 ± 30.15	37.40 ± 35.94	< 0.0001
Serum glucose	89.96 ± 14.63	92.54 ± 15.02	96.93 ± 21.64	109.17 ± 41.56	< 0.0001
Serum phosphate	3.70 ± 0.53	3.64 ± 0.53	3.63 ± 0.54	3.57 ± 0.54	0.0004
Total bilirubin	0.66 ± 0.33	0.64 ± 0.30	0.65 ± 0.35	0.61 ± 0.28	0.0468
Total protein	7.14 ± 0.42	7.14 ± 0.42	7.15 ± 0.42	7.15 ± 0.42	0.9900
Hemoglobin	13.99 ± 1.37	14.32 ± 1.41	14.48 ± 1.36	14.87 ± 1.42	< 0.0001
Diabetes					< 0.0001
Yes	2.32	2.19	4.86	11.83	
No	97.68	97.81	95.14	88.17	
High blood pressure					< 0.0001
Yes	13.04	20.12	23.43	32.01	
No	86.96	79.88	76.57	67.99	

Table II. Linear regression analysis between CMI and LSBMD

	Model 1 β (95 % CI) *p*-value	Model 2 β (95 % CI) *p*-value	Model 3 β (95 % CI) *p*-value
CMI (continuous)	-0.018 (-0.022 to -0.014) < 0.001	-0.024 (-0.029 to -0.020) < 0.001	-0.011 (-0.018 to -0.004) 0.002
CMI (quartile)			
Q1	Reference	Reference	Reference
Q2	-0.012 (-0.018 to -0.007) < 0.001	-0.011 (-0.015 to -0.008) < 0.001	-0.010 (-0.017 to -0.002) 0.017
Q3	-0.012 (-0.019 to -0.006) < 0.001	-0.013 (-0.022 to -0.004) < 0.001	-0.009 (-0.016 to -0.001) 0.023
Q4	-0.016 (-0.022 to -0.010) < 0.001	-0.019 (-0.022 to -0.016) < 0.001	-0.012 (-30.020 to -0.005) 0.0020

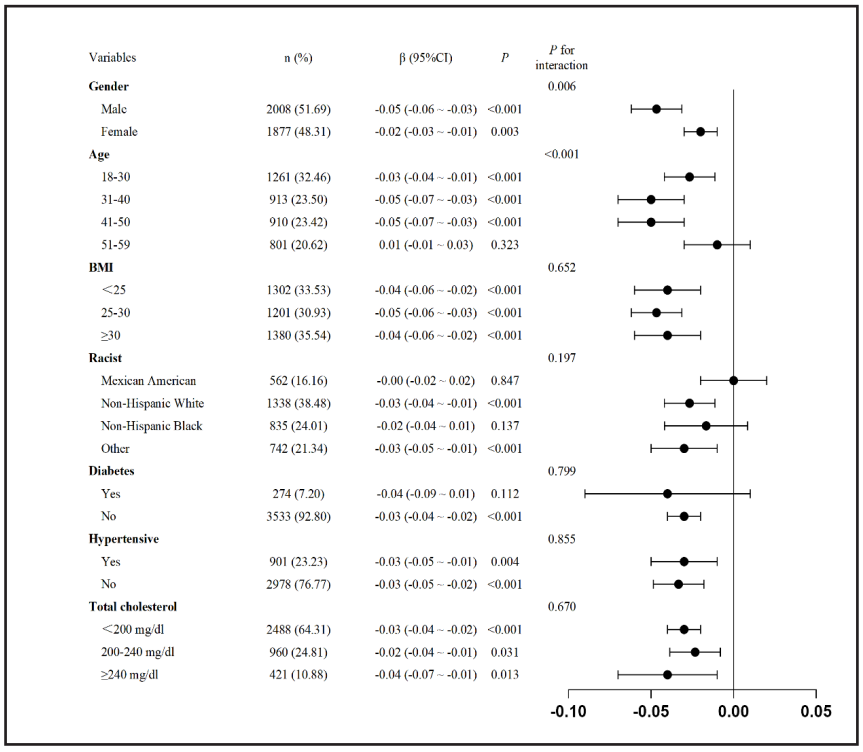

Figure 2.

Subgroup analysis of the associations between CMI and LSBMD.

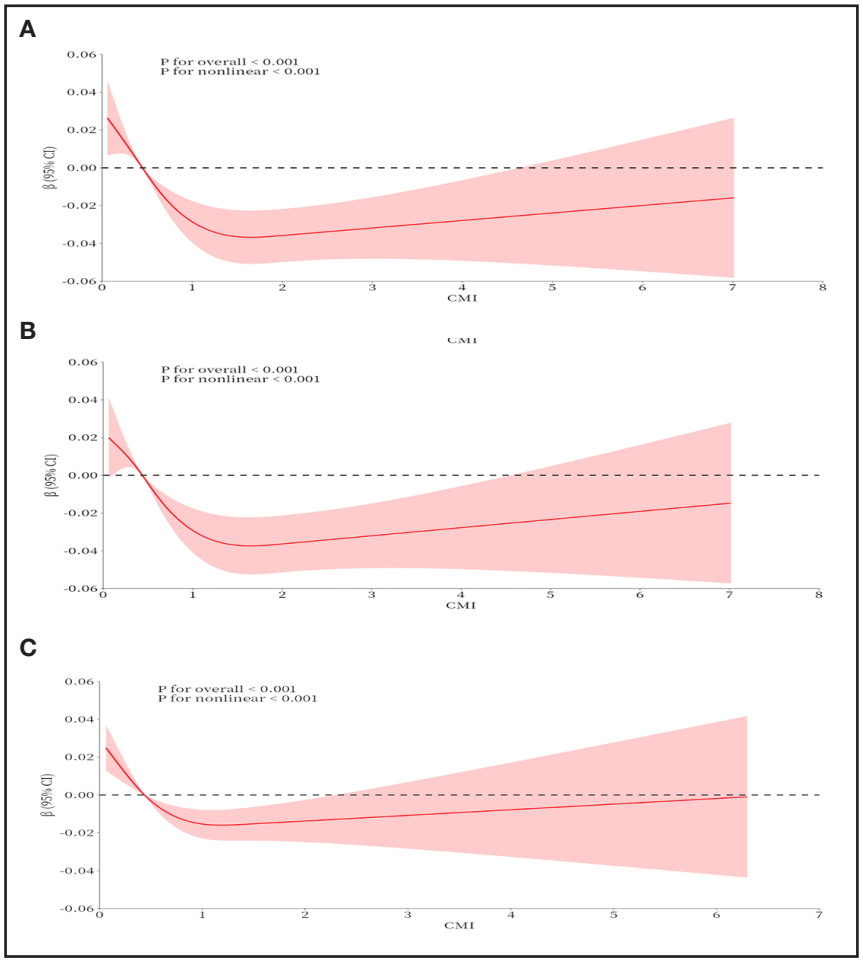

Figure 3.

The RCS curve diagram of CMI and LSBMD. A. Unadjusted variables. B. Adjusted for sex, age, race/ethnicity, BMI. C. Adjustment of all variables.

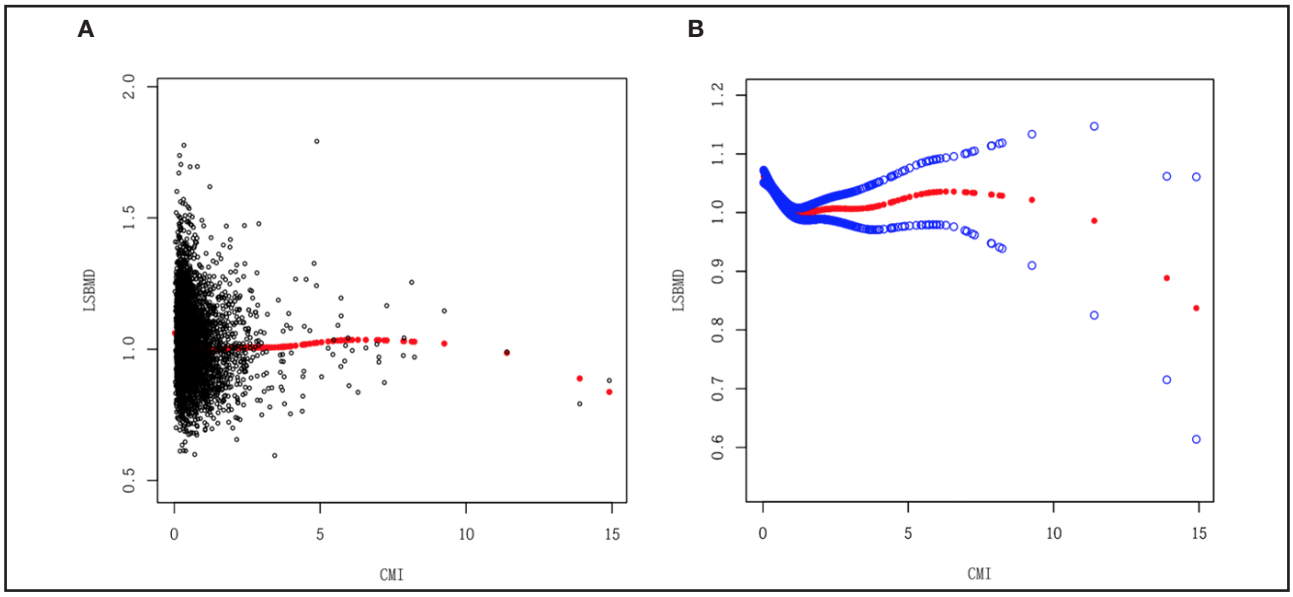

Figure 4.

Association of CMI with LSBMD. A. Scatterplot, each black dot represents a sample. B. Smoothed plot of the fit, the red line represents the fitted curve between the variables and the blue line indicates the 95 % confidence interval.

Table III. Two-stage linear regression analysis of the association between CMI and LSBMD

LSBMD	β (95 % CI)	*p*-value
Model 1		
one-line effect	-0.010 (-0.015 to -0.004)	0.0005
Model 2		
Inflection point (K)	0.797	
< K point effect 1	-0.077 (-0.097 to -0.058)	< 0.0001
> K point effect 2	0.006 (-0.001 to 0.012)	0.113
Effect 2 minus effect 1	0.083 (0.060 to 0.106)	< 0.0001
Predicted value of the equation at the folding point	1.007 (0.998 to 1.015)	
Log-likelihood ratio test		< 0.0001

Currently, there is inconsistency in the literature regarding the impact of CMI on BMD. One study found a positive correlation between CMI and BMD in the femur and intertrochanteric region (8), while another study reported a negative correlation between CMI and lumbar BMD (9). These findings suggest that the effects of CMI may vary across different skeletal sites. Therefore, this study aims to further investigate the relationship between CMI and lumbar BMD to clarify influencing factors and provide a more reliable theoretical basis. The current study analyzed the relationship between CMI and LSBMD in Americans aged 18-59 and found a significant negative correlation. The distribution of CMI varied significantly across quartiles, especially in terms of gender, age, BMI, race, and several biochemical indicators (such as alanine aminotransferase and total cholesterol). Individuals in the higher quartiles of CMI were at greater likelihood of being older, having a higher body mass index, and belonging to non-Hispanic white or Mexican American populations. These groups also exhibited generally higher biochemical markers, suggesting that changes in CMI may be driven by a variety of factors, such as liver and kidney function. In particular, unfavorable metabolic changes in participants with high CMI may be linked to reduced bone mineral density.

The underlying mechanism of the adverse effect of CMI on LSBMD is not known. Reduced levels of high-density lipoprotein cholesterol (HDL-C) and elevated levels of triglycerides are often associated with lipid metabolism disorders. Additionally, Low HDL-C levels can inhibit osteoblast differentiation by altering specific bone-related chemokines and signaling pathways (10). Additionally, low HDL-C is relevant to the formation of an inflammatory microenvironment, which promotes adipocyte differenti-

ation. The accumulation of fatty acids and oxidative byproducts exacerbates oxidative stress and inflammatory responses, further affecting the bone remodeling process. These metabolic disturbances can suppress osteoblast activity, reduce bone matrix formation, and enhance osteoclast activity, leading to bone loss and a consequent decrease in bone mineral density. On the other hand, the Waist-to-Height Ratio (WHtR) is one of the key indicators of central obesity. A higher WHtR suggests an increased risk of abnormal fat distribution. Some studies (11) have proposed that fat may have a beneficial effect on bone metabolism, with individuals exhibiting higher levels of abdominal fat showing greater bone density. However, other studies present opposing viewpoints. In obese patients, bone formation markers are relatively lower compared to bone resorption markers (12), and elevated serum parathyroid hormone levels can exert catabolic effects on cortical bone (13). Additionally, reduced testosterone levels in obese men and abnormal estrogen levels in obese women negatively impact bone metabolism (14,15). This is primarily because the decrease in sex steroids reduces the promotion of osteoclast apoptosis and increases the sensitivity of bone to mechanical loading (16). This study found that, after model adjustments, the impact of the CMI on LSBMD was somewhat attenuated. This may be due to the introduction of additional confounding variables. Previous research has shown that factors such as age (17), sex (18), BMI (19), liver function indicators (20), and kidney function indicators (21) significantly influence LSBMD. After controlling for these confounding factors, the independent effect of CMI on LSBMD may be weakened or partially masked. The interactions among multiple metabolic factors could also contribute to the observed reduction in the negative correlation.

This study found a significant threshold effect of CMI on LSBMD. When CMI is below the threshold of 0.797, LSBMD decreased significantly with increasing CMI ($\beta = -0.077$, $p < 0.0001$). However, when CMI exceeds this threshold, the negative correlation weakens or even levels off ($\beta = 0.006$, $p = 0.113$). The confirmation of this threshold was based on the optimal fitting model from regression analysis, aimed at identifying the critical point of CMI's influence on LSBMD. Further analyses showed the presence of a biological mechanism or compensatory effect that diminishes the impact of CMI on LSBMD at higher levels, leading to a "saturation" phenomenon. Previous studies have demonstrated an interaction between lipid metabolism disorders and bone metabolism. In individuals with high CMI, although abnormalities in lipid metabolism and the influence of hormones and cytokines secreted by adipose tissue, such as leptin (22), promote increased bone resorption, leading to bone loss (23), lipids may regulate bone formation or inhibit bone resorption through fatty acid metabolism. This process potentially buffers further declines in LSBMD. High CMI is typically associated with insulin resistance, which affects bone metabolism, though its impact is dual in nature (24). Under moderate insulin resistance, elevated insulin levels promote bone formation, as insulin acts as a stimulatory factor for bone formation. It can directly influence osteoblasts, enhancing bone formation and mineral deposition. Therefore, when CMI is higher, the increase in insulin resistance may partially offset its negative impact on bone density, creating a compensatory effect. High CMI may affect the amount of fat in the bone marrow. The relationship between bone marrow fat and bone metabolism is complex, and under conditions of high CMI, bone marrow fat may increase. Tencerova's study (25) confirmed that adults with morbid obesity have higher total bone marrow adipose tissue in the lumbar spine and femoral metaphysis. However, a regulatory mechanism may exist in the body that limits the excessive suppression of bone formation by bone marrow fat within a certain range. Some scholars currently suggest that netrin-2 secreted by bone marrow macrophages can trigger bone marrow fat lipolysis (26), and bone marrow adipose tissue contribute to systemic glucose and fatty acid clearance (27). Therefore, when CMI exceeds a certain threshold, this regulatory mechanism may be activated to prevent further bone loss. The threshold effect of CMI on LSBMD involve the combined influence of multiple factors, including metabolism, lipid regulation, and insulin resistance. At higher CMI levels, a balance or compensatory mechanism may exist among these factors, stabilizing the negative impact on bone density.

In the subgroup analysis, the negative association of CMI with LSBMD remained stable, with the exception of the subgroups of Mexican Americans, non-Hispanic Blacks, individuals aged 51-59, and those diagnosed with diabetes. This suggests that the link is in general stable in relation to CMI and LSBMD. However, these specific subgroups exhibited exceptions, likely due to significant differences in their physiological characteristics and metabolic states. For Mexican Americans and non-Hispanic Blacks, differences in insulin sensitivity, fat distribution, and metabolic function among racial/ethnic groups (28) may affect the relation with CMI and LSBMD. Bone metabolism is significantly affected in diabetic patients due to metabolic dysregulation and chronic inflammation (29). Additionally, the metabolic environment in diabetic individuals may weaken the negative correlation between CMI and LSBMD. For those aged 51-59, significant hormonal changes occur, and bone density may rapidly decline due to decreased estrogen levels. This transitional phase may thus alter the relationship between CMI and LSBMD.

Despite the fact that this study reduced population heterogeneity through a larger sample size and adjusted for confounders to be sure of the robustness of the findings, and also to be the first NHANES study to explore the relevance of CMI to BMD, it remains unable to account for all confounding factors that influence lumbar spine BMD, nor can it establish a cause-and-effect relationship among the variables. Therefore, future research should employ more refined techniques for analyzing bone microstructure, conduct longitudinal studies, and integrate clinical data with laboratory indicators to comprehensively evaluate the dynamic impact of CMI on lumbar spine BMD.

In summary, the current study found a meaningful adverse correlation on CMI and LSBMD, suggesting that CMI is not only an independent risk factor for decreased LSBMD but that its impact may vary across different CMI ranges. This highlights the importance of paying special attention to the potential adverse effects on bone density when managing cardiometabolic risk.

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Nutrición Hospitalaria

Trabajo Original

Otros

Efectividad de la administración de un complemento dietético (urea oral) para el tratamiento de la hiponatremia en el SIADH

Effectiveness of the administration of a dietary supplement (oral urea) for the treatment of hyponatremia in SIADH

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Resumen

Antecedentes y objetivos: la causa más frecuente de hiponatremia en el ámbito hospitalario es el síndrome de secreción inadecuada de hormona antidiurética (SIADH). Este estudio compara la eficacia y la seguridad de la urea frente a la restricción hídrica en el tratamiento de la hiponatremia causada por SIADH.

Material y métodos: se realizó un estudio observacional de cohortes en 212 pacientes con hiponatremia ($Na^+ < 135$ mmol/L) por SIADH en el Complejo Hospitalario Universitario de Pontevedra entre enero de 2015 y mayo de 2022. De estos, 112 recibieron urea (15 g/día) y 100 fueron tratados con restricción hídrica (1 litro/día). El objetivo principal fue normalizar los niveles de sodio ($Na \geq 135$ mmol/L).

Resultados: la urea fue significativamente más eficaz que la restricción hídrica. Los niveles de sodio aumentaron de 126,35 a 133,9 mmol/L con la urea, frente a un incremento de 126,44 a 130,5 mmol/L con la restricción hídrica ($p < 0,001$). La normalización del sodio se logró de promedio en 6 días con la urea frente a 8 días con la restricción hídrica ($p = 0,04$). Al alta, el 59,8 % de los pacientes tratados con urea alcanzaron niveles normales de sodio, en comparación con el 42 % del grupo tratado con restricción hídrica ($p = 0,007$). La mortalidad a 60 días fue menor en el grupo de la urea (16,1 %) que en el grupo de la restricción hídrica (32,8 %) ($p < 0,007$).

Conclusión: la urea es más eficaz que la restricción hídrica para normalizar los niveles de sodio, con un mejor perfil de seguridad y menor mortalidad a 60 días.

Palabras clave:

SIADH. Hiponatremia. Urea. Restricción hídrica. Euvolemia.

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Abstract

Background and objectives: the most common cause of hyponatraemia in hospital settings is the syndrome of inappropriate antidiuretic hormone secretion (SIADH). This study compares the efficacy and safety of urea versus fluid restriction in the treatment of hyponatraemia caused by SIADH.

Material and methods: an observational cohort study was conducted with 212 patients suffering from hyponatremia ($Na^+ < 135$ mmol/L) due to SIADH at the Complejo Hospitalario Universitario de Pontevedra between January 2015 and May 2022. Of these, 112 patients received urea (15 g/day) and 100 were treated with fluid restriction (1 liter/day). The primary objective was to normalize sodium levels ($Na \geq 135$ mmol/L).

Results: urea was significantly more effective than fluid restriction. Sodium levels increased from 126.35 to 133.9 mmol/L with urea, compared to an increase from 126.44 to 130.5 mmol/L with fluid restriction ($p < 0.001$). Sodium normalization was achieved in an average of 6 days with urea, compared to 8 days with fluid restriction ($p = 0.04$). At discharge, 59.8 % of patients treated with urea reached normal sodium levels, compared to 42 % in the fluid restriction group ($p = 0.007$). The 60-day mortality rate was lower in the urea group (16.1 %) compared to the fluid restriction group (32.8 %) ($p < 0.007$).

Conclusion: urea is more effective than fluid restriction in normalizing sodium levels, with a better safety profile and lower 60-day mortality.

Keywords:

SIADH. Hyponatremia. Urea. Fluid restriction. Euvolemia.

INTRODUCCIÓN

La hiponatremia es la anomalía electrolítica más frecuente, afectando al 7-8 % de los pacientes ambulatorios de edad avanzada y al 15-20 % de los hospitalizados. Los síntomas varían desde leves (mareos, náuseas) hasta graves (convulsiones, coma). La causa principal es el síndrome de secreción inadecuada de hormona antidiurética (SIADH). El tratamiento del SIADH depende de la duración y la gravedad de la hiponatremia. La corrección mejora los síntomas, aunque su impacto a largo plazo es debatido. No obstante, una corrección rápida puede ser perjudicial (1,2).

Incluso la hiponatremia leve se asocia con morbilidad significativa, como inestabilidad de la marcha, caídas y osteoporosis. Su prevención y tratamiento son esenciales, especialmente en el contexto hospitalario, donde se relaciona con estancias prolongadas y peores resultados clínicos (3,4).

La restricción de líquidos es el tratamiento principal para la hiponatremia moderada por SIADH, aunque es incómoda y desafiante para los pacientes, especialmente durante tratamientos como la quimioterapia, debido al riesgo de deshidratación y lesión renal aguda. Si no se tolera o el paciente no responde en 24-48 horas, se consideran las intervenciones farmacológicas. Se han utilizado diversos tratamientos farmacológicos, como demeclociclina, litio, diuréticos de asa y tabletas de urea, sin que exista un consenso claro sobre la mejor estrategia (5).

El tolvaptán, un antagonista del receptor de vasopresina autorizado en Europa, tiene mayor afinidad y selectividad por el receptor V2 que la AVP endógena. Esto reduce la reabsorción de agua y aumenta la excreción de agua libre (acuaresis), elevando las concentraciones séricas de sodio sin aumentar la excreción de iones de sodio o potasio. Los estudios han mostrado que los bloqueadores de los receptores V2 pueden mejorar de manera segura el sodio sérico y la calidad de vida de los pacientes (6-11).

La urea es un suplemento dietético que actúa como un diurético osmótico no tóxico y económico que aumenta su concentración en la médula renal, mejorando la extracción de agua y la concentración de sodio. Esto reduce las pérdidas de sodio por la orina y aumenta la excreción de agua por efecto osmótico. La principal limitación era su mal sabor pero las nuevas formulaciones con sabores de frutas han mejorado su aceptación, estando disponibles en sobres de 21 gramos con 15 gramos de urea (12,13).

El presente estudio se llevó a cabo debido a la ausencia de estudios comparativos y de ensayos clínicos que evaluasen la eficacia y la seguridad de la urea y la restricción hídrica, dos estrategias terapéuticas de uso frecuente en el tratamiento del SIADH.

MATERIAL Y MÉTODOS

TIPO DE ESTUDIO

Se realizó un estudio observacional analítico de cohortes retrospectivas en un ámbito de vida real.

OBJETIVOS EVALUADOS

Se evaluó como objetivo principal con ambos fármacos la eficacia en la normalización del sodio ($Na \geq 135$ mmol/L) en términos tanto de la velocidad de normalización en días como del porcentaje de pacientes que alcanzan niveles normales de sodio.

También se evaluaron el perfil de seguridad y la mortalidad a los 60 días con ambas estrategias terapéuticas.

ÁMBITO

El estudio se llevó a cabo en el Complejo Hospitalario de Pontevedra (norte de España).

PERIODO DE ESTUDIO

Los datos se recolectaron desde enero de 2015 hasta mayo de 2022.

PARTICIPANTES

Criterios de inclusión

Pacientes con hiponatremia ($Na < 135$ mmol/L) y diagnóstico de SIADH, definido según los siguientes criterios:

– Sodio sérico < 135 mmol/l.

- Osmolaridad plasmática < 275 mOsm/kg.
- Osmolaridad urinaria > 100 mOsm/kg.
- Hiponatremia hipotónica con euvolemia clínica.
- Ausencia de signos de hipovolemia (valores normales de presión ocular, presión venosa normal, sin ortostatismo).
- Ausencia de signos de hipervolemia (ascitis, edemas).
- Sodio urinario > 40 mmol/l (en presencia de sodio en la dieta).
- Ausencia de hipotiroidismo, insuficiencia suprarrenal (hipocortisolismo) o insuficiencia renal.
- Sin ingesta reciente de diuréticos.
- Ausencia de estímulos fisiológicos para la secreción de AVP (cirugía reciente, dolor severo, fármacos que estimulen la secreción de AVP, etc.).

Criterios de exclusión

Edad menor de 18 años y disfunción hepática o renal grave antes del tratamiento.

CRITERIOS DE ELECCIÓN DEL TRATAMIENTO

El tratamiento con urea o restricción hídrica se seleccionó según el perfil clínico de cada paciente. En aquellos pacientes con dificultades para cumplir con la restricción hídrica o en los que se anticipaba un fracaso terapéutico con esta estrategia se inició el tratamiento con urea desde el principio. En cambio, la restricción hídrica fue el tratamiento de primera línea en la mayoría de los casos, siguiendo las guías clínicas para el manejo de la hiponatremia dilucional. En los pacientes que no respondieron a la restricción hídrica se optó por un cambio a la urea como tratamiento de segunda línea.

TRATAMIENTOS ADMINISTRADOS

Se incluyeron un total de 112 pacientes tratados con urea, con una dosis media de 15 g al día, y 100 pacientes tratados con una restricción hídrica media de 1 litro de líquidos diarios. La decisión de iniciar el tratamiento con restricción hídrica se basó en criterios clínicos, considerando la severidad de la hiponatremia y la capacidad de cumplimiento del paciente.

En aquellos pacientes en los que existían dudas sobre la respuesta a la restricción hídrica se utilizó la fórmula de Furst como herramienta adicional para evaluar la capacidad del paciente de excretar agua libre. El cálculo de esta fórmula permitió predecir el grado de respuesta a la restricción hídrica a partir de la relación entre la osmolaridad urinaria y la osmolaridad plasmática, reflejando la eficiencia renal en la eliminación de agua libre. Los pacientes con osmolaridad urinaria persistente por encima de 500 mOsm/kg se identificaron como probables no respondedores a la restricción hídrica estándar de 1 litro/día.

Para estos pacientes se consideró la necesidad de una mayor restricción hídrica (< 1 litro al día) o la introducción de la urea como alternativa terapéutica más efectiva para alcanzar niveles normales de sodio. Esta estrategia permitió la individualización del tratamiento, ajustándose las intervenciones según la capacidad fisiológica de cada paciente para excretar agua libre y optimizándose así los resultados clínicos.

En los casos en que la urea se inició como tratamiento, se siguió un protocolo de ajuste de la dosis en función de la evolución de los niveles de sodio sérico y la tolerancia del paciente.

VARIABLES RECOGIDAS

Se recopilaron datos clínicos y sociodemográficos, así como la evolución de las variables relacionadas con el efecto de ambas terapias, incluyendo el sodio y el potasio séricos, la urea plasmática y la creatinina sérica. También se evaluaron los efectos adversos y la mortalidad a los 60 días del inicio de la terapia.

CONSIDERACIONES ÉTICAS

El estudio fue aprobado por el Comité de Ética e Investigación de Galicia (Código de Registro: 2023/146). Todos los participantes firmaron el consentimiento informado. Se siguieron las recomendaciones de las guías STROBE para estudios observacionales.

ANÁLISIS ESTADÍSTICO

Se realizó un análisis descriptivo de los datos utilizando el programa estadístico SPSS 19.0. Las variables cuantitativas se describieron mediante medidas de tendencia central y dispersión (media, desviación estándar), y las variables cualitativas mediante frecuencias y porcentajes. Para analizar la evolución de las variables antes y después del tratamiento con urea oral, se utilizaron la prueba t de Student para datos relacionados o pruebas no paramétricas (como el test de Wilcoxon) en función de si los datos seguían o no una distribución normal. La normalidad de los datos se evaluó utilizando el test de Shapiro-Wilk. Los resultados se consideraron estadísticamente significativos con un valor de $p < 0.05$.

RESULTADOS

Se incluyeron 112 pacientes tratados con urea en una dosis media de 15 g y 100 pacientes tratados con restricción hídrica media de 1 litro de líquidos al día.

Las características clínicas y sociodemográficas de ambos grupos, al inicio del tratamiento con urea y con restricción hídrica, se resumen en la tabla I.

La tabla I muestra las características clínicas y sociodemográficas de ambos grupos al inicio del tratamiento con urea y

restricción hídrica. La edad media se presenta en años con el rango de edad indicado en cada grupo. La función renal se clasifica en función del filtrado glomerular (FG) con los porcentajes correspondientes para cada categoría. La etiología del síndrome de secreción inadecuada de hormona antidiurética (SIADH) se detalla por causas: medicamentosa, tumoral, trastornos del sistema nervioso central, trastornos pulmonares no malignos e idiopática. Los parámetros de laboratorio al inicio del tratamiento incluyen: sodio plasmático, urea plasmática, potasio plasmático, creatinina sérica y osmolalidad plasmática, con sus respectivas medias y desviaciones típicas (DT).

La evolución de los parámetros analíticos tras el inicio del tratamiento con la urea y la restricción hídrica se resumen en la tabla II.

La tabla II muestra los resultados de un estudio comparativo sobre la eficacia del tratamiento con urea oral frente a la restricción hídrica en pacientes con hiponatremia. Los hallazgos sugieren que el tratamiento con urea oral es superior en la normalización de la natremia.

La evolución temporal de las concentraciones de sodio plasmático en mmol/L tras la adición de la urea oral y la instauración de la restricción hídrica, respectivamente, se muestra en la figura 1.

El grupo tratado con urea mostró un aumento significativo del sodio plasmático, pasando de 126,35 ± 4,41 mmol/l a 133,9 ± 4,12 mmol/l ($p < 0,001$). Por otro lado, el grupo de restricción hídrica también experimentó un aumento pero que fue menos pronunciado, pasando de 126,44 ± 5,52 mmol/l a 130,5 ± 5,41 mmol/l ($p < 0,001$). Esta diferencia indica que la urea oral fue más eficaz para corregir la hiponatremia ($p < 0,001$).

El incremento de la urea plasmática en el grupo de la urea, de 45,02 ± 25,53 mg/dL a 62,35 ± 28,75 mg/dL ($p < 0,001$), es un efecto esperado debido a la administración de urea oral. Este aumento refleja una mayor retención de solutos, lo cual es beneficioso para la normalización del sodio. En contraste, el grupo de la restricción hídrica no mostró ningún cambio significativo en la urea plasmática (de 38,24 ± 35,72 mg/dL a 42,21 ± 28,46 mg/dL, $p = 0,177$).

Tabla I. Características clínicas y sociodemográficas de ambos grupos, al inicio del tratamiento con urea oral y de la restricción hídrica, respectivamente

Variables *n* (%)	Grupo urea (*n* = 112)	Restricción hídrica (*n* = 100)
Edad (años), media	75	81,25
Rango de edad	68-87	78,5-84
Hombres, *n* (%)	64 (57,1 %)	55 (55 %)
Función renal por filtrado glomerular (FG)		
- FG > 60 ml/min/m^2	62 (55,35 %)	60 (60 %)
- FG 30-60 ml/min/m^2	50 (44,64 %)	40 (40 %)
Etiología SIADH, n (%)		
- *Medicamentosa*	42 (37,5 %)	51 (51 %)
• Diuréticos	16 (38,09 %)	20 (39,21 %)
• Antidepresivos	13 (30,95 %)	13 (25,49 %)
• Antiepilépticos	8 (19,04 %)	10 (19,60 %)
• Antipsicóticos	3 (7,14 %)	5 (9,80 %)
• Otros	2 (4,76 %)	3 (5,88 %)
- *Tumoral*	24 (28,9 %)	23 (23 %)
• Cáncer pulmonar	19 (79,16%)	19 (82,6 %)
• Cáncer de cabeza y cuello	3 (12,5%)	4 (18,2 %)
• Cáncer de mama	1 (4,2 %)	0
• Otros	1 (4,2 %)	0
- *Trastornos del sistema nervioso central*	7 (6,25 %)	5 (5 %)
• Trastornos pulmonares no malignos	23 (20,53 %)	14 (14 %)
• Idiopático	16 (21,42 %)	7 (7 %)
Parámetros de laboratorio, día 0		
- Sodio plasmático, mmol/l (media, DT)	123,02 ± 3,4	124,91 ± 6,12
- Urea plasmática, mg/dL (media, DT)	35,14 ± 17,34	47,13 ± 42,32
- Potasio plasmático, mEq/L (media, DT)	4,27 ± 0,63	4,17 ± 0,65
- Creatinina sérica, mg/dL (media, DT)	0,68 ± 0,23	0,86 ± 0,47
- Osmolalidad plasmática, mOsm/kg (media, DT)	259,84 ± 10,32	262,72 ± 14,25

DT: desviación típica.

Tabla II. Evolución de parámetros analíticos tras inicio del tratamiento de la urea oral y restricción hídrica

Parámetros de laboratorio	Urea de 24 horas	Urea de fin de terapia	Restricción hídrica de 24 horas	Restricción hídrica de fin de terapia	Valor *p*
Sodio plasmático, mmol/l (media, DT)	126,35 ± 4,41; $p < 0,001$	133,9 ± 4,12; $p < 0,001$	126,44 ± 5,52; $p < 0,001$	130,5 ± 5,41; $p < 0,001$	Basal: 0,320 24 h: 0,210 Fin: < 0,001
Urea plasmática, mg/dL (media, DT)	45,02 ± 25,53; $p < 0,001$	62,35 ± 28,75; $p < 0,001$	38,24 ± 35,72; $p = 0,276$	42,21 ± 28,46; $p = 0,177$	Basal: 0,230 24 h: < 0,001 Fin: < 0,001
Potasio plasmático, mEq/L (media, DT)	4,24 ± 0,75; $p = 0,142$	4,39 ± 0,79; $p = 0,237$	3,91 ± 0,70; $p = 0,008$	4,15 ± 0,61; $p = 0,989$	Basal: 0,340 24 h: 0,004 Fin: 0,430
Creatinina sérica, mg/dL (media, DT)	0,719 ± 0,29; $p = 0,071$	0,72 ± 0,26; $p = 0,056$	0,992 ± 0,796; $p < 0,001$	0,999 ± 0,765; $p < 0,001$	Basal: 0,400 24 h: < 0,025 Fin: < 0,020
Osmolalidad plasmática, mOsm/kg (media, DT)	267,92 ± 10,76; $p < 0,001$	285,29 ± 10,76; $p < 0,001$	268,26 ± 13,92, $p < 0,04$	280,77 ± 9,74; $p < 0,001$	Basal: 0,420 24 h: 0,310 Fin: 0,010

DT: desviación típica.

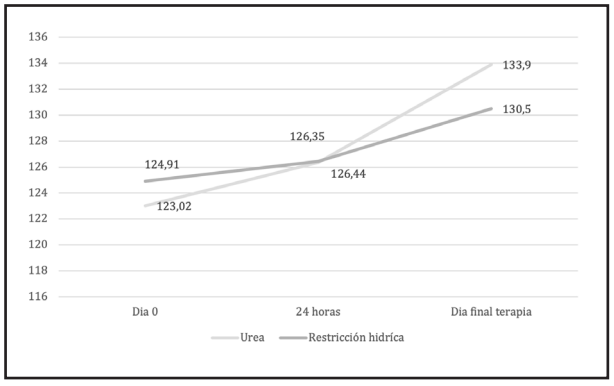

Figura 1.

La gráfica muestra la evolución temporal de las concentraciones de sodio plasmático, en mmol/L, tras la adición de urea oral y la instauración de la restricción hídrica, respectivamente. La terapia con urea muestra un aumento más pronunciado del sodio en comparación con la restricción hídrica, especialmente al final de la terapia.

En el grupo de la urea no se observaron cambios significativos en los niveles de potasio plasmático (de 4,24 ± 0,75 mEq/L a 4,39 ± 0,79 mEq/L, $p = 0,237$). El grupo de la restricción hídrica mostró una disminución significativa a las 24 horas (de 3,91 ± 0,70 mEq/L a 4,15 ± 0,61 mEq/L, $p = 0,004$) pero no al final del tratamiento ($p = 0,430$).

En el grupo de la urea no se observaron cambios significativos en los niveles de creatinina sérica (de 0,719 ± 0,29 mg/dL a 0,72 ± 0,26 mg/dL, $p = 0,056$). Sin embargo, en el grupo de la restricción hídrica se observaron aumentos en los niveles de creatinina, de 0,992 ± 0,796 mg/dL a 0,999 ± 0,765 mg/dL, con significación estadística tanto a las 24 horas ($p < 0,025$) como al final del tratamiento ($p < 0,020$).

Ambos tratamientos resultaron en un aumento significativo de la osmolalidad plasmática. El grupo de la urea mostró un incremento de 267,92 ± 10,76 mOsm/kg a 285,29 ± 10,76 mOsm/kg ($p < 0,001$), mientras que el grupo de la restricción hídrica pasó de 268,26 ± 13,92 mOsm/kg a 280,77 ± 9,74 mOsm/kg ($p < 0,001$). La mejora en la osmolalidad plasmática fue superior en el grupo de la urea ($p = 0,010$).

Los pacientes del grupo de la urea alcanzaron la normalización de la natremia en un tiempo medio de 6 ± 3,6 días mientras que, en el grupo de la restricción hídrica, el tiempo medio de normalización de la natremia fue de 8 ± 3,4 días ($p = 0,04$). Respecto a la proporción de pacientes que alcanzaron la normalización de la natremia al final de la terapia (momento del alta hospitalaria) con ambas estrategias terapéuticas, esta fue en el grupo de la urea del 59,8 %, mientras que en el grupo tratado con restricción hídrica fue del 42 % ($p = 0,007$).

Los datos del perfil seguridad y la mortalidad a los 60 días en ambos grupos del estudio, se resumen en la tabla III.

Los efectos secundarios más destacados en el grupo de la urea son la disgeusia (7,14 %) y el dolor abdominal (4,46 %), con una diferencia significativa en la aparición de disgeusia comparada con el grupo de la restricción hídrica ($p < 0,01$). No se reportaron casos de hipercorrección del sodio ni de síndrome de desmielinización osmótica en ninguno de los grupos.

Tabla III. Perfil de seguridad de la urea y restricción hídrica

Efecto secundario	Urea (N = 112), *n* (%)	Restricción hídrica (N = 100), *n* (%)	Valor *p*
Disgeusia	8 (7,14 %)	0 (0 %)	< 0,01
Dolor abdominal	5 (4,46 %)	0 (0 %)	0,54
Estreñimiento	3 (2,6 %)	0 (0 %)	0,73
Hipercorrección de sodio	0 (0 %)	0 (0 %)	N/A
Síndrome de desmielinización osmótica	0 (0 %)	0 (0 %)	N/A
Sed intensa	0 (0 %)	18 (18 %)	< 0,001
Deshidratación	0 (0 %)	15 (15 %)	< 0,001
Cefalea	0 (0 %)	10 (10 %)	0,19
Calambres	0 (0 %)	8 (8 %)	0,08
Mortalidad a los 60 días	16,1 %	32,8 %	< 0,007

Por otro lado, la sed intensa (18 %) y la deshidratación (15 %) fueron significativamente más frecuentes en el grupo de la restricción hídrica ($p < 0,001$), en contraste con su ausencia en el grupo de la urea. Otros efectos secundarios como la cefalea (10 %) y los calambres (8 %) se presentaron exclusivamente en el grupo tratado con restricción hídrica, aunque sin alcanzar la significación estadística.

Finalmente, la mortalidad a los 60 días fue significativamente menor en el grupo tratado con urea (16,1 %) en comparación con el grupo tratado con restricción hídrica (32,8 %), con un valor de $p < 0,007$.

DISCUSIÓN

Nuestra muestra del estudio es de experiencia en la vida real y representa uno de los análisis más extensos en la literatura sobre el uso de la urea para el tratamiento de la hiponatremia en pacientes con SIADH.

La hiponatremia, definida como una concentración plasmática de sodio (PNa) < 135 mmol/L, es el trastorno electrolítico más común en la práctica clínica. Se clasifica en leve, moderada y grave, y puede ser aguda o crónica. La pequeña proporción de pacientes con hiponatremia severa y/o aguda generalmente presentan síntomas neurológicos evidentes y requieren hospitalización y tratamiento urgente (14). Sin embargo, la mayoría de los pacientes con hiponatremia crónica no grave no requieren hospitalización inmediata ni tratamiento urgente. A pesar de que en muchos casos se presenta de forma asintomática, cualquier nivel de hiponatremia se asocia con un aumento de la comorbilidad y la mortalidad, lo que subraya la importancia de identificar tratamientos seguros, bien tolerados y efectivos para el manejo a largo plazo de esta afección (1,2,7).

La etiología más común de la hiponatremia en los pacientes hospitalizados y ambulatorios es el síndrome de secreción inadecuada de hormona antidiurética (SIADH), causado frecuentemente por medicamentos y por trastornos oncológicos y del sistema nervioso central, entre otros (15,16). Las intervenciones terapéuticas actuales para tratar la hiponatremia por SIADH se basan en su fisiopatología, pero muchos de estos tratamientos, incluidos los diuréticos de asa, las tabletas de cloruro de sodio y la restricción de líquidos, carecen de sólida evidencia respecto a su eficacia a largo plazo y presentan desafíos importantes para el cumplimiento del paciente (17,18).

La restricción hídrica es una intervención tradicional para el manejo del SIADH y se basa en la reducción del volumen de ingesta de líquidos para disminuir la retención hídrica y aumentar la concentración de sodio plasmático. Aunque es un enfoque relativamente simple y sin costo significativo, su eficacia puede ser limitada y su cumplimiento difícil para muchos pacientes. La restricción hídrica puede llevar a síntomas de deshidratación y sed intensa, lo que disminuye la adherencia a largo plazo y puede afectar negativamente a la calidad de vida del paciente. Además, su efectividad varía significativamente entre los pacientes y puede no ser suficiente para corregir la hiponatremia en los casos más severos (17,18).

El tolvalptán, un antagonista de la vasopresina, ha demostrado en ensayos clínicos ser efectivo para elevar las concentraciones de sodio en los pacientes con SIADH. Su mecanismo de acción implica bloquear los receptores de vasopresina, lo que reduce la retención de agua sin afectar a la excreción de sodio. Aunque el tolvaptán es efectivo, su uso está limitado por varios factores, incluyendo su alto costo y la necesidad de una monitorización estrecha para evitar la corrección rápida de la natremia, que puede llevar a complicaciones (19). A pesar de su efectividad, no se ha convertido en una solución de tratamiento de uso generalizado debido a estas limitaciones prácticas y económicas.

La urea, con una masa molar de 60 g/mol, actúa como un osmol efectivo en los segmentos de la nefrona con alta permeabilidad al agua y baja permeabilidad a la urea. Sus efectos sobre la excreción de agua libre pueden explicarse mejor por la relación entre la excreción de agua libre y la excreción de solutos. En el SIADH, la urea ayuda a reducir la natriuresis y a crear un balance positivo de sodio, lo que contribuye a la mejora del sodio plasmático (8-13). A pesar de su mal sabor, recientes avances en la formulación de la urea han mejorado significativamente su

tolerancia, al presentarse en sobres con sabores de frutas que contienen 15 g de urea (8,9).

Nuestros resultados demuestran que la urea oral es eficaz para normalizar los niveles de sodio sérico. El tratamiento se inició con dosis de 15 g/24 h, con ajustes graduales según fuese necesario, logrando niveles normales de sodio en un tiempo medio de 6 días. La dosis media de urea empleada fue de 15 g al día.

Comparado con la restricción hídrica, el tratamiento con urea mostró una mayor eficacia en la corrección de la hiponatremia. Los pacientes tratados con urea alcanzaron la normalización de la natremia en un tiempo medio de 6 ± 3,6 días, mientras que el grupo de la restricción hídrica lo hizo en 8 ± 3,4 días. Además, una mayor proporción de pacientes del grupo de la urea logró la normalización de la natremia al alta hospitalaria (59,8 % *vs.* 42 %). Estos hallazgos sugieren que la urea no solo es más efectiva, sino que también podría ofrecer beneficios en términos de supervivencia, con una menor mortalidad a los 60 días en el grupo tratado con urea (16,1 % *vs.* 32,8 %).

En términos del perfil de seguridad, el tratamiento con urea mostró una tolerancia general favorable comparado con la restricción hídrica. Los efectos secundarios más comunes en el grupo de urea fueron la disgeusia (7,14 %) y el dolor abdominal (4,46 %), siendo la disgeusia significativamente más frecuente en comparación con el grupo de la restricción hídrica ($p < 0,01$). No se reportaron casos de hipercorrección del sodio ni de síndrome de desmielinización osmótica en ninguno de los grupos. En contraste, la restricción hídrica estuvo asociada con una mayor frecuencia de sed intensa (18 %) y deshidratación (15 %), que no se observaron en el grupo de la urea. Otros efectos secundarios, como la cefalea (10 %) y los calambres (8 %), también fueron exclusivos de la restricción hídrica, aunque sin alcanzar la significación estadística. La mortalidad a los 60 días fue notablemente menor en el grupo tratado con urea (16,1 %) en comparación con el grupo tratado con restricción hídrica (32,8 %) ($p < 0,007$), sugiriendo que la urea no solo es más eficaz, sino que también ofrece un perfil de seguridad superior.

La principal limitación de nuestro estudio radica en que no se trata de un ensayo clínico aleatorizado ni a doble ciego; por ello existe riesgo de sesgo de asignación y de ausencia de enmascaramiento. Se necesitan estudios más amplios con muestras más representativas para confirmar los hallazgos de este estudio. Se desconocen la eficacia y la seguridad a largo plazo de estos tratamientos. Se necesitan estudios de seguimiento a largo plazo para evaluar ambos aspectos.

CONCLUSIÓN

El estudio muestra que la urea es superior a la restricción hídrica para normalizar el sodio en los pacientes con hiponatremia por síndrome de secreción inadecuada de hormona antidiurética (SIADH), con una corrección más rápida y una mayor tasa de éxito al alta. También presenta un perfil de seguridad más favorable, con menos efectos secundarios graves y menor mortalidad a 60 días en comparación con la restricción hídrica.

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ARÁN

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Revisión

Intermittent fasting for glycemic control in patients with type 2 diabetes: a meta-analysis of randomized controlled trials

Ayuno intermitente para el control glucémico en pacientes con diabetes de tipo 2: un metaanálisis de ensayos controlados y aleatorizados

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Abstract

Objective: to systematically evaluate the efficacy and safety of Intermittent Fasting (IF) in patients with type 2 diabetes (T2DM).

Method: randomized controlled trials (RCTs) on the efficacy of IF intervention in T2DM were systematically searched from PubMed, The Cochrane Library, Web of Science, MEDLINE and CNKI, and retrieval time was set from database onset to September 2024. A meta-analysis was performed using the RevMan 5.3 software.

Results: sixteen articles were included, with a total of 5369 patients. The meta-analysis showed that, compared with the control group, IF could improve patients' glycated hemoglobin, fasting plasma glucose, body weight, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, low density lipoprotein, and cholesterol levels ($p < 0.05$). However, there was no significant difference in improving the levels of postprandial plasma glucose, high-density lipoprotein, and triglyceride levels compared to the control group ($p > 0.05$).

Conclusion: IF may help people with T2DM manage their blood sugar levels effectively. In addition, IF can reduce body weight, reduce waist circumference, maintain stable blood pressure, and reduce low-density lipoprotein and total cholesterol levels, and is considered safe and feasible to implement. However, more high-quality studies are needed to provide further evidence on the benefits of IF in improving other lipid levels.

Keywords:

Intermittent fasting. Type 2 diabetes *mellitus*. Blood glucose. Meta.

Resumen

Objetivo: evaluar sistemáticamente la eficacia y seguridad del ayuno intermitente (IF) en pacientes con diabetes *mellitus* de tipo 2 (T2DM).

Métodos: se realizaron búsquedas sistemáticas de ensayos controlados y aleatorizados (ECA) en PubMed, The Cochrane Library, Web of Science, MEDLINE y CNKI sobre la eficacia de las intervenciones de IF en la T2DM, desde la construcción de la base de datos hasta septiembre de 2024. Se realizó un metanálisis con el software RevMan 5.3.

Resultados: se incluyeron 16 ensayos con un total de 5369 pacientes. El metaanálisis mostró que el IF mejoró la hemoglobina glicada, la glucosa en ayunas, el peso corporal, el IMC, el perímetro de la cintura, la presión arterial sistólica y diastólica, el LDL y el colesterol en los pacientes, comparados con los controles ($p < 0,05$). No hubo diferencias estadísticamente significativas ($p > 0,05$) en la mejora de los niveles postprandiales de glucosa, HDL y triglicéridos en comparación con los controles.

Conclusión: el IF puede ayudar a los pacientes con T2DM a controlar los niveles de glucosa de manera efectiva. Además, el IF puede reducir el peso, reducir la cintura, mantener la presión arterial estable y reducir los niveles de LDL y colesterol total. Se considera seguro y viable. Sin embargo, se necesitan más estudios de alta calidad para demostrar más los beneficios del IF en la mejora de los niveles de otros lípidos.

Palabras clave:

Ayuno intermitente. Diabetes tipo 2. Glucosa en sangre. Meta.

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INTRODUCTION

Type 2 diabetes *mellitus* (T2DM) has become a chronic disease with a global epidemic and poses a significant challenge to public health (1). The dramatic rise in prevalence is the result of multiple factors, including unhealthy lifestyle habits, obesity, sedentary behavior, and genetic predisposition. As the global population ages and lifestyles change, the prevalence of T2DM is expected to continue to grow. According to a study published in the Lancet in 2023 (2), the number of people with diabetes worldwide is likely to surge to 1.31 billion by 2050, of which T2DM patients will make up the vast majority, more than 96 %.

Fasting, or the restriction or avoidance of food intake for a specified period of time, can extend from 12 hours to three weeks (3). Numerous studies have shown that fasting can extend the lifespan of a variety of experimental organisms. In addition, a series of prospective clinical trials have also indicated that fasting can help reduce disease risk factors associated with aging, including cardiovascular disease, diabetes, and certain types of cancer. Fasting also increases the body's resistance to oxidative stress, such as during acute surgical stress. There are also studies showing that fasting may improve the effectiveness of some cancer treatments. A variety of dietary interventions have been tried to address a range of metabolic dysfunction, of which intermittent fasting (IF) stands out because of its popularity. Table I (4-6) details the different IF patterns and their respective characteristics.

Recently, researchers from the University of Utah, the University of Wisconsin-Madison and other institutions published a study (7) in the Journal of the American Medical Association. The study pooled meta-analyses of 11 published randomized clinical trials that assessed 104 unique associations between four types of IF (including alternate-day fasting, modified alternate-day fasting, 5:2 diet, time-restricted eating) and obesity-related health outcomes. In particular, high-quality evidence supports that 1-2 months of modified IF is associated with a modest reduction in body mass index in healthy adults and in people with overweight, obesity, or non-alcoholic fatty liver disease. The paper suggests that IF may play a positive role in improving weight and cardiometabolic outcomes, particularly in adults who are overweight or obese. As a dietary management strategy, IF has attracted a lot of attention in patients with T2DM. Numerous studies have shown that IF may confer a range of metabolic health benefits. Despite this, there is currently a lack of systematic reviews or meta-analyses incorporating randomized controlled trials (RCTS) to fully evaluate the safety and efficacy of IF in T2DM treatment. Given the controversial effects of IF on the improvement of blood glucose, blood lipids, HbA1c and body weight in T2DM patients, and with the continuous development of this dietary pattern in global T2DM studies, meta-analysis is particularly necessary. The gaps in the literature in this area highlight the need for rigorous research on IF as an adjunct therapy for T2DM. Therefore, the purpose of this study was to systematically evaluate the safety and effectiveness of IF in the treatment of T2DM, and to provide evidence-based medical evidence for dietary intervention programs for T2DM patients (8).

DATA AND METHODS

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

1) Study design: RCT in Chinese/English; 2) Subjects: diagnosed with T2DM, ≥ 18 years old, no other complications; 3) Intervention measures: the intervention group implemented IF; 4) Outcome measures: the main measures were blood glucose results (HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose (PPG)), cholesterol, and triglycerides. Secondary outcome measures were anthropometric measures (including body weight, BMI, waist circumference), systolic blood pressure (SBP), diastolic blood pressure (DBP), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

Exclusion criteria

1) The data are incomplete or the full text of the literature cannot be obtained; 2) Case reports, abstracts, reviews, lectures and other non-original research literature; 3) Repeated publications (only one of them was retained for analysis).

Table I. Different regimens of intermittent fasting patterns

Pattern	Frequency	Duration	Extra detail
Time-limited fasting	Everyday	16 h	Eat within the remaining 8 hours, usually after getting up in the morning
Alternate day fasting	Every other day	24 h	Eat only one meal on the fasting day, mostly Chinese food, about 400-500 kcal, and eat normally the next day
5:2 diet	Twice a week	24 h	Fasting 2 days a week, fasting day control calories of 500-600 kcal
Fasting once a week	Once a week	24 h	A water-only fast
Simulated fasting	Once a month	120 h	Low-calorie non-fasting ketogenic diet
The 10-day juice method	Irregular frequency	240 h	Drink juice and avoid solid foods during fasting times
Other patterns	Polytropic	Polytropic	Many may be based on frequency and time

LITERATURE SEARCH STRATEGY

Two researchers (HX and HG) independently searched the databases of PubMed, The Cochrane Library, Web of Science, MEDLINE and CNKI from their setup to September 2024, using a combination of subject words and free words. The terms were as follows: diabetes *mellitus,* type 2 diabetes *mellitus,* T2DM; intermittent fasting, IF, intermittent energy restriction, intermittent caloric restriction, time restricted feeding; randomized controlled trial, RCT.

LITERATURE SCREENING AND DATA EXTRACTION

Two researchers (HX and HG) independently screened the literature and extracted data according to established inclusion and exclusion criteria. In the event of disagreement, the differences are resolved through discussion or, if necessary, the intervention of a third researcher to make a final judgment. In the literature selection process, the EndNote literature management software was first used to eliminate duplicates, and then a preliminary screening was conducted by reading the title and abstract of the article to eliminate the literature that did not meet the inclusion criteria. For literature that is considered likely to be eligible after initial screening, the researchers will further read the full text to make a final decision. Excel 2019 software was used to extract literature data, and the extracted information included key data such as first author, publication year, study location, sample size, intervention methods and outcome indicators.

LITERATURE QUALITY EVALUATION

Two investigators (HX and HG) will independently evaluate literature quality according to Cochrane Randomized Controlled trial literature quality evaluation criteria. In case of disagreement during the evaluation process, a third researcher or domain expert will decide. The specific evaluation criteria are as follows: If the study fully meets the evaluation criteria, it indicates that the possibility of various biases is low, and the quality of the literature is rated as grade A. If the part of the study meets the evaluation criteria, it indicates that the possibility of bias is moderate, and the literature quality grade is B. If the study does not meet the evaluation criteria at all, it indicates that the possibility of bias is high, and the quality of the literature is set at grade C (9).

STATISTICAL METHODS

In this study, the RevMan 5.3 software was used for meta-analysis. First, heterogeneity among included studies was assessed by chi-square tests and I^2 statistics. If the I^2 value is less than or equal to 50 %, heterogeneity between studies is low, and the fixed effect model is selected for the meta-analysis. If the value of I^2 is greater than 50 %, it indicates that there is significant heterogeneity among the studies, and then a random effects model is used for analysis. For the data of continuous variables, when the measurement units used in different studies were the same, we used the weighted mean difference (WMD) and its 95 % confidence interval (CI) to represent the results. When the units of measurement did not agree, the results are presented using the standardized mean difference (SMD) and its 95 % CI.

RESULTS

BASIC CHARACTERISTICS OF THE INCLUDED LITERATURE

A total of 148 papers meeting the requirements were preliminarily retrieved, and 16 were finally included through layer by layer screening. The basic characteristics of the included references are shown in table II (10-25).

RESULTS OF THE META-ANALYSIS

On a global scale, modern humans are facing a number of complex chronic health challenges, including obesity, diabetes, metabolic diseases, and cardiovascular disease. Over the past decade, large-scale clinical trials have demonstrated that IF can reduce body weight and body fat, improve insulin sensitivity, lower blood sugar and insulin levels, reduce blood pressure, improve lipid levels, and reduce biomarkers of inflammation and oxidative stress. This meta-analysis included 16 randomized controlled trials involving a total of 5369 patients.

Blood glucose results (Fig. 1)

Thirteen studies evaluated the effect of IF on controlling HbA1c in T2DM patients. Heterogeneity testing showed that there was heterogeneity among the studies ($p < 0.0001$, $I^2 = 77$ %). Random effects model analysis showed that, IF significantly improved HbA1c levels (WMD = -0.36, 95 % CI = -0.50, -0.21, $p < 0.0001$).

Six studies evaluated the effect of IF on fasting plasma glucose in T2DM patients. There was heterogeneity among studies ($p = 0.05$, $I^2 = 54$ %). The random effects model analysis showed that IF could significantly improve FPG levels (WMD = -12.38, 95 % CI = -16.6, -8.15, $p < 0.0001$).

Three studies evaluated the effect of IF on postprandial plasma glucose control in patients with T2DM. There was heterogeneity among the studies ($p = 0.0004$, $I^2 = 82$ %). Random effects model analysis showed that there was no statistically significant difference in postprandial plasma glucose reduction between the IF group and the control group (WMD = -0.60, 95 % CI = -1.82, 0.61, $p = 0.33$).

Table II. Basic features of the included articles

Number	Study	Country	Samples (*n*) IG/CG	Intervention measure		Duration	Outcome measure
				IG	CG		
1	Williams, 1998 (10)	United States	18/18	One day per week (400-600 kcal/day), the rest of the time 1500-1800 kcal/day. The average energy intake is estimated at 1486 kcal/day	Regular diet	20 weeks	① ③ ⑩ ⑫ ⑬ ⑯
2	Patel, 2007 (11)	Oman, Dhahira region	334	93.1 % of the participants fasted for 30 days, with specific energy not mentioned	Regular diet	20 weeks	①
3	Siaw, 2014 (12)	Singapore	153	Fasting for at least 10 days during Ramadan, the specific energy is not mentioned	Regular diet	4 weeks	⑦ ⑯
4	Bener, 2014 (13)	Qatar	1301	Fasting for at least 11-12 days during Ramadan, the specific energy is not mentioned.	Regular diet	NA	⑤ ⑥ ⑦ ⑧ ⑩ ⑪ ⑫
5	Clifton, 2016 (14)	South Australia	31/32	Two days of severe energy restriction (400-600 kcal/day), weekly follow-up for 2 consecutive days, and the remaining 5 days of habitual diet	Regular diet	12 Weeks	① ② ③ ⑤ ⑥ ⑦
6	Li, 2017 (15)	Germany	16/16	Consumed only 300 kcal per day through liquids, then gradually reintroduced solid foods	Regular diet	4 months	① ③ ④ ⑤ ⑥ ⑦ ⑩ ⑪
7	Hassanein, 2017 (16)	Middle East, Lebanon, Kuwait, and the United Arab Emirates	155/162	Fasting for about 15 hours a day, the specific energy is not mentioned	Regular diet	8 weeks	① ⑦
8	Bashier, 2017 (17)	UAE (Dubai)	417	Ramadan	NA	20 days	① ⑦ ⑯
9	Carter, 2018 (18)	Australia	70/67	Limit intake of calories for 2 consecutive days per week: 500-600 kcal/d, regular diet for the remaining 5 days	Continuous limited capacity: 1200-1500 kcal/d	12 months	① ③ ⑦ ⑧ ⑩ ⑪ ⑫ ⑬ ⑯
10	Sundfør, 2018 (19)	Norway	54/58	For 2 consecutive days (400 kcal/d for women and 600 kcal/d for men), the remaining 5 days on normal diet.	Total daily energy expenditure minus 400 kcal/600 kcal (female/male).	6 months	① ③ ④ ⑤ ⑥ ⑦ ⑩ ⑪ ⑫
11	Hassanein, 2019 (20)	Middle East and North Africa	1749	Fasting	Regular diet	15 days/30 days	① ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩ ⑪ ⑫ ⑬
12	Xiaohua, 2019 (21)	Changchun City, China	32/33	For one day a week, 500 kcal/d were eaten, and for the remaining 6 days a diabetic diet.	Diabetic diet	12 weeks	⑧ ⑨ ⑩ ⑪ ⑭ ⑮

(Continues on next page)

Table II (cont.). Basic features of the included articles

Number	Study	Country	Samples (*n*) IG/CG	Intervention measure		Duration	Outcome measure
				IG	CG		
13	Raza, 2021 (22)	Pakistan	220	Fasting	Regular diet	NA	① ⑦ ⑧
14	Hassanein, 2021 (23)	UAE, Dubai	343	Fasting	Regular diet	Within 3 months	① ⑦
15	Kramer, 2024 (24)	Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, Toronto	23/16	TRE (20 h-fasting/4 h-eating)	Standard lifestyle	6 weeks	① ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩ ⑪ ⑫
16	Deshmane, 2024 (25)	India	26/25	Time-restricted IF	Continuous calorie restriction diet	6 months	⑦

IG: intervention group; CG: control group; ① weight (kg); ② height; ③ BMI; ④ Waist circumference, cm; ⑤ SBP: systolic blood pressure, mmHg; ⑥ DBP: diastolic blood pressure, mmHg; ⑦ HbA1c: glycated hemoglobin; ⑧ FPG: fasting plasma glucose, mg/dL; ⑨ PPG: postprandial plasma glucose, mmol/L; ⑩ LDL: low-density lipoprotein, mmol/L; ⑪ HDL: high-density lipoprotein, mmol/L; ⑫ Cholesterol; ⑬ Triglycerides; ⑭ TC; ⑮ TG; ⑯ Adverse events.

Anthropometry and other general information (Fig. 2)

Twelve studies evaluated the effect of IF intervention on body mass in T2DM patients. There was heterogeneity among the studies ($p = 0.94$, $I^2 = 0$ %). The fixed-effect model analysis showed that IF could improve body mass (WMD = -0.65, 95 % CI = -1.38, 0.09, $p = 0.08$).

Six studies evaluated the effect of IF intervention on BMI in T2DM patients. There was heterogeneity among studies ($p = 0.14$, $I^2 = 40$ %). Fixed-effect model analysis showed that IF could improve BMI level (WMD = -0.79, 95 % CI = -1.70, 0.12, $p = 0.09$).

Four studies evaluated the effect of IF on waist circumference in patients with T2DM. There was heterogeneity among studies ($p = 0.32$, $I^2 = 14$ %). The fixed-effect model analysis showed that IF could improve waist circumference (WMD = -1.07, 95 % CI = -2.08, -0.07, $p = 0.04$).

Six studies evaluated the effect of IF intervention on blood pressure in T2DM patients. When it comes to the effect of IF on SBP in T2DM patients, there is heterogeneity among studies ($p = 0.05$, $I^2 = 54$ %). Random effects model analysis shows that IF can significantly improve SBP (WMD = -3.51, 95 % CI = -3.82, 5.82, $p < 0.0001$).

Six studies evaluated the effect of IF on DBP in T2DM patients, and there was heterogeneity among the studies ($p < 0.0001$, $I^2 = 88$ %). Random effects model analysis was used, and the results showed that IF could significantly improve DBP (WMD = -2.28, 95 % CI = -4.80, 0.23, $p = 0.07$).

This meta-analysis showed that IF significantly reduced SBP and DBP. The reduced blood pressure may be attributed to significant weight loss. It is well known that there is a strong association between weight and blood pressure in obese patients. IF is expected to improve the lifestyle of patients with pre-diabetes and T2DM. Future RCTS with higher quality and longer follow-up are needed to confirm the findings (26).

Lipid profile (Fig. 3)

Eight studies evaluated the effect of IF on LDL in T2DM patients, and there was heterogeneity among the studies (P=0.036, I^2=9%). Fixed-effect model analysis showed that IF could significantly improve LDL (WMD = -0.19, 95 % CI = -0.25, -0.13, $p < 0.0001$).

Eight studies evaluated the effect of IF on HDL in T2DM patients, and there was heterogeneity among the studies ($p = 0.03$, $I^2 = 56$ %). Random effects model analysis was used, and the results showed that there was no statistically significant difference in HDL reduction between the IF group and the control group (WMD = -0.03, 95 % CI = -0.11, 0.05, $p = 0.45$).

Six studies evaluated the effect of IF on cholesterol in T2DM patients, and there was heterogeneity among the studies ($p < 0.0001$, $I^2 = 83$ %). Random effects model analysis showed that IF could significantly improve cholesterol (WMD = -0.44, 95 % CI = -0.75, -0.13, $p = 0.0005$).

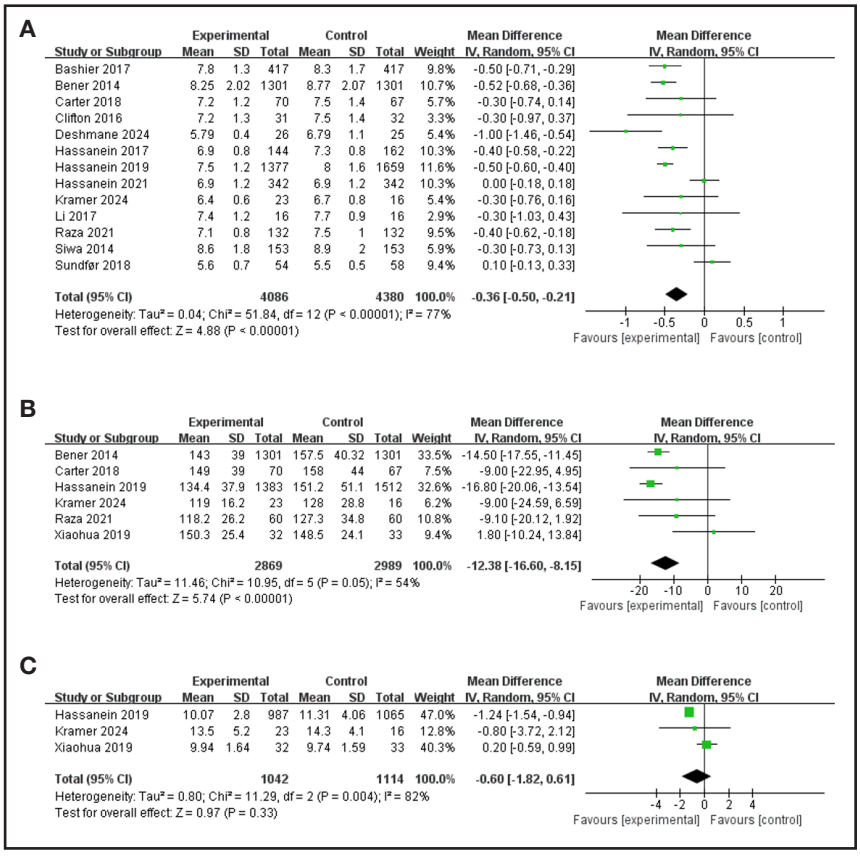

Figure 1.

Meta-analysis of blood glucose status and IF in T2DM patients: A. HbA1c. B. Fasting plasma glucose. C. Postprandial plasma glucose.

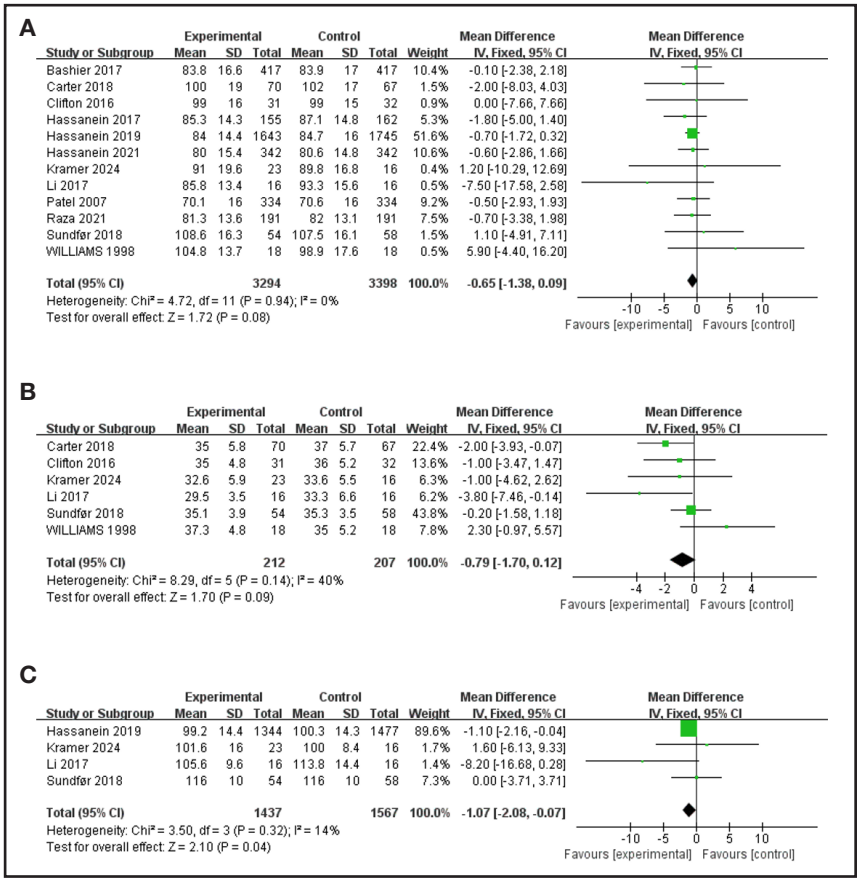

Figure 2.

Meta-analysis of anthropometry and other general information and IF in T2DM patients: A. Weight; B. BMI; C. Waist circumference (continues on next page).

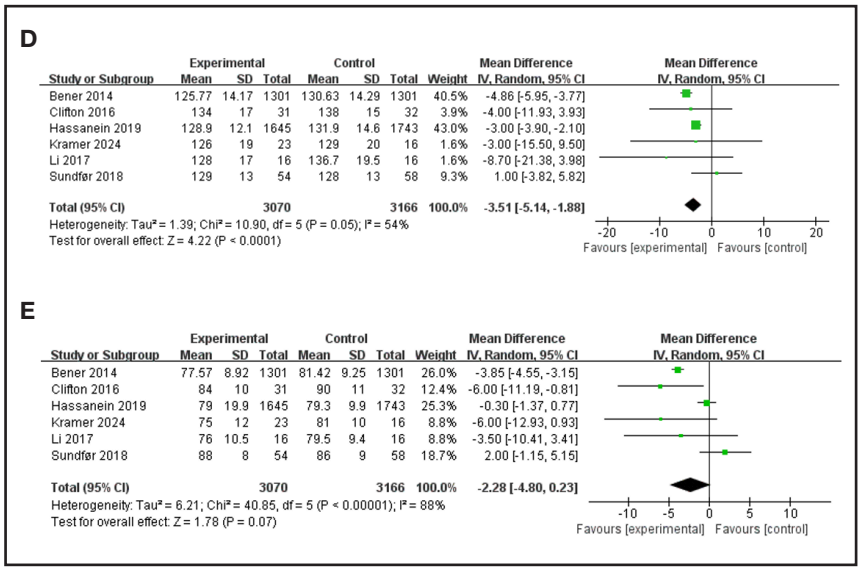

Figure 2 (cont.).
D. SBP. E. DBP.

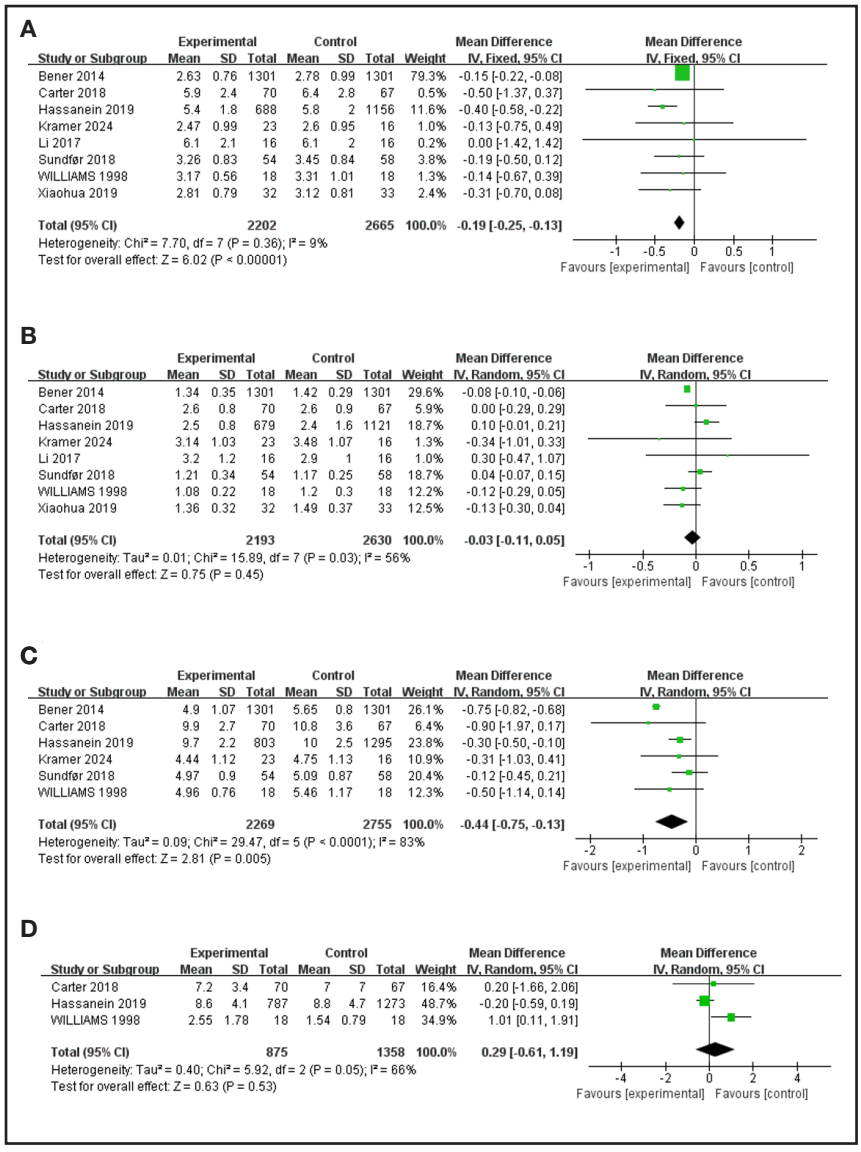

Figure 3.
Meta-analysis of lipid profile and IF in T2DM patients: A. LDL. B. HDL. C. Cholesterol. D. Triglycerides.

Three studies evaluated the effect of IF on triglycerides in T2DM patients, and there was heterogeneity among the studies ($p = 0.05$, $I^2 = 66$ %). Random effects model analysis was adopted, and the results showed that there was no statistically significant difference in the reduction value of triglycerides in the IF group compared with the control group (WMD = 0.29, 95 % CI = -0.61, 1.19, $p = 0.53$).

Security and compliance

Adverse events during the study were reported in four articles. Of these, no serious adverse events occurred in 3 studies. One study reported a 78/417 incidence of hypoglycemic events, but these adverse effects improved after the intervention. Wliiams and other studies included in this study showed that the compliance of the subjects was 86.11 % at 5 months; Carter et al. showed that the compliance of the subjects was 72.86 at 12 months. Thus, IF is safe and feasible.

DISCUSSION

IF IS BENEFICIAL FOR BLOOD GLUCOSE CONTROL IN T2DM PATIENTS

Multiple studies have shown that IF can significantly improve blood glucose control in patients with T2DM. Specifically, IF is able to reduce FPG and HbA1c levels. In addition, IF also helps to improve insulin sensitivity and reduce insulin resistance, which is an important benefit for people with T2DM, as insulin resistance is one of the core features of the disease. IF is also able to help people with T2DM lose weight, which has a positive impact on improving blood sugar control and promoting overall health.

IF IS BENEFICIAL FOR T2DM PATIENTS TO REDUCE BODY WEIGHT, BMI, WAIST CIRCUMFERENCE AND LDL-C LEVEL

In recent years, IF as a dietary pattern has received a lot of attention in terms of health promotion and disease management. The study by Professor Gong Tingting´s team points out that for adults who are overweight or obese, IF may have a range of health benefits, including reduced waist circumference and body fat mass, improved lipid levels, and lower fasting insulin levels. In an RCt-based umbrella review that analyzed 351 unique associations, it was found that IF significantly reduced waist circumference, body fat mass, LDL, triglycerides, and blood pressure levels. In addition, some studies have observed that IF improves cardiovascular health indicators, such as lowering blood pressure and cholesterol levels, and these findings are consistent with our findings. In patients with T2DM, IF may help improve blood sugar control. It is important to note that the effects of IF may vary from individual to individual, so before trying IF, patients are advised to consult a professional physician or dietitian for personalized advice and guidance. In addition, future studies are needed to further evaluate the effects of IF on various health outcomes and explore its potential mechanisms of action (27).

IF IS SAFE AND FEASIBLE IN T2DM PATIENTS

Common IF patterns include the 5:2 pattern (restricting caloric intake for two days a week and eating normally for the remaining five days) and time-restricted eating (eating only during certain periods of time each day) (28). Different IF patterns may have different effects on blood sugar control. Overall, as a diet management strategy, IF has shown potential to improve blood sugar control and overall health in patients with T2DM. However, because there may be differences between individuals, it is recommended that patients try IF under the guidance of a healthcare professional.

COMPARISON WITH OTHER STUDIES

Different from previous studies, which mainly focused on the effects of IF on body weight and blood glucose level, this meta-analysis specifically focused on the effects of IF on blood pressure. To our knowledge, this is the first meta-analysis of this relationship. In this meta-analysis of ten studies, we found that IF significantly reduced systolic blood pressure and similarly significantly reduced diastolic blood pressure in patients who had reached 12 weeks of intervention. These findings are significant because they offer a new perspective on lowering blood pressure. While there is plenty of evidence in basic and clinical research to support the multiple health benefits of IF, there is still room for further research in the following areas. First, this study found that the effects of IF on heart rate and lipid levels were not significant, which is a difference from the results of basic studies, suggesting that more convincing clinical study data is needed to clarify this. Second, future studies need to consider how to generalize the conclusions of this study to groups of patients at high risk of prediabetes and T2DM to more fully assess the potential of IF in blood pressure management (29).

LIMITATIONS AND PROSPECTS

The literature review showed that IF was able to reduce body weight by 3-5 kg over 12 weeks, an effect comparable to sustained energy restriction. However, it is not clear what the best dietary strategy should be during fasting. Common IF patterns include the 16:8 pattern (fasting for 16 hours a day) and the 5:2 pattern (restricting calorie intake two days a week). The interaction between IF and lifestyle factors such as skipping breakfast and using medications may have an impact on physical and mental health, especially in the adolescent population. Although short-term IF has shown some benefit in animal models and

human studies, its role in non-obese individuals and its impact on risk factors for type 2 diabetes in adolescents needs further study. It is important to note that low-carb diets may increase risk factors for type 2 diabetes in adolescents compared to low-fat, high-carb diets promoted by adult guidelines. Overall, although IF has shown some advantages in weight management and health, more rigorous research is urgently needed to identify best practice approaches and assess their potential risks (30).

Although the IF model has received a lot of attention as an emerging weight loss method, there are still many key questions that need to be answered. Currently, there is insufficient information on the safety, acceptability and effectiveness of IF strategies in the wider population. In addition, most of the existing study samples are mainly from Western populations, which limits the general applicability of the findings. Although multiple studies have explored IF, there is no consensus on the ideal dietary pattern for fasting days. Previous studies have mainly described caloric restriction on fasting days, such as recommending consuming 75 % of recommended calories on fasting days (31), but have lacked clear guidance on dietary patterns on non-fasting days. In addition, it is unclear whether a high-protein diet is recommended during fasting. Some previous studies have pointed out that a high-protein diet may help enhance sustained satiety, thereby reducing the hunger associated with prolonged fasting. What's more, whether the recent popularity of meal replacement products can provide additional health benefits for IF is also a question that deserves further research. In conclusion, in order to fully assess the potential benefits and risks of IF, future research needs to explore the long-term effects and best practices of IF in different population and cultural contexts.

Previous research (32) has shown that long-term light or moderate fasting, such as IF, can have a positive effect on health and may extend life. In addition, proteomic analysis of white blood cells revealed that short-term intensive fasting not only increased neutrophil degranulation, but also promoted cytokine secretion. This suggests that short-term intensive fasting can enhance immune function, especially innate immune function, at least in part by altering the expression profile of white blood cells. As a popular dietary intervention, IF is considered relatively easy to adhere to and has been associated with multiple health benefits, including promoting weight loss and improving blood sugar levels. Although the specific mechanism behind the beneficial effects of IF is not fully understood, it may be related to the regulation of the gut microbiome.

There are several limitations to this study that need to be taken into account when interpreting the results. First, there was a degree of heterogeneity between the included trials and the dietary regimen, and the length of the intervention may have been the main cause of this heterogeneity. To address this issue, a random effects model was used for data consolidation and sensitivity analysis was performed for possible sources of heterogeneity. Secondly, the number of RCTS that met the inclusion criteria was limited, and the sample size was generally small, especially for T2DM patients. In addition, this study focused on alternative outcome measures (such as HBA1c, FPG, etc.) with intervention spans ranging from 8 weeks to 12 months, which limits our ability to draw definitive conclusions about the effects of IF on blood glucose control. Although there may have been some selection bias in the current study, as the relevant studies were not registered in a public database, we still strictly followed the steps of the systematic review, following a pre-set flow chart. Longer-term clinical trials are needed in the future to evaluate the long-term effects and safety of intermittent fasting in different populations. Delve into how intermittent fasting can promote health by altering the gut microbiome or other biological pathways. Explore the differences in individual responses to intermittent fasting and how to tailor a personalized eating plan based on an individual's genetic background, lifestyle, and health status. Research on optimal eating patterns during non-fasting periods and how to combine high-protein diets or meal replacement products to enhance the health benefits of intermittent fasting. Expand the study to include populations in diverse cultural and geographic contexts to assess the universal applicability and cultural adaptation of intermittent fasting (33).

CONCLUSION

So far, there have been few experimental studies using IF in people with type 2 diabetes, because not all people with diabetes are suitable for IF diet therapy. In addition to improving blood sugar and promoting weight loss, the IF diet may also help improve other risk factors for T2DM, including insulin resistance and high blood sugar levels. Although further research is needed to validate these findings, the IF diet strategy provides clinicians with a range of intervention options to recommend to younger patients at risk for T2DM. Future studies should further explore the long-term impact of IF on risk factors for type 2 diabetes in adolescents and assess its applicability in different populations and cultural contexts to develop a better dietary pattern for T2DM patients to manage and control blood sugar, lipids, and body weight, leading to a better quality of life for people with diabetes (34).

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Revisión

Disinformation about diet and nutrition on social networks: a review of the literature

Desinformación sobre dieta y nutrición en las redes sociales: revisión de la literatura

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Abstract

Background: social networks have become indispensable for global communication, offering unparalleled access to information. However, the lack of content regulation has allowed health and nutrition misinformation to thrive, posing significant public health risks.

Objectives: this study aimed to identify the social networks most frequently used for spreading nutrition-related misinformation and evaluate the primary topics, including diseases and dietary claims, featured in these messages.

Methods: a systematic review of the literature was conducted, analyzing studies focused on nutrition-related misinformation across platforms such as Twitter, Instagram, TikTok, and YouTube. Data collection adhered to PRISMA guidelines, and findings were synthesized narratively to address the study objectives.

Results: this study analyzed 28 documents focusing on nutrition-related misinformation on social networks. Instagram (50 %) and YouTube (39.28 %) were identified as the most prevalent platforms for spreading such content, followed by TikTok (5.13 %) and Twitter (10.72 %). Over 62 % of the reviewed studies addressed misinformation linked to miracle diets, often associated with orthorexia (14.28 %) and COVID-19 (14.28 %). These diets frequently included unverified claims of rapid health improvements. Notably, credible nutrition content was predominantly shared by healthcare professionals and academic organizations, highlighting their key role in fight against misinformation.

Conclusions: misinformation about nutrition on social networks is a growing public health concern. Public health institutions must implement strategies to improve digital literacy and provide tools for assessing information credibility. Healthcare professionals should leverage social media to disseminate evidence-based knowledge, counteracting the influence of unreliable sources. Collaborative efforts are essential to ensure social networks serve as platforms for reliable health promotion and education.

Keywords:

Diet. Health disinformation. Healthcare professionals. Nutrition. Public health. Social networks.

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Resumen

Antecedentes: las redes sociales han desempeñado un papel esencial en la difusión de información relacionada con la nutrición durante años. Los usuarios pueden seguir cualquier cuenta y ver el contenido publicado por los usuarios que siguen. El principal problema con la información difundida a través de las redes sociales es la falta de calidad y fiabilidad. En los últimos años ha habido una creciente preocupación en la población por la alimentación y la dieta. El aumento del uso de las redes sociales, combinado con la preocupación de la gente por su nutrición o dieta, ha llevado a un aumento significativo de las búsquedas relacionadas con la alimentación en las redes sociales.

Objetivo: a través de una revisión de la literatura, este estudio examinó el uso de las redes sociales en relación con la desinformación sobre dieta y nutrición.

Métodos: este estudio siguió las pautas de PRISMA. Se realizaron búsquedas en las bases de datos Medline, Web of Science y Scopus el 14 de diciembre de 2022. Nos centramos en la desinformación sobre nutrición en las redes sociales, como Twitter, TikTok, Instagram, YouTube y Facebook.

Resultados: se analizaron un total de 28 artículos para comprender la influencia de las redes sociales en la nutrición. Los resultados destacan Instagram (50 %) y YouTube (39.28 %) como las redes sociales predominantes, lo que sugiere un cambio desde los medios tradicionales. La desinformación es generalizada (100 %) y los usuarios difunden prácticas no verificadas, especialmente en Instagram (64.70 %). El auge de las dietas milagro es preocupante, con COVID-19 (14.28 %) y la ortorexia (14.28 %) recibiendo la mayor atención. La ortorexia está vinculada a la difusión de desinformación, lo que exacerba su prevalencia. Además, el análisis revela cambios en los patrones dietéticos, generando preocupación por la disminución de la popularidad de la dieta mediterránea.

Conclusión: la desinformación sobre nutrición, a través de las redes sociales, se está convirtiendo en un grave problema de salud. En nuestro estudio hemos encontrado que una gran parte de los artículos incluidos estaban relacionados con dietas milagro, pero también difundían mensajes sobre, supuestamente, superalimentos que pueden ayudar a curar enfermedades como COVID-19 o la ortorexia. Esta situación debe ser vista como un importante problema de salud pública que debe ser abordado y combatido por las instituciones de salud, así como por los profesionales de la salud.

Palabras clave:

Dieta. Desinformación sanitaria. Profesionales sanitarios. Nutrición. Salud pública. Redes sociales.

INTRODUCTION

The Internet has become the largest and fastest-growing source of health information, with millions of individuals conducting daily searches (1-3). Unlike traditional media such as newspapers, radio, or television, the Internet and social media platforms enable active participation in the communication process, fostering connection and engagement among users (3,4). These platforms wield significant social influence, empowering users to express opinions on critical issues and shaping attitudes and perceptions on a broad range of topics (5).

Platforms such as X (formerly Twitter), TikTok, Instagram, and YouTube have emerged as powerful tools for sharing information, engaging in political discourse, discussing healthcare practices, promoting health behaviors, and connecting with diverse audiences, including patients, caregivers, students, and healthcare professionals (6). Their ability to rapidly disseminate information and mobilize large groups enhances progress toward public health objectives, positioning social media as an essential medium for health education (5,6). Among these platforms, microblogging networks like Twitter are especially noteworthy for their real-time updates, brief format, and unique capacity to support social interaction (7). These platforms serve as a critical source of big data for public health researchers, facilitating the analysis of crowd behaviors, monitoring health trends, and even predicting disease outbreaks (8,9).

Understanding the distinction between social media and social networks is fundamental. Social media encompasses a broad range of digital tools, platforms, and strategies that enable interaction and content sharing, including blogs, forums, and video platforms. In contrast, social networks are specific online platforms, such as Facebook, Instagram, and LinkedIn, designed to foster connections and content exchange among users with shared interests (10). Microblogging platforms, like Twitter, offer a dynamic environment for the rapid exchange of concise updates and are a particularly valuable resource for public health research due to their accessibility and real-time content.

The widespread use of social media has also amplified discussions around food and diet, reflecting growing public concerns about long-term health risks associated with nutrition. Studies reveal that 60 % of individuals are increasingly worried about these risks (11). This heightened awareness, combined with the pervasive use of social media, has fueled a significant rise in food-related searches across platforms (12-14). However, the quality and reliability of health information shared on these platforms remain critical challenges. The interactive nature of social media exacerbates the spread of misinformation—false information shared by individuals who believe it to be true—and disinformation—intentionally false information shared to mislead others (6,15,16).

Instagram, for instance, pioneered the integration of visual content into digital marketing strategies, enabling users to discover and interact with images more effectively. Similarly, YouTube, the second most visited website globally as of 2017, provides a user-friendly platform for sharing videos (1). TikTok, as the preferred social network to millions of young users to create, share, and comment on videos worldwide (17,18). Despite these advantages, the potential for misinformation dissemination underscores the need for vigilance and quality control on these platforms.

This review synthesizes findings from over 182 studies on diet and misinformation across Twitter, Instagram, YouTube, and TikTok, encompassing more than 2 million Instagram posts, 1,000 YouTube videos, and 46,000 tweets. The primary objective is to characterize existing research and develop a taxonomy to i) identify the social networks most frequently associated with spreading misinformation, and ii) evaluate the predominant themes used in disseminating this information.

METHODS

We conducted a systematic review of the literature, in which the preferred reporting items for systematics reviews and meta-analyses (PRISMA) (19).

The aim was to review the available international literature on the use of social media and the potential impact on diet and nutrition disinformation. In addition, this work highlights possible risks found, identify signs of dangerous use, and provide recommendations based on these findings.

SEARCH METHODOLOGY

To identify relevant studies, a literature search was conducted covering a wide range of published health-related research from the following databases: Medline, Web of Science and Scopus. The time frame studied included articles published from 1st of January 2017 to 30th June 2024.

The search terms used in the different databases were focused on obtaining the appropriate result to answer the objectives set out in this study, these are as follows: terms used for nutrition included "nutrition" OR "nutrition facts" OR "diet" OR "diets", On the other hand, search terms related to social networks included: "social networks" OR "Twitter" OR "X" OR "TikTok" OR "X" OR "Instagram" OR "YouTube" OR "Facebook".

INCLUSION AND EXCLUSION CRITERIA

Studies eligible for inclusion in the review were retrieved according to predefined criteria. It is important to highlight that articles that did not meet all these criteria were excluded (Table I).

SELECTION OF ARTICLES

After retrieving the studies from the databases, duplicate reports were removed, and the titles and abstracts of the remaining articles were screened to exclude studies that did not meet the eligibility criteria. To avoid error and bias, three independent researchers conducted the review process to identify articles that met the inclusion criteria (SSF, BJG and PJJH), using the Zotero bibliographic reference manager, which allows for the detection and elimination of duplicate articles (20). Titles and abstracts were then analyzed to exclude irrelevant articles. Finally, the full texts were evaluated using PRISMA criteria, to determine whether the articles met the eligibility criteria. During this selection phase, any disagreements among the investigators were resolved by discussion and consultation with a reviewer who was not actively involved in the study selection (IHP).

ARTICLE CLASSIFICATION

After selecting relevant articles, these were analyzed following 4 criteria: i) manuscript's focus, ii) pathology/disease addressed in the manuscript, iii) use of social network, iv) health information.

Due to the heterogeneity of the studies included in this paper, a narrative synthesis was conducted according to these criteria: a content analysis was performed with the aim of obtaining information about the focus of the manuscripts, the social networks included, and the disease/pathology or situation associated with health and nutrition describe in the manuscripts. Finally, about the "health information" criteria, an analysis of the manuscripts was performed to explore how the health disinformation or information that is not based on scientific evidence, were analyzed.

Finally, we grouped the articles into two categories: i) articles focused on miracle diets and ii) articles focused on health disinformation or non-verified health information.

RESULTS

SELECTION OF SOURCES OF EVIDENCE

Our search initially identified 673 articles within the 3 databases. After removing duplicates, a total of 548 articles were screened to determine if they met the eligibility criteria, finally 487 articles were removed for not meeting these inclusion criteria, leaving 61 articles to be analyzed by reading the full text (Fig. 1).

Table I. Inclusion and exclusion criteria

Criteria	Language	Publishing media	Type of article	Subject of the article	Social network	Date of publication
Inclusion	English	Peer-reviewed journal	Research articles, and reviews	Disinformation on nutrition	Twitter, X, TikTok, Instagram, YouTube, or Facebook	Between January 1, 2017, and June 30, 2024
Exclusion	Other languages	No peer-reviewed journal, books, others	Editorial letters, comments, preprints, abstracts, proceedings, book reviews	Disinformation on non-nutrition subjects, others (like eHealth literacy instrument, educational programs, etc.)	Others (like Weibo, Reddit, etc.)	Before January 1, 2017. After December 1, 2022

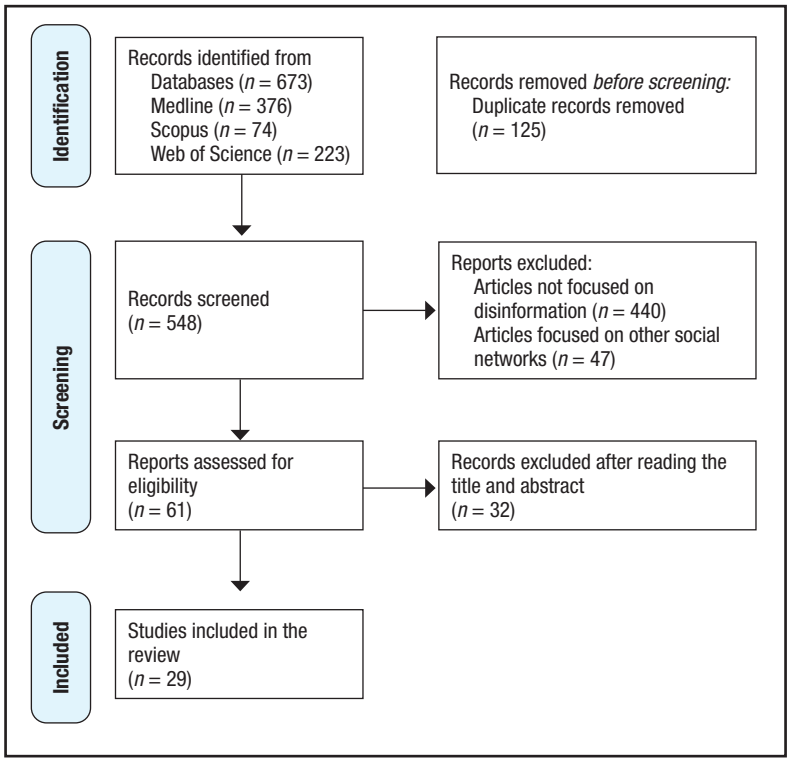

Figure 1.

Flow chart of the article selection process. Adapted from the PRISMA guideline (19).

The selected articles were divided into two main categories: on the one hand, papers dealing with miracle diets and associated misinformation (Table II). On the other hand, the documents that analyzed the misinformation disseminated through social networks about food without being associated with miracle diets (Table III).

A total of 18 articles (62.06 %) were found that were categorized as studies that addressed the relationship between nutrition, the emergence of miracle diets and the misinformation generated among users who consume information about miracle diets through social networks.

GENERAL DESCRIPTION OF RESULTS

The most frequently mentioned social media were Instagram (50 %), YouTube (39.28 %), and Twitter (10.72 %). On the other hand, the least mentioned social media were Facebook (18.75 %) and TikTok (5.13 %).

It is striking that the most widely used social network in the world, Facebook, is in this case one of the least used for sharing information related to nutrition. On the other hand, the most relevant are Instagram or YouTube, social media focused on sharing videos or audiovisual material. Therefore, this feature becomes relevant when getting information across to the public (21).

Regarding the misinformation that exists on the platforms analyzed in the different articles, we observed that 100 % confirm the existence of misinformation on diets and health. The approach to this misinformation in the different articles is quite similar, as they all deal with the increasing amount of content shared by channels or users not related to the health field, without following any scientific method or contrasting the information posted (22-33).

Nevertheless, there are also articles which analyze this context of misinformation in greater depth. One of these articles' links misinformation to the promotion of some brands by Youtubers (22). The case of these content generators is analyzed in another article, revealing that up to 87.3 % of the accounts analyzed on Instagram provide unhealthy nutritional information (23). We see the importance of these new profiles dedicated to sharing information on social media, and how they do not always seek veracity in the shared content, but to achieve relevance. One of the articles goes so far as to associate the utilization of some content to attract women with low self-esteem (22).

This can be seen in the article by Bradley P., which analyzes publications that have low veracity, but still, they get more views and likes (23). This may explain why in the results of this review we find 100 % of the articles that talk about misinformation.

In these 29 articles we found different pathologies, highlighting two of them above the rest: COVID-19 (14.28 %) and orthorexia (14.28 %). Other pathologies that appeared were acne, gout, osteoporosis, renal disease, diabetes, irritable bowel syndrome and celiac disease. (Tables II and III).

Diet is a key and very important element for people's health (24). It is important to distinguish attempts to distort the information, to deceive the population with diets claiming to cure different conditions in a short period of time, without providing any scientific evidence. These types of diets, colloquially called 'miracle diets'—although they are also referred to using many euphemisms such as "superfoods" or "healthy diets"—are present in 18 of the 29 studies analyzed.

Table II. Miracle diet and misinformation on social networks

Author, year, reference	Pathology/ Disease	Social media	Summary
O'Connor et al. (2022) (31)	Acne	Tiktok, Facebook, Instagram, Twitter	This study aimed to assess the content of acne-related misinformation available online. Websites promoting misinformation were frequently affiliated with companies selling products that promised to cure acne, often in a remarkably short time
Niknam et al. (2021) (26)	COVID-19	Instagram	To characterize the representation of public health information related to COVID-19 on Instagram. Analysis of 1,612 posts from 92 accounts revealed 23 themes, including epidemiology and statistics, training and caring, general prevention guidelines, hygiene, healthy diet, and lifestyle. This content analysis provides new insights into public concerns during health crises
Inder et al. (2021) (41)	Gout	YouTube	The aim of this study was to assess the reliability and quality of YouTube videos pertaining to gout. This study demonstrated that many YouTube videos on gout provide useful information
Valente et al. (2022) (27)	Orthorexia	Instagram	This study delved into the relationship between orthorexia nervosa (ON) and Instagram. People who share ON-related content on Instagram were found to be primarily young women. Most of the other interviewees said that Instagram affected development to a certain extent. Content that was considered most harmful concerned diets, especially clean eating
Zemlyanskaya et al. (2022) (28)	Orthorexia	Instagram	This study explored the conversation around orthorexia nervosa (ON) on Instagram from a Russian-speaking perspective. Instagram appears to have a dual effect; it has the potential to both trigger the onset of ON and encourage recovery
Jenkins et al. (2020) (29)	Orthorexia	Instagram	This study aimed to explore young adults' perceptions of the authenticity and trustworthiness of Instagram posts by social media influencers (SMIs) and nutrition professionals (NPs). Findings indicated that a strong heroic message appeal significantly enhanced the perceived authenticity of NPs' posts, which in turn increased their trustworthiness. However, this effect was not observed for SMIs
Sina et al. (2022) (42)	No	Instagram, Facebook	This systematic literature review aimed to explore the role of social media in children's and adolescents' diets and related behaviors, considering the underlying mechanisms. The review found that social media use was associated with skipping breakfast, increased consumption of unhealthy snacks and sugar-sweetened beverages, and lower intake of fruits and vegetables, regardless of age
Rodríguez-Martín & Castillo (2017) (43)	No	Twitter	Study aims to understand conceptualizations of carbohydrate consumption and dietary patterns related to carbo-phobia through Twitter activity. Four broad categories emerge that portray conceptualizations about carbohydrates: carbohydrates as a suspect or culprit for training plateau and weight problems, carbo-phobia as a lifestyle, carbo-phobia as a religion, and the love/hate relationship with carbohydrates
Giménez-Pérez et al. (2020) (44)	Diabetes	YouTube	This study evaluates the usefulness of YouTube videos as an educative tool for type 2 diabetes self-management. Of the 393 videos included, 42.2 percent ($n=166$) classified as "alternative medicine." 40.2 percent ($n=158$) contained useful information. 25.7 percent ($n=101$) videos contained misleading information
Schier et al., (2019) (45)	No	YouTube	The objective of this qualitative netnography was to describe the food and nutrition messages shared among the transgender community using video blogs on YouTube. Six major themes were generated from the data analysis. These included the following: functions of diet and exercise; diet and exercise philosophies; "how to" vlogs; advice for success; using dietary supplements; and effects of hormone therapy

(Continues on next page)

Table II (cont.). Miracle diet and misinformation on social networks

Author, year, reference	Pathology/ Disease	Social media	Summary
Saura et al. (2020) (30)	Orthorexia	Instagram	Using user-generated content (UGC) on Twitter, the present study identifies the main themes that revolve around the concept of healthy diet and determine user feelings about various foods. Our findings suggest that the collective UGC knowledge is lacking on such healthy foods as fish, poultry, dry beans, nuts, as well as yogurt and cheese
Kabata et al. (2022) (25)	No	Instagram, Twitter	This study aimed to investigate whether Instagram® profiles can be reliable sources of information and knowledge about nutrition and dietetics. A total of 1189 posts were reviewed. The overall quality of the content regarding nutritional knowledge was extremely low (93.9 % of all posts)
Alnajrany et al. (2021) (46)	COVID-19	Twitter	The utilization rate of herbal and dietary supplements among the Saudi population is reported to be high. However, the utilization rate and types of herbal and dietary supplements during the COVID-19 pandemic are largely unknown. 64 % of the 1473 participants reported using herbal and/or dietary supplements for the purpose of boosting their immune system to prevent COVID-19 infection. In addition, 88.2 % of the respondents were misinformed about the manifestation of COVID-19 symptoms
Sidhu (2018) (47)	No	Twitter, YouTube, Instagram	In the present study triangulation method of research is applied to evaluate the awareness and application of information related to diet for health, fitness and reduce body weight. This study reveals that usually people on social media blindly follow their 'friends' endangering health. The likes and comments not only substantiate the results but also create a pressure to 'do it' on others
Yousaf et al. (2020) (32)	Acne	Youtube, Instagram	The purpose of the study sought to characterize the influence of social media use on acne treatment. Social media-influenced acne treatment advice is prevalent, especially among women, adolescents, and young adults. This treatment advice frequently does not align with AAD guidelines, with notably 40 % of respondents choosing dietary modification for acne management. These results suggest that dermatologists should inquire about social media acne treatment advice and directly address misinformation
Wagner et al. (2020) (48)	COVID-19	Instagram	"Immune boosting" is a trending topic during the COVID-19 pandemic. The concept of "immune boosting" is scientifically misleading and often used to market unproven products and therapies. This paper presents an analysis of popular immune-boosting posts from Instagram. Of the sampled posts, all promoted "immune boosting" as beneficial, nearly all involved commercial interests, and many used scientific and medical rhetoric in their messaging
Parbey et al. (2022) (49)	No	YouTube, Facebook, WhatsApp	A rapid evidence review conducted during the development of Ghana's Food-Based Dietary Guidelines (FBDGs) revealed that children are highly exposed to targeted food advertisements employing strategies such as promotional characters, animations, billboards, front-of-store displays, product-branded books, and toys. The primary sources of health and nutrition information identified were television, radio, social media, health professionals, families, and friends
Fiuza, A & Rodgers, R. (2023) (50)	No	TikTok	A study involving 421 U.S. women aged 18 to 21 examined the impact of brief diet and anti-diet TikTok videos on body image and mood. Findings indicated that anti-diet videos fostered a more compassionate and accepting self-view compared to diet and neutral videos. Conversely, exposure to diet culture content led to negative effects on mood and body image, aligning with prior research on the detrimental impacts of "thinspiration" and "fitspiration" content

Table III. Misinformation about nutrition on social networks

Title	Pathology/ Disease	Social media	Summary
Onder et al. (2022) (41)	Osteoporosis	YouTube	A study assessed the quality of 238 English-language YouTube videos on osteoporosis, finding that 86.1 % provided useful information, while 13.9 % were misleading. Quality evaluations revealed that 48 % were high quality, 34 % moderate, and 18 % low. Videos from universities and professional organizations scored highest in reliability and quality
The Mellouli et al. (2022) (33)	COVID-19	Twitter	The purpose of this study was to compare tweets on nutrition in times of COVID-19 published by 2 groups, namely, a preidentified group of dietitians and a group of general users. Differences in tweets between groups, notably ones related to content accuracy, themes, and engagement in the form of likes, shed light on potentially useful and relevant elements to include in timely social media interventions aiming at fighting the COVID-19-related infodemic or future infodemics
Pilgrim et al. (2019) (22)	No	YouTube	An exploratory study analyzed non-campaign health communication by influencers on social networks, focusing on content, techniques, and visible impact. Findings indicate that influencers build trust with followers through body-focused visuals and targeted communication, portraying diet and exercise as controllable factors for achieving body perfection. They often promote dietary supplements and branded sportswear as simplified means to enhance appearance, suggesting this leads to happiness
Pilar et al. (2021) (39)	Miscellaneous	YouTube	Researchers found that the use of social networking sites impacts adolescents' eating behavior. This study aims to identify the main topic associated with healthy food on the Instagram social network via hashtag and community analysis based on 2,045,653 messages created by 427,936 individual users. The results show that users most associate Healthy food with healthy lifestyle, fitness, weight loss and diet. In terms of food, these are foods that are Vegan, Homemade, Clean and Plant-based
Lambert et al. (2017) (34)	Renal disease	YouTube	The present study describes the accuracy, quality, and health literacy demand of renal diet information for adults with kidney disease obtained from the Internet and YouTube. The most frequent renal diet topic found online was generic dietary information for people with chronic kidney disease. The proportion of renal diet information obtained from websites that was accurate was 73%. However, this information was mostly of poor quality with extensive shortcomings, difficult to action and written with a high health literacy demand
Pérez-Pérez et al. (2019) (38)	Irritable colon	Twitter	This study aimed to characterize the bowel disease (BD) community on Twitter, in particular how patients understand, discuss, feel, and react to the condition. This study evidence that Twitter is becoming an influential space for conversation about bowel conditions, namely, patient opinions about associated symptoms and treatments. So, further qualitative, and quantitative content analyses hold the potential to support decision making among health-related stakeholders, including the planning of awareness campaigns
Al Sharky (2020) (36)	Celiac disease	Instagram, Twitter	The aim of this study was to investigate social media usage patterns among celiac patients and explore the potential factors that may influence the frequency of its usage. Celiac patients are highly involved in social media activities for purposes related to their disease. We encourage healthcare providers to be available online to provide trustable and high-quality educational materials
Jammadass et al. (2019) (35)	Kidney stone disease	Twitter, Youtube	We wanted to determine whether social media and search engines play a role in the management and/or prevention of Kidnsey Stone Disease (KSD). Social Media and search engines provide valuable information to patients with KSD. However, while the information provided regarding dietary aspects and fluid management was good, it was not comprehensive enough to include advice on other aspects of KSD prevention
Turnwald et al. (2022) (23)	No	Instagram	A study analyzing 3,065 social media posts from highly followed celebrities found that 87.3 % featured foods and 89.5 % featured beverages classified as less healthy, predominantly snacks, sweets, and alcoholic drinks. These items would not meet the UK's legal standards for youth advertising
Álvarez-Mon et al. (2022) (40)	No	Twitter	We investigated tweets posted between January 2009 and December 2019 by 25 major US media outlets about MedDiet and its components as well as the retweets and likes generated. The US media outlets analyzed showed reduced interest in MedDiet as a whole, while Twitter users showed greater interest in the overall dietary pattern than in its components
Verma AK et al. (2024) (37)	Celiac disease	Facebook	This study investigates the authenticity of information about celiac disease on Facebook pages. A total of 155 celiac-related Facebook pages from Italy, the USA, and India were analyzed. It was found that 13% of these pages shared misleading information, including unverified alternative treatments. Patients are advised to verify information with healthcare professionals before relying on social media

MIRACLE DIETS AND MISINFORMATION

These studies address miracle diets in different ways, such as claiming that they can help you boost your immune system, along with the advertisement for a brand of supplements, (25) or how to protect yourself from COVID-19 by taking vitamins or cooking meat in a particular way (26) (Table II).

In all, 64.70 % of the studies advocating for these miracle diets are linked to the social network Instagram, 41.17 to YouTube, 29.41 % to Twitter and 21.12 % to Facebook (Table II).

It is observed that social networks that use videos and images as the primary means of communication are the most common. Likewise, it is noteworthy that the most used social media to share this kind of information are those platforms designed to share information along with images and sound.

When it comes to miracle diets, there is no pattern with respect to the various pathologies mentioned above, and they are present in infectious diseases as well as in chronic diseases. The articles in which these diets are discussed cover diseases as diverse as acne, COVID, gout or diabetes.

However, it is noteworthy that in 100 % of the articles in which orthorexia is mentioned, miracle diets are also present (27-30). There seems to be a link between this disorder, which is characterized by an unhealthy obsession with food quality, and the promotion of diets that are not always scientifically based, taking advantage of people suffering from this condition (27) (Table II).

MISINFORMATION ABOUT NUTRITION ON SOCIAL NETWORKS

These studies address misinformation in nutrition observed from different pathologies and social networks such as how information about kidney disease (34,35), celiac disease (36,37), or irritable bowel syndrome (38) are treated with nutrition (Table III).

In all, 54.54 % of the studies are linked to the social network YouTube, the same as Twitter. Furthermore, 27.27 % of the studies are related to Instagram while Facebook only has 11.75 % of the articles (Table III).

Likewise, we can observe that social networks that use videos and images as the primary means of communication are the most common. Also, 18.18 % of the articles focus on the role of influencers in diet, although in one article we can see how social networks are misused to encourage consumers to consume dietary supplements to achieve quick and easy results in fitness (22), while in another one the Instagram community relates the term “healthy food” with a healthy lifestyle, fitness, and diet (39). One of the studies analyzed the accounts of different celebrities, who recommended less healthy food and beverages based on nutrition scores in 87.3 % of the cases (23) (Table III).

There is no pattern with respect to pathologies and misinformation, which is present in infectious diseases as well as in chronic diseases. There is also no pattern regarding the social networks in which the most misinformation is shared (Table III).

Through the analysis of the eating patterns, we observed how are changing in recent years. On the one hand, we have the hoaxes that we see on different social networks and how they can affect people’s diet (39) and even make their health condition worse as they are not quality information (34). We can also see how sometimes this information if verified, can raise awareness among the lifestyle population and make them improve it (40). Finally, we can even observe how the Mediterranean diet has been generating less interest over the last few years (40) (Table III).

DISCUSSION

PRINCIPAL FINDINGS

This study aimed to review the current literature on the dissemination of nutrition-related misinformation on social networks. The objectives were: i) to identify the social networks most frequently used for spreading this misinformation, and ii) to evaluate the main topics, including diseases and dietary claims, utilized in these messages.

In addressing the first objective, the findings indicate a predominant use of audiovisual social networks such as Instagram, YouTube, and TikTok for spreading nutrition-related misinformation. These platforms, which emphasize visual and interactive content, appear to attract younger audiences, particularly those under 30 years old, who engage more actively with these mediums. This shift from text-based to audiovisual platforms has been previously noted in the literature, reflecting changing user preferences and the platforms’ suitability for conveying engaging yet unverified content (1,18,21). The ease of access, coupled with minimal content regulation, amplifies the spread of misinformation, particularly on topics such as diets and nutrition (50,51).

Regarding the second objective, the study highlights two major themes within the misinformation disseminated on social networks: miracle diets and general dietary misinformation related to specific pathologies. Miracle diets were frequently associated with claims of rapid health improvements, such as immune system enhancement or COVID-19 prevention, without scientific backing (25,26). Particularly concerning is the strong link between miracle diets and orthorexia, with 100 % of studies mentioning orthorexia also referencing miracle diets. This underscores the exploitation of vulnerable populations by promoting unrealistic dietary ideals under the guise of health benefits (27,30).

The results also reveal the proliferation of misinformation during public health crises, such as the COVID-19 pandemic. For example, during the pandemic, a surge in misinformation about diets aimed at preventing or curing COVID-19 was observed on platforms like Instagram and Twitter (26,33). This highlights the dual role of social networks as both sources of valuable information and breeding grounds for unverified claims. Importantly, nutrition-related content from credible sources, such as dietitians and healthcare organizations, was found to be more accurate, emphasizing the need for increased visibility of these voices (33,34).

IMPLICATIONS FOR PUBLIC HEALTH

The widespread dissemination of misinformation on social networks poses a significant public health challenge. Users often lack the necessary tools to critically evaluate the credibility of the information they encounter. As a result, low-quality content, such as posts advocating miracle diets or unverified health claims, garners significant engagement, potentially influencing user behaviors and perceptions negatively (22,23).

Public health institutions and healthcare professionals play a crucial role in combating misinformation. These entities should prioritize creating and promoting accessible, evidence-based content on social media to counteract false narratives. Additionally, targeted interventions, such as digital literacy programs, can empower users to discern credible information from misinformation.

LIMITATIONS AND STRENGTHS

This study's limitations include its focus on English-language articles and the selected social media platforms, which may exclude broader trends. Additionally, the heterogeneity of methodologies and data collection processes among the reviewed studies posed challenges in synthesizing the findings. Future research should explore the underlying motivations for disseminating misinformation and evaluate the effectiveness of interventions aimed at mitigating its impact.

Despite these limitations, the study's strengths lie in its comprehensive analysis of multiple social networks and pathologies, offering a nuanced understanding of the issue. By including studies from various platforms and focusing on diverse diseases, this review provides a robust foundation for addressing the challenges posed by nutrition-related misinformation on social networks.

CONCLUSIONS

Social networks have revolutionized global communication, offering unprecedented access to information. However, the absence of rigorous content oversight has made misinformation a pervasive issue, particularly in topics as critical as health and nutrition. This phenomenon has been compounded by the public's growing reliance on these platforms as primary sources of health information.

Our analysis underscores that nutrition is integral to human health and a subject widely discussed across platforms like Twitter, Instagram, TikTok, and YouTube. Consequently, these discussions are often influenced by misinformation, as evidenced by the prevalence of miracle diets in more than half of the studies reviewed. These diets, which promise quick results with minimal effort, pose significant public health risks, including the exacerbation of conditions like orthorexia and the spread of unverified claims about disease prevention, such as COVID-19.

This study brings to light a critical public health challenge: the widespread acceptance and influence of misinformative content on social networks. Public health institutions must take proactive measures to address this issue, including developing accessible tools to help users evaluate the credibility of the information they consume. These efforts should be complemented by targeted campaigns to promote digital literacy and critical thinking skills among the public.

Healthcare professionals also have a pivotal role to play on control of disinformation, in example establishing a strong presence on social media, they can disseminate accurate, evidence-based information and counteract the spread of false narratives. Embracing these platforms as allies rather than adversaries will enable professionals to reach broader audiences and foster informed, health-conscious communities.

Wherefore, tackling misinformation on social networks requires a concerted effort from public health authorities, healthcare professionals, and the platforms themselves. Only through collaborative action can we ensure that social networks serve as a source of reliable information and a tool for promoting public health.

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Artículo Especial

Guía de la OMS sobre edulcorantes no nutritivos: un análisis reflexivo

WHO guidance on non-nutritive sweeteners - A critical analysis

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Resumen

El uso de edulcorantes sin azúcar (ESA) ha adquirido cada vez mayor importancia como alternativa para reducir la ingesta de azúcares libres, y forma parte de la respuesta mundial a la creciente prevalencia de enfermedades no transmisibles (ENT). Los ESA ofrecen dulzor sin aportar energía calórica, lo que los posiciona como una herramienta potencial para combatir las ENT. Sin embargo, sus efectos a largo plazo sobre la salud siguen siendo controvertidos, en particular entre los profesionales de la salud. En 2023, la Organización Mundial de la Salud (OMS) publicó una guía que examina el papel de los ESA en la promoción de una alimentación saludable, la prevención del aumento de peso y el tratamiento de las ENT relacionadas con la dieta. Aunque algunos estudios incluidos en la guía sugieren beneficios, como la reducción del peso corporal y la menor ingesta de energía, la evidencia aún no es concluyente. La mayoría de los estudios disponibles, predominantemente observacionales, destacan los posibles riesgos asociados al uso de ESA. Sin embargo, estos hallazgos son limitados a la hora de establecer la causalidad debido a sesgos y factores de confusión. Esta revisión ofrece un análisis crítico de las directrices de la OMS y destaca la necesidad de realizar investigaciones más exhaustivas para comprender mejor los riesgos y los beneficios de las ESA tanto para la población general como para las personas con ENT. La evidencia científica actual revela importantes brechas de conocimiento sobre las implicaciones a largo plazo del uso de las ESA.

Palabras clave:

Edulcorantes no nutritivos. Guía. Organización Mundial de la Salud. Azúcares. Enfermedades no transmisibles. Práctica clínica basada en la evidencia.

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Conflicto de interés: los autores manifiestan que el Centro Latinoamericano de Nutrición (CELAN) ha recibido pagos por parte de Boydorr SAS y Alpina Productos Alimenticios SA en razón a asesorías, elaboración de documentos técnicos y conferencias. Adicionalmente, Patricia Savino actúa como asesora científica de Boydorr SAS. Sin embargo, los autores indican que no presentan ningún tipo de conflicto con el contenido de este artículo.

Inteligencia artificial: los autores declaran no haber usado inteligencia artificial (IA) ni ninguna herramienta que use IA para la redacción del artículo.

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Abstract

The use of non-sugar sweeteners (NSS) has gained prominence as an alternative to reduce free sugar consumption, aligning with global efforts to combat the growing prevalence of non-communicable diseases (NCDs). By providing sweetness without caloric energy, NSS are viewed as potential tools in addressing diet-related health challenges. However, their long-term effects on health remain contentious, especially within the medical community. In 2023, the World Health Organization (WHO) released guidelines evaluating the role of NSS in promoting healthy eating, preventing weight gain, and mitigating NCDs. While some studies highlight benefits, such as lower body weight and reduced energy intake, the evidence is inconclusive. Observational research predominantly raises concerns about potential risks associated with NSS, but these studies face limitations, including biases and confounding variables that hinder causal conclusions. This analysis underscores the urgent need for comprehensive, high-quality research to clarify the risks and benefits of NSS. Current evidence is limited in scope and fails to address critical knowledge gaps, particularly regarding their long-term implications for the general population and individuals with NCDs. Expanding the scientific understanding of NSS is essential to inform public health recommendations and clinical guidelines effectively.

Keywords:

Non-nutritive sweeteners. Guideline. World Health Organization. Sugars. Noncommunicable diseases. Evidence-based practice.

INTRODUCCIÓN

Los edulcorantes son sustancias que proveen sabor dulce a los alimentos o a las preparaciones. Existen edulcorantes naturales (como el azúcar de mesa) o artificiales, que son elaborados químicamente. Estos últimos también son conocidos como edulcorantes no nutritivos, edulcorantes artificiales o sustitutos del azúcar. La guía de la Organización Mundial de la Salud (OMS) utiliza el término edulcorantes sin azúcar (ESA), y los define como edulcorantes sintéticos, naturales o modificados, no nutritivos y no clasificados como azúcares, excluyendo los alcoholes de azúcar y los azúcares bajos en calorías (1).

El uso de ESA ha venido cobrando relevancia como una alternativa para reducir el consumo de azúcares libres, especialmente ante el alarmante aumento de la prevalencia de enfermedades no transmisibles (ENT) vinculadas con la alimentación. Estas enfermedades contribuyen al 74 % de las muertes a nivel mundial, principalmente en países de ingresos bajos y medios según la OMS (2). Una de estas enfermedades es la obesidad, cuya prevalencia a nivel mundial es de 37 % (IC 95 % 33 a 42 %) (3) y contribuye al desarrollo de otras ENT, mediante cambios patológicos y mecánicos relacionados con el exceso de adiposidad e incremento en el peso corporal. Entre ellas se encuentran la apnea obstructiva del sueño, la enfermedad cardiovascular, la osteoartritis, algunos tipos de cáncer, la diabetes tipo 2 y el síndrome metabólico. Además, la obesidad aumenta el riesgo de mortalidad asociada a estas condiciones en más de 2,5 veces (4).

Un estilo de vida sedentario y la adopción de patrones de alimentación poco saludables, han contribuido al aumento en la prevalencia de las ENT, creando una carga significativa para los sistemas de salud en términos de atención y de costos. La relación entre la alimentación y las enfermedades crónicas es crucial para comprender la magnitud de este problema. Un patrón de alimentación que incluya frutas, verduras, granos enteros, y que sea bajo en sodio, grasas saturadas y trans, así como azúcares libres, ha demostrado ser efectivo para reducir el riesgo de incidencia de este grupo de enfermedades (5). En respuesta a esta necesidad, la industria de alimentos ha implementado el uso de ingredientes que cumplen funciones tecnológicas al ser incorporados en los alimentos, como asegurar su inocuidad, extender su vida útil y mantener su calidad sensorial (sabor, olor, color y textura). La incorporación de este tipo de ingredientes ha contribuido a la reducción del contenido de algunos nutrientes críticos relacionados con efectos adversos sobre la salud como el sodio, las grasas saturadas y los azúcares libres. Con respecto a estos últimos, la disminución en su consumo es una medida fundamental para combatir la creciente incidencia de las ENT, por lo cual se han implementado diversas estrategias, una de ellas es el uso de los ESA como una opción para mantener el sabor dulce en los alimentos y bebidas sin aportar energía. Sin embargo, su impacto sobre la salud a largo plazo sigue siendo un tema de debate en la comunidad científica.

La OMS ha sido una de las principales entidades que ha intervenido en este debate, con la publicación de su guía en 2023 sobre el uso de los ESA (1). Este documento ofrece una recomendación sobre el uso de los ESA en el contexto de la prevención del aumento de peso y la reducción del riesgo de ENT. A pesar de que los ESA son comúnmente promovidos como una herramienta para controlar el peso y mejorar la salud metabólica, la evidencia científica que respalda estos beneficios no es concluyente. La guía de la OMS se basa en el análisis de estudios clínicos y ensayos observacionales, cuyos resultados han sido variados y no conclusivos, salvo por la única recomendación reportada por esta guía. Esto ha derivado en interpretaciones erróneas de la información y hasta en la posibilidad equivoca de eliminar el consumo de los ESA y remplazarlo por el azúcar. Este artículo tiene como objetivo proporcionar una visión crítica y reflexiva de la guía de la OMS sobre el uso de los ESA, como aporte a la discusión sobre su uso en la población general, incluyendo pacientes con ENT.

GENERALIDADES SOBRE LOS EDULCORANTES SIN AZÚCAR

DEFINICIÓN

Los ESA son aditivos alimentarios que confieren sabor dulce a un alimento (6). Su principal objetivo de uso es remplazar el azúcar libre y contribuir a la reducción del contenido energético de los alimentos. Son considerados alimentos seguros o *Generally Recognized as Safe* (GRAS). No aportan energía y son sintetizados de manera artificial, a excepción de los glucósidos de esteviol. Los ESA son 20 a 20 000 veces más potentes en su dulzor que la sacarosa, y cuando son utilizados en combinación este dulzor presenta una mayor potencia, razón por la cual tienden a ser ampliamente utilizados de esta manera (7). Los ESA tienen diferentes funciones tecnológicas en la industria de alimentos como acentuadores de sabor, humectantes, estabilizadores y espesantes, entre otras (8), su característica principal es incrementar la intensidad de dulzura, persistencia del sabor dulce y efecto en el retrogus-

to (9). Los ESA se utilizan ampliamente debido a su bajo contenido energético y su capacidad de no afectar el apetito y la respuesta glucémica posterior a la ingesta de alimentos. Esto es particularmente beneficioso para las personas con diabetes, sobrepeso u obesidad que buscan sustitutos del azúcar (10). En este sentido, en los Estados Unidos se ha observado un aumento en el uso de los ESA, de aproximadamente 200 % entre los niños y 54 % entre los adultos, en una posible respuesta a las campañas para hacer menor uso de azúcares libres como una alternativa para hacer frente a la elevada prevalencia de esta enfermedad (11).

DIGESTIÓN Y METABOLISMO DE ALGUNOS EDULCORANTES SIN AZÚCAR

Los ESA tienen una composición química diferencial y de esto depende su grado de digestión y absorción a nivel intestinal:

- El aspartamo se compone de un éster metílico de dipéptido que contiene dos aminoácidos: el ácido L-aspártico y L-fenilalanina. Tras su consumo, las peptidasas y esterasas gastrointestinales descomponen casi por completo el aspartamo, lo que da como resultado que cantidades insignificantes del compuesto entren en el torrente sanguíneo (12).
- El acesulfame K es derivado de un ácido orgánico hidrofílico que se absorbe casi en su totalidad a nivel del intestino delgado y se distribuye por la sangre a diferentes tejidos. Sin sufrir ningún metabolismo, más del 99 % del acesulfame K ingerido se excreta por vía urinaria en las primeras 24 horas y el restante en las heces.
- La sucralosa es un disacárido compuesto por 1,6-dicloro-1,6-didesoxifructosa y 4-cloro-4-desoxigalactosa, tiene un nivel de absorción muy bajo (menos del 15 %) y prácticamente no se metaboliza, siendo su eliminación por vía urinaria (13).
- Los glucósidos de esteviol, sólo 18 de las 150 a 300 especies del género Stevia exhiben propiedades edulcorantes, y los dos edulcorantes principales son el estevióside (~9,1 %) y el rebaudiósido A (~3,8 %). Estos no presentan afectación por la presencia de ácido gástrico y no es digerido por las enzimas intestinales, por tanto, no se absorbe a nivel de intestino delgado debido a su alto peso molecular. El estevióside puede ser degradado por la flora intestinal bacteriana, transformándolo en esteviol libre, un aglicón de los glicósidos de esteviol (14).
- El ciclamato es un edulcorante artificial cuya composición química es *N-ciclohexilsulfamato*, y se caracteriza por la presencia de un anión sulfamato unido a un anillo de ciclohexilo. Se absorbe en el intestino delgado y se excreta principalmente sin cambios en la orina, aunque una fracción puede ser metabolizada a ciclohexilamina por la microbiota intestinal, con una considerable variabilidad interindividual en esta capacidad metabólica (15).

LÍMITES EN SU CONSUMO

El consumo de los ESA debe estar en concordancia con los límites permitidos para su uso. La ingesta diaria admisible (IDA) es una estimación efectuada por el Comité Mixto FAO/OMS de Expertos en Aditivos Alimentarios (JECFA, por su sigla en inglés) de la cantidad de aditivo alimentario (en este caso ESA), expresada en relación con el peso corporal, que una persona puede ingerir diariamente durante toda la vida sin riesgo apreciable para su salud (8). Actualmente existen diferencias en la IDA de cada ESA según la región. A noviembre de 2024, en Estados Unidos, existen seis ESA aprobados para el consumo por parte de la Administración de Alimentos y Medicamentos (FDA, por su sigla en inglés) (16), mientras que en la Unión Europea, la gama de ESA aceptados por la Autoridad Europea de Seguridad Alimentaria (EFSA, por su sigla en inglés) y el Comité Científico de Alimentos (SCF, por su sigla en inglés) es más amplia e incluye el ciclamato (Tabla I).

Una de las preocupaciones es que, al sustituir el consumo de azúcar libre por ESA, se superen las IDA y pueda generar efectos no deseados para la salud. En 2018, Martyn et al. (17) publicaron una revisión exhaustiva que caracteriza las estimaciones de exposición a nivel mundial basado en el análisis de diferentes cohortes nacionales para siete ESA (acesulfame K, aspartamo, ciclamato, sacarina, glucósidos de esteviol, sucralosa y taumatina). Los hallazgos identificaron que los niveles de exposición se encuentran por debajo de los límites de la IDA definida para cada ESA (Tabla II).

Tabla I. Edulcorantes sin azúcar disponibles en los EE. UU. y la Unión Europea, y sus niveles de ingesta diaria admisible, según lo definen los organismos reguladores

ESA	Ingesta diaria admisible definida por la FDA (mg/kg)	Ingesta diaria admisible definida por el SCF/EFSA (mg/kg)
Acesulfame K	15	9
Aspartame	50	40
Ciclamato	No aprobado	7
Neohesperidina DC	No aprobado	5
Neotamo	0,3	2
Sacarina	15	9
Sucralosa	5	15
Glucósidos de esteviol	4	4
Taumatina	No aprobado	No especificado

ESA: edulcorante sin azúcar; FDA: U.S. Food and Drug Administration; SCF: Scientific Committee on Food; EFSA: European Food Safety Authority; mg: miligramos; kg: kilogramos. Basado en las referencias (39-41).

Tabla II. Consumo promedio del ADI por cada ESA según región

Región	Población estudiada	ESA	Consumo promedio (%) del ADI para cada ESA
Asia	Participantes de la Encuesta de nutrición y salud (China)	Ciclato	11,6 a 33,8
	Cohorte de supuestos grandes consumidores (India)	Acesulfame K Aspartame Sacarina Sucralosa	2,8 a 5,2 2,1 a 4,8 16,7 a 22,4 0,5 a 2,1
	Participantes de la Encuesta especial sobre la frecuencia y la ingesta de consumo de alimentos (2010) (Japón)	Esteviol Aspartamo Acesulfame K Sacarina Sucralosa	0,20 a 0,47 0,001 a 0,004 0,13 a 0,26 0,03 a 0,06 0,07 a 0,15
	Participantes de todas las edades (*n* = 34706) KNHANES (2010-2014) (Corea)	Acesulfame K Aspartamo Sacarina Sucralosa	1,7 0,9 3,6 2,2
Australia – Nueva Zelanda	Población general australiana y de Nueva Zelanda 2010-2011	Esteviol	10 a 55
	Población general australiana y de Nueva Zelanda 2015.	Acesulfame K	5 a 7
Europa	Estados miembros de la UE, EFSA, 2013	Aspartamo	1 a 40,8
	Estados miembros de la UE, EFSA, 2015	Esteviol	2,5 a 60
	Evaluación de los programas de alimentación y nutrición en niños pequeños, EFSA, 2016	Sucralosa	19,3 a 80,7
	Francia, Italia, Reino Unido, Irlanda. Población general	Acesulfame K Aspartamo	2 a 69 0 a 30
	Estados miembros de la UE, 2017	Esteviol	2,5 a 75
América Latina	Cohorte de niños y adolescentes que asisten a escuelas públicas y privadas (Argentina)	Acesulfame K Aspartamo Ciclato Sacarina	4,6 7 23,7 5,6
	Cohorte de niños escolarizados en la región de Valparaíso, 6 a 14 años (Chile)	Acesulfame K Aspartamo Ciclato Sacarina Sucralosa	11,3 11,8 4,5 0,4 18
	Cohorte de escolares de Viña del Mar y Santiago, 10 a 16 años (Chile)	Acesulfame K Aspartamo Ciclato Sacarina Sucralosa	0,1 a 0,7 3,5 a 14 0 a 2,3 0 a 42,8 7,8 a 17,5
	Cohorte de adultos que asisten a la universidad de cada país, de 18 a 26 años (Chile, Panamá, Guatemala y Perú)	Acesulfame K Aspartamo Sucralosa	3,1 a 7,7 2,9 a 4,5 2,4 a 9,2
	Cohorte de adultos que asisten a 4 universidades diferentes (Chile)	Esteviol	6 a 14
América del Norte	No se identificaron evaluaciones en América del Norte que presentaran estimaciones reales de exposición diaria a ESA	-	-

Adaptado de Martyn, 2014 (17). ESA: edulcorantes sin azúcar; ADI: acceptable daily intake; *EFSA: European Food Safety Authority; UE: Unión Europea.*

USO DE EDULCORANTES SIN AZÚCAR: GUÍA DE LA OMS

En 2023, la OMS publicó el informe titulado "Uso de edulcorantes sin azúcar", cuyo objetivo era proporcionar recomendaciones basadas en la evidencia sobre el consumo de ESA en adultos, mujeres gestantes y niños aparentemente sanos, incluyendo a personas con un índice de masa corporal (IMC) alto. Estas recomendaciones están dirigidas a tomadores de decisiones en distintos ámbitos de atención y a profesionales de la salud, entre otros (1). La guía se desarrolló mediante la búsqueda y selección sistemática de literatura científica, mientras que la certeza de la evidencia fue evaluada utilizando la metodología GRADE (*Grading of Recommendations, Assessment, Development, and Evaluations*) (18).

Después de la revisión y análisis de toda la evidencia científica, la guía de la OMS elaboró una única recomendación: "*La OMS propone que no se utilicen edulcorantes sin azúcar como medio para controlar el peso o reducir el riesgo de enfermedades no transmisibles (recomendación condicional)*". Esta recomendación está dirigida exclusivamente a la población para la cual se obtuvo la evidencia, es decir, niños, adultos y mujeres gestantes aparentemente sanos, así como personas con un IMC alto. Por esta razón, no es adecuado aplicar esta recomendación a otras poblaciones, especialmente aquellas que presentan enfermedades asociadas. Del mismo modo, se debe evitar formular conclusiones en forma de recomendaciones a partir de la información de la guía, ya que su construcción requiere la implementación de un análisis metodológico que evalúe el conjunto de la evidencia, su grado de certeza y otras implicaciones para la práctica.

El carácter condicional de la recomendación se debe a que la certeza global de la evidencia fue clasificada como baja, lo que redujo la confianza del grupo desarrollador de la guía para emitir una recomendación definitiva en la que los efectos indeseables superen a los deseables.

En cuanto a la evidencia científica, la guía incluyó el análisis de 50 ensayos clínicos controlados aleatorizados, 97 estudios de cohortes prospectivas y 47 estudios de casos y controles. En general, la evidencia de ensayos clínicos en adultos indicó una reducción en el peso (diferencia de medias -0,71 kg IC 95 % -1,13 a -0,28 kg), una disminución en la ingesta de energía (diferencia de medias -569 kj/d IC 95 % -859 a -278 kj/d) y una reducción en el consumo de azúcares libres (diferencia de medias -38,4 g/d IC 95 % -57,8 a -19,1 g/d) asociada al uso de ESA, aunque con una baja certeza de la evidencia.

Los hallazgos de los ensayos clínicos difieren de los resultados identificados por los estudios observacionales (casos y controles, y cohortes). La certeza de este tipo de estudios fue calificada de baja a muy baja. Los estudios observacionales detectaron asociaciones entre el uso de los ESA y el incremento del IMC (diferencia de medias +0,14 kg/m^2 IC 95 % 0,03 a 0,25 kg/m^2), aumento en la incidencia de obesidad (HR 1,76 IC 95 % 1,25 a 2,49), incremento en la incidencia de diabetes tipo 2 (HR - bebidas 1,23 IC 95 % 1,14 a 1,32; HR - disponibles en mesa 1,34 IC 95 % 1,21 a 1,48), elevación de la mortalidad por cualquier causa (HR 1,12 IC 95 % 1,05 a 1,19) y por causas cardiovasculares (HR 1,19 IC 95 % 1,07 a 1,32). Además, aumento en la incidencia de la enfermedad coronaria (HR 1,32 IC 95 % 1,17 a 1,50), el accidente cerebrovascular (HR 1,19 IC 95 % 1,09 a 1,29), la hipertensión (HR 1,13 IC 95 % 1,09 a 1,17) y el cáncer de vejiga (HR 1,31 IC 95 % 1,06 a 1,62).

Al contrario del volumen de evidencia identificada en adultos, la información sobre el uso de ESA en niños es muy limitada. Por ejemplo, las asociaciones a favor del uso de los ESA, derivan de un único ensayo clínico que mostró una reducción del perímetro abdominal (diferencia de medias -0,66 cm IC 95 % -1,23 a -0,09 cm), así como para la disminución de la masa grasa corporal (diferencia de medias -0,57 kg IC 95 % -1,02 a -0,12 kg), ambos con una certeza moderada de la evidencia. No se identificaron asociaciones entre el consumo de los ESA y la incidencia de sobrepeso, diabetes tipo 2, enfermedades cardiovasculares, cáncer cerebral y caries, así como alteraciones negativas con la neurocognición, ni aumento en la ingesta de energía y azúcares libres (1).

En el caso de las gestantes, la evidencia también fue escasa. El análisis conjunto de los estudios observacionales identificó una asociación entre un alto consumo de ESA y un mayor riesgo de parto pretérmino (OR 1,25 IC 95 % 1,07 a 1,46), con certeza de evidencia muy baja. Ante la ausencia de evidencia, no fue posible elaborar un metaanálisis para identificar un efecto consolidado de las asociaciones entre el uso de los ESA y la grasa corporal, el asma, las alergias y la neurocognición en hijos de mujeres que consumieron ESA durante la gestación. Sin embargo, una cohorte prospectiva (19) identificó una asociación en contra de los ESA y el riesgo de desarrollar asma a los 18 meses o a los 7 años (OR ajustado 1,14 IC 95 % 1,00 a 1,28 y OR ajustado 1,2 IC 95 % 1,07 a 1,35; respectivamente) con una certeza de evidencia muy baja. Los autores de este estudio reportan limitaciones en torno a la clasificación de consumo de los ESA, lo cual pudo modificar el efecto estimado. Por otro lado, en el desenlace de neurocognición, una cohorte prospectiva elaborada por Cohen y colaboradores (20) encontró cambios únicamente relacionados con la capacidad verbal de la escala KBIT-II para niños con una mediana de edad de 7,7 años (-3,2 IC 95 % -5,0 a -1,5), pero esta diferencia, a pesar de ser estadísticamente significativa, no se considera clínicamente importante debido a que el puntaje total de la escala es 100 puntos. Los resultados de este estudio fueron considerados con muy baja certeza.

Desde una perspectiva de salud pública, la guía de la OMS busca no solo proporcionar directrices sobre el uso de ESA, sino también motivar una reflexión más amplia sobre los patrones dietéticos y el consumo de productos alimenticios ultraprocesados. La OMS advierte que remplazar el azúcar libre con edulcorantes en productos alimenticios ultraprocesados no mejora sustancialmente la calidad de la alimentación. De igual manera, es muy importante mantener los esfuerzos para redu-

cir el consumo de productos alimenticios con azúcares libres dentro de una estrategia más amplia que promueva la ingesta de alimentos sin procesar y mínimamente procesados.

POSIBLES LIMITACIONES DE LA GUÍA DE LA OMS

La guía de la OMS representa un paso importante hacia una mejor comprensión del papel de los ESA en la alimentación humana, pero también señala que quedan muchas preguntas sin responder. En particular, la incertidumbre sobre los efectos a largo plazo de los ESA subraya la necesidad de más investigaciones rigurosas y de largo plazo que puedan ofrecer respuestas más concluyentes sobre su seguridad y efectividad.

Al revisar la guía de la OMS, un aspecto relevante es el tipo de estudios incluidos. Estos fueron ensayos clínicos, estudios de cohortes prospectivos y estudios de casos y controles. En cuanto a los ensayos clínicos, son los únicos estudios a los que se les puede atribuir un efecto de causalidad debido a su diseño experimental y prospectivo. Generalmente, estos estudios asignan aleatoriamente una intervención y un placebo a una población definida y, mediante un control riguroso de las variables, evalúan y analizan su efecto tras un periodo determinado de tiempo. Además, los ensayos clínicos se consideran el estándar más alto para decidir sobre la implementación de una intervención (por ejemplo, vacunas) debido a las fortalezas inherentes a su metodología.

Por otro lado, los estudios de cohortes prospectivos y los estudios de casos y controles tienen una naturaleza observacional, lo que significa que no se realiza ninguna intervención. En este caso, se evalúa la relación o asociación entre una exposición y la presencia de una condición o enfermedad, lo que implica que no se puede determinar causalidad. Por esta razón, identificar una asociación en un estudio observacional no equivale a establecer una causa entre la exposición y el evento. Además, estos tipos de estudios son más propensos a sesgos propios de su diseño, incluso cuando se controlan múltiples variables de confusión (21).

Un aspecto importante para considerar dentro del análisis de los estudios observacionales es la posibilidad de presentar causalidad inversa. Esta se puede explicar de siguiente manera: en la actualidad un individuo con alto riesgo de diabetes tipo 2 comienza a hacer uso de los ESA, pero al cabo de un tiempo desarrolla la enfermedad, por lo cual se desconoce si la causa de la enfermedad es debida específicamente al uso de los ESA, o a otras situaciones que actúan como factores de confusión como los antecedentes familiares de patologías crónicas, la carga genética o el patrón global de la alimentación. Para reducir el efecto de la causalidad inversa, se debe realizar el control de las variables de confusión, para lo cual existen diferentes alternativas durante el análisis de la información como la estratificación, la regresión multivariada, el uso de los puntajes de propensión y los análisis de sensibilidad. En esta línea, los autores de la guía de la OMS concluyeron que "la causalidad inversa y los factores de confusión residuales pueden contribuir a las asociaciones encontradas en los estudios observacionales entre el consumo de ESA y los resultados de salud, pero que no hay evidencias que permitan descartarlas por ser atribuibles exclusivamente a la causalidad inversa o a la confusión residual" (1). Por este motivo la certeza de la evidencia de los estudios observacionales tiende a ser menor que la que incorpora los ensayos clínicos, lo cual puede modificar los desenlaces evaluados.

En relación con lo anterior, los estudios observacionales en comparación con los ensayos clínicos pueden sobre o subestimar la dirección del efecto y su magnitud. Por esta razón una buena parte de los estudios observacionales concluyen que es necesario el diseño y ejecución de ensayos clínicos para confirmar los hallazgos identificados, cuando estos son éticamente posibles. En este sentido, los datos agrupados de los ensayos clínicos de la guía de la OMS tienen un efecto significativo en la disminución del peso corporal en adultos, por el contrario, el metaanálisis de los estudios observacionales no identifica un efecto significativo a favor o en contra. En el caso del IMC, el conjunto de los datos de los estudios observacionales concluye que existe un efecto sobre la ganancia de peso, mientras que los ensayos clínicos no lo hacen (22,23).

En cuanto a la certeza de la información o el grado de confianza en la magnitud del efecto, según la metodología GRADE, los ensayos clínicos inician con una certeza alta en su evaluación, mientras que los estudios de cohortes prospectivos tienen mayor riesgo de sesgo, lo que los sitúa en un nivel de baja certeza cuando se utiliza esta metodología. Cuando la evidencia proviene tanto de ensayos clínicos como de estudios de cohortes, se da mayor peso a los ensayos clínicos en términos de confiabilidad. Ante la ausencia de estudios clínicos para la mayoría de los desenlaces evaluados en la guía de la OMS, el grupo desarrollador utilizó la información derivada de estudios observacionales (24).

Otro de los aspectos relevantes de la guía, es la ausencia en la incorporación de metodologías de análisis secuenciales y modelamiento de sustitución de los azúcares libres por ESA en estudios de cohorte prospectivos. El uso de estas metodologías dentro de estudios de cohorte prospectivos de larga duración permitiría reducir el sesgo inherente en los estudios observacionales retrospectivos y de caso control, así como pueden proveer un mejor estimador del riesgo asociado. El uso de este tipo de análisis fue realizado por Khan y colaboradores (25) estima de manera agrupada los desenlaces cardiometabólicos y el uso de ESA, según el tipo de análisis de la cohorte (análisis prevalente, por cambio o por sustitución). En síntesis, se identifica que los estudios de cohorte prevalentes tienden a sobreestimar el efecto e identificar asociaciones adversas, mientras que las cohortes con análisis por cambio o sustitución reportan efectos favorables en el consumo de ESA sobre los desenlaces cardiometabólicos.

Adicional a todo lo anterior, durante 2023 y 2024 se ha publicado nueva evidencia basada en revisiones sistemáticas y metaanálisis que resultan contradictorios a los hallazgos pre-

sentados en la guía de la OMS. Un ejemplo de los resultados en contra de los ESA es el metaanálisis de Chen Z y colaboradores (26) quien identificó que un elevado consumo de ellos se asociaba con mortalidad por cualquier causa o específica, sin embargo, los propios autores indican que existen varias limitaciones en los hallazgos por lo cual las conclusiones deben ser interpretadas con cautela. No obstante, otros autores han encontrado asociaciones a favor para el cáncer colorrectal, pero negativas para la incidencia de leucemia (27) y la enfermedad cardiovascular (28). Mientras tanto, otros autores han identificado resultados a favor del uso de los ESA para la reducción del peso corporal en niños y adultos (29,30) y ningún riesgo de desarrollar cáncer de endometrio (31), de vejiga (32) o de seno (33).

Otro aspecto que aborda la guía es la diversidad de los efectos de los diferentes tipos de edulcorantes. Aunque todos los ESA se agrupan bajo una misma categoría, existen diferencias en la estructura química, el metabolismo y el impacto fisiológico de cada uno de ellos. Por ejemplo, edulcorantes como la sucralosa, el aspartame o la estevia entre otros, pueden tener efectos distintos sobre el metabolismo de la glucosa y la microbiota intestinal, tales como una reducción en las bacterias benéficas y aumento de bacterias patógenas, aumento del pH intestinal y efectos no conclusivos al respecto de la alteración en la producción de ácidos grasos de cadena corta y expresión de genes involucrados en el metabolismo microbiano (9). Conz et al. (10) reportan que la principal limitación de los estudios asociados al consumo de ESA y el impacto en la microbiota intestinal es la diferencia en el número de participantes, los hábitos dietéticos y los estilos de vida que influyen directamente en la composición inicial de la microbiota y su respuesta con los ESA. Por otro lado, la ingesta de ESA es sólo uno de los múltiples factores que pueden impactar la composición y variedad de la microbiota, por lo que se hace necesario formular investigaciones para dar respuesta a estas inquietudes. Esta heterogeneidad ha complicado la interpretación de los resultados de los estudios, y la OMS ha señalado que se necesita más investigación para comprender completamente cómo afectan estas sustancias a largo plazo.

EDULCORANTES Y ENFERMEDADES CRÓNICAS

Como se mencionó anteriormente, la población objetivo de la guía de la OMS incluye adultos, niños, mujeres gestantes aparentemente sanas y personas con un IMC alto. La recomendación principal de la guía es proporcionar directrices para la prevención del aumento de peso no saludable y reducir la incidencia de enfermedades no transmisibles relacionadas con la alimentación. Cabe destacar que la guía no tiene como objetivo ofrecer pautas para el manejo de la diabetes tipo 2 o la prediabetes (1). Además, la evidencia disponible sobre la relación entre los ESA y el manejo de otras condiciones clínicas, como la desnutrición, el cáncer, enfermedades infecciosas, pulmonares o renales, es escasa o inexistente. En una búsqueda sistemática de la literatura realizada durante la elaboración de este artículo (Anexo 1), solo se identificaron estudios en humanos que relacionan el consumo de ESA con la incidencia de recidivas de cáncer y mortalidad por esta enfermedad (34) así como efectos sobre marcadores bioquímicos y resultados en salud en pacientes con diabetes (35). Sin embargo, el estudio relacionado con cáncer es de tipo observacional, lo que introduce un alto riesgo de sesgo debido a la presencia de variables de confusión, como la medición de la ingesta de bebidas con adición de ESA a partir de una frecuencia de consumo de los tres últimos meses, por lo cual no es posible cuantificar la cantidad y tipo de ESA que se asoció con el desenlace. Por otro lado, la publicación sobre diabetes es una revisión sistemática de la colaboración Cochrane, que busca evaluar los efectos de los ESA sobre esta enfermedad, concluye que la evidencia disponible es inconclusa y de muy baja certeza (35).

A partir de lo anterior, es evidente la necesidad de realizar investigaciones sobre el efecto o las posibles asociaciones del uso de ESA en pacientes con comorbilidades ya existentes distintas al exceso de peso (9). Adicionalmente, los profesionales de la salud, especialmente nutricionistas dietistas, deben evaluar el uso seguro de los ESA sin exceder la IDA definida para cada tipo de edulcorante, en el contexto del tratamiento nutricional indicado para los pacientes.

OTRAS CONSIDERACIONES

MUJERES GESTANTES, MADRES LACTANTES Y NIÑOS

La gestación, la lactancia y los primeros 1000 días de vida son periodos críticos para un apropiado crecimiento y desarrollo de los niños, en donde el aspecto nutricional juega un papel de vital importancia. En cuanto al uso de los ESA en los niños menores de 2 años, el consenso de la Academia Americana de Pediatría (2019) (36) indica que no se aconseja su uso ante la ausencia de evidencia científica en este grupo de edad. Por otro lado, el consenso mexicano sobre el uso de ESA en la mujer en edad reproductiva (publicado en 2019) (37) concluyó que no hay suficiente evidencia para establecer una relación de causa-efecto para los partos prematuros, la incidencia de alergias, presencia de ESA en la leche materna y manejo del peso corporal durante la gestación. Se debe anotar que la evidencia evaluada por este consenso se consideró de baja y muy baja certeza. Sin embargo, evidencia de un metaanálisis reciente (2024) demuestra una relación entre el consumo de ESA en mujeres gestantes y el parto pretérmino, mientras que no encontró asociaciones con otros desenlaces (38). Aunque la evidencia sobre el uso de los ESA en estos grupos poblacionales es limitada o nula, la guía de la OMS subraya la necesidad de tener precaución en su uso en mujeres gestantes, madres lactantes y niños, sin embargo, esta guía no proporcionó ninguna recomendación específica sobre este tema.

EDUCACIÓN NUTRICIONAL

Los ESA siguen siendo una opción común en muchos productos alimenticios, especialmente en bebidas y alimentos procesados, que pueden contribuir a reducir la ingesta de azúcar libre a corto plazo, pero no son una solución definitiva para mejorar el perfil y calidad de la alimentación. Es así como la OMS recomienda que las políticas de salud pública se centren en promover patrones de alimentación basados en alimentos naturales, ricos en nutrientes y con fuentes de dulzor natural, como las frutas, en lugar de depender exclusivamente de los ESA para reducir el consumo de azúcares libres. Sin embargo, el acceso a una alimentación saludable varía considerablemente, especialmente en las comunidades más vulnerables y en países de América Latina, donde las políticas alimentarias y las condiciones socioeconómicas pueden limitar el acceso a una alimentación y nutrición adecuada. Esto subraya la necesidad de intervenciones integrales, entre ellas la educación alimentaria y nutricional a la población general y a los profesionales de la salud, que promuevan no solo cambios en el comportamiento individual, sino también políticas públicas que garanticen entornos alimentarios más saludables. La educación alimentaria y nutricional debe basarse en metodologías adaptadas a las diferentes poblaciones, con mensajes claros y comprensibles que le permitan tomar decisiones acertadas sobre los alimentos que adquieren y consumen.

En el caso del exceso de peso o la obesidad, la inclusión de los ESA no debe considerarse como una solución aislada al problema, pueden ser una alternativa complementaria, pero es necesario que se integre a un enfoque más amplio que considere la educación alimentaria, la actividad física y la modificación de hábitos no saludables. La educación juega un papel importante para fomentar la adopción de cambios significativos y duraderos en el comportamiento. Los ESA pueden ser aliados en el control del consumo de azúcar, pero su uso debe alinearse con un plan integral diseñado por profesionales de la salud, orientado a prevenir y manejar problemas metabólicos de manera sostenible.

CONCLUSIÓN

Los ESA son ingredientes que se utilizan ampliamente en la industria de alimentos con diferentes funciones tecnológicas. Estos son utilizados como una alternativa para sustituir el azúcar de mesa o los azúcares libres, con el fin de reducir al aporte energético. La guía de la OMS indica que no deben recomendarse como herramienta principal para el control del peso o la prevención de enfermedades crónicas, aunque existen datos que sugieren posibles beneficios en la reducción de peso y consumo de energía en adultos, también se han encontrado asociaciones potenciales entre el uso de ESA y ciertos riesgos de salud. Sin embargo, estas asociaciones han sido detectadas principalmente en estudios observacionales, limitados en su capacidad para establecer causalidad debido a la posibilidad de sesgos y factores de confusión.

A pesar de los numerosos estudios evaluados, incluyendo ensayos clínicos y estudios observacionales, la evidencia se considera de baja a muy baja certeza, especialmente para desenlaces clave como el riesgo de obesidad, diabetes tipo 2 y mortalidad, entre otros. Esta incertidumbre subraya la necesidad de realizar investigaciones adicionales, particularmente en poblaciones específicas como los niños y las mujeres gestantes, donde la evidencia es limitada. Los ESA requieren una comprensión más profunda sobre cómo interactúan a largo plazo con la salud humana. Además, los resultados contradictorios de estudios recientes refuerzan la necesidad de desarrollar métodos de análisis más robustos y específicos que permitan a los tomadores de decisiones y profesionales de la salud establecer directrices basadas en evidencia sólida y confiable.

ANEXO 1.

A continuación, se describe la estrategia de búsqueda utilizada para identificar publicaciones científicas en las que se identifique el uso de ESA en enfermedades crónicas ya presentes, y no en el riesgo de desarrollarlas.

Plataforma de búsqueda: PubMed

Fecha de búsqueda: octubre 30 de 2024

Estrategia de búsqueda:

	Términos de búsqueda
#1.	((sweet* AND (artificial[tiab] OR agent*[tiab]) OR Non-nutritive[tiab]) OR (sugar[tiab] AND substitute[ti]) OR "Sweetening Agents"[Mesh])
#2.	("Chronic Disease"[Mesh] OR "Diabetes Mellitus"[Mesh] OR "Neoplasms"[Mesh] OR "Pulmonary Disease, Chronic Obstructive" [Mesh] OR "Renal Insufficiency, Chronic" [Mesh] OR "Dementia" [Mesh])
#3.	#1 AND #2
#4.	review[pt] OR editorial[pt] OR "systematic review"[ti] OR protocol[ti] OR editorial[ti]
#5.	#3 NOT #4

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IMPORTANCIA DE LA FRECUENCIA CARDIACA DE RECUPERACIÓN TRAS EJERCICIO EN NIÑOS CON SOBREPESO Y/U OBESIDAD

Sr. Editor:

Leímos con interés el artículo titulado "Physical fitness, cardiometabolic risk and heart rate recovery in chilean children", cuyo objetivo fue establecer la asociación entre la condición física y el riesgo cardiometabólico con el tiempo de recuperación de la frecuencia cardiaca en escolares chilenos (1). La investigación analizó a 478 escolares de entre 6 a 9 años, que fueron medidos en su condición física global a través de la prueba de caminata de seis minutos, fuerza de agarre y salto hacia adelante sin impulso, siendo utilizado un monitor cardiaco para valorar la frecuencia cardiaca antes, durante y tras el ejercicio. En relación con la conclusión del trabajo, los investigadores indicaron lo siguiente: "Existe asociación entre la frecuencia cardiaca de recuperación y la condición física y sensibilidad insulínica en escolares con sobrepeso y/u obesidad, lo que refuerza la necesidad de la medición de esta variable en niños con sobrepeso y obesidad para una prevención temprana".

Basándonos en la población de estudio abordada en el trabajo científico citado previamente, es que nos gustaría aportar información relevante sobre algunas limitaciones que presenta la frecuencia cardiaca como única medida de recuperación.

Para comenzar debemos mencionar que, si bien la frecuencia cardiaca por sí sola es una métrica aceptada para el monitoreo de cargas de trabajo físico, hubiera sido interesante complementarla con medidas específicas de variabilidad del ritmo cardiaco. En este contexto, la utilización de la raíz cuadrada media de las diferencias sucesivas entre los latidos cardíacos normales (RMSSD) ha demostrado ser en la actualidad una de las métricas más utilizadas para la ponderación de cargas de trabajo físico (2,3), donde la evidencia ha planteado la no existencia de una asociación directa entre la RMSSD y los distintos componentes de la carga de trabajo externo (volumen, intensidad y densidad), mientras que por el contrario se ha observado una relación inversa con la carga de trabajo interna en poblaciones pediátricas y adultas con diverso nivel de entrenamiento (4,5).

En esta línea, la inclusión de métricas como la RMSSD de recuperación, también llamada "RMSSD-Slope", o la relación "RMSSD/RR" podría proporcionar una evaluación más completa y precisa del estado cardiovascular y metabólico tras el ejercicio, donde la comprensión de la dinámica del tono vagal es crucial para mejorar la prescripción, evaluación y adhesión de los niños chilenos con sobrepeso y/u obesidad a los programas de ejercicio, especialmente considerando que sus conductas sedentarias son cada vez más prevalentes (6-8).

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CARACTERÍSTICAS DE LOS DISEÑOS CRUZADOS

Sr. Editor:

He leído con mucho interés el artículo titulado "Evaluación sensorial de un suplemento nutricional oral específico para diabetes con aceite de oliva virgen extra en pacientes en riesgo nutricional y diabetes *mellitus* tipo 2: ensayo clínico doble ciego, aleatorizado, cruzado y multicéntrico (DIACARE)" (1) y considero relevante destacar algunas características del diseño empleado que podrían ser de interés para los lectores de su revista.

En los ensayos con diseño cruzado se administran dos o más tratamientos (p. ej., medicamentos) a los sujetos en diferentes períodos de tiempo, asignando la secuencia de tratamientos de forma aleatoria para cada participante (Fig. 1). En consecuencia, los participantes de cada grupo reciben dos intervenciones distintas y los efectos de estas intervenciones se miden en los mismos individuos (2). El hecho de que cada participante actúe como su propio control ofrece varias ventajas: en primer lugar, el efecto de las variables confundentes puede reducirse; además, al comparar entre grupos, no existe variabilidad intersujeto; y, finalmente, se requiere un tamaño muestral menor en comparación con un diseño paralelo (3). Sin embargo, este diseño también presenta algunas limitaciones. Es adecuado únicamente para patologías que se mantienen estables a lo largo del tiempo (por ejemplo, enfermedades crónicas). Además, existe un alto riesgo de que el efecto de una intervención previa influya en los resultados de la intervención posterior, lo que podría alterar los resultados. Por lo tanto, el efecto del tratamiento podría no deberse exclusivamente a la intervención en sí sino también a las interacciones entre el tratamiento y el orden o la secuencia temporal del estudio. Por esta razón es fundamental conocer la duración del "periodo de lavado", es decir, el tiempo necesario para que los efectos del primer tratamiento desaparezcan antes de iniciar el siguiente (2,4).

En conclusión, los ensayos con diseño cruzado presentan tanto ventajas como desventajas que se deben sopesar en función de la intervención y la condición a evaluar al elegir este diseño de investigación.

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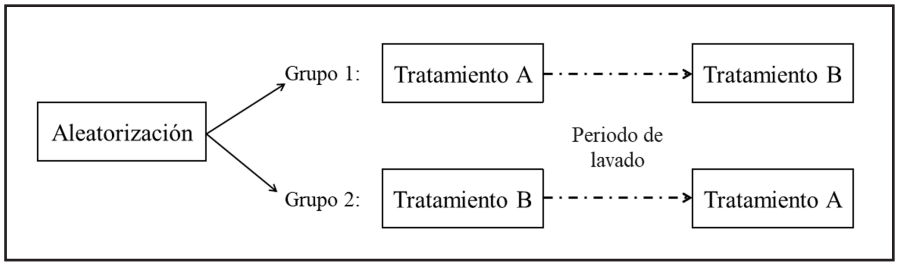

Figura 1.
Esquema de un ensayo de tipo cruzado.

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FOODS FORTIFIED WITH VITAMIN D. MITH OR REALITY?

Dear Editor,

Vitamin D is currently considered a pleiotropic hormone. In fact, in addition to its contribution to bone metabolism, vitamin D fulfils a broad spectrum of biological functions related to proliferation, differentiation and cell metabolism. Vitamin D deficiency has been involved in autoimmune diseases, infections, neuropsychiatric disorders, cardiovascular risk and several types of cancer (1-3).

Naturally, vitamin D is synthesized mainly from skin exposure to solar radiation, while a smaller amount comes from natural dietary sources. Very few foods naturally contain vitamin D and, furthermore, they are not exactly the most consumed ones. These include oily fish such as herring (27.0 µg/100 g), salmon (9.9 µg/100 g), sardines (7.9 µg/100 g), tuna (4.5 µg/100 g) and mackerel (4.0 µg/100 g), sun-dried mushrooms (3.9 µg/100 g) and, especially, cod liver oil (210 µg/100 g) (4).

The Institute of Medicine suggest that infants aged 0-1 yrs require at least 10 µg/d (400 IU) of vitamin D, and children aged 1 yr and older (1-18 yrs) require at least 15 µg/d (600 IU) to maximize bone health. It also suggests that all adults aged 19-70 and > 70 years require at least 15 µg (600 IU) and 20 µg/d (800 IU), respectively, of vitamin D to maximize bone health and muscle function. To date, vitamin D guidelines have generally been based on the beneficial effects of vitamin D on musculoskeletal health and, to a lesser extent, on non-skeletal health (6,7).

At present, vitamin D deficiency is a global health problem that affects all ages and races (3,6). This eventuality is probably related to the changes that have occurred in human lifestyle habits in recent decades (little outdoor activity, always wearing clothes and frequently using sunscreen). Systematic vitamin D food fortification is an effective and safe alternative to improve vitamin D status in the general population (7).

Vitamin D fortification policies among European countries are quite heterogeneous. The vast majority of European countries, including Spain, do not appear to have established policies to adequately fortify a relevant range of foods with vitamin D. The systematic (mandatory) vitamin D food fortification in the US, Canada and Finland may provide important guidance for health authorities in other regions (Table I) (8). In particular, the example of Finland (mass fortification of milk, margarine/fat spread; fortification of selected brands for yogurt, orange juice, plant-based milk such as soy, oat or almond milk, bread, cereals) has considerably improved vitamin D status in the general Finnish population. This experience could serve as a benchmark for future vitamin D food fortification policies in other countries (10).

Foods fortified with vitamin D are an affordable and easily implemented solution to a global public health problem. There is a long and successful experience in those countries that have already implemented systematic vitamin D food fortification. It would be advisable for health authorities to design mass mandatory vit. D fortification strategies of at least one basic food product, preferably fluid milk, and make them widely available.

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Table I. Vitamin D food fortification in the United States, Canada and Finland (adapted from [8])

Food (serving)*	United Sates	Canada	Finland
Mass fortification (usually mandatory)			
Fluid cow's milk (250 ml or 1 cup)	2.5-5.0†	2.5-5.0	2.5
Margarine/Fat spread (10 g)	-	1.5-3.0	2.0
Fortification of selected foods			
Yogurt	1.5-5.0 per 170 g	1.0 per 100 g	0.5-1.0 per 100 g
Cheese slice (16 g)	1.5	-	-
Orange juice (125 ml or 1/2 cup)	1.25	1.25	1.25
Plant-based milk (250 ml or 1 cup)	1.5-3.0	1.5-3.0	1.9-3.75
Margarine 10 g	0.75-5.0	-	-
Bread (100 g)	2,25	-	1.7
Cereals, ready-to-eat (1/2-3/4 cup)	1-2.5	1.0	3.0 per 100 g

**Vitamin D per serving in µg (1 µg = 40 IU). †FDA in 2016 permitted voluntary "doubling" of mandatory vitamin D in milk.*

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REPRODUCIBILITY AND TRANSPARENCY IN SYSTEMATIC REVIEWS

Dear Editor,

I recently came across the article titled "Treating asthma patients with probiotics: a systematic review and meta-analysis" by Xie, Yuan and Wang (1). The study provides a thorough evaluation of the role of probiotics in the treatment of asthma. I commend the authors for their comprehensive analysis, which offers valuable insights into a topic of increasing importance in the field.

However, I noticed that the authors did not provide the details of their search strategy in the main text or supplementary material. A systematic review's literature search is a crucial component, as it forms the foundation for the entire analysis. The search strategy is not only key to identifying eligible studies, but it also plays a critical role in minimizing bias and ensuring the robustness and reproducibility of the review. Without access to the search strategy, the transparency and reproducibility of this study are significantly compromised. In conclusion, the authors' work represents a significant contribution to the literature on asthma management. However, I encourage them to provide the full search strategy to maintain the integrity of their systematic review (2,3).

Lastly, I recommend that future authors submitting to *Nutrición Hospitalaria* consult the PRISMA-Search (PRISMA-S) Extension (2), which offers detailed guidance on reporting search strategies for systematic reviews. Adopting such guidelines will further enhance the transparency and reproducibility of systematic reviews in the journal.

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LA INTERSECCIONALIDAD COMO HERRAMIENTA EN EL ÁMBITO DE LA NUTRICIÓN

Sr. Editor:

Hemos leído la publicación de Vinueza-Veloz (1) donde se analizó el estado nutricional de adultos ecuatorianos considerando aspectos tales como la etnia, la edad y la pobreza. Este trabajo nos hizo reflexionar sobre la relevancia de la interseccionalidad en el campo de la nutrición como herramienta que permite comprender de manera más sistémica cómo se manifiestan las experiencias individuales de discriminación en la nutrición humana. Cada vez más, la interseccionalidad se usa como herramienta teórica para investigar cómo se cruzan las características sociales, evidenciando que las desigualdades en la salud no son meramente cuestiones individuales, sino que reflejan injusticias sociales más amplias (2). Al replantear la desigualdad en la salud en términos de relaciones de poder, podemos observar cómo ciertos grupos disfrutan de privilegios de salud a expensas de otros. El comprender la interseccionalidad permite a los profesionales de la salud reconocer y abordar las realidades complejas de sus pacientes, lo que en última instancia conduce a estrategias de atención nutricional más efectivas e inclusivas (3). Para ilustrar la aplicación de la interseccionalidad en las prácticas nutricionales podemos examinar estudios de casos específicos que revelan cómo factores como la identidad racial y la percepción de la suficiencia de ingresos pueden dar forma a la calidad de la dieta. Un estudio que investigó la relación entre estas variables utilizó el Índice de Alimentación Saludable (HEI) para definir la calidad de la dieta y descubrió que tanto la identidad racial como los niveles de ingresos influyen de forma independiente y conjunta en las elecciones dietéticas (4). Otro ejemplo es el estudio de Ortiz y cols. (5), que utilizó el enfoque interseccional para mostrar cómo los determinantes sociales de la salud interactúan entre sí, afectando a las elecciones alimentarias y al acceso a los servicios nutricionales. Estos trabajos sugieren que las políticas que solo abordan una dimensión de la desigualdad, como la pobreza, son insuficientes para enfrentar los problemas de salud de manera efectiva (6). En consecuencia, es imperativo que las prácticas nutricionales dentro de los hospitales tengan en cuenta las experiencias interseccionales de los pacientes para garantizar que las recomendaciones dietéticas sean culturalmente sensibles y equitativas (7). Un obstáculo importante para cumplir esta premisa es la falta de accesibilidad a conjuntos de datos diversos y a gran escala que puedan reflejar con precisión las experiencias interseccionales de las diferentes poblaciones. Además, las crisis políticas, económicas, ambientales y de salud contemporáneas han creado nuevos desafíos de políticas tanto a nivel nacional como internacional, lo que complica los esfuerzos para integrar la interseccionalidad en los marcos nutricionales (8). Para superar estas barreras es esencial fomentar la colaboración entre los investigadores y los profesionales de salud, así como los políticos, para desarrollar métodos sólidos de recopilación de datos que capturen las identidades interseccionales con precisión.

Al examinar las experiencias únicas de las personas a través de la lente de las identidades sociales interrelacionadas, los equipos de salud pueden desarrollar intervenciones nutricionales que den cuenta de la realidad social y cultural de nuestras comunidades.

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Inteligencia artificial: los autores declaran no haber usado inteligencia artificial (IA) ni ninguna herramienta que use IA para la redacción del artículo.

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¿CÓMO ELEGIR EL DISEÑO DE INVESTIGACIÓN?

Sr. Editor:

Con el objetivo de orientar a los lectores de su prestigiosa revista en el proceso de elaboración de proyectos de investigación, me gustaría abordar una pregunta recurrente: ¿Qué diseño de investigación (DI) es el más adecuado para emplear?

Para responder a esta interrogante, es útil recordar las palabras del matemático J. Tukey: "Es mucho mejor una respuesta aproximada a una pregunta correcta, que es a menudo vaga, que una respuesta exacta a una pregunta equivocada, que puede formularse de manera precisa" (1). Así, la elección del DI debe estar guiada principalmente por la pregunta de investigación (PI). Esta puede categorizarse en distintos tipos (2): a) terapia, seleccionar tratamientos efectivos; b) precisión diagnóstica, escoger pruebas diagnósticas con precisión y seguridad aceptables; c) pronóstico, estimar el curso clínico probable y anticipar complicaciones; d) incidencia, determinar cuántas personas se diagnostican de nuevo en un año; e) prevalencia, identificar la proporción de personas que viven con una afección; f) etiología, determinar la causa de un problema; g) prevención**,** explorar cómo se puede prevenir una afección; h) cribado, evaluar si la detección temprana de una afección influye en la salud. Para cada tipo de pregunta existen DI ideales para responderla (Tabla I), los cuales se deben sopesar en función de la jerarquía de la evidencia (3). Por ejemplo, si planteamos la siguiente pregunta: ¿Cuál es la efectividad de las intervenciones nutricionales en las personas con enfermedad de Crohn? El DI ideal sería un ensayo clínico aleatorizado (ECA). Sin embargo, no siempre es factible utilizar este diseño.

Los ECA se consideran el estándar de referencia para investigar las relaciones causales en la investigación clínica (4), aunque no siempre es ético aplicarlos. Por ejemplo, si deseamos investigar la relación entre el consumo de tabaco y el cáncer oral, no sería ético pedir a las personas que comiencen a fumar para observar el resultado, dado el amplio conocimiento de los efectos perjudiciales del tabaco. En este caso, un diseño de cohortes sería más adecuado y factible para explorar la relación entre el consumo de tabaco y el cáncer oral.

En conclusión, seleccionar un diseño de investigación adecuado requiere comprender que cada PI tiene un enfoque metodológico idóneo. Esto permite no solo responder con precisión sino también mantener la ética y la factibilidad del estudio. Además, en este manuscrito se han descrito los principales diseños utilizados en la investigación clínica y los tipos de preguntas de investigación más comunes. Sugiero revisar el libro "*Designing clinical research*" de Hulley y cols. (6) a los lectores que deseen profundizar en esta interesante e importante temática para el desarrollo de proyectos de investigación clínica.

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Conflictos de intereses: el autor declara no tener conflictos de interés.

Uso de inteligencia artificial: el autor declara no haber utilizado herramientas de inteligencia artificial para la redacción y/o en el proceso de elaboración del artículo.

Tabla I. Diseño de investigación según el tipo de pregunta (5,6)

Tipo de pregunta	Diseño de investigación
Terapia	EC
Prevalencia	Corte transversal
Incidencia	Cohortes, corte transversal
Pronóstico	Cohortes
Cribado	EC
Precisión diagnostica	Cohortes, corte transversal
Etiología	Cohortes, casos y controles

EC: ensayo clínico.

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FRECUENCIA CARDIACA EN PROGRAMAS COMUNITARIOS: ¿ES SUFICIENTE COMO INDICADOR DE CONDICIÓN FÍSICA?

Sr. Editor:

He leído con interés el artículo titulado "Evaluación de un programa dirigido por trabajadores comunitarios para promover la salud cardiometabólica en adultos de un municipio mexicano de alta marginación", publicado en Nutrición Hospitalaria (1). Este estudio evaluó una población de 429 adultos residentes en el municipio de Chimalhuacán, México, asignados a dos grupos de diferente tamaño (n = 246 en el grupo de intervención y n = 183 en el grupo de control), con el objetivo de analizar el impacto de un programa grupal de orientación alimentaria en el consumo de alimentos, la actividad física y el riesgo cardiometabólico (1).

En relación con los principales hallazgos, los autores reportan un aumento de la frecuencia cardiaca (FC) en reposo en ambos grupos, atribuible al envejecimiento. Sin embargo, se destaca que este aumento fue menor en el grupo de intervención, relacionándolo con una "menor pérdida de la condición física" (1). Basándonos en la población abordada y los resultados presentados, consideramos oportuno aportar algunas observaciones críticas respecto a las limitaciones que conlleva el uso exclusivo de la FC como indicador de recuperación y condición física.

Aunque las conclusiones del estudio son congruentes con la hipótesis planteada, estimamos que se requieren más elementos para establecer una relación causal directa entre la intervención y la mejora de la condición física. Sería particularmente relevante incluir mediciones directas que permitan evaluar parámetros como la capacidad aeróbica o la variabilidad de la frecuencia cardiaca (VFC), los cuales ofrecen un marco más sólido para interpretar los cambios observados en la FC. La literatura sugiere que la FC en reposo, aunque útil, puede estar influenciada por múltiples factores ajenos a la intervención, tales como el estrés, la calidad del sueño o las condiciones ambientales durante la medición. Sin controles estrictos sobre estas variables, resulta difícil interpretar de manera inequívoca los cambios observados en la FC como indicadores de mejoras en la condición física (2,3). Además, es importante señalar que un aumento de la actividad física no necesariamente conlleva una reducción inmediata de la FC en reposo, dado que los efectos adaptativos cardiorrespiratorios suelen requerir más tiempo, así como mayores intensidades y volúmenes de ejercicio (4).

Por lo tanto, sugerimos que los futuros estudios consideren la inclusión de mediciones objetivas, como el análisis de la VFC, para obtener una visión integral de los efectos de una intervención sobre la salud cardiometabólica. Este enfoque permitiría una evaluación más precisa de las respuestas fisiológicas y contribuiría a validar la efectividad de los programas implementados (5). La VFC, al reflejar el equilibrio entre las influencias simpáticas y parasimpáticas, ofrece una herramienta complementaria que podría mejorar la interpretación de los cambios observados en la FC y su relación con la condición física. Esta medición ha

Conflictos de intereses: los autores no declaran ninguno.

Declaración de uso de inteligencia artificial: los autores declaran que se utilizó ChatGPT para la corrección y edición del manuscrito.

Tabla I. Descripción de las principales métricas de variabilidad de la frecuencia cardíaca

Métricas	Descripción
SDNN	Variabilidad total autonómica
RMSSD	Actividad parasimpática
NN50	Variabilidad parasimpática rápida
pNN50	Actividad parasimpática
HF	Actividad parasimpática
LF	Balance simpático y parasimpático
LF/HF	Balance simpático y parasimpático
VLF	Influencias simpáticas
ULF	Regulación a largo plazo
ApEn	Complejidad de la señal
SampEn	Regularidad de la señal
DFA $\alpha 1$	Control parasimpático a corto plazo
DFA $\alpha 2$	Control parasimpático a largo plazo
SD1	Variabilidad parasimpática
SD2	Variabilidad simpática parasimpática
SD1/SD2	Balance simpático y parasimpático

Fuente: Shaffer et al. (5).

mostrado ser valiosa en la evaluación de la respuesta fisiológica a las intervenciones, especialmente en los contextos donde los factores de estrés podrían influir en los resultados.

A continuación presentamos un resumen de las principales métricas de la VFC y su aplicabilidad clínica para una evaluación más precisa del comportamiento cardiaco.

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PRECISIONES LEGISLATIVAS SOBRE EL ARTÍCULO "POSICIONAMIENTO 2024 DE LAS GUÍAS DIETÉTICAS SEEDO"

Sr. Editor:

En el número extraordinario, publicado recientemente en *Nutrición Hospitalaria* (1) con el objetivo de actualizar el Consenso FESNAD-SEEDO 2011 Recomendaciones nutriciones basadas en la evidencia para la prevención y el tratamiento del sobrepeso y la obesidad en adultos (2), se menciona en la página 9 la legislación de los sustitutivos de comidas y de los sustitutivos de la dieta completa para el control de peso que estaba en vigor en el año 2011, sin tener en cuenta los reglamentos posteriores de la Unión Europea (UE) que la modificaron considerablemente.

Hasta 2016-2017 los *sustitutivos de comidas para el control de peso de 200-400 kcal/comida*, así como los *sustitutivos de la dieta completa para el control de peso de 800-1200 kcal/día*, estaban regidos por la Directiva 96/8/CE, que se incorporó al ordenamiento jurídico español en el Real Decreto 1430/1997. Los *sustitutivos de la dieta completa con un aporte energético inferior a 800 kcal/día* no estaban regulados en la UE, aunque sí se permitía su comercialización bajo ciertos criterios. Véanse las páginas 47-53 de dicho Consenso.

El Reglamento (UE) 2016/1413 de la Comisión, de 24 de agosto de 2016, modificó el Reglamento (UE) 432/2012, que establece una lista de declaraciones autorizadas de propiedades saludables de los alimentos, y las condiciones que en él se habían fijado para las dos declaraciones de propiedades saludables permitidas en los *sustitutivos de una o dos comidas principales para el control de peso, reduciendo el intervalo energético a 200-250 kcal por comida* y fijando un mínimo por comida del 30 % del valor de referencia de nutrientes del Anexo XIII del Reglamento (UE) 1169/2011 para la mayoría de minerales y vitaminas, a excepción del sodio y el potasio para los que se fija un mínimo de 172,5 mg y 500 mg por comida, respectivamente. Para la vitamina K, el cloro, el flúor, el cromo y el molibdeno no se establecen mínimos. La Directiva 98/6/CE y, por ende, el Real Decreto 1430/1997, fue derogada por el Reglamento (UE) 609/2013 del Parlamento Europeo y del Consejo, de 12 de junio de 2013, quedando los *sustitutivos de comidas para el control de peso* fuera del ámbito de aplicación de este último.

Tal como indicaba en un artículo publicado en *Nutrición Hospitalaria* en 2020 (3), el Reglamento (UE) 609/2013 incluyó dentro de su ámbito de aplicación los *sustitutivos de la dieta completa para el control de peso*. Por ello la Comisión Europea solicitó a la EFSA un dictamen sobre su composición e información. En 2015 la EFSA emitió el correspondiente dictamen (4) que sirvió de base para la redacción del Reglamento Delegado (UE) 2017/1798 de la Comisión, de 2 de junio de 2017, que complementa el Reglamento (UE) 609/2013 en lo que respecta a los requisitos específicos aplicables a estos productos.

El Reglamento (UE) 2017/1798 es un fiel reflejo de los criterios fijados por la EFSA para los sustitutivos de la dieta completa

Conflicto de intereses: el autor declara no tener conflicto de interés.

Inteligencia artificial: el autor declara no haber usado inteligencia artificial (IA) ni ninguna herramienta que use IA para la redacción del artículo.

para el control de peso (5), con la excepción de la colina, para la cual la EFSA propuso un mínimo diario de 550 mg, basándose en la Ingesta Adecuada (AI) del Institute of Medicine de los EUA en 1998 para los hombres adultos. La Comisión hizo caso del requerimiento de la industria europea de estos productos y rebajó el *mínimo de colina a 400 mg/día*, que es la AI que estableció la EFSA en 2016 para los adultos (6).

De los *requisitos de composición del Reglamento (UE) 2017/1798* destacamos los siguientes para la ingesta diaria:

- *Energía entre 600 kcal y 1200 kcal*, pudiéndose denominar *dieta muy hipocalórica* (VLCD) las inferiores a 800 kcal y *dieta hipocalórica* (LCD) a partir de ese nivel.
- *Proteínas entre 75 g y 105 g*, cuyo índice de aminoácidos según el patrón OMS de 2007 (7), corregido por la digestibilidad de las proteínas, es de 1.
- Ácido*s linoleico y α-linolénico, mínimos 11 g y 1,4 g,* respectivamente, cuyos altos niveles dificultan su estabilidad en el tiempo.
- *Vitaminas y minerales*, con mínimos próximos a los Valores de Referencia de la Dieta (DRV) fijados por la EFSA, excepto para sodio (575 mg), cloruro (830 mg) y magnesio (150 mg) con mínimos mucho más bajos que sus DRV. Para el cromo y el flúor no se fijan mínimos.
- *Máximo de 250 mg diarios para el magnesio*, nivel máximo de ingesta tolerable para sales fácilmente disociables (8), inferior a las AI de la EFSA para adultos (9). Para los demás micronutrientes no se establecen máximos.
- *No se fija un mínimo para la fibra* pero si su cantidad alcanza al menos 10 g se permite la declaración nutricional "con fibra añadida" y si no se añade fibra debe consultarse a un profesional de la salud sobre la posibilidad de añadirla. Se prohíbe cualquier otra declaración nutricional o de propiedades saludables.

Este Reglamento establece algunos *requisitos de información alimentaria al consumidor*, entre los cuales cabe mencionar:

- Que el producto está *destinado exclusivamente a los adultos sanos obesos o con sobrepeso* que deseen bajar de peso;
- Que el producto *no debe ser consumido por* mujeres embarazadas o en período de lactancia, adolescentes o individuos que padezcan alguna dolencia sin consultar a un profesional de la salud;
- Que el producto *no debe ser utilizado durante* más de ocho semanas o repetidamente durante períodos más cortos sin consultar a un profesional de la salud.

La asociación Total Diet & Meal Replacements Europe solicitó a la Comisión europea la revisión a la baja los mínimos diarios de los ácidos linoleico y α-linolénico, así como al alza el máximo de magnesio, aportando seis publicaciones científicas, dado que la cantidad de ambos ácidos grasos que se libera del tejido adiposo durante la pérdida de peso al consumir estos preparados es suficiente para cubrir la AI de ácido linoleico y disminuir en un 40 % la de ácido α-linolénico, y que 350 mg de magnesio diarios no son motivo de preocupación por la posible inducción de diarrea. El 10 de marzo de 2020 la Comisión solicitó a la EFSA su revisión. En 2021 la EFSA emitió un nuevo dictamen (10), en el cual propuso *eliminar el mínimo de ácido linoleico, reducir a 0,8 g el de ácido α-linoleico y aumentar a 350 mg el máximo de magnesio*, que iguala la AI de los hombres adultos.

Finalmente, en 2022 se publicó el Reglamento Delegado (UE) 2022/2182 de la Comisión, de 30 de agosto de 2022, que se modifica el Reglamento (UE) 2017/1798 y recoge las modificaciones propuestas de ambos ácidos grasos y de magnesio.

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