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Nutrición Hospitalaria

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"Salud digital": tele-ejercicio en obesidad, ¿qué nos puede aportar?

"Digital health": tele-exercise in obesity, what can we expect?

Aunque la enfermedad por el SARS-CoV-2, COVID-19, se haya adjudicado el nombre propio de la "pandemia", los lectores de este editorial estarán de acuerdo en que la verdadera pandemia que asola nuestras consultas es la obesidad. Su abordaje debe ser multifactorial porque múltiples son sus causas y consecuencias (1). Dentro de este enfoque, el ejercicio físico es clave para conseguir el éxito y la no reganancia del peso perdido a largo plazo.

Gracias a unos mayores conocimientos y conciencia de los beneficios de la práctica deportiva, hemos pasado del "camine usted a diario" a recomendar ejercicio físico estructurado en obesidad, no solo aeróbico sino también ejercicio de fuerza. Además, dos conceptos han emergido con fuerza en los últimos años. De un lado, la importancia de evitar el sedentarismo (2), al mismo nivel que el entrenar de forma regular. Por otro lado, el papel del gasto calórico de la actividad física, no asociado al ejercicio (NEAT, "non-excercise activity thermogenesis") (3), ligado a la actividad diaria previamente no estructurada, como subir escaleras en vez de usar ascensor o caminar mientras se habla por teléfono, entre otros ejemplos.

Y como "nunca hay que desperdiciar una buena crisis", el contexto actual ha propiciado el desarrollo de la comunicación digital y herramientas adaptadas a este nuevo entorno. El ejercicio físico no ha sido una excepción. En este número se presentan dos estrategias digitales aplicadas al ejercicio físico en personas con sobrepeso y obesidad.

Primo y cols. (4), en este número de la revista *Nutrición Hospitalaria,* han analizado el efecto de un programa físico estructurado en 35 personas con obesidad, en vida real, a través de una plataforma "on line". Tras 12 semanas, los participantes redujeron de forma significativa su peso, índice de masa corporal, perímetro de cintura, niveles de insulina y prevalencia de síndrome metabólico mientras que aumentaron su calidad de vida, capacidad de ejercicio y masa muscular total. En el trabajo de da Silva y cols. (5), también publicado en este número, se aleatorizaron 44 mujeres con sobrepeso y obesidad a recibir una intervención en tele-ejercicio a través de vídeos frente a una intervención en tele-ejercicio sumada a *coaching* nutricional semanal. Tras 8 semanas, en ambos grupos mejoraron la fuerza muscular isométrica y la resistencia muscular dinámica, sin embargo no mejoraron otros parámetros antropométricos, de *fitness* ni calidad de vida.

Las herramientas digitales aplicadas al ejercicio físico son versátiles, como demuestran ambos trabajos. En un caso (5) se trata de vídeos a través de YouTube® en un entorno privado y, en el segundo trabajo (4), en una plataforma desarrollada a tal fin, www.vibraup.com. Permiten trabajar con diferentes dispositivos, como ordenador, tableta o móvil y son fáciles de manejar.

Ambos estudios difieren en cuanto a diseño, duración y criterios de inclusión. Sin embargo, hay 5 aspectos clave que pueden influir en los mejores resultados globales obtenidos por Primo y cols. (4). En primer lugar, el diseño de los entrenamientos y su estructura en 3 fases de progresión en volumen y tiempo está perfectamente definida. En segundo lugar, se insiste en el concepto de NEAT y como apoyo, se aconseja monitorizarlo en una *app.* En tercer lugar, si bien no se acompañó de *coaching* nutricional, previamente a la intervención se dieron unas recomendaciones concretas sobre dieta y contenido en macronutrientes, mientras que en el *coaching* se trataron aspectos nutricionales generales. En cuarto lugar, la plataforma utilizada, con comunicación bidireccional en vez de vídeos, una alternativa con menor posibilidad de interacción. Finalmente, se trata de un trabajo en vida real, integrado en la atención habitual a la persona con obesidad, lo que aporta más valor desde el punto de vida clínico. Sin embargo, necesitamos datos a largo plazo y con un mayor número de participantes, para ambas intervenciones.

editorial

Entre las quejas más frecuentes para no hacer ejercicio físico están la falta de tiempo, no disponer de centros deportivos cercanos o las limitaciones impuestas por la pandemia COVID-19. Ambas herramientas, permiten la autogestión en el tiempo, evitando desplazamientos y salvando distancias. Otro punto clave del uso de herramientas digitales, como son los "llevables" (en inglés, *wearables),* que son un apoyo en la monitorización de la actividad física, que permiten el seguimiento de los progresos y analizar el grado de consecución de los objetivos (6). Pero también este seguimiento de resultados se relaciona con una mayor motivación, superación personal y adherencia a la actividad física (7).

¿Todos nuestros pacientes van a beneficiarse de estas intervenciones digitales? Claramente, la respuesta es no. Personas con acceso limitado a recursos tecnológicos, carecer de habilidades mínimas digitales o falta de motivación, son perfiles no aconsejables. Asimismo, tampoco son buenos candidatos a este abordaje personas con lesiones osteomusculares u otras limitaciones por motivos de salud, que precisen una supervisión directa y continuada en cuanto al ejercicio físico o pacientes con trastorno de la conducta alimentaria que necesiten una intervención más cuidadosa.

Pacientes motivados, con problemas de accesibilidad a centros deportivos, con medios tecnológicos disponibles y competenciales digitales, sí que son buenos candidatos para participar en este tipo de programas. Además, aunar juego y aprendizaje digital, la *"gamificación"* (8), nos permite colar nuestro mensaje de salud en personas menos motivadas y seguir atrayendo a los que ya estén convencidos.

No podemos obviar el papel de la práctica deportiva en la socialización. Este tipo de herramientas pueden parecer *a priori* que reduzcan la interacción social, sin embargo, bien diseñadas en torno a una comunidad virtual, que favorezca la comunicación entre iguales y la sana competencia entre participantes, es un aspecto para explorar. También pueden salvar el miedo que tienen algunos pacientes a acudir a un centro deportivo, por temor al qué dirán sobre su cuerpo. Los profesionales que trabajamos en la atención a personas con obesidad tenemos la necesidad y obligación de formarnos en ejercicio físico y reclamar la integración de profesionales del deporte en nuestros equipos. Todos somos conscientes de lo importante que es hacer ejercicio físico pero, a nivel metabólico, para poder mejorar el estado de salud y obtener otros beneficios como el éxito en el abordaje de la obesidad, necesitamos mantener nuestro nivel de actividad física en el tiempo (9). Si las herramientas digitales en prescripción de ejercicio en obesidad pueden responder a esta necesidad, es una pregunta abierta, a la que esperamos responder lo antes posible.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Paciente crítico

Folic acid and vitamin B_{12} as biomarkers of morbidity and mortality in patients with septic shock

El ácido fólico y la vitamina B_{12} como biomarcadores de morbilidad y mortalidad en pacientes con shock séptico

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Abstract

Introduction and objective: a study was made of the folic acid (Fol) and vitamin B_{12} (B_{12}) serum concentrations in critical patients with septic shock upon admission and after three days of stay in the Intensive Care Unit (ICU), with an analysis of their association to inflammatory parameters and patient morbidity-mortality.

Methods: a prospective analytical study was made of 30 critically ill patients with septic shock. Demographic data, comorbidities, clinical information and severity scores were recorded. Data collected included serum Fol and B_{12} levels using the Dxl® Autoanalyzer (Beckman Coulter) based on a competitive electrochemoluminescence immunoassay.

Results: mean serum Fol was within the reference range stipulated by the laboratory on the first day. Nevertheless, a total of 21.4 % of the patients had high Fol levels, with 14.2 % being Fol deficient. An association was observed between Fol ($p < 0.012$) status and 28-day mortality, and the number of days of mechanical ventilation, fraction of inspired oxygen (FiO_2) and fibrinogen increased in patients with higher Fol levels ($p < 0.05$). In addition, 85.7 % of cases had B_{12} levels above the reference values, with a correlation being observed between B_{12} and Fol.

Conclusions: this study proposes Fol as a novel morbidity-mortality biomarker in critical septic patients, and reinforces the usefulness of B_{12} as a morbidity biomarker. It is thus suggested that the measurement of Fol upon admission and over the first 72 hours of hospital stay could provide prognostic information about the clinical course and outcome of septic shock patients.

Keywords:

Septic shock. Folic acid. Vitamin B_{12}. Morbidity. Mortality.

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Conflicts of interest: all authors declare that they have no conflicts of interest in relation to this work.

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Resumen

Introducción y objetivo: se realizó un estudio de las concentraciones séricas de ácido fólico (Fol) y vitamina B_{12} (B_{12}) en pacientes críticos con *shock* séptico al ingreso y después de tres días de estancia en la Unidad de Cuidados Intensivos (UCI), con un análisis de su asociación con los parámetros inflamatorios y la morbimortalidad de los pacientes.

Método: se realizó un estudio analítico prospectivo de 30 pacientes críticos con *shock* séptico. Se registraron datos demográficos, comorbilidades, información clínica y puntuaciones de gravedad. Los datos recopilados incluyeron los niveles séricos de Fol y B_{12} utilizando el autoanalizador DxI® (Beckman Coulter) basado en un inmunoensayo de electroquimioluminiscencia competitivo.

Resultados: la media de Fol sérico estuvo dentro del rango de referencia estipulado por el laboratorio el primer día. Sin embargo, el 21,4 % de los pacientes presentaban niveles altos de Fol y el 14,2 % presentaban deficiencia de Fol. Se observó una asociación entre el estado de Fol ($p < 0,012$) con la mortalidad a los 28 días, con el número de días de ventilación mecánica, con la fracción de oxígeno inspirado (FiO_2) y con el fibrinógeno, que aumentaron en los pacientes con niveles de Fol más altos ($p < 0,05$). Además, el 85,7 % de los casos tenían niveles de B_{12} por encima de los valores de referencia, observándose una correlación entre B_{12} y Fol.

Conclusiones: este estudio propone al Fol como nuevo biomarcador de morbimortalidad en los pacientes críticos con sepsis y refuerza la utilidad de la B_{12} como biomarcador de morbilidad. Por tanto, se sugiere que la medición de Fol al ingreso y durante las primeras 72 horas de estancia hospitalaria podría proporcionar información pronóstica sobre el curso clínico y el resultado de los pacientes con *shock* séptico.

Palabras clave:

Shock séptico. Ácido fólico. Vitamina B_{12}. Morbilidad. Mortalidad.

INTRODUCTION

Septic shock is one of the major causes of mortality and morbidity in the Intensive Care Unit (ICU), and places a strong burden on healthcare resources (1,2). Septic shock is associated with a greater risk of mortality than sepsis alone, and with an in-hospital mortality rate of over 40 %, according to the Third International Consensus Definition for Sepsis and Septic Shock (1). Sepsis is characterized by tissue infiltration by polymorphonuclear cells (PMNs) and monocytes/macrophages, with excessive production of reactive oxygen species (ROS) (e.g., superoxide anions and hydrogen peroxide) and reactive nitrogen species (RNS) (e.g., nitric oxide) (3). Such free radicals produced in excess could amplify the inflammatory response in sepsis, acting as cell signal messengers, altering expression, and intervening in inflammatory immune modulation. These processes could provoke cell damage (to membranes, proteins and DNA), generally leading to cellular dysfunction, multiorgan failure, and eventual death of the septic patient. Inflammatory biomarkers are useful for the diagnosis of infections in the emergency care setting (4,5). More studies are required to help identify and understand the pathophysiological basis and biomolecular disorders that occur in this disease, as well as studying the evolution in the ICU, to help us understand, even predict a patient's clinical outcome in the future.

Folic acid (Fol) has not been evaluated in depth as a biomarker in critical patients. The present study was therefore designed to explore the behavior of Fol in the critically ill. The results of studies on serum Fol levels in critically ill patients and individuals with sepsis are subject to controversy. A study of critically ill patients (6) revealed deficient serum Fol levels in 65 % of patients. However, other authors have found Fol levels to be within the reference values in septic patients (7,8). Folic acid levels have been inversely correlated to the clinical severity of critically ill patients, and have been found to be lower in septic and febrile patients (9). Likewise, Fol has been shown to contribute to the control of chronic inflammation *in vitro* through various mechanisms after inducing monocytes with lipopolysaccharides *in vitro.* The administration of a preparation with Fol, vitamin B_{12} and choline modified the levels of inflammatory molecules (10).

Vitamin B_{12} (B_{12}) is another key and essential nutrient that may be useful in defining the prognosis of critical patients (11). Deficiencies of some vitamins, including B_{12} and Fol, have been demonstrated in critical patients, suggesting the need for replacement measures (12). B_{12} has been claimed to have antioxidant properties that afford a glutathione (GSH) sparing effect. The underlying mechanism involves stimulation of the activity of methionine synthase and reaction with hydrogen and nitrogen free radicals. Manzanares et al. (13) proposed that high parenteral doses of B_{12} could benefit patients with septic shock. Moreover, Lin et al. (14) observed that the administration of intravenous B_{12} to patients during septic shock improved blood pressure. However, high levels of B_{12} are associated with more seriously ill critical patients (15). In contrast, elevated blood vitamin B_{12} levels have been associated with inflammatory diseases and poor prognosis in critically ill patients (16). Plasma vitamin B_{12} levels have also been associated with other acute phase biomarkers such as C-reactive protein (CRP), and with the Sequential Organ Failure Assessment (SOFA) score in critically ill patients (17,18).

The association between Fol concentration and in-hospital mortality in adult patients with septic shock has not been evaluated to date. The tentative use of Fol as a novel biomarker may allow early recognition and decreased severity of sepsis. Therefore, we initially aimed to evaluate Fol and B_{12} status in a sample of 28 patients with septic shock.

MATERIAL AND METHODS

STUDY DESIGN AND PATIENTS

An analytical study was made of Fol and B_{12} levels and clinical parameters on day 1 and day 3 of ICU stay in critically ill patients with septic shock. Over a two-year period (September 2017 to May 2019), adult patients (≥ 18 years old) admitted to the ICU were systematically screened for study inclusion. The selection of patients was made in the ICU of the hospital. Patient diagnosis was established following the consensus criteria of septic shock (16) and according to the definition of the Third Interna-

tional Consensus Definition for Sepsis and Septic Shock (1). Patients over 18 years of age with sepsis and who had severe arterial hypotension unresponsive to fluid therapy were included. These patients did not receive Fol or B_{12} as oral, enteral, parenteral supplements or any combination of them. Control samples were obtained from healthy adult subjects with ages similar to those of the study cases, and presenting blood sample values within reference ranges.

The study was approved by the Ethics Committee of the University of Granada (Ref.: 248/CEIH/2015). Patients were admitted after providing their informed consent. The study was carried out according to the principles of the Declaration of Helsinki and also in abidance with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) guidelines. The clinical and laboratory parameters of the patients were collected on day 1 and day 3 after admission to the ICU. Clinical parameters included the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, the Sequential Organ Failure Assessment (SOFA) score, days of mechanical ventilation (DMV), ICU stay, and 28-day mortality rate.

BIOCHEMICAL ASSESSMENT

Fasting blood samples were drawn from the patients by venipuncture after the hemodynamic stabilization phase of admission and after three days of ICU stay: renal function (ions and creatinine), liver function (bilirubin), nutrition parameters (Fol and B_{12}), hematological and inflammatory parameters (lactic acid, fibrinogen, lactate dehydrogenase [LDH], CRP and procalcitonin [PCT]) were measured by the hospital laboratory using standard techniques.

ASSESSMENT OF FOLIC ACID AND VITAMIN B_{12}

The patients had blood drawn on day 1 and day 3 of their stay in the ICU. The samples were processed immediately. They were centrifuged at 3500 rpm for 10 min at 4 °C and frozen at -80 °C until further analysis. Samples of healthy controls were processed in the same way as the case samples. Fol and B_{12} were measured using a Dxl® Autoanalyzer (Beckman Coulter, CA, USA) employing a competitive electrochemoluminescence immunoassay for quantitative determinations. The reference values considered for Fol levels were 3.10 to 20.0 ng/mL and 116.0 to 513.0 pg/mL for B_{12}. The Fol analytical method involved binding of the Fol in the sample to a folate binding protein. The excess folate binding protein bound to a folate-alkaline phosphatase conjugate that in turn was bound to murine capture anti-antibodies coating paramagnetic particles. By applying a magnetic field in the reaction vessel, these particles were recovered; the light generated only by the molecules of the recovered particles was measured using a luminometer – the light generated being inversely proportional to Fol concentration in the sample.

The B_{12} analytical method involved the following steps: the proteins were first denatured with alkaline potassium cyanide and dithiothreitol. The B_{12} in the sample was then exposed to an intrinsic factor alkaline phosphatase conjugate and paramagnetic particles with anti-intrinsic factor were added to bind the excess conjugate. After applying a magnetic field and washing, only the intrinsic factor-alkaline phosphatase particles bounded to the paramagnetic particles were recovered; the remaining conjugate was measured with a luminometer, and the light generated was inversely proportional to the concentration of B_{12} in the sample.

STATISTICAL ANALYSIS

The statistical analysis was performed using the SPSS version 21.0 statistical package (IBM SPSS, Armonk, NY, USA). Qualitative variables were reported as frequencies and percentages, while quantitative variables were shown as the mean ± standard deviation (SD). The assumption of normality was tested using the Shapiro-Wilk test. The chi-squared test was performed to calculate the frequencies of the variables between groups. The association between quantitative variables and mortality, and between the cases and controls, was explored by applying the Mann-Whitney U-test. Folic acid was stratified according to the median (6.20 ng/mL) into two groups (high and low Fol levels) and compared with the rest of the variables using the Mann-Whitney U-test. Comparison of the quantitative variables between day 1 and day 3 of admission was carried out using the Wilcoxon test in order to study the evolution of the critical patients with septic shock during ICU stay. Spearman's correlation coefficient was used to establish correlations between the primary outcomes and the inflammatory and clinical outcomes. Statistical significance was considered for $p < 0.05$.

RESULTS

PATIENT CHARACTERISTICS

A total of 30 patients admitted to the ICU with septic shock were enrolled after agreeing to participate in the study. However, two patients did not continue because their samples had to be discarded. Twenty-eight patients therefore were finally recruited for the study. Table I shows demographic and clinical characteristics of the patients, as well as the evolution over three days of ICU stay. The differences in mechanical ventilation data (PaO_2/FiO_2: partial oxygen arterial pressure/fraction of inspired oxygen; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PEEP: positive end-expiratory pressure, and C_{st}: static compliance) between the first and third day were not significant. The microorganisms causing infection were *Streptococcus* (n = 3), *Acinetobacter* (n = 1), *Pseudomonas* (n = 1), *Campylobacter* (n = 1), *Clostridium* (n = 1), *Candida albicans* (n = 1) and *Escherichia coli* in the rest of the cases.

A majority of cases had underlying diseases such as cardiocirculatory diseases, hyperlipidemia, diabetes, chronic obstructive pulmonary disease, malignancy, etc. Two cases had hepatitis B

Table I. Demographic and clinical characteristics and evolution over three days of ICU stay in critically ill septic shock patients

	1st day (n = 28) (mean ± SD)	3rd day (n = 14) (mean ± SD)	*p*-value
Age (years)	61.9 ± 14.1	-	-
Male, number (%)	22.0 (78.6 %)	-	-
SOFA score	12.40 ± 2.60	8.88 ± 4.40	$p < 0.05$
APACHE II score (range)	22.0 (17.0-27.0)	-	-
SBP (mm Hg)	67.1 ± 15.9	79.6 ± 10.9	$p < 0.05$
FiO_2 (%)	0.56 ± 0.17	0.40 ± 0.14	$p < 0.001$
Etiology of sepsis (number of subjects)			
Abdominal	14.0	-	-
Respiratory	8.00	-	-
Urinary	6.00	-	-

Values are expressed as mean ± standard deviation (SD), as ranges or percentages. SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation; SBP: systolic blood pressure; FiO_2: fraction of inspired oxygen. A p-value less than 0.05 was considered statistically significant.

virus (HBV), another human immunodeficiencyvirus (HIV) disease and another only hypothyroidism, which could interfere in the depletion of antioxidants.

As expected, the APACHE II and SOFA scores were high, with a significant decline in SOFA score ($p < 0.011$) during ICU stay. A total of 15 patients needed mechanical ventilation (53.6 %), and the mean number of days spent in the ICU was 7.04 ± 10.5. The 28-day mortality rate was 42.9 % (12 patients).

BIOCHEMICAL PARAMETERS

The descriptive statistics and comparative bivariate analysis between the biochemical parameters upon admission and on the third day of ICU stay are shown in table II. In general, abnormal laboratory parameters were observed in our 28 cases of septic shock. Acute markers of inflammation and infection such as CRP and PCT were found to be above the reference values. At follow-up a statistically significant decrease was found for lactic acid, PCT, hemoglobin and platelet count on the third day ($p < 0.05$). Serum Fol and B_{12} levels showed no significant changes over the three days of ICU stay.

Table III shows the serum Fol and B_{12} levels of the patients with septic shock and the healthy controls. A total of 84 serum samples from healthy patients were used as controls. There were statistically significant differences in serum Fol and B_{12} levels between the two groups, with higher values among the cases ($p < 0.047$ and $p < 0.001$, respectively). No significant differences were found for Fol and B_{12} in our group of cases during ICU stay. However, the chi-squared test revealed that 21.4 % and 28.6 % of the patients were deficient in Fol, and that 14.2 % and 14.3 % of the patients presented high Fol values, on the first and third day of stay, respectively. Moreover, a total of 85.7 % of the patients presented high levels of B_{12} at the beginning of the study, versus 92.3 % of the patients after three days of ICU stay.

Table IV in turn describes the association between serum Fol and B_{12} levels and in-hospital morbidity-mortality. The serum Fol levels in the patients who died were compared with the serum Fol levels in the patients who survived: those who died had significantly higher levels of Fol on the first day of ICU stay ($p < 0.017$). In addition, there were significant differences in lactic acid concentration and platelet count between the patients who died and those who survived. No differences were observed in the case of B_{12}, CRP, PCT, LDH, fibrinogen, leukocytes or hemoglobin.

Table V shows the matrix correlations between folic acid and B_{12} and clinical outcome and severity markers. A statistically significant correlation was recorded between Fol and days of mechanical ventilatión (DMV) ($r = 0.459$; $p < 0.05$) on the first day of ICU stay. However, no statistically significant differences were observed between Fol versus SOFA, Fol versus APACHE II, or Fol versus days of stay in the ICU. After associating Fol and B_{12} with other acute phase parameters, we found statistically significant correlations between Fol versus fibrinogen ($r = 0.382$; $p < 0.045$) and Fol versus B_{12} ($r = 0.374$; $p < 0.05$) on the first day of ICU stay. A correlation was also observed between Fol on the first day and Fol on the third day of ICU stay ($r = 0.939$; $p < 0.001$).

Figure 1 shows DMV, fraction of inspired oxygen (FiO_2) and fibrinogen levels in patients with low and high serum Fol levels. The results showed the subjects with higher serum Fol levels to have more DMV ($p < 0.012$), higher percentages of FiO_2 ($p < 0.012$) and higher fibrinogen levels ($p < 0.008$).

Table II. Biochemical parameters and their evolution over three days of ICU stay in patients with septic shock

	1st day (n = 28) (mean ± SD)	3rd day (n = 14) (mean ± SD)	Reference values	*p*-value 1st day *vs.* 3rd day
Lactic acid (mmol/L)	4.72 ± 1.98	2.39 ± 2.17	0.60-2.50	p < 0.05
Sodium (mmol/L)	137.0 ± 7.2	136.8 ± 82.0	136.0-146.0	ns
Potassium (mmol/L)	4.26 ± 0.91	3.92 ± 0.71	3.50-5.10	ns
Anion gap (mmol/L)	12.1 ± 4.3	7.3 ± 10.8	7.00-16.0	ns
Creatinine (mg/dL)	2.99 ± 1.47	2.35 ± 1.64	0.67-1.20	ns
Total bilirubin (mg/dL)	2.37 ± 3.04	2.79 ± 3.07	0.30-1.20	ns
Fibrinogen (mg/dL)	513 ± 183	514 ± 290	200-350	ns
LDH (U/L)	620 ± 473	1286 ± 2131	110-295	ns
CRP (mg/L)	35.1 ± 28.9	46.7 ± 53.5	0.02-5.00	ns
Procalcitonin (ng/mL)	75.5 ± 59.3	42.6 ± 65.9	< 0.50	p < 0.05
Leukocytes (x 10^3/µL)	15.3 ± 17.9	13.3 ± 68.4	3.5-10.5	ns
Hemoglobin (g/dL)	11.2 ± 2.6	9.4 ± 2.1	11.0-17.0	p < 0.001
Platelets (x 10^3/µL)	122.3 ± 96.0	86.8 ± 59.4	120.0-450.0	p < 0.05
INR (ratio)	2.01 ± 1.40	1.90 ± 2.39	0.80-1.16	ns
aPTT (sec)	49.2 ± 30.3	40.8 ± 12.4	26.0-37.0	ns

Values are expressed as mean ± standard deviation (SD). LDH: lactate dehydrogenase; CRP: C-reactive protein; INR: international normalized ratio; aPTT: activated partial thromboplastin time. A p-value less than 0.05 was considered statistically significant. ns: not significant.

Table III. Serum folic acid and vitamin B_{12} levels in patients with septic shock and healthy controls

	Controls (n = 84) (mean ± SD)	Cases 1st day (n = 28) (mean ± SD)	Cases 3rd day (n = 14) (mean ± SD)	*p*-value 1st day	*p*-value 3rd day
Folic acid (ng/mL)	8.71 ± 3.16	9.61 ± 7.86	7.49 ± 7.08	p < 0.05	p < 0.05
Vitamin B_{12} (pg/mL)	466 ± 152	976 ± 511	1119 ± 192	p < 0.001	p < 0.001

A p-value less than 0.05 was considered statistically significant.

Table IV. Association between biochemical parameters and 28-day mortality in septic shock patients

	1st day (n = 28)			3rd day (n = 14)		
	Survivors (mean ± SD)	Non-survivors (mean ± SD)	*p*-value	Survivors (mean ± SD)	Non-survivors (mean ± SD)	*p*-value
Folic acid (ng/mL)	6.48 ± 5.33	13.80 ± 8.93	p < 0.05	7.04 ± 6.63	9.10 ± 10.1	ns
Vitamin B_{12} (pg/mL)	1000 ± 533	943 ± 500	ns	1141 ± 421	1363 ± 238	ns
Platelets (x 10^3/µL)	141 ± 88	96 ± 103	p < 0.05	104 ± 55	29 ± 26	p < 0.05

(Continues on next page)

Table IV (Cont.). Association between biochemical parameters and 28-day mortality in septic shock patients

	1st day (n = 28)			3rd day (n = 14)		
	Survivors (mean ± SD)	**Non-survivors (mean ± SD)**	***p*-value**	**Survivors (mean ± SD)**	**Non-survivors (mean ± SD)**	***p*-value**
Lactic acid (mmol/L)	3.94 ± 1.77	5.76 ± 1.82	p < 0.05	1.45 ± 0.36	5.23 ± 2.98	p < 0.05
CRP (mg/L)	40.0 ± 36.2	27.9 ± 10.5	ns	35.6 ± 36.9	72.6 ± 85.8	ns
PCT (ng/mL)	72.0 ± 57.8	80.3 ± 63.8	ns	47.0 ± 69.3	4.90 ± 3.30	ns
LDH (U/L)	630 ± 578	607 ± 323	ns	713 ± 910	3767 ± 4208	ns
Fibrinogen (mg//dL)	482 ± 146	557 ± 223	ns	523 ± 322	489 ± 203	ns
Leukocytes (x 10^3/µL)	15.9 ± 10.5	14.2 ± 25.8	ns	13.3 ± 4.5	13.2 ± 12.6	ns
Hemoglobin (g/dL)	11.5 ± 2.3	11.0 ± 3.0	ns	9.4 ± 2.1	9.7 ± 2.5	ns

CRP: C-reactive protein; PCT: procalcitonin; LDH: lactate dehydrogenase. A p-value less than 0.05 was considered statistically significant. ns: not significant.

Table V. Matrix correlations between folic acid and vitamin B_{12} and clinical outcome and severity markers

	Fol 1st day (n = 28)	Fol 3rd day (n = 14)	B_{12} 1st day (n = 28)	B_{12} 3rd day (n = 14)
SOFA	ns	ns	ns	ns
APACHE	ns	-	ns	-
DMV (day)	p < 0.05	ns	ns	ns
Stay (day)	ns	ns	ns	ns
Fibrinogen	p < 0.05	p < 0.05	ns	ns
Folic acid	-	p < 0.05	p < 0.05	ns

SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation; DMV: days of mechanical ventilation. A p-value less than 0.05 was considered statistically significant. ns: not significant.

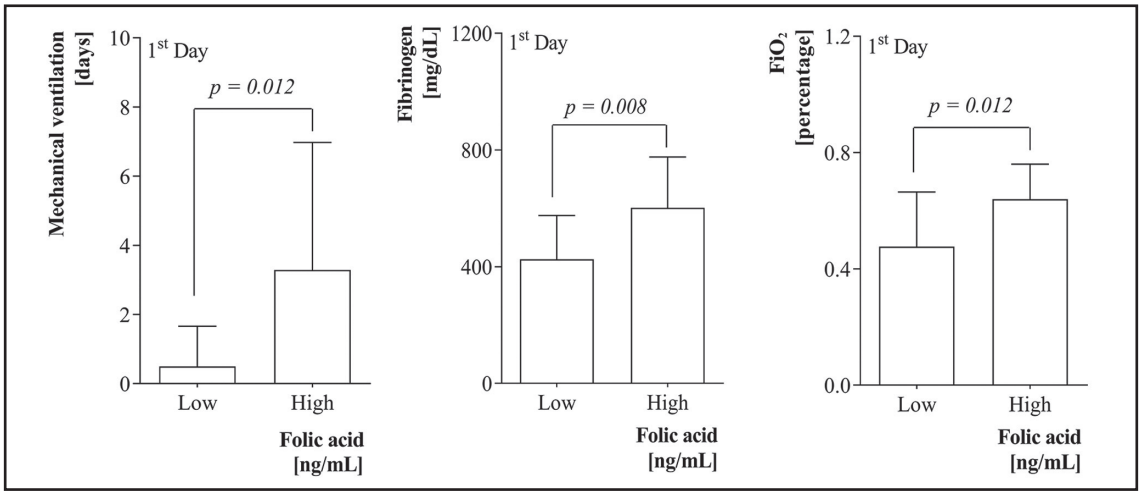

Figure 1.

Days of mechanical ventilation (DMV), fibrinogenand FiO_2 according to serum folic acid. FiO_2: fraction of inspired oxygen. A p-value less than 0.05 was considered statistically significant.

DISCUSSION

The aim of the present study was to investigate Fol and B_{12} behavior in critical care patients with septic shock upon admission and after three days in the ICU, and to assess their association to inflammatory parameters and patient morbidity-mortality. Our main findings were that the Fol levels were high in nearly one-third of the patients, being positively associated to mortality and to clinical outcomes such as the number of days of mechanical ventilation, FiO_2 and fibrinogen. Moreover, serum B_{12} levels were seen to be elevated in patients with septic shock.

An association between low Fol levels and mortality has been documented in the literature in patients with cardiovascular diseases and cancer (19). To the best of our knowledge, the present study is the first one to associate Fol levels with morbidity and mortality in patients with septic shock. However, no association between Fol and mortality was observed on the third day, possibly due to hemodynamic stabilization during ICU stay, and also because deceased patients were no longer included in the evaluation on the third day. In a previous study (7), Fol and B_{12} were measured in patients with severe sepsis, and no significant differences were observed with respect to the healthy control group. Another study (6) found 65 % of the critical patients admitted to the ICU to have decreased Fol levels (< 3.40 ng/mL), with a more pronounced decrease 24 hours after admission. Similarly, B_{12} and Fol were measured in 102 patients with severe sepsis, with results similar to our own, recording higher levels of B_{12} and levels of Fol within reference ranges (8). When Fol was analyzed in septic patients and compared with healthy individuals, no significant differences were found between the two groups (7,8), as also occurred in our study. A sample of 105 critical patients was studied, and 19 % were found to have Fol deficiency (< 2.70 ng/mL) upon admission to the ICU, with the observation of a negative correlation between Fol levels and the clinical severity of patients, and the identification of lower Fol levels in septic and febrile patients (9). In our study, the average Fol level on the third day was lower than on the first day, but higher in those patients who died during ICU stay. We believe that the Fol levels increased in more severe patients in response to decreased antioxidant status (20), since folic acid has the ability to suppress ROS (21,22). In fact, an *in vivo* study (21) found that supplementation with Fol could prevent apoptosis as induced by oxidative stress, reducing ROS levels, through negative regulation of vascular peroxidase 1 as a consequence of changes in DNA methylation. Also, the *in vitro* administration of Fol has been shown to suppress hypoxia-induced inflammation (22). Moreover, a study found that the administration of Fol, vitamin B_6 and B_{12} significantly increased fibrinogen levels in women at increased risk of cardiovascular disease (23). This consequently would confirm our observation of higher fibrinogen levels in patients with high Fol levels ($p < 0.008$).

Some of the cases in this study (12 of them) developed acute kidney injury as shown in the mean creatinine at ICU admission shown in table II. These patients have been on continuous renal replacement therapy. Altered micronutrient status has been found to be common in patients with acute common insufficiency, including Fol (24). Furthermore, it has been described in a recent study that 33 % of the critical ill patients investigated with continuous renal replacement therapy had serum Fol deficiency (25). This could explain the 14 % of Fol deficiencies in our study.

A number of studies have also associated B_{12} levels with other inflammatory biomarkers and patient morbidity-mortality (11,12,18,26,27). In a study on critically ill patients, B_{12} levels were seen to be significantly linked to inflammatory markers such as CRP on day one and two of ICU admission, and to severity parameters such as the SOFA score during patient stay in the ICU (18). Another study also confirmed the association between B_{12} and CRP in critically ill patients (12). Therefore, B_{12} could be considered a predictor of patient morbidity. Other studies (11,26) have supported the association between high levels of B_{12} and morbidity and mortality among critically ill patients, with higher B_{12} concentrations being found in those who died versus the survivors. Recently, elevated plasma B_{12} levels have been associated with an increased risk of all-cause mortality in the general population of The Netherlands (27). No association between B_{12} and mortality was observed in our study, however.

High plasma levels of B_{12} have been linked to functional deficiency of B_{12} (28). High plasma B_{12} concentrations may be a consequence of low levels of B_{12} within the cell, caused by an efflux of B_{12} from the cell towards the plasma compartment. Vitamin B_{12} functional status can only be measured by the enzymatic activity of cobalamin-dependent enzymes within the cell (28). In this study, B_{12} was considered a marker of plasma inflammation regardless of B_{12} levels within the cell. This explanation could also be applied to Fol. Thus, the fact that Fol was elevated in plasma in some patients does not guarantee folic acid functionality, since cell deficiency of Fol may actually exist.

The SOFA score is the gold standard for assessing severity in patients with sepsis in the ICU. However, groups of potential biomarkers evaluated jointly can increase diagnostic performance as well as morbidity-mortality prognostic yield compared to use of the SOFA score alone. Such biomarkers include PCT (29). Lactic acid is contemplated in the definition of sepsis and septic shock in the 2016 Consensus (1). Similarly to our own study, another paper has suggested lactic acid to be a predictor of mortality in patients with infection in the emergency care setting (30). In short, this biomarker has proven useful in the diagnosis, prognosis and evolution of septic patients (1,30,31).

Since methionine is necessary for the synthesis of DNA, both folic acid and B_{12} contribute to the production of leukocytes and red blood cells, which are necessary for defense against infection. Figure 2 shows the dependence of Fol and B_{12} upon the synthesis of methionine, since these vitamins favor the conversion from homocysteine to methionine. Furthermore, a study (32) found metabolites of methionine (S-adenosylmethionine and S-adenosylhomocysteine) to be elevated and related to the sepsis mortality. On the other hand, the administration of group B vitamins (including B_{12} and Fol) has been shown to

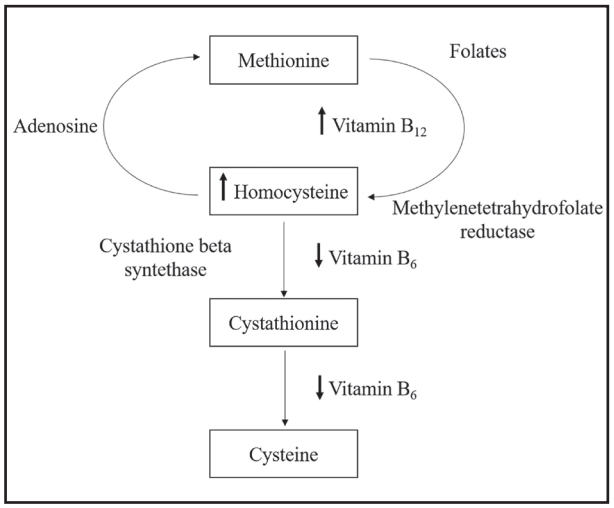

Figure 2.

Homocysteine cycle. In the present study, Fol and B_{12} were seen to be consumed in the synthesis of methionine. On using homocysteine, and when vitamin B_6 is decreased, little cysteine is produced. The latter molecule forms part of the structure of glutathione – a primary molecule for protection against the oxidative stress generated in these patients.

decrease homocysteine levels (33). In another study, the authors believed that dietary differences were unlikely to explain the route of homocysteine, but rather that hyperhomocysteinemia causes a prothrombotic disorder that alters the coagulation-anticoagulation balance, which is related to patient prognosis (7). In our study, we found an association between Fol and fibrinogen, and between thrombocytopenia and mortality. In another study, a relationship was observed between coagulopathy and organic dysfunction, since the authors found a correlation between the SOFA score and thrombocytopenia (34). As seen in figure 2, homocysteine is not available for synthesizing the cysteine necessary for glutathione, since through B_{12} and Fol it goes on to synthesize the methionine needed for cell development. It has also been observed that vitamin B_6 is decreased in patients with inflammation (35-37). In fact, another study (20) documented a positive correlation between B_{12} and glutamic acid in patients with septic shock. Accordingly, we attempted to explain the importance of the alteration of these two vitamins – Fol and B_{12} – since many pathways on which they depend are altered, and this may cause patient clinical status to worsen.

The present study has several strengths and limitations. As strengths, to our knowledge, it is the first to report on the association between Fol levels and morbidity-mortality in patients with septic shock. With regard to the limitations, the measurement of biomarkers in serum might not reflect their status within the cell. On the other hand, although we would have obtained greater statistical power with a larger sample size, it should be taken into account that the study group was limited to patients with septic shock in a very serious and labile state – a fact that made it difficult to recruit a greater number of patients.

CONCLUSIONS

In sum, this study contributes a possible novel biomarker – folic acid – which could be useful for the prognosis of morbidity-mortality during ICU stay in critical patients, with B_{12} levels acting as a biomarker of morbidity. Further studies are needed to elucidate the behavior and response of Fol in critically ill patients with septic shock during ICU stay.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Paciente crítico

Nutritional status and its association with in-hospital major adverse cardiac events in patients with severe heart failure: a prospective study

Estado nutricional y su asociación con eventos cardíacos adversos mayores intrahospitalarios en pacientes con insuficiencia cardíaca grave: un estudio prospectivo

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Abstract

Objectives: this study aimed to evaluate the relationship of Nutritional Risk Screening 2002 (NRS2002) and in-hospital major adverse cardiac events (MACE) in patients with severe heart failure.

Methods: an observational study was conducted at the emergency intensive care units (EICU) of Shandong University Qilu Hospital from January 2017 to December 2019. Nutritional screening and assessment were performed at the time of admission to hospital with the NRS2002.

Results: of the 209 patients included, 16 cases (7.66 %) were not at nutritional risk, and 193 cases (92.34 %) were at risk. Among them, 12 cases (5.74 %) were malnourished, 38 cases (18.18 %) were at high nutritional risk, and 115 cases (55.02 %) were overweight and obese. The differences in prealbumin (PA) and N-terminal B-type natriuretic peptide precursor (NT-proBNP) between the 2 groups were statistically significant ($p < 0.05$). A total of 134 cases (64.12 %) received nutrition treatment support, of which 39 cases (29.10 %) received enteral nutrition (EN), 77 cases (57.46 %) parenteral nutrition, and 18 cases (13.43 %) enteral nutrition combined with parenteral nutrition (EN + SPN) support treatment. In all, 31 cases (54.39 %) reached 100 % of the target dose. Patients in the EN and EN + SPN groups had 37 MACE (64.91 %) and 31 enteral nutrition complications (54.39 %), with differences between the 3 groups being statistically significant ($p < 0.05$).

Conclusion: the nutritional risk of patients with severe heart failure is high, and age and heart function are positively correlated with nutritional risk. The complications rate of patients with high nutritional risk is significantly higher than in those with low risk; the higher the nutritional risk, the higher the hospital mortality rate — that is, nutritional risk affects disease outcome.

Keywords:

Severe heart disease. Heart failure. Nutritional risk. Malnutrition.

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Resumen

Objetivos: este estudio tuvo como objetivo evaluar la relación del *Nutritional Risk Screening* 2002 (NRS2002) con los eventos cardiacos adversos mayores intrahospitalarios (MACE) en pacientes con insuficiencia cardiaca grave.

Métodos: se realizó un estudio observacional en las unidades de cuidados intensivos de emergencia (UCIE) del Hospital Qilu de la Universidad de Shandong desde enero de 2017 a diciembre de 2019. Se realizaron un cribado y una evaluación nutricional en el momento del ingreso hospitalario con el NRS2002.

Resultados: de los 209 pacientes incluidos, 16 casos (7,66 %) no tenían riesgo nutricional y 193 casos (92,34 %) sí lo tenían. Entre ellos, 12 casos (5,74 %) estaban desnutridos, 38 casos (18,18 %) tenían un alto riesgo nutricional y 115 casos (55,02 %) tenían sobrepeso u obesidad. Las diferencias de prealbúmina (PA) y precursor del péptido natriurético de tipo B N-terminal (NT-proBNP) entre los 2 grupos fueron estadísticamente significativas ($p < 0,05$). En total, 134 casos (64,12 %) recibieron soporte de tratamiento nutricional, de los que 39 casos (29,10 %) recibieron nutrición enteral (NE), 77 casos (57,46 %) nutrición parenteral y 18 casos (13,43 %) nutrición enteral combinada con nutrición parenteral (NE + SPN) como tratamiento de apoyo. Treinta y un casos (54,39 %) alcanzaron la dosis objetivo al 100 %. Los pacientes de los grupos EN y EN + SPN tuvieron 37 MACE (64,91 %) y 31 complicaciones de la nutrición enteral (54,39 %), siendo la diferencia entre los 3 grupos estadísticamente significativa ($p < 0,05$).

Conclusiones: el riesgo nutricional de los pacientes con insuficiencia cardíaca grave es alto; la edad y la función cardiaca se correlacionan positivamente con el riesgo nutricional. La complicación de los pacientes con alto riesgo nutricional es significativamente mayor que la de los de bajo riesgo; cuanto mayor es el riesgo nutricional, mayor es la tasa de mortalidad hospitalaria, es decir, el riesgo nutricional afecta el resultado de la enfermedad.

Palabras clave:

Enfermedad cardiaca grave. Insuficiencia cardiaca. Riesgo nutricional. Desnutrición.

INTRODUCTION

Cardiovascular diseases, mainly manifesting as heart failure, are the most common critical illness in the emergency department. Heart failure is the severe and terminal stage in the development of various cardiovascular diseases. It is the main cause of hospitalization and disability in the elderly, and the cause of one in nine deaths in the United States (1). Malnutrition is a common complication that affects the prognosis of elderly hospitalized patients. At present, there are few studies on the nutritional risk and nutritional support of patients with severe cardiac diseases. This study aimed to study the nutritional status and clinical nutritional support of patients with severe cardiac disease through the NRS2002 nutritional risk screening tool, to understand the relationship between nutrition-related factors of severe cardiac patients and the severity of cardiac function and prognosis.

METHODS

STUDY POPULATION

From January 2017 to December 2019 there were 209 patients with severe cardiovascular disease hospitalized in the emergency intensive care unit (EICU) of Qilu Hospital. According to the New York Heart Association (NYHA) Cardiac Function Classification and Killip Cardiac Function Classification, these patients were classified into 2 groups. In our study, we divided the 209 cases into the non-heart failure group (47 cases) and the heart failure group (162 cases). Among the 47 cases in the non-heart failure group, there were 9 cases categorized as NYHA grade I and 38 cases as Killip grade I. According to the Cardiac Function Classification, 10 cases of grade II, 25 cases of grade III, 41 cases of grade IV, a total of 76 cases were classified into the heart failure group. According to Killip's classification, 36 cases of grade II, 14 cases of grade III, 36 cases of grade IV, and a total of 86 cases were classified into the heart failure group. All patients with related treatments had signed an informed consent form.

RESEARCH METHODS

Sample size calculation

This study was a cross-sectional study, which used the formula $n = K \times Q / P$. The allowable error of the research project was 15 %, so constant $K = 178$. n represents the number of people surveyed, P represents the probability of nutritional risk, 51 % (2). $Q = 1 - P$, so it could be calculated that $n = K \times Q / P = 178 \times 49\ \% / 51\ \% = 171$ cases. Considering a 20 % loss to follow-up rate (data insufficiency, etc.), there were 205 cases. A total of 209 cases were finally included in the sample size.

NRS2002 score

The initial evaluation of the NRS2002 scoring scale was completed in the inpatient system by doctors and nurses who had undergone intense professional training. On admission to hospital, to measure and calculate body mass index we used BMI = body mass (kg) / height^2 (m^2). (After admission, body mass and height were also measured: BMI = body mass [kg] / height^2 [m^2].) Patients with fluid retention are given adequate diuresis and have dry body mass measured to calculate the BMI index. For patients with obvious edema, ascites, pleural effusion, or unable to stand up, serum ALB < 30 g/L is > 3 points. Assessment was completed after the APACHE II score test data of the inpatient system was issued within 24 hours. Malnutrition was defined as hospitalized cardiac patients with BMI < 18.5, while BMI ≥ 24 was overweight, and BMI ≥ 28 was obesity. NRS2002 scoring standard: 0-2, no nutritional risk; ≥ 3 points, low nutritional risk; ≥ 5 points, high nutritional risk; among them, those with ≥ 3 points or more were defined as having malnutrition risk.

Specimen collection

After admission, all patients underwent radial artery blood sampling, using a bedside blood gas analyzer to detect blood glucose (BS), lactic acid (LAC), blood potassium (K^+), blood calcium (Ca^{++}), blood sodium (Na^+) and other indicators. In the immediate resting state, venous blood was collected in the supine position, and the bedside immunofluorescence method was used to detect troponin I (CTNI), myoglobin (MYO), creatine phosphokinase and its isoenzymes (CK-MB), and N-terminal forebrain natriuretic peptide (NT-proBNP). All subjects were in a resting state in the early morning of the next day, and venous blood was collected from the supine position to determine hemoglobin (Hb), albumin (ABL), prealbumin (PA), triacylglycerol (TG), and cholesterol (TC), etc. The target dose of nutritional support was 20-30 kcal/(kg · d).

STATISTICAL ANALYSIS

The SPSS 25.0 statistical software was used for the analysis. Measurement data conforming to a normal distribution were represented as $\bar{x} \pm s$. Data not conforming to a normal distribution was represented as M (P_{25}, P_{75}), and transformed into a normal distribution with the natural logarithm (Ln). Pairwise comparisons between groups used Student's t-test. One-way analysis of variance was used for comparison between multiple groups, and the SNK-q test was used for multiple comparisons between groups when the difference was statistically significant. The count data are expressed as number of cases or rate, and comparison between groups was performed through the chi-squared test. A $p < 0.05$ indicated that the difference was statistically significant.

RESULTS

The age of patients ranged from 14 to 90 years old, with an average age of 69.23 ± 13.42 years. There were 123 males (58.85 %) with an average age of 66.98 ± 13.51 years, and 86 females (41.15 %) with an average age of 72.45 ± 12.69 years in our study.

The results of the NRS2002 nutritional risk screening are shown in table I. The degree of aging of patients with severe cardiac diseases was high, of which 144 cases (68.90 %) were ≥ 65 years old, and 116 cases (55.50 %) were over 70 years old. There were 14 cases (6.70 %) that were not at nutritional risk, 195 cases (92.34 %) were at nutritional risk, and 87 cases (18.18 %) were at high nutritional risk— among them, 83 patients (97.65 %) with NYHA classification had nutritional risk, as was also the case with 112 patients (90.32 %) with Killip classification. Among them, 12 cases (5.74 %) were malnourished. In addition to malnutrition, overweight accounted for 47.85 %, and obese accounted for 7.18 % of the sample. There were 139 cases (66.51 %) with abnormal food intake at the time of admission, of which 117 cases (55.98 %) had a weight decrease of 25 % to 75 %, and 22 cases (10.53 %) had a weight decrease of 76 % to 100 %. Twenty-three patients (11.00 %) had had a weight loss of 5 % in the past 3 months. There were 66 cases (31.57 %) with fluid retention. There were 193 cases (92.34 %) with APACHE II score > 10 points.

The information on the nutritional support is shown in table II. There were 134 cases (64.12 %) of critically ill patients receiving nutritional support, EN 39 cases (29.10 %), EPN 77 cases (57.46 %), EN + SPN 18 cases (13.43 %); 23 cases (40.35 %) had EN start time in 48 h, 34 cases (59.65 %) were over 48 h; 31 cases (54.39 %) met the 100 % target. Among the enteral nutritional preparations, 42 cases (61.76 %) were non-elemental and special preparations. The initial dose was ≤ 500 ml (93.22 %), the final dose was 500 ml in 24 cases (41.38 %), and 1000 ml in 24 cases (41.38 %), of which 43 (EN and EN + SPN) (75.44 %) used prokinetic drugs. In this group of patients, 110 cases (52,63 %) used ventilator-assisted ventilation, 87 cases (41.63 %) used analgesia and sedation, and 164 cases (78.47 %) used vasoactive drugs.

A comparison of the basic data of different patients with NRS2002 score is shown in table III. According to the table, we found that the nutritional risk of patients with severe cardiac disease increased significantly with age. The Cr and NT-proBNP values of NRS2002 low-nutrition and high-risk patients were higher than those of non-risk patients; the lower the TC value, the higher the nutritional risk, and the difference between low-risk patients and non-risk patients was statistically significant. In addition to the above indicators, there was no statistically significant difference in other related nutritional indicators among different nutritional risk groups.

A comparison of the basic data of patients with different scores in the Killip classification in NRS2002 is shown in tables IV and V. Killip-graded cardiac patients with severe cardiac function had a worsened nutritional risk, and the differences between groups, including the non-heart failure and the heart failure groups, were statistically significant. The PA value of the nutritional high-risk group was significantly lower than in the other groups. The CTNI value was negatively correlated with nutritional risk, and the comparison between the high-risk group and low-risk group was statistically significant. The higher the NT-proBNP value, the higher the nutritional risk of patients, and the comparison between the three groups was not statistically significant.

A comparison of basic data of the NYHA-graded patients with different scores in NRS2002 is shown in tables VI and VII. The nutritional risk of patients with severe cardiac diseases in the NYHA classification increases with age, and the worse the heart function, the higher the nutritional risk. The nutritional risk of the non-heart failure group was lower than that of the heart failure group, and the differences between the different nutritional risk groups were statistically significant. Besides, we also found that the higher the CTNI value and NT-proBNP value, the higher the nutritional risk of patients, and the comparison between the three groups was not statistically significant.

Table I. Results of the NRS2002 Nutrition Risk Screening

Objects		Number of cases	Percentage (%)	Objects	Number of cases	Percentage (%)
Age (years)	> 70	116	55.50	Liver cirrhosis	1	0.48
Nutrition screening score	< 3	14	6.70	Hip fracture	2	1.12
	3-5	108	51.67	Acute onset of chronic disease or complications	91	43.54
	> 5	87	41.63	COPD	3	1.44
BMI	< 18.5	12	5.74	General malignant tumor	13	6.22
	24-28	100	47.85	Diabetes	119	56.94
	≥ 28	15	7.18	Major abdominal surgery	9	4.3
Time to lose 5 % of body weight (months)	< 3	14	6.70	Stroke	70	33.49
	< 2	2	0.96	Severe pneumonia	1	0.48
	< 1	7	3.35	Fluid retention	66	31.57
Reduction in eating compared to before (%)	25-50	95	45.45	Pitting edema	44	21.05
	51-75	22	10.53	Pericardial effusion	7	3.35
	76-100	22	10.53	Pleural effusion	13	6.22
APACHE II (score)	> 10	193	92.34	Ascites	2	0.96

Table II. Basic information of nutritional treatment support

Objects		Number of cases	Percentage (%)	Objects		Number of cases	Percentage (%)
Nutritional treatment support		134	64.12		150	4	7.02
EEN		39	29.1		450	2	3.51
EPN		77	57.46		500	47	82.35
EN + SPN		18	13.43		1000	4	7.02
Oral nutritional supplement (ONS)		6	10.53	Use of prokinetic drugs		43	75.44
Nasogastric tube		49	85.96	EN final daily dose (ml)	150	2	3.51
Naso-intestinal tube		2	3.51		300	2	3.51
EN start time (hours)	≤ 24	15	26.32		450	2	3.51
	> 24	8	14.04		500	24	42.11
	> 48	34	59.65		600	1	1.75
Time to reach target dose (hours)	≤ 24	13	22.8		1000	24	42.11
	24-48	7	12.28		1500	3	5.26
	48-72	33	57.89	Ventilator-assisted breathing		110	52.63
	72	4	7.02	Invasive ventilator		47	22.49

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Table II (Cont.). Basic information of nutritional treatment support

Objects		Number of cases	Percentage (%)	Objects		Number of cases	Percentage (%)
Dose target achievement ratio (%)	60	9	16.18	Non-invasive ventilator		60	28.71
	80	17	29.824	High-flow humidification oxygen therapy		3	1.44
	100	31	54.39	Analgesia and sedation		87	41.63
EN preparation	Elemental	26	38.23	Duration (hours)	≤ 24	14	16.09
	Non-elemental	14	20.59		> 24	20	22.99
	Special	28			41.18	> 72	60.92
EN daily initial dose (ml)	100	2	3.51	Use of vasoactive drugs		164	78.47

Table III. Comparison of basic data of patients with different scores in NRS2002

Objects	NRS2002 < 3 (n = 14)	NRS2002 3 (n = 108)	NRS2002 ≥ 5 (n = 87)	F/χ^2	*p*
Age ($\bar{x} \pm s$, years)	59.21 ± 16.41	67.05 ± 12.45*	73.55 ± 12.69*†	10.764	< 0.05
Gender (n)				116.411	< 0.05
Male	39	41	43		
Female	12	32	42		
ALB ($\bar{x} \pm s$, g/L)	39.14 ± 7.70	37.96 ± 8.80	36.30 ± 8.88	1.174	> 0.05
PA ($\bar{x} \pm s$, g/L)	17.72 ± 6.32	18.14 ± 7.62	16.68 ± 16.09	0.503	> 0.05
Hb ($\bar{x} \pm s$, g/L)	123.64 ± 30.55	118.50 ± 4.33	115.02 ± 25.25	0.560	> 0.05
TG ($\bar{x} \pm s$, mmol/L)	1.74 ± 1.40	1.42 ± 0.84	1.36 ± 0.76	1.328	> 0.05
TC ($\bar{x} \pm s$, mmol/L)	4.41 ± 0.99	3.74 ± 1.09*	3.74 ± 1.27	0.634	< 0.05
Bs ($\bar{x} \pm s$, mmol/L)	8.27 ± 4.17	7.63 ± 3.37	8.13 ± 5.56	0.358	> 0.05
Na^+ ($\bar{x} \pm s$, mmol/L)	138.86 ± 4.47	137.73 ± 10.12	139.90 ± 8.58	1.324	> 0.05
K^+ ($\bar{x} \pm s$, mmol/L)	4.21 ± 0.43	4.36 ± 0.55	4.27 ± 0.91	0.525	> 0.05
Ca^{++} ($\bar{x} \pm s$, mmol/L)	2.14 ± 1.29	2.12 ± 1.92	2.09 ± 0.43	0.346	> 0.05
Lac ($\bar{x} \pm s$, mmol/L)	1.99 ± 1.39	2.53 ± 2.90	2.35 ± 2.91	0.223	> 0.05
Cr ($\bar{x} \pm s$, mmol/L)	91.14 ± 30.69	154.06 ± 141.52*	136.06 ± 109.34*	1.772	< 0.05
CTNI ($\bar{x} \pm s$, μg/L)	9.05 ± 9.41	7.61 ± 13.03	5.30 ± 9.55	1.281	> 0.05
NT-proBNP (P_{25}, P_{75}), ng/L	2207 (467, 9845)	7240 (2830, 19400)*	9940 (2745, 22610)*	4.814	< 0.05

*Compared with NRS2002 without risk, *p < 0.05; compared with NRS2002 of low-risk group, †p < 0.05.*

Table IV. Comparison of basic data of patients with different scores in Killip grading of NRS2002

Objects	NRS2002 < 3 (n = 14)	NRS2002 3 (n = 108)	NRS2002 ≥ 5 (n = 87)	F/χ^2	*p*
Age ($\bar{x} \pm s$, years)	63.00 ± 10.81	67.83 ± 11.86*	75.00 ± 10.89*†	7.399	< 0.05
Gender (n) Male Female	 10 2	 43 21	 25 23	112.000	< 0.05
ALB ($\bar{x} \pm s$, g/L)	38.67 ± 6.60	38.12 ± 9.20	36.67 ± 8.84	0.462	> 0.05
PA ($\bar{x} \pm s$, g/L)	16.83 ± 6.15	18.96 ± 6.05	15.89 ± 5.50†	3.876	< 0.05
Hb ($\bar{x} \pm s$, g/L)	119.50 ± 47.38	114.02 ± 25.14	112.76 ± 26.90	0.730	> 0.05
TG ($\bar{x} \pm s$, mmol/L)	1.61 ± 0.91	1.48 ± 0.88	1.31 ± 0.80	1.318	> 0.05
TC ($\bar{x} \pm s$, mmol/L)	3.50 ± 1.47	3.56 ± 1.28	3.55 ± 1.33	2.280	> 0.05
Bs ($\bar{x} \pm s$, mmol/L)	8.22 ± 5.73	6.80 ± 2.65	7.19 ± 4.40	0.271	> 0.05
Na^+ ($\bar{x} \pm s$, mmol/L)	139.00 ± 1.41	135.71 ± 14.92	137.74 ± 12.00	0.175	> 0.05
K^+ ($\bar{x} \pm s$, mmol/L)	4.69 ± 0.22	4.40 ± 0.62*	4.26 ± 0.62*†	0.353	> 0.05
Ca^{++} ($\bar{x} \pm s$, mmol/L)	2.14 ± 0.18	2.12 ± 0.21	2.14 ± 0.54	1.726	> 0.05
Lac ($\bar{x} \pm s$, mmol/L)	1.67 ± 0.98	2.04 ± 0.28	2.03 ± 2.63	1.328	> 0.05
Cr ($\bar{x} \pm s$, mmol/L)	110.50 ± 3.54	172.70 ± 151.64	141.04 ± 116.43	0.353	> 0.05
CTNI ($\bar{x} \pm s$, μg/L)	10.16 ± 9.75	9.85 ± 10.24	5.70 ± 6.76†	3.207	< 0.05
NT-proBNP (P_{25}, P_{75}), ng/L	6359 (1993.50, 18625)	4532 (1700,14349)	9748 (3380,22520)	0.104	> 0.05

*Compared with NRS2002 without risk, *p < 0.05; compared with NRS2002 low risk, †p < 0.05.*

Table V. Comparison of NRS2002 scores in patients with Killip classification of cardiac function

Object/Group	n (%)	NRS2002 Score	$^*\chi^2$	$^\dagger\chi^2$	$^\ddagger\chi^2$	*p*
Killip Grade I	38 (30.65)	4.67 ± 2.08				
Grade II	36 (29.03)	4.70 ± 1.16*	159.093			< 0.05
Grade III	14 (11.29)	4.83 ± 1.17*†	224.202	178.617		< 0.05
Grade IV	36 (29.03)	4.18 ± 1.08*†‡	66.834	116.125	65.998	< 0.05
Grade II-Grade IV	86 (69.11)	4.20 ± 1.14*	343.679			< 0.05

*Compared with grade I, *p < 0.05; compared with grade II, †p < 0.05; compared with grade III, ‡p < 0.05.*

Table VI. Comparison of basic data of NRS2002 patients with different NYHA grades

Object	NRS2002 < 3 (n = 2)	NRS2002 3 (n = 44)	NRS2002 ≥ 5 (n = 39)	F/χ^2	*p*
Age ($\bar{x} \pm s$, years)	36.5 ± 31.82	69.00	71.00	12.000	< 0.05
Gender (n) Male Female	 2 0	 25 19	 22 17	12.000	< 0.05

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Table VI (Cont.). Comparison of basic data of NRS2002 patients with different NYHA grades

Object	NRS2002 < 3 (n = 2)	NRS2002 3 (n = 44)	NRS2002 ≥ 5 (n = 39)	F/χ^2	*p*
ALB ($\bar{x} \pm s$, g/L)	42.00 ± 16.55	37.74 ± 8.29	35.83 ± 9.03	0.816	> 0.05
PA ($\bar{x} \pm s$, g/L)	23.10 ± 6.08	16.28 ± 7.05	17.71 ± 23.72	0.202	> 0.05
Hb ($\bar{x} \pm s$, g/L)	124.33 ± 29.92	121.56 ± 23.48	119.98 ± 24.00	0.075	> 0.05
TG ($\bar{x} \pm s$, mmol/L)	1.82 ± 1.50	1.38 ± 0.81	1.41 ± 0.74	0.484	> 0.05
TC ($\bar{x} \pm s$, mmol/L)	4.56 ± 0.88	3.86 ± 0.94	3.89 ± 1.22	0.003	> 0.05
Bs ($\bar{x} \pm s$, mmol/L)	8.28 ± 4.19	8.21 ± 3.70	8.88 ± 6.27	0.233	> 0.05
Na^+ ($\bar{x} \pm s$, mmol/L)	138.23 ± 4.84	139.11 ± 10.17	139.79 ± 9.53	1.341	> 0.05
K^+ ($\bar{x} \pm s$, mmol/L)	4.13 ± 0.41	4.34 ± 0.50	4.29 ± 1.10	0.883	> 0.05
Ca^{++} ($\bar{x} \pm s$, mmol/L)	2.15 ± 0.13	2.12 ± 0.18	2.04 ± 0.31	0.039	> 0.05
Lac ($\bar{x} \pm s$, mmol/L)	1.67 ± 0.98	2.46 ± 2.21	2.21 ± 2.63	0.061	> 0.05
Cr ($\bar{x} \pm s$, mmol/L)	87.67 ± 31.17	140.92 ± 132.91	130.68 ± 106.66	0.875	> 0.05
CTNI ($\bar{x} \pm s$, μg/L)	2.35 ± 1.63	4.36 ± 15.84	4.80 ± 12.23†	0.034	> 0.05
NT-proBNP (P_{25}, P_{75}), ng/L	5955 (1810, 10100)	11100 (4460, 21400)	16266 (1580, 2346.36)	0.104	> 0.05

*Compared with NRS2002 without risk, *p < 0.05; compared with NRS2002 low risk, †p < 0.05.*

Table VII. Comparison of NRS2002 scores of patients with NYHA classification of cardiac function

Object/Group	n (%)	NRS2002 Score	*χ^2	†χ^2	‡χ^2	*p*
NYHA Grade I	9 (10.59)	2.78 ± 1.72				
Grade II	10 (11.76)	4.60 ± 1.43*	218.083			< 0.05
Grade III	25 (29.41)	4.08 ± 1.12*†	100.381	197.692		< 0.05
Grade IV	41 (48.23)	4.12 ± 1.53*††	372.000	372.000	248.000	< 0.05
Grade II-Grade IV	76 (89.41)	4.17 ± 1.39*	218.083			< 0.05

*Compared with NRS2002 without risk, *p < 0.05; compared with NRS2002 low risk, †p < 0.05.*

The comparison of hospital outcome indicators for severe cardiac patients is shown in table VIII and table IX. There were 223 cases (155.33 %) of major adverse cardiac events during the hospitalization of severe cardiac patients, and 193 cases (86.55 %) of cardiac arrest, arrhythmia, and heart failure were the main ones. Among arrhythmias, 43 cases of atrial fibrillation (37.07 %), 24 cases of ventricular fibrillation (20.69 %), and 21 cases of ventricular tachycardia (18.10 %) stood out. What is more, there were 151 cases (72.25 %) of gastrointestinal complications, and 133 cases (40.62 %) were mainly caused by weakened or disappeared bowel sounds, abdominal distension, and interruption of EN. The incidence of major adverse cardiac events in EN patients was 37 cases (64.91 %), and the incidence of enteral nutrition complications was 31 cases (54.39 %). The higher the nutritional risk, the higher the incidence, and the difference between risk groups was statistically significant. The in-hospital mortality rate of patients with severe cardiac disease was 28.23 %. The higher the nutritional risk, the higher the mortality rate, and the difference between risk groups was statistically significant. The higher the nutritional risk of patients with severe cardiac diseases, the longer the average length of hospital stay, but the difference between the groups was not statistically significant.

Table VIII. Inpatient outcome index data of severe cardiac patients

Object	Number of cases	Percentage (%)	Object	Number of cases	Percentage (%)
Cardiac event occurred	210	100.48	Atrioventricular block	2	1.72
Angina pectoris	25	11.21	EN complication	151	264.91
Myocardial infarction	5	2.24	EN interrupt	24	15.89
Heart failure	57	25.56	Bloating	16	10.60
Cardiac arrest	68	30.49	Decreased or disappeared bowel sounds	93	61.59
Arrhythmia	68	30.49	Nausea	4	2.65
Ventricular premature beats are duality	11	9.48	Vomiting	5	3.31
Short burst velocities	7	6.03	Gastric retention	3	1.99
Atrial fibrillation	43	37.07	Diarrhea	11	7.28
Atrial flutter	3	2.59	Gastrointestinal bleeding	12	7.95
Supraventricular tachycardia	4	3.45			
Ventricular tachycardia	21	18.10			
Ventricular fibrillation	24	20.69			
Sinus bradycardia	1	0.86			

Table IX. Comparison of outcome indexes of inpatients with severe heart disease

Outcome indicators			NRS2002							
			< 3		*3*		≥ 5		χ^2/F	*p*
	n	%	n	%	n	%	n	%		
EN complication rate	31	54.39	1	7.14	13	12.04*	17	19.54*†	58.000	< 0.05
EN major cardiac events rate	37	64.91	0	0	17	15.74	20	23.00†	37.000	< 0.05
EN EICU fatality rate	23	11.00	3	13.04	15	65.22	5	21.74	35.357	> 0.05
EICU fatality rate	59	28.23	4	6.78	21	35.59	34	57.63†	21.000	< 0.05
EN EICU average hospital stay		16.10 ± 11.12	17.80 ± 14.49	16.97 ± 12.06	0.140	> 0.05				
EICU average hospital stay		18.54 ± 14.94	19.23 ± 15.96	16.92 ± 12.06	0.302	> 0.05				

*Compared with NRS2002 low risk (< 3), *p < 0.05; compared with NRS2002 medium risk (3), †p < 0.05.*

DISCUSSION

The incidence of nutritional and metabolic disorders in critically ill patients with heart failure is high. Chronic heart failure, gastrointestinal dysfunction, insufficient nutrient intake and increased consumption can easily lead to malnutrition risks. Malnutrition is a common complication in patients with heart failure and an independent predictive risk factor for death. Obesity is an important risk factor for heart failure (3).

Adequate nutrition, which has an established role in the prevention of heart failure, is known to promote health-related quality of life by addressing malnutrition and promoting optimal functioning

among older adults (4). NRS-2002 is a reliable screening tool in an in-patient sample with chronic heart failure (5). In our study, 68.90 % of patients in this group are ≥ 65 years old, with an average age of 69.23 ± 13.42 years. The overall nutritional status of patients with severe cardiac disease is manifested as nutritional disorders. The ratio of nutritional risk is 92.34 %, which is significantly higher than the 37.6 %-51.41 % reported by Zhu MW. The incidence of malnutrition of 5.26 % is lower than that of 10 %-20 % reported in other studies (2-6), which may be related to a 52.80 % of patients with first-onset acute heart failure admitted to the emergency department. Among them, there were 3 cases (25 %) with Killip classification grade I (25 %), 9 cases (75 %) with Killip classification and NYHA classification grades III and IV (75 %); 115 cases (55.02 %) were overweight and obese. The proportion of patients whose diet was reduced by 25 % to 100 % compared with before accounted for 66.51 %, while the proportion of patients who had lost 5 % of weight in the past 3 months accounted for 11.00 %, and that of fluid retention was 31.57 %. Complex nutritional status requires a higher and more refined balance of nutritional support and energy requirements, fluid management and heart load.

The high nutritional risk rate is related to the serious condition of patients with severe cardiac diseases. The APACHE II score in this group of cases > 10 points accounted for 92.34 %, of which acute onset of chronic diseases and complications, diabetes, and stroke accounted for 90.61 %. Acute attacks in patients with severe cardiac disease often have infections, which increase the risk of malnutrition (7). The mechanism is that heart failure with gastrointestinal congestion and ischemia lead to poor appetite, decreased serum protein production in liver congestion, and gastrointestinal dysfunction leading to insufficient nutrient intake, digestion, and absorption. Besides, the release of inflammatory factors participates in ventricular remodeling, muscle atrophy and other aggravations of malnutrition. What is more, the application of mechanically-assisted positive-pressure ventilation therapy, analgesic and sedative drugs, and vasoactive drugs has increased the difficulty of nutritional therapy support (8). In this group of patients, invasive mechanical assisted ventilation was used for 52.63 %, analgesic and sedative drugs were used for 41.63 %, and vasoactive drugs were used for 78.47 % of subjects.

Considering the clinical harm of nutritional risks for patients, we should screen patients for nutritional risk as soon as possible. Subsequently, we can choose the appropriate nutritional pathways and nutritional preparations, and implement personalized nutritional support treatment. If enteral nutrition is difficult to implement, you can start with light enteral nutrition to gradually improve tolerance, improve nutritional status, and improve body stress protection (9). High energy-density nutritional preparations can not only improve the nutritional indicators of patients with severe heart failure, but also reduce their level of inflammatory factors to improve heart function, which is more in line with the needs of fluid intake restriction management (7,10). Resting energy expenditure (REE) is currently considered to be the gold standard for measuring human energy expenditure, especially in elderly patients (11). Studies have pointed out that the REE of hospitalized patients with different body mass index (BMI) is not the same: the average REE of patients with a BMI lower than 21 kg/m^2 is 21.4 kcal/kg · d, while the average REE of patients with a BMI higher than 21 kg/m^2 is 18.4 kcal/kg · d. For critically ill patients with overweight, obesity, and poor tolerance to cardiac function, nutritional support based on individual needs is more conducive to risk control. That is to prevent, manage, treat diseases and optimize health through personalized nutrition support treatment of human beings. Daily negative balance for patients to keep weight loss per week at about 0.45-0.9 kg is 500-750 kcal; in other words, that is to control daily intake at 1200-1500 kcal for women or 1500-1800 kcal for men. Especially those with BMI ≥ 35 kg/m^2 need control to reduce body weight by 5 %-10 % (6). The nutritional preparations of this group of patients are mainly non-elemental and special-application high-energy density preparations accounting for 61.76 %. An 84.22 % of the achieved dose was concentrated in 500 ml-1000 ml. Promoting gastrointestinal motility drugs and probiotics can improve the control of enteral nutrition complications and promote enteral nutrition to achieve the dose target. In the choice of nutritional support for this group of patients, parenteral nutrition and supplemental parenteral nutrition accounted for 42.54 %, while only 40.35 % of patients started enteral nutrition within 48 hours. The delay in the implementation of early enteral nutrition is not conducive to the protection of intestinal barrier function, and increases the risk of intestinal bacterial translocation and infection.

The nutritional risk of patients with severe cardiac disease is positively correlated with age, and the older the age, the higher the risk (12). Malnutrition and nutritional risks are mainly manifested as hypoproteinemia, anemia, and high capacity load accompanied by deterioration of heart and kidney function, which leads to a higher prognostic risk for patients (13). In this study, the Cr and NT-proBNP values of the malnutrition risk group were higher than those of the no-risk group. B-type natriuretic peptide (brain natriuretic peptide, BNP) and N-terminal B-type natriuretic peptide precursor (NT-pro BNP) as biological markers for the diagnosis of cardiac insufficiency are widely used in clinical practice. They are important indicators for judging the severity of heart failure, risk stratification and prognosis, and to evaluate the effect of treatment. Ventricular myocytes produce amino acid residue-containing precursor B-type natriuretic peptide (pre-pro BNP) under the pathological conditions of increased ventricular pressure and volume load, and then divide it into amino acid-containing B-type natriuretic peptide precursor (pro BNP), which is cleaved into two parts under the action of endonuclease. The biologically active BNP containing amino acids and the non-biologically active NT-pro BNP containing amino acids are secreted into the blood circulation by the cardiomyocytes in equal numbers of molecules. BNP can accurately reflect the degree of cardiac insufficiency, while NT-proBNP is affected by renal insufficiency and changes more significantly (14). TC is one of the main variables that stably predicts the death of long-term hospitalized patients with heart failure (15). In this study, the TC value of the nutritional risk group was lower than that of the no-risk group, and the difference between the no-risk group and the low-risk group was statistically significant. Blood TC levels are affected by many factors such as

diet, drug control, and lifestyle. Fat, cholesterol, especially saturated fatty acids, can increase blood cholesterol levels; plant-based dietary patterns, dietary fiber, plant sterols, etc., can affect the absorption of cholesterol or reduce blood cholesterol levels (16). Insufficient exogenous intake and endogenous regulatory synthesis disorders in disease states can cause blood levels to drop.

Killip's heart function classification and the NYHA classification are used to evaluate heart function — the worse the heart function, the higher the nutritional risk. Cardiac function classification can be used as a predictor of nutritional risk (13). In the subgroup with Killip cardiac function classification, the higher the nutritional risk, the lower the PA value, and the difference between the high-risk and low-risk groups is statistically significant. Lourenço et al. (17) found that patients with PA ≤ 15 mg/dL have a higher disability and mortality rate than patients with heart failure and PA > 15 mg/dL. CABASSI et al. (18) proposed that PA is a more accurate predictor of death in elderly heart failure patients with increased BNP, and is of great significance in screening and identifying high-risk heart failure patients with high nutritional risk.

In 1/3-1/2 of patients with heart failure, especially chronic heart failure combined with renal insufficiency, poor gastrointestinal function entails a risk of enteral nutrition intolerance and complications (19). The amount and rate of nutritional support and heart function influence each other. In this study, the incidence of major adverse cardiac events in severe EN cardiac patients reached 64.91 %, and the incidence of enteral nutrition-related complications was 54.39 %, which was between 36.7 % and 95.1 % in related reports (20-22). The overall hospital mortality rate of patients with severe cardiac disease is 28.23 %. The higher the nutritional risk, the higher the mortality rate, which is positively correlated with nutritional risk. The in-hospital mortality rate of EN patients with severe cardiac disease was 11.00 %, and the difference between risk groups was not statistically significant. This may be related to the small sample size, and further research is needed.

CONCLUSION

Patients with severe heart disease have a high nutritional risk with complex conditions, and the worse the cardiac function, the higher the nutritional risk. The high incidence of EN support-related complications is positively correlated with nutritional risk, and EN is difficult to implement. Early nutritional assessment and selection of appropriate individualized nutritional treatment support methods are required. Close observations should be made to strengthen the monitoring of high-risk factors and the identification and treatment of complications; to improve the quality and effect of nutritional support, and to achieve the treatment goal of improving patient outcome.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

Complicaciones asociadas a la nutrición parenteral en los enfermos con infección por SARS-CoV-2

Parenteral nutrition-associated complications in patients with SARS-CoV-2 infection

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Resumen

Introducción: se desconoce si los pacientes diagnosticados de infección respiratoria aguda por SARS-CoV-2 (COVID-19) presentan más riesgo de complicaciones asociadas a la nutrición parenteral (NP).

Objetivo: conocer la incidencia, los factores de riesgo y la mortalidad de las complicaciones asociadas a la NP en esta población.

Métodos: estudio de cohortes prospectivo de 87 pacientes diagnosticados de infección por SARS-CoV-2. Se analizan la tasa de incidencia de las complicaciones y las *odds ratio* (OR) de diferentes factores.

Resultados: la edad ≥ 65 años (OR: 2,52, IC 95 %: 1,16 a 5,46), los antecedentes de obesidad (OR: 3,34, IC 95 %: 2,35 a 4,33) y el tratamiento con propofol (OR: 2,45, IC 95 %: 1,55 a 3,35) o lopinavir/ritonavir (OR: 4,98, IC 95 %: 3,60 a 6,29) se asociaron al desarrollo de hipertrigliceridemia. Los pacientes con obesidad (OR: 3,11, IC 95 %: 1,10 a 8,75) o dislipemia (OR: 3,22, IC 95 %: 1,23 a 8,40) y los tratados con propofol (OR: 5,47, IC 95 %: 1,97 a 15,1) presentaron mayor riesgo de infección asociada al catéter (IAC). No se observó ningún factor de riesgo relacionado con el desarrollo de hiperglucemia. La mortalidad fue mayor en los pacientes con IAC (46,7 % *vs.* 10,8 %, p = 0,014). El riesgo de mortalidad fue superior en los enfermos de ≥ 65 años (OR: 2,74, IC 95 %: 1,08 a 6,95) o con IAC (OR: 3,22, IC 95 %: 1,23 a 8,40).

Conclusiones: la incidencia de complicaciones asociadas a la NP en pacientes diagnosticados de infección por SARS-CoV-2 es elevada. El riesgo de mortalidad es superior en los enfermos mayores de 65 años o con IAC.

Palabras clave:

Hiperglucemia. Hipertrigliceridemia. Hepatopatía. Infección asociada al catéter. Nutrición parenteral.

Abstract

Background: it is unknown whether patients with acute respiratory distress syndrome (ARDS) secondary to COVID-19 are at greater risk of developing complications associated with parenteral nutrition (PN).

Aim: to describe the incidence, risk factors, and clinical impact of complications in patients with ARDS-COVID-19 receiving PN.

Methods: a prospective cohort study of 87 patients with ARDS-COVID-19 infection. The incidence of complications and odds ratios of risk factors were analysed.

Results: age ≥ 65 years (OR, 2.52, 95 % CI: 1.16 to 5.46), obesity (OR, 3.34, 95 % CI: 2.35 to 4.33) and treatment with propofol (OR, 2.45, 95 % CI: 1.55 to 3.35) or lopinavir/ritonavir (OR, 4.98, 95 % CI: 3.60 to 6.29) were risk factors for hipertriglyceridemia. Obesity (OR, 3.11, 95 % CI: 1.10 to 8.75), dyslipidemia (OR, 3.22, 95 % CI: 1.23 to 8.40) or treatment with propofol (OR, 5.47, 95 % CI: 1.97 to 15.1) were risk factors for intravascular catheter-related infection. No risk factors were described for hiperglycemia. Mortality was higher in patients with intravascular catheter-related infection (46.7 % vs 10.8 %, p = 0.014). Mortality risk was higher in older patients (OR, 2.74, 95 % CI: 1.08 to 6.95) or patients with intravascular catheter-related infection (OR, 3.22, 95 % CI: 1.23 to 8.40).

Conclusions: the incidence of complications associated with PN in patients with COVID-19-related ARDS is frequent. The mortality risk is higher in older patients or those with catheter-related infection.

Keywords:

Hyperglycemia. Hypertriglyceridemia. Liver disease. Intravascular catether-related infection. Parenteral nutrition.

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INTRODUCCIÓN

Una cepa nueva de coronavirus se describió en Wuhan (China) en diciembre de 2019. Desde entonces, este virus se ha diseminado por prácticamente la totalidad de los países del mundo. El espectro de la enfermedad es muy variable: va desde la infección asintomática hasta la neumonía complicada con síndrome respiratorio agudo severo (SARS), el shock séptico y el fallo multiorgánico. Las personas de edad avanzada o con enfermedades crónicas presentan un cuadro clínico más grave (1). Aproximadamente, 1 de cada 5 individuos que padecen la enfermedad desarrollan insuficiencia respiratoria aguda, con necesidad de ingreso en una unidad de cuidados intensivos (UCI) (2).

Una terapia nutricional precoz en el paciente crítico, preferiblemente utilizando la vía enteral, ha demostrado ser una estrategia terapéutica que puede reducir la severidad de la enfermedad y disminuir las complicaciones y el tiempo de estancia en la UCI (3). Algunos enfermos requieren nutrición parenteral (NP) cuando la nutrición enteral (NE) está contraindicada o no es capaz de cubrir la totalidad de las necesidades nutricionales. La NP no está exenta de riesgo: se asocia a diferentes complicaciones, como hiperglucemia, alteración del perfil lipídico, infección asociada al catéter venoso central (IAC) y enfermedad hepática asociada a la NP (4). Se han descrito diferentes factores de riesgo relacionados con estas complicaciones, como la presencia de obesidad, diabetes *mellitus* (DM) o sepsis; el uso de fármacos, como corticoides, inhibidores de la bomba de protones, benzodiacepinas y antibióticos, y el tipo de lípidos aportado en la NP (5). Además, los pacientes críticos por SARS-CoV-2, debido a la respuesta inflamatoria sistémica y al uso de fármacos concomitantes, pueden presentar resistencia a la insulina, aumento de la lipólisis y alteración del metabolismo de las proteínas, con mayor riesgo de complicaciones asociadas a la NP (6). Se desconoce el papel que tienen estas complicaciones en la evolución de los enfermos con SARS-CoV-2.

El objetivo de este estudio fue conocer la incidencia, los factores de riesgo relacionados y el efecto sobre la mortalidad de las complicaciones asociadas a la NP en los pacientes ingresados con infección por coronavirus en la UCI durante la pandemia de 2020.

MATERIAL Y MÉTODOS

TIPO Y ÁMBITO DEL ESTUDIO

Estudio observacional, analítico, longitudinal, prospectivo, de cohortes, según la práctica clínica habitual, que incluyó a todos los pacientes mayores de 18 años diagnosticados de infección por SARS-CoV-2 con distrés respiratorio (7) y necesidad de ventilación mecánica, ingresados en la UCI de un hospital terciario, a cargo del servicio de anestesia y reanimación, durante la primera ola de la pandemia de primavera de 2020.

POBLACIÓN ESTUDIADA

Se incluyeron todos los pacientes atendidos por la unidad de nutrición clínica que presentaron intolerancia gastrointestinal a la dieta oral o a la NE. La indicación de NP fue la presencia de íleo adinámico, diarrea intratable, ausencia de acceso enteral o intolerancia gastrointestinal durante la pronación. Ningún paciente tenía diagnóstico de error congénito del metabolismo lipídico, ni gestación. Los enfermos terminaban el estudio cuando presentaban tolerancia gastrointestinal a la dieta oral o la nutrición enteral o fallecían.

COMPOSICIÓN DE LA NP

La formulación de la NP fue individualizada. Los requerimientos calóricos se calcularon mediante la fórmula de Harris Benedict, multiplicado por un factor de enfermedad de 1,3. En los pacientes obesos se utilizó el peso ajustado para el cálculo energético según la fórmula:

$$\text{Peso ajustado} = (\text{peso actual} - \text{peso ideal}) \times 0{,}25 + \text{peso ideal}$$

La composición de la NP se ajustó a las recomendaciones para el soporte nutricional del paciente crítico según el consenso de la Sociedad Española de Medicina Intensiva (SEMICYUC) y la Sociedad Española de Nutrición Clínica y Metabolismo (SENPE) (8). Todos los pacientes recibían una mezcla de NP 3 en 1 por vía central, a través de la vena yugular derecha, colocada en condiciones de máxima asepsia. En todos los casos se utilizó una emulsión lipídica que contiene aceite de pescado: SMOFlipid® (Fresenius Kabi), teniendo la mezcla un 30 % de aceite de soja, 30 % de MCT, 25 % de aceite de oliva y 15 % de aceite de pescado, o Lipoplus® (Braun), teniendo la mezcla un 40 % de aceite de soja, 50 % de MCT y 10 % de aceite de pescado. Los electrolitos se ajustaron de acuerdo con las necesidades diarias del paciente. Todas las bolsas aportaron diariamente oligoelementos (Supliven®, Fresenius) y vitaminas (Cernevit®, Baxter). El volumen final de la NP fue de aproximadamente 1 ml/kcal, salvo que el paciente necesitara una restricción hídrica. La NP se administró diariamente durante 24 h mediante un catéter conectado a un filtro de 1,2 micras para limitar la infusión de partículas extrañas, siguiendo las recomendaciones de la *Federal Drug Addministation* (FDA) (9).

En los pacientes que lo necesitaron, se añadió insulina regular en la bolsa de NP a razón de 1 unidad por cada 10 g de glucosa aportados, con la idea de mantener un rango de glucosa de entre 140 y 180 mg/dl. Dos tercios de la insulina regular subcutánea extra requerida en las 24 h anteriores para mantener la glucemia dentro del rango se añadían a la bolsa de NP al día siguiente.

VARIABLES CLÍNICAS

Las variables del estudio fueron: edad (años), sexo (hombre/mujer), antecedentes de DM, dislipemia u obesidad (sí/no), índice de masa corporal (IMC, definido como peso en kilos/talla^2

en metros), composición de la NP por kg de peso del paciente en kilocalorías (kcal), aminoácidos en gramos (g), glucosa (g), lípidos (g), dosis de insulina (unidades/día) y necesidad de tratamiento con propofol (Fresenius Kabi) (sí/no), tocilizumab (Roactemra®, Roche) y lopinavir/ritonavir (Kaletra®, Abbvie Farmacéutica) (sí/no). También se recogieron los días de duración de la NP, la presencia de complicaciones asociadas a la NP (hiperglucemia, hipertrigliceridemia, IAC y hepatopatía secundaria a NP) (sí/no) y la mortalidad (sí/no).

Se definió la hiperglucemia como la presencia de al menos un valor de glucemia plasmática o capilar > 180 mg/dl; la hipertrigliceridemia, como al menos un valor de triglicéridos (TG) plasmáticos > 400 mg/dl; la IAC como la presencia de cualquier episodio de cultivo positivo de la punta del catéter en caso de retirada o hemocultivos simultáneos positivos por el mismo germen de una vena periférica y de sangre extraída del catéter venoso central en los pacientes con clínica de sepsis, y en ausencia de otra causa de infección; y la hepatopatía secundaria a NP, como el aumento de ambas enzimas de colestasis, gamma-GT y fosfatasa alcalina, dos veces por encima del límite superior de la normalidad señalado por el laboratorio. Se calculó la tasa de incidencia de cada una de estas complicaciones por separado, definida como el número de pacientes que desarrolló la complicación dividido por el número total de pacientes por 100 días de NP en el caso de la hiperglucemia, la hipertrigliceridemia y la hepatopatía, y por 1000 días de utilización del catéter de NP en el caso de la IAC.

VARIABLES BIOQUÍMICAS

Según el protocolo habitual, en todos los pacientes se realizó la extracción de una muestra de sangre venosa al menos una vez al día. El análisis incluía hemograma, creatinina, iones, perfil hepático, albúmina, ferritina y proteína C-reactiva. Semanalmente se midieron los niveles plasmáticos de TG en plasma mediante espectrometría, utilizando un método enzimático (autoanalizador Roche/Hitachi Cobas 8000, modelo c70, Roche Diagnostics®).

CRITERIOS ÉTICOS

El estudio se llevó a cabo de acuerdo con la práctica clínica habitual, sin realizar ninguna intervención diagnóstica o terapéutica diferente de las habituales, buscando una mejora en la asistencia a los pacientes con COVID-19. Los datos se analizaron de forma anónima en todo momento.

ANÁLISIS ESTADÍSTICO

Se realizó una estadística descriptiva, calculándose la media y la desviación estándar para las variables cuantitativas y la frecuencia relativa para las variables cualitativas. Las diferencias entre los grupos se compararon empleando el test de la "t" de Student para variables cuantitativas y la prueba del chi^2 para las variables cualitativas. Se estimaron las *odds ratios* (OR) de presentar cada una de las complicaciones estudiadas, con sus correspondientes intervalos de confianza al 95 % (IC 95 %), para los diferentes factores de riesgo considerados, utilizándose un análisis de regresión logística multivariante.

Los datos se procesaron mediante el programa SPSS, versión 18.0. Se consideró significativa toda $p < 0,05$.

RESULTADOS

Las características de los 87 pacientes incluidos en la cohorte, los fármacos utilizados y las variables relacionadas con la NP se señalan en la tabla I. El 66,7 % eran varones (59,1 ± 11,4 años, 28,4 ± 4,7 kg/m^2) y el 33,3 %, mujeres (62,2 ± 9,5 años, 30,5 ± 6,9 kg/m^2). La relación pO_2/FiO_2 en el primer día de la estancia en la UCI fue de 180 ± 62. El índice de estrés al ingreso en la UCI, medido por los niveles plasmáticos de albúmina (2,9 ± 0,3 g/dl), ferritina (2069 ± 291 g/dl) y proteína C-reactiva (15,2 ± 12,6 mg/dl), fue elevado. Los valores iniciales de gama GT y fosfatasa alcalina fueron 127 ± 125 UI/L y 94 ± 60 UI/L, respectivamente.

Tabla I. Características de la población y composición de la NP al inicio del tratamiento

	Total (n = 87)
Edad (media ± DE, años)	60,1 ± 10,8
Mujeres, n (%)	29 (33,3 %)
Hombres, n (%)	58 (66,6 %)
IMC (media ± DE, kg/m^2)	29,1 ± 5,6
Obesidad, n (%)	25 (28,7 %)
Dislipemia, n (%)	29 (33,3 %)
Diabetes *mellitus,* n (%)	21 (24,1 %)
Tocilizumab, n (%)	48 (55,2 %)
Lopinavir/ritonavir, n (%)	62 (71,2 %)

(Continúa en la página siguiente)

Tabla I (Cont.). Características de la población y composición de la NP al inicio del tratamiento

	Total (n = 87)
Propofol® n (%)	49 (56,3 %)
Calorías (media ± DE, kcal/kg/día)	26,9 ± 4,0
Aminoácidos (media ± DE, g/kg/día)	1,3 ± 0,2
Glucosa (media ± DE, g/kg/día)	3,2 ± 0,7
Lípidos (media ± DE, g/kg/día)	0,9 ± 0,2
Tipo de lípidos (SMOFlipid®) n (%)	58 (66,6 %)
Dosis de insulina (media ± DE, unidades/día)	34,1 ± 15,6
Días de NP (media ± DE, días)	8,5 ± 4,6

DE: desviación estándar; IMC: índice de masa corporal; NP: nutrición parenteral.

La tasa de incidencia de la hiperglucemia fue de 33 x 100 pacientes por día de NP y la de hipertrigliceridemia de 37 x 100 pacientes por día de NP. De los pacientes con perfil hepático normal al ingreso, únicamente 2 (2,3 %) presentaron elevación de la gamma-GT y la fosfatasa alcalina por encima de dos veces el límite superior de la normalidad, definido por el laboratorio, durante el seguimiento. Treinta y siete pacientes tuvieron un hemocultivo positivo por IAC, lo que equivale a una tasa de incidencia de 4,25 x 1000 pacientes por día de utilización del catéter. El germen aislado más común fue un *Staphyloccocus* coagulasa-negativo (Fig. 1).

Los pacientes con IMC elevado presentaron más frecuentemente hiperglucemia, hipertrigliceridemia o IAC, mientras que el uso de propofol o de lopinavir/ritonavir se asoció a una mayor frecuencia de hipertrigliceridemias o de IAC (Tabla II). No existían diferencias en la composición de la NP, ni en la dosis de insulina, ni en el uso de SMOFlipid® o Lipoplus® en cuanto al desarrollo de complicaciones (Tabla III). La duración de la NP fue mayor en los enfermos que presentaron hiperglucemia frente a los que no la presentaron (11,9 ± 4,6 *vs.* 7,5 ± 4,2, p = 0,000), hipertrigliceridemia (10,7 ± 4,6 *vs.* 7,2 ± 4,2, p = 0,001) o IAC (10,7 ± 4,1 *vs.* 7,0 ± 4,0, p = 0,000).

En el análisis multivariante (Tabla IV), ningún factor de riesgo analizado se asoció al desarrollo de hiperglucemia. La edad ≥ 65 años (OR: 2,52, IC 95 %: 1,16 a 5,46), el antecedente de obesidad (OR: 3,34, IC 95 %: 2,35 a 4,33) y el tratamiento con propofol (OR: 2,45, IC 95 %: 1,55 a 3,35) o lopinavir/ritonavir

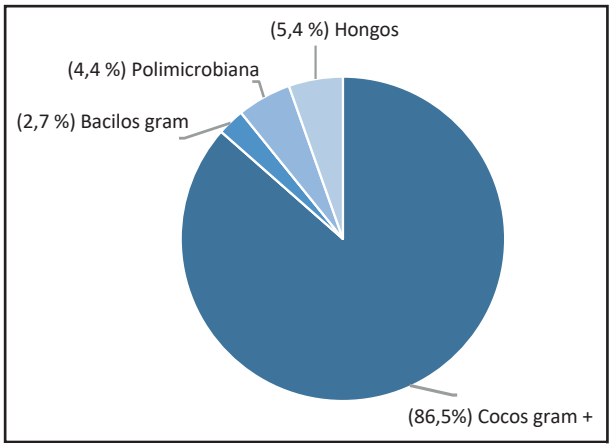

Figura 1.

Aislamiento microbiológico en las infecciones asociadas al catéter.

Tabla II. Factores relacionados con las complicaciones de la nutrición parenteral

	Hiperglucemia (n = 20)	Hipertriglicerideмia (n = 32)	IAC (n = 37)
Edad (media ± DE, años)	54,8 ± 9,2*	54,2 ± 9,7†	56,9 ± 11,0‡
Edad ≥ 65 años (n, %)	3 (15,0 %)	6 (18,7 %)	14 (37,8 %)
Sexo, varón (n, %)	15 (75,0 %)	23 (71,9 %)	23 (62,1 %)
IMC (media ± DE, kg/m^2)	31,3 ± 7,6*	31,3 ± 7,2†	31,2 ± 6,9‡
Obesidad (n, %)	9 (45,0 %)	13 (40,6 %)†	15 (40,5 %)‡
Dislipemia (n, %)	9 (45,0 %)	12 (37,5 %)	17 (53,1 %)‡
DM tipo 2 (n, %)	6 (30,0 %)	8 (25,0 %)	10 (27,0 %)
Propofol® (n, %)	15 (75,0 %)	23 (71,9 %)†	28 (75,7 %)‡
Lopinavir/ Ritonavir (n, %)	18 (90,0 %)	29 (90,6 %)†	28 (75,7 %)‡
Tocilizumab (n, %)	11 (55,0 %)	20 (62,5 %)	20 (54,0 %)

*IAC: infección asociada al catéter; DE: desviación estándar; IMC: índice de masa corporal; *p < 0,05, hiperglucemia frente a sin hiperglucemia; †p < 0,05, hipertrigliceridemia frente a sin hipertrigliceridemia; ‡p < 0,05, IAC frente a sin IAC.*

Tabla III. Composición y duración de la nutrición parenteral y desarrollo de complicaciones

	Hiperglucemia (n = 20)	Hipertriglice-ridemia (n = 32)	IAC (n = 37)
Calorías (media ± DE, kcal/kg/día)	28,2 ± 3,3	28,1 ± 3,8	27,3 ± 4,5
Aminoácidos (media ± DE, g/kg/día)	1,4 ± 0,1	1,4 ± 0,1	1,4 ± 0,2
Glucosa (media ± DE, g/kg/día)	3,4 ± 0,6	3,4 ± 0,6	3,3 ± 0,7
Lípidos (media ± DE, g/kg/día)	0,9 ± 0,1	0,9 ± 0,2	0,9 ± 0,2
Tipo de lípidos SMOFlipid® (n, %)	9 (45,0 %)	20 (62,5 %)	19 (45,0 %)
Dosis de insulina (media ± DE, unidades/día)	42,2 ± 21,8	36,3 ± 18,9	40,0 ± 19,5
Días de NP (media ± DE, días)	11,9 ± 4,6*	10,7 ± 4,6†	10,7 ± 4,1‡

*IAC: infección asociada al catéter; DE: desviación estándar; *p < 0,05, hiperglucemia frente a sin hiperglucemia; †p < 0,05, hipertrigliceridemia frente a sin hipertrigliceridemia; ‡p < 0,05, IAC frente a sin IAC.*

(OR: 4,98, IC 95 %: 3,60 a 6,29) se asociaron al desarrollo de hipertrigliceridemia. De igual forma, los pacientes con historia previa de obesidad (OR: 3,11, IC 95 %: 1,10 a 8,75) o dislipemia (OR: 3,22, IC 95 %: 1,23 a 8,40) y los tratados con propofol (OR: 5,47, IC 95 %: 1,97 a 15,1) presentaron mayor riesgo de IAC.

La mortalidad total fue del 33,3 % (29 pacientes). La mortalidad fue menor en los enfermos que desarrollaron hiperglucemia frente a aquellos otros con normoglucemia (15,0 % *vs.* 37,3 %, p = 0,042) o hipertrigliceridemia frente a normotrigliceridemia (18,7 % *vs.* 41,8 %, p = 0,020). La mortalidad fue mayor en presencia de IAC (46,7 % *vs.* 10,8 %, p = 0,014) (Fig. 2). No existieron diferencias en cuanto a mortalidad entre los pacientes que recibieron SMOFlipid® y aquellos que recibieron Lipoplus® (29,3 % *vs.* 31,0 %, p = 0,478). Sin embargo, en el análisis multivariante, la mortalidad se asociaba únicamente con la edad ≥ 65 años (OR: 2,74, IC 95 %: 1,08 a 6,95) o con la IAC (OR: 3,22, IC 95 %: 1,23 a 8,40).

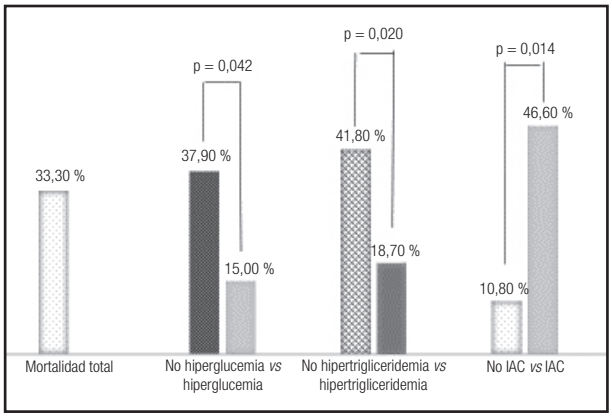

Figura 2.
Mortalidad asociada a complicaciones (IAC: infección asociada al catéter).

Tabla IV. Factores de riesgo y mortalidad para cada una de las complicaciones mediante el análisis de regresión logística

	Hiperglucemia OR (IC 95 %)	Hipertrigliceridemia OR (IC 95 %)	IAC OR (IC 95 %)
Edad ≥ 65 años (sí/no)	2,93 (0,99-8,60)	*2,52 (1,16-5,46)*	1,14 (0,46-2,80)
Sexo (hombre/mujer)	0,65 (0,20-2,02)	1,64 (0,98-2,30)	1,49 (0,59-3,78)
Obesidad (sí/no)	2,38 (0,78-7,25)	*3,34 (2,35-4,33)*	*3,11 (1,10-8,78)*
Dislipemia (sí/no)	2,07 (0,73-5,87)	1,41 (0,69-2,13)	*3,22 (1,23-8,40)*
Diabetes *mellitus* (sí/no)	1,57 (0,50-4,83)	0,88 (0,06-1,80)	1,38 (0,50-3,80)
Tipo de lípidos (SMOFlipid/Lipoplus)	0,64 (0,21-2,24)	1,10 (0,44-1,76)	1,01 (0,35-2,87)
Tocilizumab (sí/no)	0,78 (0,28-2,17)	1,19 (0,31-2,07)	1,21 (0,48-3,08)
Lopinavir/Ritonavir (sí/no)	3,36 (0,74-17,90)	*4,98 (3,60-6,29)*	1,89 (0,63-5,65)
Propofol® (sí/no)	2,47 (0,59-7,64)	*2,45 (1,55-3,35)*	*5,47 (1,97-15,10)*
Mortalidad (sí/no)	0,28 (0,07-1,10)	0,31 (0,01-1,30)	*3,22 (1,23-8,40)*

OR: odds ratio; *IC: intervalo de confianza; IAC: infección asociada al catéter.*

DISCUSIÓN

Entre las complicaciones asociadas a la NP, la hiperglucemia, la hipertrigliceridemia, la hepatopatía y la IAC son las más frecuentes. Este estudio prospectivo demuestra que los pacientes diagnosticados de infección por SARS-CoV-2 desarrollan frecuentemente complicaciones asociadas a la NP, especialmente hiperglucemia, hipertrigliceridemia e IAC. La prevención y detección precoz de estas complicaciones tiene relevancia en la práctica clínica, dado que su control asegura una mejor evolución, especialmente en el paciente crítico.

La incidencia de la hiperglucemia en los pacientes sometidos a NP es del 50 % (10). En los enfermos con SARS-CoV-2 de nuestro estudio fue de 33 x 100 días de NP. Un adecuado control glucémico ha demostrado reducir la morbimortalidad (11), así como las complicaciones cardiovasculares asociadas (12). Para controlar la glucemia se recomienda disminuir el aporte de glucosa en la NP a 3 g/kg/día y añadir insulina al tratamiento (13), medidas ambas que se garantizaron en nuestra población. Se ha descrito que el riesgo de hiperglucemia está incrementado en los enfermos de ≥ 65 años, obesos o con historia previa de DM (14). En nuestro estudio, entre el 25 y el 35 % de los enfermos tenían un diagnóstico de obesidad, dislipemia o DM, pero ninguna de estas patologías ni la edad ≥ 65 años se asoció con el desarrollo de hiperglucemia.

La hipertrigliceridemia asociada a la NP tiene una frecuencia de entre el 6 y el 60 %. Este porcentaje tan amplio se debe al punto de corte utilizado para su definición, a las características de la población estudiada y a la composición de la NP (15,16). Los expertos de la ASPEN sugieren que el riesgo de efectos adversos es mayor cuando los niveles de TG en plasma superan los 400 mg/dl (17). Considerando este punto de corte, en nuestro estudio, la incidencia de hipertrigliceridemia fue de 37 x 100 pacientes-días de NP. Esta complicación se ha relacionado con factores como la obesidad y la DM (18), la composición de la NP, especialmente la cantidad y el tipo de emulsión lipídica utilizada (19), y el uso de fármacos como el propofol (20), el tolicilizumab (21) y el lopinavir/ritonavir (22). En nuestro estudio, la edad mayor o igual a 65 años (OR: 2,52, IC 95 %: 1,16-5,46), la obesidad (OR: 3,34, IC 95 %: 2,35-4,33) y el tratamiento con propofol (OR: 2,45, IC 95 %: 1,55-3,35) o lopinavir/ritonavir (OR: 4,98, IC 95 %: 3,60-6,29) se asociaron a un mayor riesgo de desarrollar hipertrigliceridemia. No se encontraron diferencias significativas en cuanto al tipo de emulsión lipídica utilizada, estando ambas enriquecidas con aceite de pescado.

Otra complicación relacionada con la NP es la IAC (23). En nuestro estudio, la incidencia de la IAC fue de 4,25 x 1000 pacientes-día de NP, que es similar a la descrita en la literatura (24). El factor principal relacionado con la IAC es la falta de medidas estrictas de asepsia cutánea durante la colocación y manipulación del catéter venoso central. Otros factores son el lugar de inserción, el número de luces, el tipo y el tiempo de permanencia del catéter insertado, la existencia de focos adicionales de infección, la hiperglucemia, la edad, el sexo y la inmunosupresión (25). En nuestro estudio, factores como la edad, el sexo, la composición de la emulsión y la necesidad de insulina en la NP no demostraron aumentar el riesgo de infección. Los antecedentes de obesidad o dislipemia o el uso de propofol se asociaron a las IAC. Probablemente esto sea debido, al menos en parte, a que los pacientes obesos presentan mayor riesgo de infección y a que el uso del propofol puede suponer un aumento del número de veces que se manipula el catéter.

La duración de la NP es un factor de riesgo descrito para el desarrollo de complicaciones. En nuestra población, el número de días con NP fue mayor en los pacientes que presentaban hiperglucemia, hipertrigliceridemia o IAC.

La mortalidad del paciente hospitalizado por SARS-CoV-2 es elevada, en torno al 28 % (26). En nuestra serie, la mortalidad fue similar, del 33 %. El riesgo de mortalidad fue superior en los enfermos mayores de 65 años y en aquellos que presentaban IAC, con una odds ratio de *exitus* dos y tres veces superior, respectivamente.

Este estudio tiene algunas limitaciones. En primer lugar, el escaso tamaño de la muestra, que puede dificultar la validación externa de los resultados. En segundo lugar, no existe un grupo de control de pacientes críticos sin infección por coronavirus. Nuestro estudio se diseñó como un estudio de cohortes prospectivo, válido para analizar la asociación pero no la causalidad, como base para generar hipótesis. En tercer lugar, aquellos enfermos que fallecieron precozmente tuvieron menos tiempo para desarrollar las complicaciones asociadas a la NP. Esto puede explicar por qué se observó menor mortalidad en los pacientes con hiperglucemia e hipertrigliceridemia. Por último, en relación a la IAC hay que tener en cuenta que, probablemente, en los primeros días de la oleada de la pandemia, el acceso y la manipulación de los catéteres venosos los realizó personal menos experto y con medidas de asepsia menos estrictas que las de las unidades de críticos habituales.

En conclusión, los pacientes con SARS-CoV-2 que reciben NP tienen un riesgo elevado de desarrollar hiperglucemia, hipertrigliceridemia e IAC. La mortalidad de los enfermos que presentan alguna de estas complicaciones está incrementada. Estos eventos son detectables y tratables en la mayoría de los casos. Por este motivo, es importante diseñar e implementar protocolos de actuación para monitorizar la glucemia y los niveles de TG en plasma, así como colocar y manipular los catéteres venosos con las máximas condiciones de asepsia y vigilar los signos de infección para prevenir y tratar precozmente el desarrollo de estas complicaciones.

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Nutrición Hospitalaria

Trabajo Original

Pediatría

Changes in body composition and cardiometabolic risk factors in relation to the reduction in body mass index in adolescents with obesity

Cambios en la composición corporal y factores de riesgo cardiometabólico en relación con la reducción del índice de masa corporal en adolescentes con obesidad

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Abstract

Introduction: there are controversial data in relation to the reduction in body mass index standard deviation score (BMI-SDS) needed to improve adiposity in the pediatric population with obesity. The aim of this work was to determine the minimum variation in BMI-SDS required to improve the values of adiposity markers and cardiometabolic risk factors in growing adolescents with obesity.

Methods: a longitudinal study consisting of clinical evaluation (waist circumference, waist-to-height ratio, fat mass index, and blood pressure) and blood testing (insulin resistance and lipid profile) was conducted in 350 adolescents with obesity (152 boys and 198 girls) aged 10.2-14.3 years who went through a combined intervention (12 months).

Results: a decrease in SDS-BMI ≤ 0.5 was not associated with any significant improvement in the clinical features and blood testing recorded. A decrease in BMI-SDS > 0.5, and especially if > 1.0, was linked to a significant improvement in adiposity markers. A decrease in BMI-SDS > 0.5 was associated with a significant improvement in insulin resistance, and a decrease in BMI-SDS > 1.0 was associated with a significant decrease in the percentage of patients who showed high values of systolic blood pressure, HOMA-IR, and lipid profile

Conclusions: improvement in body composition, insulin resistance, and lipid profile can be observed with reductions in BMI-SDS ≥ 0.5 in obese adolescents, while extended benefits are obtained by losing at least 1.0 BMI-SDS.

Keywords:

Adolescents. Body composition. Body mass index reduction. Cardiometabolic risk factors. Lipid profile. Obesity.

Resumen

Introducción: los datos en relación con la reducción del índice de masa corporal (IMC-SDS) necesario para mejorar la adiposidad en la población pediátrica con obesidad son controvertidos. El objetivo de este trabajo es determinar la variación mínima del IMC-SDS necesaria para mejorar los valores de los marcadores de adiposidad y los factores de riesgo cardiometabólico en adolescentes obesos.

Métodos: estudio longitudinal clínico (perímetro de cintura, índice cintura-estatura e índice de masa grasa y presión arterial) y analítico (HOMA-R y perfil lipídico) realizado en 350 adolescentes con obesidad (152 niños y 198 niñas) de entre 10,2 y 14,3 años de edad que completaron una intervención combinada (12 meses).

Resultados: una disminución en el índice de masa corporal (SDS-BMI) ≤ 0,5 no se asoció con ninguna mejora significativa de las características clínicas y analíticas registradas. Una disminución del IMC-SDS > 0,5, y especialmente si > 1,0, se relacionó con una mejora significativa de los marcadores clínicos de adiposidad. Una disminución del IMC-SDS > 0,5 se asoció con una mejora significativa de la resistencia a la insulina y una disminución del BMI-SDS > 1,0 se asoció con una disminución significativa del porcentaje de pacientes que mostraban valores altos de presión arterial sistólica, HOMA-IR y perfil lipídico

Conclusiones: con una reducción del IMC-SDS ≥ 0,5 se observa una mejoría tanto en la composición corporal como en los factores de riesgo cardiovascular en los adolescentes obesos; no obstante, estos beneficios son mayores si la reducción del IMC-SDS es superior a 1.0.

Palabras clave:

Adolescentes. Composición corporal. Factores de riesgo cardiometabólico. Reducción del índice de masa corporal. Perfil lipídico. Obesidad.

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INTRODUCTION

Childhood obesity has progressed in a sustained increase in most industrialized countries, and currently depicts the most relevant nutritional disorder in our environment (1,2). In addition, childhood obesity is related to a greater immediate risk of cardiometabolic complications in relation to adiposity, such as high levels of blood pressure, increased lipid serum concentration, insulin resistance (metabolic syndrome) and non-alcoholic fatty liver disease (3-7).

Waist circumference (WC) and waist-to-height ratio (WtHr) are good predictors of cardiovascular disease risk factors (8,9). In spite of this, body mass index (BMI) has been frequently used in the diagnosis and follow-up of children with obesity (10,11) since it shows a good correlation with body fat as measured by dual-energy X-ray absorptiometry (gold standard to define obesity) and cardiovascular risk factors (3,12-15).

The implementation of a combined dietary-behavioral-physical activity intervention has proved to have a positive effect in adolescents with obesity. As body mass index standard deviation score (BMI-SDS) decreases, so does fat mass in the absence of changes in fat-free mass and, consequently, in longitudinal growing (16,17). Despite this, there are controversial data in relation to the reduction in BMI-SDS needed to improve adiposity in the pediatric population with obesity. A recently published meta-regression study (18) concluded that a minimum 0.6 decrease in BMI-SDS is imperative in order to attain any improvement in fat mass. Furthermore, a systematic review with meta-analysis (19) and several meta-regression studies (20,21) concluded that reductions in BMI-SDS are likely to improve cardiovascular outcomes in childhood and adolescent obesity; nevertheless, at present, they are unable to recommend a definite value of BMI-SDS reduction indispensable to improve markers of metabolic health. In other words, the reduction in BMI-SDS required to improve both body composition and the profile of cardiovascular risk factors by means of lifestyle interventions has not yet been fully established.

The objective of this study was the identification of the minimum change in BMI-SDS required to improve adiposity markers and cardiometabolic risk factors in adolescents with obesity enrolled in a combined intervention. We hypothesized that exclusive weight loss is not imperative in order to optimize body composition and cardiometabolic risk factors since, in accordance to the old aphorism: "the child becomes slim by means of keeping a stable weight because he/she is growing".

MATERIAL AND METHODS

PARTICIPANTS

This was a longitudinal study (convenience sample) that was conducted in 350 adolescents (152 boys and 198 girls) aged 10.2 to 14.3 years and previously diagnosed with obesity (BMI-SDS > 2.0). All patients included in the study were Caucasian and completed a clinical assessment (clinical evaluation was performed every 3 months) and blood testing before and after their participation in a one-year intervention program that comprises a combination of dietary-behavioral-physical activity measures. Medical care was provided in the Pediatric Endocrinology Unit of the Navarra Hospital Complex (Pamplona, Spain) in the period from January 2016 to December 2019. All participants had previously experienced pubertal changes (Tanner stages: II-V). Exclusion criteria included obesity secondary to genetic, metabolic or endocrine disease.

Appropriate information on proceedings and potential implications was delivered to the parents and/or legal guardians, and the corresponding written consent was a requirement prior to subject incorporation to this study in all cases. The study was then submitted to the Ethics Committee for Human Investigations of the Navarra Hospital Complex (in accordance with the ethical standards stated in the Declaration of Helsinki, 1964 and later amendments) for final acceptance.

COMBINED DIETARY-BEHAVIORAL-PHYSICAL ACTIVITY INTERVENTION

The combined intervention has been previously addressed (17,22). The central idea of the program corresponds to the following maxim: "the child becomes slim by keeping a stable weight because he/she is growing," and includes nutritional education, a nutritional intervention, the promotion of physical activity and healthy lifestyles, and self-monitoring of body weight (weekly registration of weight).

Acquisition of the basic practical and theoretical skills enabling self-monitoring was mandatory in order to be included in this study. A multidisciplinary team (pediatrician, nurse and dietitian) educated the patients and their families on nutrition, synchronizing the education and the first visit. The contents of these structured sessions (nutritional value of the different food groups, food pyramid, physical activity, etc.) were personalized according to the characteristics of each patient and family, and continuous guidance was provided for all of them. The program was developed or extended depending on the needs of the patient in subsequent visits.

The approach to weight maintenance was accomplished by means of a diversified and well balanced diet for the whole family with no strict restrictions or immediate or exaggerated weigh loss. The Mediterranean diet, adapted to family customs or the preferences of the patients, was our dietary model. It was mandatory to ensure five daily meals, with the requirement that meal schedules were respected. The participants were instructed to avoid eating between meals and to increase the time of intake (eating slowly and adequately chewing the food).

In addition, an individualized scheme to increase physical activity was proposed to every participant and consisted of a daily, regulated (60 min) free-choice activity (swimming, walking, cycling, martial arts, etc.) and an increase in daily activity (such as walking up the stairs rather than using the elevator, walking, helping in house tasks, etc.).

Every family was given a leaflet with general recommendations on usual diet, physical activity (sports and home activity), and a healthy lifestyle.

The participants were divided into four groups in line with their changes in BMI-SDS in the course of the combined intervention (between the beginning and after 12 months of follow-up):

- Group I: participants with increased BMI-SDS.
- Group II: participants with BMI-SDS decreased by > 0 to ≤ 0.5.
- Group III: participants with BMI-SDS decreased by > 0.5 to ≤ 1.0.
- Group IV: participants with BMI-SDS decreased by > 1.0 to ≤ 1.5.

CLINICAL ASSESSMENT

The anthropometric measurements were taken following a protocol that had been previously published (17,22). The following anthropometric measurements were registered in the first appointment and every 3 months thereafter: weight, height, skinfold thickness (biceps, triceps, subscapular, and suprailiac) and waist circumference.

The subjects had to be in underwear and barefoot in order to take weight and height measurements. Weight was determined using an Año-Sayol scale (reading interval, 0 to 120 kg and a precision of 100 g), and height was measured using a Holtain wall stadiometer (reading interval, 60 to 210 cm; precision, 0.1 cm). BMI was calculated after applying the corresponding formula: weight (kg)/height^2 (m).

Skinfold thickness values were measured with an accuracy of 0.1 mm on the left side of the body with Holtain skinfold calipers (CMS Weighing Equipment, Crymych, United Kingdom). The percentage of total body fat and fat mass (kg) was estimated using the equations reported by Slaughter et al., adjusted for sex and age (23). The FMI was calculated using the following formula: fat mass (kg)/height^2 (m).

WC was quantified using a tape measure (reading interval, 0 to 150 cm; precision, 0.1 cm) placed on a horizontal line equidistant from the last rib and the iliac crest, and the WtHR was calculated in accordance to the formula: waist (m)/height (m). All these measurements were reported by the same trained individual.

The SDS values for weight, height, BMI and WC were quantified using the program *Aplicación Nutricional*, by the Spanish Society of Pediatric Gastroenterology, Hepatology and Nutrition (Sociedad Española de Gastroenterología, Hepatología y Nutrición Pediátrica, available at http://www.gastroinf.es/nutritional/). The graphs by Ferrández et al. (Centro Andrea Prader, Zaragoza 2002) were the reference charts used for this assessment (24).

The subjects were placed in the supine position in order to measure blood pressure (BP) in the right arm using a Visomat comfort 20/40 (Roche Diagnostics Inc., Amman, Jordan) digital blood pressure monitor, selecting the lowest of three measurements. Arterial hypertension was defined when systolic (SBP) and/or diastolic pressure (DBP) was equal to or higher than the 95th percentile for age, sex, and height, in accordance to the American reference charts (National high blood pressure Program in Children and Adolescents) (25).

BLOOD TESTING

Fasting glucose, insulin, triglycerides (TGC), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were determined in the course of the combined intervention (at the onset and after 12 months of follow-up) by means of standardized methodologies. In accordance to the International Diabetes Federation consensus report for children and adolescents (26), serum TC levels higher than 200 mg/dL, TGC levels higher than 150 mg/dL, LDL-C levels higher than 130 mg/dL, or HDL-C levels lower than 40 mg/dL were accepted as dyslipidemia, and fasting blood glucose higher than 100 mg/dL was considered dysglycemia.

The HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) indexes were calculated from fasting glucose and insulin concentrations (fasting glucose in mmol/L x fasting insulin in mU/L) / 22.5) with the aim of assessing insulin resistance. An HOMA-IR value equal to or higher than 4.0 was considered to represent insulin resistance (27).

STATISTICAL ANALYSIS

Results are displayed as percentages (%) and means (M), with their corresponding standard deviations (SDS). The Chi-square test was used to compare percentages within and between groups according to changes in BMI-SDS. Student's *t*-test was used to compare mean values for the variables recorded within groups. ANOVA was used to compare mean values for variables between groups. Pearson's test was used to quantify the degree of linear association between quantitative variables. Statistical analyses were performed using the program Statistical Packages for the Social Sciences, version 20.0 (Chicago, IL, USA). Statistical significance was accepted when the p-value was < 0.05.

RESULTS

The mean values of clinical and biochemical features registered in individuals of both sexes before the implementation of the combined intervention are displayed in table I, as well as the comparison. Mean values of age, weight, height, BMI and waist were significantly higher in boys ($p < 0.01$). There were no significant differences in the mean values of weight-SDS, height-SDS, BMI-SDS, WC-SDS, WtHr and FMI, as well as in SBP or DBP, and the biochemical characteristics registered between the participants of both sexes.

At baseline, there was a statistically significant positive correlation ($p < 0.01$) between BMI-SDS and FMI (boys: $r = 0.899$, girls: $r = 0.829$), WC-SDS (boys: $r = 0.913$, girls: $r = 0.824$) and WtHr (boys: $r = 0.843$, girls: $r = 0,830$).

Table I. Clinical and biochemical data before combined intervention in both sexes (mean ± SDS)

Characteristics	All (n = 350)	Boys (n = 152)	Girls (n = 198)	p-value*
Clinical data				
Age (years)	12.1 ± 1.6	12.5 ± 1.5	11.7 ± 1.8	0.001
Weight (kg)	69.9 ± 13.8	76.2 ± 14.1	65.1 ± 11.9	0.001
Weight-SDS	2.94 ± 1.12	3.14 ± 0.96	2.92 ± 0.88	0.20
Height (cm)	155.5 ± 10.6	159.3 ± 10.9	152.5 ± 9.6	0.001
Height-SDS	0.82 ± 0.91	0.88 ± 0.91	0.76 ± 0.81	0.90
BMI (kg/m^2)	28.4 ± 3.8	29.4 ± 3.9	27.6 ± 3.5	0.001
BMI-SDS	3.05 ± 1.01	3.36 ± 0.99	2.88 ± 0.98	0.15
WC (cm)	92.6 ± 9.1	97.6 ± 9.2	89.7 ± 8.2	0.001
WC-SDS	2.40 ± 0.9	2.85 ± 0.91	2.44 ± 0.84	0.31
WtHr	0.59 ± 0.05	0.61 ± 0.04	0.59 ± 0.05	0.23
FMI (kg/m^2)	10.7 ± 2.0	10.6 ± 2.0	10.7 ± 1.8	0.69
Systolic BP (mmHg)	123.1 ± 11.4	124.9 ± 11.3	122.0 ± 11.9	0.40
Diastolic BP (mmHg)	70.2 ± 8.6	70.4 ± 8.5	70.2 ± 9.1	0.32
Laboratory data				
Fasting glucose (mg/dL)	87.5 ± 6.7	88.6 ± 7.4	86.6 ± 7.0	0,60
Insulin (mU/L)	19.7 ± 9.1	18.1 ± 9.8	20.9 ± 12.1	0.89
HOMA-IR	4.28 ± 2.19	3.99 ± 2.22	4.51 ± 2.9	0.27
Triglycerides (mg/dL)	106.7 ± 37.6	104.0 ± 35.7	110.3 ± 39.4	0.19
Total cholesterol (mg/dL)	164.6 ± 27.1	167.4 ± 31.9	162.4 ± 24.7	0.72
HDL-C (mg/dL)	44.8 ± 8.2	45.7 ± 8.1	44.2 ± 8.3	0.11
LDL-C (mg/dL)	100.1 ± 23.5	102.3 ± 25.1	98.1 ± 21.3	0.69

**Student's t-test. BMI: body mass index; WC: waist circumference; WtHR: waist-to-height ratio; FMI: fat mass index; BP: blood pressure; HOMA-IR: homeostasis model assessment of insulin resistance; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.*

The mean initial and final values for weight and BMI-SDS of these groups are shown in table II. The comparison of the groups confirmed that there were no significant differences between the mean values of both weight and BMI-SDS at the onset of the combined intervention. There were no significant differences in the changes in weight at 12 months of follow-up in the groups with a decrease in BMI-SDS (groups I, II and III).

The modifications in clinical features in relation to variations in BMI-SDS at 12 months of follow-up are shown in table III. The comparison of the groups uncovered no significant differences in any of the clinical features registered at the onset of the combined intervention. However, at 12 months of follow-up, the analysis identified that a decrease in BMI-SDS had was related to a significant decrease in WC-SDS, WtHR and FMI, while height-SDS and SBP and DBP revealed a non-significant decrease (ANOVA). In group I patients, the increase in BMI-SDS was linked to a significant increase in WC-SDS, FMI and SBP, while height-SDS, WtHr and DBP showed a non-significant increase. A decrease in SDS-BMI by > 0 to ≤ 0.5 (group II) was not associated with any significant decrease in any of the clinical features recorded (height-SDS, WC-SDS, WtHr, FMI, and SBP and DBP). A decrease in SDS-BMI by > 0.5 to ≤ 1.0 (group III) was associated with a significant decrease in WC-SDS, WtHr and FMI, while height-SDS, SBP and DBP showed a non-significant decrease. Finally, a decrease in SDS-BMI by > 1.0 to ≤ 1.5 (group IV) was related to a significant decrease in WC-SDS, WtHr, FMI and SBP, while height-SDS and DBP showed a non-significant decrease.

Table II. Groups formed in relation to changes in BMI-SDS at 12 months of follow-up

Variable	Group I (increased) (n = 156)	Group II (decreased > 0 to ≤ 0.5) (n = 68)	Group III (decreased > 0.5 to ≤ 1.0) (n = 70)	Group IV (decreased > 1.0 to ≤ 1.5) (n = 56)	p-values*
Boys/girls		30/38	76/80	26/44	20/36
Weight (kg)					
Initial mean	71.1 ± 14.7	70.6 ± 14.7	71.4 ± 15.8	70.2 ± 12.1	N.S.
Final mean	80.8 ± 16.6	74.3 ± 14.1	70.2 ± 13.4	70.7 ± 1 2.9	p < 0.05
p-value†	p < 0.01	N.S.	N.S.	N.S.	
BMI (SDS)					
Initial mean	2.91 ± 0.91	3.00 ± 0.93	3.10 ± 0.81	3.12 ± 0.84	N.S.
Final mean	3.50 ± 1.10	2.77 ± 1.10	2.25 ± 0.78	1.96 ± 0.79	p < 0.01
p-value†	p < 0.01	N.S.	p < 0.01	p < 0.01	
BMI change (range)	0.63 ± 0.39 (0.2-2.0)	-0.23 ± 0.12 (-0.1 to -0.47)	-0.85 ± 0.22 (-0.51 to 0.99)	-1.35 ± 0.15 (-1.01 to -1.49)	p < 0.01

**ANOVA. †Student's t-test. BMI: body mass index.*

Table III. Changes in clinical characteristics according to changes in BMI-SDS at 12 months of follow-up

Variable	Group I (increased) (n = 156)	Group II (decreased > 0 to ≤ 0.5) (n = 68)	Group III (decreased > 0.5 to ≤ 1.0) (n = 70)	Group IV (decreased > 1.0 to ≤ 1.5) (n = 56)	p-values*
Height (SDS)					
Initial mean	0.73 ± 0.91	0.79 ± 0.91	0.67 ± 0.98	0.66 ± 0.94	N.S.
Final mean	0.70 ± 1.07	0.75 ± 1.11	0.65 ± 1.09	0.65 ± 0.97	N.S.
p-value†	N.S.	N.S.	N.S.	N.S.	
WC-SDS					
Initial mean	2.45 ± 1.25	2.46 ± 0.93	2.44 ± 1.2	2.47 ± 1,38	N.S.
Final mean	2.84 ± 1.21	2.47 ± 0,99	1,85 ± 1.2	1.80 ± 1.31	p < 0.01
p-value†	p < 0.01	N.S.	p < 0.01	p < 0.01	
WtHr					
Initial mean	0.59 ± 0.05	0.59 ± 0.04	0.60 ± 0.05	0.60 ± 0.06	N.S.
Final mean	0.61 ± 0.09	0.59 ± 0.05	0.57 ± 0.07	0.57 ± 0.07	p = 0.03
p-value†	N.S.	N.S.	p < 0.01	p < 0.01	
FMI (kg/m²)					
Initial mean	10.7 ± 2.1	10.6 ± 2.1	11.1 ± 2.0	10.9 ± 2.3	N.S.
Final mean	11.3 ± 1.8	10.3 ± 2.2	10.0 ± 2.4	9.6 ± 2.0	p < 0.01
p-value†	p = 0.01	N.S.	p < 0.01	p < 0.01	
Systolic BP					
Initial mean	122.2 ± 13.3	121.6 ± 11.5	124.7 ± 11.9	126.4 ± 10.4	N.S.
Final mean	126.9 ± 14.1	121.4 ± 12.6	123.1 ± 10.1	122.1 ± 8.5	N.S.
p-value†	p = 0.01	N.S.	N.S.	P = 0.04	
Diastolic BP					
Initial mean	70.7 ± 9.1	68.5 ± 8.9	71.7 ± 9.1	71.1 ± 9.2	N.S.
Final mean	72.2 ± 9.7	68.5 ± 6.8	70.4 ± 9.8	70.7 ± 9.9	N.S.
p-value†	N.S.	N.S.	N.S.	N.S.	

**ANOVA. †Student's t-test. WC: waist circumference; WtHR: waist-to-height ratio; FMI: fat mass index; BP: blood pressure.*

There were no significant differences in the variations in clinical features in relation to changes in BMI-SDS at 12 months of follow-up between boys and girls.

Modifications in biochemical characteristics in relation to changes in BMI-SDS at 12 months of follow-up are discussed in table IV. The comparison of the groups at the onset of the combined intervention revealed no significant differences in any of the biochemical characteristics recorded. However, at 12 months of follow-up, the analysis evinced that a decrease in BMI-SDS was related to a significant decrease in insulin, HOMA-IR tryglicerides, TC and LDL-C, while HDL-C showed a non-significant decrease (ANOVA). In group I patients, the increase in BMI-SDS did not entail any significant decrease in each of the biochemical characteristics recorded (glucose metabolism and lipid profile). In group II patients, the decrease in BMI-SDS (from > 0 to ≤ 0.5) was not related to any significant decrease in each of the recorded biochemical characteristics either (glucose metabolism or lipid profile). And finally, a decrease in SDS-BMI by > 0.5 to ≤ 1.0 (group III) or by > 1.0 to ≤ 1.5 (group IV) was related to a significant decrease in glucose, insulin, HOMA-IR and TGC, while TC, LDL-C and HDL-C showed a non-significant decrease. There were no significant differences in the changes in glucose metabolism and lipid profile in relation to changes in BMI-SDS at 12 months of follow-up between boys and girls.

Table IV. Changes in glucose metabolism and lipid profile in relation to changes in BMI-SDS at 12 months of follow-up

Variable	Group I (increased) (n = 156)	Group II (decreased > 0 to ≤ 0.5) (n = 68)	Group III (decreased > 0.5 to ≤ 1.0) (n = 70)	Group IV (decreased > 1.0 to ≤ 1.5) (n = 56)	p-values*
Glucose (mg/dL)					
Initial mean	87.6 ± 8.2	85.3 ± 5.9	88.7 ± 7.1	88.7 ± 8.0	N.S.
Final mean	87.2 ± 6.9	86.7 ± 6.7	84.1 ± 7.0	83.0 ± 6.81	N.S.
p-value†	N.S.	N.S.	p = 0.01	p < 0.01	
Insulin (mU/L)					
Initial mean	19.2 ± 12.5	20.0 ± 13.4	22.0 ± 17.5	21.8 ± 19.0	N.S.
Final mean	21.1 ± 13.4	21.6 ± 14.6	14.6 ± 13.5	14.9 ± 10.9	p = 0.03
p-value†	N.S.	N.S.	p < 0.01	p < 0.01	
HOMA-IR					
Initial mean	4.2 ± 2.1	4.3 ± 2.5	4.8 ± 3.1	4.7 ± 3.5	N.S.
Final mean	4.65 ± 2.5	4.47 ± 2.4	2.65 ± 2.1	2.3 ± 1.7	p < 0.01
p-value†	N.S.	N.S.	p < 0.01	P < 0.01	
Tryglicerides					
Initial mean	100.5 ± 33.2	104.8 ± 35.9	108.3 ± 36.5	105.2 ± 33.9	N.S.
Final mean	105.7 ± 37.6	112.4 ± 39.7	89.3 ± 29.9	86.3 ± 27.6	p = 0.01
p-value†	N.S.	N.S.	p < 0.01	p < 0.01	
TC (mg/dL)					
Initial mean	167.4 ± 28.8	163.2 ± 29.1	163.3 ± 29.5	161.8 ± 28.1	N.S.
Final mean	166.3 ± 26.1	166.8 ± 29.5	154.5 ± 29.9	153.3 ± 21.9	p < 0.01
p-value†	N.S.	N.S.	N.S.	N.S.	
HDL-C (mg/dL)					
Initial mean	45.8 ± 9.5	43.2 ± 8.5	44.2 ± 8.9	44.0 ± 8.4	N.S.
Final mean	44.1 ± 8.3	44.5 ± 6.6	46.0 ± 8.3	44.6 ± 4.7	N.S.
p-value†	N.S.	N.S.	N.S.	N.S.	
LDL-C (mg/dL)					
Initial mean	101.7 ± 18.5	100.2 ± 17.8	99.9 ± 18.9	95.3 ± 18.8	N.S.
Final mean	102.9 ± 17.4	101.1 ± 18.4	94.5 ± 17.0	93.2 ± 15.7	p < 0.05
p-value†	N.S.	N.S.	N.S.	N.S.	

**ANOVA. †Student's t-test. HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.*

Table V. Changes in percentage of cardiometabolic risk factors in relation to changes in BMI-SDS at 12 months of follow-up

Variable	Group I (increased) (n = 156)	Group II (decreased > 0 to ≤ 0.5) (n = 68)	Group III (decreased > 0.5 to ≤ 1.0) (n = 70)	Group IV (decreased > 1.0 to ≤ 1.5) (n = 56)	p-value*
SBP > 95th					
Initial mean	24 (21.8 %)	12 (23.1 %)	14 (26.9 %)	12 (28.6 %)	N.S.
Final mean	38 (33.9 %)	8 (15.4 %)	10 (25 %)	0 (0 %)	p < 0.01.
p-value†	p < 0.05	N.S.	N.S.	p < 0.01	
DBP > 95th					
Initial mean	5 (4.5 %)	3 (5.7 %)	3 (5.7 %)	3 (7.1 %)	N.S.
Final mean	5 (4.5 %)	2 (3.8 %)	2 (3.8 %)	2 (4.7 %)	N.S.
p-value†	N.S.	N.S.	N.S.	N.S.	
HOMA-IR > 4.0					
Initial mean	60 (41.1 %)	30 (41.7 %)	32 (50 %)	198 (39.6 %)	N.S.
Final mean	66 (44.6 %)	28 (37.8 %)	8 (12.1 %)	6 (14.2 %)	p < 0.01
p-value†	N.S.	N.S.	p < 0.01	p < 0.01	
TGC > 150 mg/dl					
Initial mean	28 (18.7 %)	18 (24.3 %)	16 (25 %)	12 (25 %)	N.S.
Final mean	26 (17.6 %)	12 (16.2 %)	6 (9.1 %)	0 (0 %)	p < 0.01
p-value†	N.S.	N.S.	p < 0.05	p < 0.01	
TC > 200 mg/dL					
Initial mean	22 (14.1 %)	10 (13.2 %)	10 (14.7 %)	6 (12.5 %)	N.S.
Final mean	18 (11.8 %)	10 (13.5 %)	2 (2.9 %)	0 (0 %)	p <`0.01
p-value†	N.S.	N.S.	p < 0.05	p < 0.05	
HDL-C < 40 mg/dL					
Initial mean	54 (36.5 %)	30 (40.5 %)	24 (37.5 %)	20 (41.6 %)	N.S.
Final mean	53 (35.8 %)	18 (24.3 %)	14 (21.2 %)	0 (0 %)	p < 0.01
p-value†	N.S.	p < 0.05	p < 0.05	p < 0.01	
LDL-C > 130 mg/dL					
Initial mean	22 (14.9 %)	8 (10.8 %)	8 (12.5 %)	6 (12.5 %)	N.S.
Final mean	22 (14.9 %)	8 (10.8 %)	4 (6.1 %)	0 (0 %)	p < 0.05
p-value†	N.S.	N.S.	N.S.	p < 0.05	

**χ^2 inter-groups. †χ^2 intra-groups. SBP: systolic blood pressure; DBP: diastolic blood pressure; HOMA-IR: homeostasis model assessment of insulin resistance; TGC: tryglicerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.*

Changes in percentage values for the cardiometabolic risk factors in relation to changes in BMI-SDS at 12 months of follow-up are shown in table V. The comparison of the groups at the beginning of the combined intervention exhibits no significant differences in each of the cardiometabolic risk factors recorded (SBP and DBP, HOMA-IR and lipid profile). However, at 12 months of follow-up, it was observed that a decrease in BMI-SDS was associated with a significant decrease in the percentage of patients who showed SBP values higher than 95th percentile for the applied reference, as well as percentages of HOMA-IR index values higher than 4.0, plasma TGC higher than 150 mg/dl, TC higher than 200 mg/dL, LDL-C higher than 130 mg/dL and HDL-C values lower than 40 mg/dL; simultaneously; DBP values higher than 95th percentile for the applied reference showed a non-significant decrease. In group I patients, the increase in BMI-SDS was not associated with any significant decrease in percentage of patients who showed high values in DBP, HOMA-IR index and lipid profile; however, the percentage of patients with higher values in SBP showed a significant increase. In group II patients, the decrease in BMI-SDS (from < 0 to > 0.5) was not associated with any significant decrease in percentage of patients who showed high values in SBP and DBP, HOMA-IR index and lipid profile, but the percentage of patients with HDL-C values lower than 40 mg/dL showed a significant decrease. In group III patients, the decrease in BMI-SDS (from > 0.5 to ≤ 1.0) was not associated with any signif-

icant decrease in the percentage of patients who showed high values in SBP and DBP; at the same time, the percentage of patients with higher values in HOMA-IR index and lipid profile, except in LDL-C, experienced a significant decrease. And finally, a decrease in SDS-BMI by > 1.0 to ≤ 1.5 (group IV) was associated with a significant decrease in the percentage of patients who showed high values of SBP, HOMA-IR and lipid profile, while the percentage of patients with higher values in DBP showed a non-significant increase. There were no significant differences in the changes in percentages of the cardiometabolic risk factors recorded in relation to changes in BMI-SDS at 12 month period of follow-up between boys and girls.

DISCUSSION

This study features that a significant improvement in body composition and cardiovascular risk factors associated with obesity is observed in adolescents with obesity when BMI-SDS decreases at least 0.5 in a 12-month period, and, especially, when the decrease is greater than 1.0. In our experience, losing weight would not be necessary since, in accordance with the old aphorism: "the child becomes slim by means of keeping a stable weight because he/she is growing" (17,22).

This study was designed on the basis of previous data regarding the change in BMI-SDS required to reduce adiposity or to improve cardiovascular outcome in children and adolescents with obesity through lifestyle interventions (27-29). Nevertheless, it differs from previous reports since the sample is much larger and the definition of the groups in relation to the decrease in BMI-SDS is distinct. And, above all, because those studies were based on weight loss as a condition to achieve an improvement in body composition (decrease in adiposity) and modify the profile of cardiovascular risk factors associated with obesity (18-21,27,28,30).

One of the main objectives in the treatment of childhood obesity is to reduce the percentage of body fat mass without negatively affecting longitudinal growth. In compliance with several authors, our experience leads us to consider that maintaining a constant weight during a combined intervention in a growing adolescent would be sufficient to reduce BMI-SDS and, consequently, to decrease body fat without altering growth (13,17,22,30). Dual-energy X-ray absorptiometry (DEXA) has been considered a "quasi gold standard" to define obesity (31), but its complex and expensive use makes it not feasible for daily clinical practice or epidemiological research. Anthropometric measures such as BMI, WC, WtHr, and FMI have been used as alternatives, as they are readily available and can serve as inexpensive tools to identify obesity (8,9,32-35). A recently published systematic review and meta-analysis found that both BMI and WtHr were strongly correlated with body fat measured by DEXA; therefore, both could be used to diagnose obesity in pediatric populations when more sophisticated techniques are not available (15). In this study, BMI was applied for the definition of obesity, despite its limitations (it does not differentiate between fat mass and fat-free mass), precisely because it correlates well with body fat and cardiovascular risk factors (3,12-14,32). It is noteworthy that in this study we also found a significant correlation between the BMI-SDS values and the adiposity parameters recorded (WC-SDS, WtHr and FMI).

In the present study we observed no improvement in body composition parameters and cardiovascular risk factors associated with obesity (hypertension, increase in HOMA-IR, TGC, TC and LDL-C, and decrease in HDL-C) with a BMI-SDS decrease lower than 0.5 in a 12-month period. In contrast with previous studies (27-29), we found that an improvement in body composition and some cardiometabolic risk factors associated with obesity (decrease in HOMA-IR and TGC) can be noticed with BMI-SDS reductions by > 0.5 to ≤ 1.0 in adolescents with obesity, but the reduction in BMI-SDS required to simultaneously to improve body composition and cardiovascular outcomes in adolescents with obesity (decrease in hypertension, HOMA-IR, TGC, TC and LDL-C, and increase in HDL-C) should be greater than 1.0.

On the other hand, our results corroborate that a reduction in BMI-SDS greater than 0.5 can be achieved if weight remains practically stable for a period of 1 year in growing adolescents with obesity under a combined program of physical activity intervention (17,22). In fact, 36 % of participants in this study (group III and IV) achieved a reduction in BMI by > 0.5 to ≤ 1.0, and in 16 % (group IV) the reduction was greater than 1.0. That is to say, to reduce adiposity in this patients it would not be necessary to force a weight loss that could condition their linear growth, but rather it would be enough to comply with the aphorism taken as a reference in this study.

Insulin resistance is considered as the determining pathogenic factor in the onset of lipid profile and lipoprotein alterations that are highly atherogenic and concur in obesity. The insulin resistance induces hypertriglyceridemia and, consequently, a higher proportion of low density lipoproteins, as well as a decline in the formation of high density lipoproteins, with capacity of endothelial toxicity and deposition in the arterial wall (3-7,36,37). A balanced diet and increased physical activity are known to improve dyslipidemia; therefore, a reasonable strategy in obese patients would be lifestyle interventions such as maintaining an adequate diet and physical activity. In fact, the observed changes in body composition and cardiometabolic risk factors in relation to the reduction in BMI-SDS in our sample of adolescents with obesity represented the effects of a combined intervention, which included nutritional education, a balanced diet and lifestyle modification through increased physical activity (13,17,22,38-40).

In conclusion, the fact that the adiposity parameters recorded (WC-SDS, WtHr and FMI) improved significantly with a reduction in BMI-SDS ≥ 0.5, and that at this level the indices of insulin sensitivity and lipid profile also improved, suggests that improving the level of adiposity is essential to improve metabolic health. Indeed, our findings suggest that any intervention should aim to reduce body mass index in obese children by at least 0.5 for clinical and biochemical effectiveness, while greater benefits may accumulate with reductions of 1.0 or more. However, more evidence is needed before such parameters can be identified and used in a clinical setting.

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ARÁN

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Trabajo Original

Pediatría

Frequency of malnutrition in children and adolescents with child maltreatment

Frecuencias de mala nutrición en niños y adolescentes con maltrato infantil

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Abstract

Introduction: child maltreatment (CM) can have a negative impact on physical and mental health in childhood and throughout life.

Objective: to determine the frequency of malnutrition in cases of CM from the Clínica de Atención Integral al Niño Maltratado (CAINM) of the Instituto Nacional de Pediatría (INP), Mexico.

Material and methods: this was a cross-sectional, retrospective, descriptive study of children with CM. Height/age, weight/height, and body mass index/age were used to determine malnutrition status (undernutrition and overweight or obesity). The frequency of malnutrition by age group and sex were compared using χ^2 tests. The prevalence of malnutrition at CAINM was compared to that expected in Mexico (ENSANUT-2012), serving as a reference for children without CM, using one-sample Poisson tests.

Results: of the 117 cases, 41 % presented wasting or overweight/obesity, and 25 % were growth-stunted. Neither wasting nor stunting displayed any difference between age groups ($p > 0.05$). Overweight/obesity was observed more frequently in adolescents than in schoolchildren ($p < 0.05$). Being overweight or obese was most frequently associated with sexual abuse, and wasting and stunting were most often associated with neglect. Compared to the population without CM, the group under 5 years of age had a higher prevalence of wasting ($p < 0.01$), and those aged 5 to 11 years had a higher prevalence of both wasting and stunting ($p < 0.001$).

Conclusions: CM cases were characterized by acute undernutrition and stunting as well as by adolescents who were overweight or obese. Malnutrition in the pediatric population should be analyzed from a wider perspective, including possible CM.

Keywords:

Child maltreatment. Malnutrition. Overweight/obesity. Undernutrition. Stunting. Children/adolescents.

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Resumen

Introducción: el maltrato infantil (MI) puede afectar la salud física y mental en la niñez y a largo plazo.

Objetivo: determinar las frecuencias de mala nutrición en casos de MI de la Clínica de Atención Integral al Niño Maltratado (CAINM), perteneciente al Instituto Nacional de Pediatría de México.

Métodos: estudio transversal, retrospectivo y descriptivo. Se utilizaron los cocientes de peso/talla, talla/edad e IMC/edad. Las frecuencias de mala nutrición (desnutrición y sobrepeso/obesidad) se compararon entre los grupos de edad y sexo a través de la prueba del χ^2. Utilizando pruebas de Poisson para una sola muestra se compararon las prevalencias de la mala nutrición con las esperadas en México (ENSANUT-2012).

Resultados: de los 117 casos de MI, el 41 % presentaban emaciación o sobrepeso/obesidad, y el 25 % talla baja. Ni por emaciación ni por talla baja hubo diferencias entre los grupos de edad ($p > 0,05$). La frecuencia del sobrepeso/obesidad fue mayor en los adolescentes que en los escolares ($p < 0,05$). En el grupo de abuso sexual destacó el sobrepeso/obesidad; en el de negligencia, la emaciación y la talla baja. En comparación con las prevalencias de los niños sin MI, los niños < 5 años tuvieron prevalencias más altas de emaciación ($p < 0,01$); los de 5 a 11 años, de emaciación y talla baja (para ambas, $p < 0,001$).

Conclusiones: los niños con MI se caracterizaron por desnutrición y talla baja, así como también por sobrepeso/obesidad en los adolescentes. La mala nutrición en las poblaciones pediátricas debe analizarse desde una perspectiva amplia, incluido el posible maltrato infantil.

Palabras clave:

Maltrato infantil. Mala nutrición. Sobrepeso/obesidad. Desnutrición. Talla baja. Niños/adolescentes.

INTRODUCTION

The World Health Organization defines child maltreatment (CM) as abuse and neglect involving children and adolescents under 18 years of age (1). The diagnosis and care of a child with CM is not simple due to variations in the nature of the abuse or neglect, along with its clinical manifestations, severity, lack of knowledge, and the deficit of specialized interdisciplinary and multidisciplinary centers.

CM most often occurs in a combined form (2). The negative effects of CM, either due to neglect or physical and psychological/emotional abuse, can lead to malnutrition (3-5).

Malnutrition refers to deficiencies or excesses in nutrient intake, imbalance of essential nutrients, or impaired nutrient utilization. The double burden of malnutrition consists of both undernutrition and overweight and obesity, as well as diet-related noncommunicable diseases. Undernutrition manifests in four broad forms: wasting, stunting, underweight, and micronutrient deficiencies (6).

Malnutrition, such as acute undernutrition (wasting), stunting, overweight or obesity, involves a complex interaction of medical and psychosocial factors. Characteristics of acute undernutrition are the loss of lean and fatty tissue, manifested by wasting or thinness, which confers a greater risk for infections and death. Stunting is the most common manifestation of chronic undernutrition in low-income and middle-income countries, reflecting the cumulative negative effects of suboptimal health conditions and inadequate nutrition and psychosocial care over time. Stunting has medium- and long-term implications, such as lower school achievement, cognitive deficits, and diminished work capacity. Conversely, obesity is a complex and multifactorial disease characterized by an excess of body fat; it is associated throughout life with the earliest risk of suffering from chronic degenerative diseases and death (7,8).

Several reports show a relationship between malnutrition status and CM: between undernutrition and neglect (9,10) and between overweight/obesity and CM (mainly physical or sexual abuse) (11,12). However, most studies link a history of CM with overweight and obesity in adulthood (12-15). Little is known about the frequency of the different malnutrition conditions in children who have experienced CM (16-18).

It has been reported that the relationship between nutritional status and CM (specifically, physical and sexual abuse in children under 12 years) has a greater frequency of acute undernutrition and stunting in girls who were physically abused, and of overweight and obesity in girls who were sexually abused (18). However, there is no information among an important group of youth affected by CM: adolescents. Therefore, the aim of this study was to describe the frequency of undernutrition, stunting, overweight and obesity in children and adolescents admitted to the *Clínica de Atención Integral al Niño Maltratado* (CAINM) of our institution, the *Instituto Nacional de Pediatría* (INP), who experienced different types of CM.

METHODS

STUDY DESIGN

This was a cross-sectional, retrospective, descriptive study.

SETTING

A third-level pediatric hospital, INP, registered the cases of CM patients who were admitted for a year in the care of CAINM. This work was approved by the Institutional Review Board (Record No. 2020/015).

PARTICIPANTS

It included 131 medical records of cases of underage patients (under 18 years old) obtained from June 2013 to May 2014 who were admitted at CAINM-INP. The inclusion criteria were the availability of medical records of cases with a diagnosis of CM in any of its forms that contained complete information on registry number, birthdate, sex, weight, height, and family socio-economic status (SES), resulting in 117 cases.

In total, 90 % of all cases of CM came from the outpatient and emergency services of the INP; the remaining cases came from the orthopedics, internal medicine, gastronutrition, neonatology, and neurology services.

VARIABLES

Weight, height, body mass index (BMI), wasting, stunting, overweight/obesity, CM, and type of CM (physical abuse, sexual abuse, psychological/emotional abuse, neglect and polyvictimization).

CHILD MALTREATMENT

Four types of CM, physical abuse, sexual abuse, psychological/emotional and neglect, and polyvictimization, were considered. Polyvictimization cases refer to situations in which the medical records contain a description of more than one type of CM.

The child or adolescent was taken to the third level hospital by a parent or tutor (the father, mother, relative or foster care staff) in cases of the following: sexual abuse in any of its forms, physical injuries and trauma, neglect, abandonment, inappropriate behavior or emotional symptoms, or other situations.

Pediatricians who had initial contact with children with suspected CM referred them to CAINM. This clinic consists of an interdisciplinary group of experts in the CM area, including the following specialties:paediatrics, nutrition, mental health, social work and law. These experts are also trained according to the Consensus for the Study and Comprehensive Care of Maltreated Children (20,21). The records provide information on the SES of the patient based on the INP classification (22). SES was categorized as follows: level IX, which is the one that is exempt from payment of fees for medical services (they are mainly for foster children and adolescents); levels 1 and 2 have low SES, level 3 has medium-low SES, levels 4 and 5 have medium-high SES, level 6 has high SES or social security, and K level has higher SES (22).

NUTRITIONAL STATUS

All the participants were measured and weighed when they entered CAINM. The anthropometric evaluation was performed by the same nutrition expert at each consultation (the one who subscribes) according to Lohman's methodological criteria (23).

Before noon, the children were weighed and measured with minimal clothing. Recumbent length was measured until the age of two years with the help of a nurse. One measurer placed a hand on the child´s feet and kept the heels against the vertical board to ensure that the knee was extended. The subject's head was held with the Frankfort Plane aligned perpendicular to the plane of the measuring table.

Stature was measured in the vertical stadiometer with the child's body weight distributed evenly on both feet, placing the head in the horizontal Frankfort Plane with arms hanging freely at the sides of the trunk.

BIAS

We identified selection bias because the patients included were those who attended a referral hospital. Furthermore, information bias was also included because CM diagnostic practices depend on place and time of evaluation. Last, we identified an information bias during the analysis, as it lacked a multivariate analysis, and possible confounding variables were not considered.

STUDY SIZE

The sample was non-probabilistic for convenience using the records of diagnosed CM cases collected over a year. Sample size was determined for a descriptive study based on the malnutrition frequencies of a study in the reference center for maltreated children under 11 years of age (18,19). The sample size was calculated according to an estimate based on previous results from the study by Martin-Martin and Loredo-Abdala 2010, resulting in the following sample sizes for wasting, stunting and overweight/obesity: 114, 115, and 117, respectively. This study was then analyzed by age group (< 5, 5-11 and 12-17 years).

NUTRITIONAL STATUS

The following indices were calculated based on age and sex: height or length/age (H/A), weight/length or weight/height (W/H) and BMI/age; [BMI = weight (kg) / height^2 (m^2)]. The Z-score indices from the OMS-2006 child growth standards were used as the reference for children younger than 2 years, and the Centers for Disease Control and Prevention (CDC-2000) standards were used for children over 2 years old. Overweight and obesity diagnoses were calculated by means of the BMI/age ratio. In children younger than 5 years old, the cut-off points for BMI/age were $Z = 2$ to 3 for overweight and $Z \geq 3$ for obesity. In children 5 to 17 years old, the cut-off points for BMI/age were $Z = 1$ to 2 for overweight and $Z \geq 2$ for obesity.

To determine acute undernutrition in children younger than five years old, the W/H indicator was used, whereas BMI/age was used for the remaining age groups. The classifications were as follows: for mild undernutrition, wasting (W/H) or thinness (BMI/age) ($Z = -1$ to -2); for moderate undernutrition, wasting (W/H) or thinness (BMI/age) ($Z = -2$ to -3); and for severe undernutrition, wasting (W/H) or thinness (BMI/age) ($Z \leq 3$). Chronic undernutrition (stunting) was determined by the index H/A ($Z \leq 2$) (24-26).

STATISTICAL METHODS

Descriptive statistics were used for age, sex and anthropometric variables; the chi-square (χ^2p) test was used to compare the frequencies of the nutrition states across age groups. The frequencies of acute undernutrition (moderate-severe), overweight/obesity and stunting of the groups were compared with those of the study mentioned above that described malnutrition states in a population of 178 children under 5 and 5-11 years old with only two types of CM — physical and sexual abuse; the children belonged to the same clinic as the children in this study (18).

The prevalence of malnutrition in CM was compared using a one-sample Poisson test, with the population prevalence of malnutrition expected in Mexico (ENSANUT-2012) serving as a reference for children without CM (27,28). In all cases, $p < 0.05$ was considered statistically significant.

RESULTS

PARTICIPANTS

Of a total of 131 cases of CM within a one-year period at the reference centre for maltreated children of a third level hospital, fourteen clinical files were excluded because they did not fulfil the inclusion criteria. Of the 117 remaining cases, 53 % were females.

The age ranged from 0.1-17.7 years old, with an average age of 6.8 ± 4.2 years (Table I describes the characteristics of the population studied). In total, 81 % of the population had a low SES (1X, 1N and 2N) whereas 16 % had a medium SES (3N).

CHILD MALTREATMENT TYPE

The most prevalent form of CM was physical abuse, and the least prevalent form was psychological/emotional abuse. With respect to age range, the most frequent types of CM were as follows: physical abuse in children younger than 5 years old, sexual abuse among schoolchildren, and physical abuse and polyvictimization among adolescents. However, polyvictimization had the same prevalence among both schoolchildren and adolescents (Table I). It is worth mentioning that 19.6 % of the studied sample also experienced domestic violence.

NUTRITIONAL STATUS

In total, 41 % (n = 48) of the sample suffered from acute undernutrition (mild, moderate and severe) or overweight/obesity. The distribution was 26 % (n = 31) undernutrition, 11 % (n = 13) overweight and 3 % (n = 4) obesity; however, there was no difference among the age groups or sexes ($p > 0.05$) (Table II).

Table I. Characteristics of the population studied

Characteristics	Children aged < 5 yrs n = 48	School-aged children (5-11 yrs) n = 46	Adolescents (12-17 yrs) n = 23	Total n = 117
Age, SD	2.1 ± 1.5	8.0 ± 2.0	14.4 ± 1.6	6.8 ± 4.2
Sex, n (%)				
Female	22 (46)	25 (54)	15 (65)	62 (53)
Male	26 (54)	21 (46)	8 (35)	55 (47)
Child maltreatment, n (%)				
Physical abuse	20 (42)	10 (22)	(30)	37 (32)
Sexual abuse	8 (17)	12 (28)	3 (13)	23 (20)
Psychological/emotional abuse	3 (6)	2 (4)	4 (17)	9 (8)
Neglect	12 (25)	10 (22)	3 (13)	25 (21)
Polyvictimization	5 (10)	12 (26)	6 (26)	23 (20)
*Anthropometric measurements**				
Weight (kg)	10.9 ± 4.7	24.6 ± 10.1	48.3 ± 16.1	23.6 ± 16.9
Height (cm)	80.9 ± 17.0	119.7 ± 13.7	150.2 ± 10.3	109.8 ± 30.3
BMI (kg/m^2)	15.9 ± 1.9	16.5 ± 3.4	20.9 ± 5.2	17.1 ± 3.8
Z height/age	-1.0 ± 1.5	-1.1 ± 1.7	-1.3 ± 1.6	-1.1 ± 1.6
Z weight/height	-0.3 ± 1.3	-----	-----	----
Z BMI/age	-0.17 ± 1.4	-0.38 ± 1.8	0.12 ± 1.47	-0.20 ± 1.6

**Values represent means and SDs.*

Table II. Nutritional status by age group

Age group	Children < 5 yrs n = 48	School-aged children n = 46	Adolescents n = 23	Total n = 117
Nutritional status	n (%)	n (%)	n (%)	n (%)
Normal	34 (71)	25 (54)	10 (43)	36 (31)
Overweight	2 (4)	6 (13)	5 (22)	13 (11)
Obesity	0 (0)	2 (4)	2 (9)	4 (3)
Undernutrition[a+b+c]	12 (25)	13 (28)	6 (26)	31 (26)
Mild[a]	8 (17)	7 (15)	4 (17)	19 (16)
Moderate[b]	3 (6)	2 (4)	1 (4)	6 (5)
Severe[c]	1 (2)	4 (9)	1 (4)	6 (5)
Stunting	9 (19)	12 (26)	8 (35)	29 (25)

**Degree of undernutrition (a, b and c).*

Overweight and obesity

Obesity was not present in children younger than five years old; however, 4 % (n = 2) of these children were overweight. In the other age groups, the frequency of the combination of overweight and obesity was 17 % (n = 8) and 30 % (n = 7) in schoolchildren and adolescents, respectively, and statistically significant differences were found between these two age groups ($\chi^2p = 9.13$, $p < 0.05$) (Table II).

Undernutrition

According to the level of undernutrition, 10 % (n = 12) of the cases presented moderate to severe undernutrition. The frequencies were similar across the age groups; additionally, there were no differences between sexes ($p > 0.05$) (Table II).

Stunting

In total, 25 % of the population presented stunting. The frequency of stunting was 9 %, 26 % and 35 % in children younger than five years old, in school-aged children and in adolescents, respectively; however, there were no differences between age groups or between sexes ($p > 0.05$) (Table II).

FREQUENCY OF STUNTING ACCORDING TO NUTRITION STATUS

There were no cases of obesity or stunting coexisting. Nevertheless, the frequency of stunting was accompanied by overweight in 15 % of the total population, with a predominance in males (females 0 % and males 50 %; $\chi^2p = 5.31$, $p < 0.05$).

However, the coexistence of stunting with undernutrition (moderate to severe) was 67 % (females 100 % and males 43 %; $\chi^2p = 4.28$, $p < 0.05$) (Fig. 1).

FREQUENCY OF CHILD MALTREATMENT FOR TYPE OF MALNUTRITION

In children with overweight/obesity, sexual abuse was the most frequent form of CM. In children with undernutrition and stunting, it was neglect (Table III).

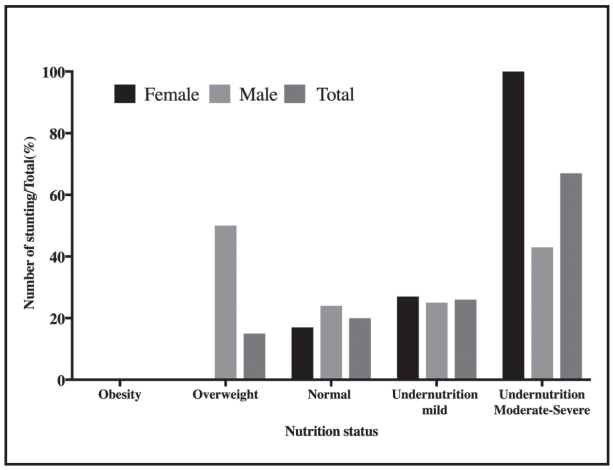

Figure 1.
Frequency of stunting according to nutrition status.

Table III. Nutritional status in different types of child maltreatment

	Nutritional status				
Child maltreatment	**Normal 69**	**Overweight-obesity 17**	**Undernutrition* 31**	**Total 117**	**Stunting 29**
n	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Physical n = 37	25 (68)	4 (11)	8 (22)	37/37 = 100	7 (19)
Sexual n = 23	12 (52)	7 (30)	4 (17)	23/23 = 100	1 (4)
Psychological/emotional n = 9	7 (78)	1 (11)	1 (11)	9/9 = 100	1 (11)
Neglect n = 25	14 (56)	1 (4)	10 (40)	25/25 = 100	14 (56)
Polyvictimization n = 23	11 (48)	4 (17)	8 (35)	23/23 = 100	6 (26)

**Moderate-severe.*

COMPARISON STUDIES

The frequencies of malnutrition as compared with those of the study by Martín-Martín and Loredo-Abdala (18) in 2010 were not significantly different for undernutrition (moderate-severe) between the age groups under 5 years (8.3 % vs. 10.7 %, $p > 0.05$) or between the 5- to 11-year-old groups (13 % vs. 9.5 %, $p > 0.05$). Furthermore, there were no significant differences in the overweight-obesity frequencies among children under 5 years of age (4.2 % vs. 4.2 %, $p > 0.05$) or among those aged 5 to 11 (17.4 % vs. 22.6 %, $p > 0.05$). However, in the present study, the frequency of stunting in the age group 5 to 11 years was higher (26 % vs. 12 %, $p < 0.05$).

When the results were compared with those from ENSANUT-2012 (27) we observed that children under 5 years old with CM had a higher prevalence of undernutrition (moderate-severe) than expected for this population of children based on the national prevalence ($p < 0.01$).

For school-aged children with CM, the prevalence was higher than that expected based on the general population prevalence of undernutrition (moderate-severe) ($p < 0.001$) and stunting ($p < 0.001$).

In adolescents with CM, the prevalences of undernutrition and overweight/obesity did not differ from those expected based on the general population prevalence ($p > 0.05$).

The prevalence of stunting could not be compared with that expected in the population without CM because there was no information for this age group (Table IV).

DISCUSSION

The results of the study reveal the frequency of malnutrition status in children and adolescents with CM. The findings provide an indication of the presence of the two extremes of malnutrition (undernutrition and overweight/obesity).

Although the frequencies of stunting tended to increase with age, they did not differ between children and adolescents, nor did undernutrition. This study highlights the prominence in the frequency of undernutrition and stunting in all age groups, which can be attributed to the fact that one of the long-term consequences of undernutrition is stunting, as described by Mehta et al. (26).

The presence of CM is related to undernutrition in childhood (29). Some reports mention undernutrition as primarily a characteristic of neglect (9,30), since undernutrition is a prime example of neglect in childhood; stunting is also related to CM (31).

Undernutrition and stunting in some countries of the world remain unresolved (32). However, children with CM may be more vulnerable to these conditions. The presence of a higher prevalence of undernutrition and stunting in children with CM than in children without CM could be indicative of sequelae or causes of CM. Similarly, one study found a higher frequency of undernutrition in children with CM than in those without CM (33). Although it was not possible to compare the prevalence of stunting in adolescents vs. ENSANUT-2012, its prevalence is striking; however, the group of children under 5 years of age had a higher prevalence of undernutrition, and the school-age group had higher prevalences of undernutrition and stunting, which suggests a relationship of CM with undernutrition. Although the duration of CM (34) was not explored in this study, it is possible that at an older age, there is greater exposure to CM, which leads to chronic undernutrition reflected by stunting.

Additionally, socioeconomic factors are important because more than three-quarters of the study population had a low SES,

Table IV. Comparison of observed and expected prevalences of malnutrition in Mexican children with child maltreatment

Age group	Nutrition status	Observed cases	Observed prevalence (%)	95 % CI for observed prevalence	Expected prevalence by ENSANUT 2012 2012 (%)	1 sample Poisson Test p-value	
Children < 5 yrs (n = 48)	Overweight-obesity	2	*4.2*	0.5	15.1	*9.7*	0.4615
	Undernutrition	4	*8.3*	0.5	21.3	*1.6*	0.0079
	Stunting	9	*18.7*	8.6	35.6	*13.6*	0.3217
School-aged children (n = 46)	Overweight-obesity	8	*17.4*	7.5	34.3	*34.4*	0.0441
	Undernutrition	6	*13.0*	4.8	28.4	*1.5*	0.0001
	Stunting	12	*26.1*	13.5	45.6	*7.0*	0.0001
Adolescents (n = 23)	Overweight-obesity	7	*30.4*	12.2	6.2	*35.0*	0.8604
	Undernutrition	2	*8.7*	1.0	31.4	*1.9*	0.4583

and both undernutrition and stunting have been associated with low SES (35). On the other hand, we noticed that all the girls who presented with acute undernutrition also presented stunting, indicating that they are more affected than boys. This finding could be explained by discrimination against girls, which is conducive to undernutrition and a delay in obtaining medical attention (36).

With respect to overweight/obesity, adolescents had higher frequencies than school-aged children. Although the aetiology of obesity is multifactorial, the results could be related to hormonal-metabolic changes during this stage or to child maltreatment, as a possible consequence of CM is obesity (3). Additionally, there is a risk of obesity in adolescents who have suffered from CM (37,38).

Physical and sexual abuse have been related to the presence of overweight/obesity (39-41). Some reports also indicate a relationship between neglect and obesity in adolescents (5,42). In this study, within the group of adolescents, physical abuse and polyvictimization were the most frequent forms of CM, which may indicate a synergy between abuse and higher frequencies of overweight/obesity.

Conversely, children and adolescents with and without CM did not show any differences in overweight/obesity, suggesting that the frequency of this form of malnutrition may also be due to the overweight/obesity epidemic, which is a problem in Mexico (27).

Other studies have also failed to identify a difference in the prevalence of overweight and obesity in children and adolescents who are maltreated compared to those who are not maltreated (11,12).

This study has the strength that the cases were diagnosed by an interdisciplinary group and used anthropometric assessments conducted by a standardized researcher.

LIMITATION

There are few descriptive studies about malnutrition frequency in children with CM; they refer only to children, not to adolescents, and they apply to only two specific types of CM (18). A limitation of the present study was that we did not have data that allowed us to determine whether the states of malnutrition described were a cause or consequence of CM. The high prevalence of malnutrition in our country, along with the multiple risk factors in its development, are confounding variables that were not considered in this study.

INTERPRETATION

In this studied population of CM, undernutrition and stunting were present in children, while overweight/obesity was present in adolescents. Malnutrition can be a reflection of CM, so its possible causes must be analysed, including this phenomenon.

GENERALITY

The frequencies observed in our study must be taken with caution, considering the national nutritional health problem of Mexican children. The high prevalence of malnutrition identified in patients with CM in this study must be considered only in countries with a similar prevalence of malnutrition in the general population.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Pediatría

Riesgo cardiometabólico en niños con obesidad grave

Cardiometabolic risk in children with severe obesity

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Resumen

Introducción: la obesidad grave ha tenido un mayor aumento que la obesidad no grave en los escolares chilenos durante los últimos años. Desconocemos si el punto de corte actualmente utilizado para definir la obesidad grave (IMC ≥ + 3 DE, curvas OMS-2007) se asocia a un mayor daño biológico en nuestra población pediátrica.

Objetivo: describir y comparar el riesgo cardiometabólico en escolares con obesidad grave y no grave.

Método: se realizó un análisis secundario de una muestra de 3325 escolares en los que se estudiaron los factores de riesgo cardiometabólico. Se comparó la prevalencia de estos factores en los que presentaban obesidad según fuera esta grave o no, calculándose los OR respectivos.

Resultados: de los 589 sujetos con obesidad, con una media de edad de 11,4 ± 0,98 años, el 46 % eran de género femenino y el 11,5 % presentaban obesidad grave, con mayor prevalencia de la mayoría de los factores estudiados y sin diferencias en cuanto a antecedentes parentales de enfermedad crónica u obesidad, educación de los padres y actividad física del niño. Los niños con obesidad grave tenían un mayor riesgo de obesidad central (OR: 12,9), resistencia insulínica (OR: 3,2), HTA (OR: 2,67) y síndrome metabólico (OR:1,92).

Conclusión: esta definición de obesidad grave en la niñez favorece la identificación de los niños con mayor comorbilidad cardiometabólica, lo cual permite focalizar los esfuerzos de prevención secundaria y su tratamiento más oportuno.

Palabras clave:

Obesidad. Obesidad grave. Pediatría. Riesgo cardiovascular. Riesgo cardiometabólico.

Abstract

Introduction: severe obesity has had a greater increase than non-severe obesity in Chilean schoolchildren during the last years. We do not know whether the cut-off point currently used to define severe obesity in children (BMI ≥ + 3 DE, WHO-2007 curves) is associated with a greater biological risk in our population.

Objective: to describe and compare cardiometabolic risk in schoolchildren with severe vs. non-severe obesity.

Methods: a secondary analysis of a sample of 3,325 schoolchildren was performed, in which cardiometabolic risk factors were studied. The prevalence of these was compared in the subsample of 589 schoolchildren with obesity according to whether it was severe or not, and the respective ORs were calculated.

Results: mean age was 11.4 ± 0.98 years, 46 % were girls, and 11.5 % of the sample had severe obesity, with a higher prevalence of most of the factors studied and no differences in chronic disease, obesity or education in parents, or physical activity of the child. The risk of those with severe obesity for central obesity, insulin resistance, high blood pressure, and metabolic syndrome reached an OR of 12.9, 3.2, 2.67, and 1.92, respectively, as compared to those with non-severe obesity.

Conclusion: this definition of severe obesity in childhood favors the identification of children with higher cardiometabolic comorbidity, which allows to focus the efforts of secondary prevention and its most timely treatment.

Keywords:

Obesity. Severe obesity. Pediatrics. Cardiovascular risk. Cardiometabolic risk.

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INTRODUCCIÓN

La comisión para acabar con la obesidad infantil de la OMS señala que, durante las últimas cuatro décadas, la obesidad en los niños de 5 a 19 años se ha multiplicado por 10 en el mundo. Dado que la población menor de 5 años con sobrepeso u obesidad aumentó de 32 a 41 millones desde 1990 a 2016, estas cifras alcanzarían los 70 millones hacia 2025 (1).

En la población pediátrica, la evaluación antropométrica se contrasta con patrones de crecimiento que ajustan el peso y la talla de acuerdo con la edad y el sexo, utilizándose en muchos países las curvas de la OMS de 2006 para evaluar a los menores de 5 años (2). En los mayores se usan las de la OMS de 2007 o curvas de los propios países (3). En la evaluación anual de los escolares en Chile, se reportó en 2019 que, de forma conjunta, todos los niveles educativos (prekínder, kínder, 1º básico, 5º básico, 1º medio) presentaron un 23 % de obesidad y que el 6 % del total correspondía a una obesidad grave. Al comparar con el año precedente, la obesidad grave aumentó en mayor proporción que la obesidad global, tendencia descrita también en otros países (4-7).

Desde hace más de 20 años, diversos autores han descrito que la probabilidad de persistir con obesidad hacia la adultez aumenta con la edad, desde un 50 % para un niño de 6 años con obesidad hasta un 75 % en los adolescentes de 10 a 14 años, acentuándose ambas si al menos uno de sus progenitores tiene obesidad (8-10). Por otra parte, la mayor gravedad de la obesidad en la niñez y la adolescencia incrementa aun más este riesgo (11).

Las consecuencias cardiometabólicas de la obesidad se expresan tempranamente en la niñez, con agregación de diferentes factores de riesgo cardiometabólico; está estrechamente asociada con la resistencia insulínica y es mayor en los niños con obesidad que en aquellos con sobrepeso (12,13). Particularmente, se ha descrito en una población de escolares que el 32 % presentaban alguna de las formas clínicas de dislipidemia, porcentaje que aumentaba hasta el 56 % en aquellos con obesidad (14). Los puntos de corte para definir los factores de riesgo cardiovascular (FRCV) en la niñez tienen variación pero, incluso usando umbrales conservadores, se ha demostrado que su prevalencia está directa e independientemente relacionada con el grado de obesidad y la resistencia insulínica (15,16). Esta última es un mecanismo etiopatogénico central en la génesis del daño biológico producido por el exceso de tejido adiposo (17).

No existe consenso en la definición de obesidad grave en la niñez y se han planteado diferentes puntos de corte para el IMC en distintas curvas de crecimiento con el objetivo de mejorar la estimación del riesgo biológico asociado. Si se identifica mejor a aquellos niños con mayor riesgo, se favorecerán el diagnóstico oportuno, la focalización de recursos económicos para el tratamiento y la prevención de enfermedades crónicas futuras asociadas al mayor riesgo cardiovascular (18).

Para la evaluación nutricional de los escolares se utilizan las curvas de la OMS de 2007 para las edades de 5 a 19 años, y se ha consensuado el puntaje zIMC igual o mayor que +3 para definir la obesidad grave. Sin embargo, no disponemos de estudios que evalúen el riesgo biológico asociado a este punto de corte, por lo cual nos cuestionamos si los niños con obesidad grave así definida presentan mayor comorbilidad cardiometabólica que los niños con obesidad no grave, y nos planteamos como objetivo el describir y comparar la prevalencia y la agregación de los factores de riesgo cardiovascular (FRCV) entre ambos grupos.

METODOLOGÍA

Se trata de un análisis secundario realizado a partir de una muestra poblacional del estudio "Estado nutricional, síndrome metabólico y resistencia a la insulina, en una muestra poblacional de escolares", conformada por 3325 escolares de 10 a 15 años, reclutados durante 2009-2011 en 20 escuelas públicas de la comuna de Puente Alto, de Santiago, Chile. Este estudio incluyó a los alumnos de 5º y 6º básico asistentes a dichas escuelas, cuyos apoderados/tutores aceptaron participar (3.325/5.614), excluyéndose los que hubieran presentado alguna enfermedad aguda durante los 15 días previos (13).

Para este análisis secundario se construyó una base de datos anonimizada que incluyó a todos los escolares con obesidad, una muestra conformada por 589 sujetos con los datos completos demográficos, de evaluación antropométrica, desarrollo puberal y resultados de exámenes de laboratorio de interés. Se consideraron además las encuestas disponibles respondidas por los padres sobre enfermedades crónicas familiares, escolaridad del jefe del hogar y la actividad física reportada por el alumno.

Las variables demográficas fueron la edad (en años), el género (masculino/femenino) y la maduración puberal, definida según los estadios de Tanner (I a V) por autorreporte a partir de su identificación privada mediante cartillas ilustradas.

Para el diagnóstico del estado nutricional se calculó el IMC (peso en kg/talla en m^2), expresado en términos absolutos y ajustado a la edad y el sexo, como puntaje z (zIMC), utilizando la referencia OMS 2007 y el programa Anthro Plus (20). Como variable categórica se definió la obesidad no grave como un zIMC $\geq +2$ a $< +3$ y la obesidad grave como un zIMC $\geq +3$.

El perímetro de la cintura (PC) se midió en cm, con cinta métrica inextensible y el sujeto de pie, a un centímetro sobre el reborde lateral superior de la cresta ilíaca derecha, a nivel medio-axilar, con la cinta paralela al suelo, sin comprimir la piel y al final de una espiración normal. Se consideró como obesidad central toda medición superior al percentil 90 de una referencia internacional (21), y la razón entre el pliegue cutáneo subescapular y el tricipital (PSE/PTC) como indicadora de grasa troncal, medidos ambos pliegues del modo estandarizado (22).

Se registraron los antecedentes familiares de uno o ambos padres de obesidad, diabetes *mellitus,* hipertensión arterial, dislipidemia e infarto/accidente vascular encefálico o trombosis. La escolaridad del jefe del hogar se consideró como indicador del nivel socioeconómico, categorizándola como "básica" (primaria), "media" (secundaria) y "universitaria". Para aproximarnos a la actividad física del escolar, se incluyó la respuesta a la pregunta: "El día de ayer: ¿anduviste en bicicleta o caminaste al menos durante una hora?" como variable dicotómica.

La presión arterial sistólica o diastólica (PAS o PAD), medidas de modo estandarizado, se expresaron en mm Hg y se definieron presión arterial normal (< p90), la presión arterial normal alta (p90 a p94) y la hipertensión arterial (≥ p95), según las recomendaciones (23).

En una muestra sanguínea con ayuno de 12 horas se midieron distintos parámetros. Los lípidos plasmáticos —colesterol total (CT), colesterol de HDL (C-HDL) y triglicéridos (TG)— se expresaron en mg/dL y se midieron con un método enzimático-colorimétrico (equipo Modular P-800. Roche Diagnostics GmbH, Mannheim, Alemania), estando el coeficiente de variación entre el 1,3 y el 2,5 %. El colesterol de LDL (C-LDL) se calculó con la fórmula de Friedewald excepto si los TG excedían de 400 mg/dL o en presencia de quilomicrones, situaciones en las que el C-LDL se midió directamente. El colesterol no HDL se calculó restando el C-HDL del CT. Los valores se interpretaron según las recomendaciones del comité internacional de expertos (24) y de la Sociedad Chilena de Pediatría (25). Se consideró el CT como aceptable o normal (< 170), de riesgo (170 a 199) o de riesgo alto (≥ 200). El C-LDL se clasificó como normal (< 110), de riesgo (110 a 129) o de riesgo alto (≥ 130). Los TG como normales (< 90), de riesgo (90 a 129) o de riesgo alto (≥ 130). Finalmente, el C-HDL seclasificó como normal (> 45), de riesgo (40 a 45) o de alto riesgo (< 40).

La glicemia (método Gluco-quant, Glucosa/Hexoquinasa, Roche Diagnostics GmbH, Manheim, Alemania) se consideró elevada si ≥ 100 mg/dL; la insulinemia (técnica de inmunoensayo quimio-luminométrico directo, ADVIA CentaurR XP, y equipo Bayer HealthCare LLC, Kyowa Medex Co, Japón) se expresó en µU/mL y se calculó el índice de HOMA como estimador de la resistencia insulínica (RI), definida por un valor > p95 (26).

Se utilizaron los criterios de Cook para definir el síndrome metabólico (SM) como la presencia de 3 o más de los cinco siguientes criterios: PC ≥ p90 (obesidad central); PAS o PAD ≥ p90 (hipertensión arterial); TG ≥ 110 mg/dl (hipertrigliceridemia); C-HDL ≤ 40 mg/dl (C-HDL bajo) y glicemia ≥ 100 mg/dl (glicemia de ayuno alterada) (27).

ANÁLISIS ESTADÍSTICO

Se realizó un análisis descriptivo de las variables numéricas, verificando su distribución con test de normalidad y expresando las medidas de tendencia central como promedio (DE) o mediana (RIC) según si la distribución era normal o no, respectivamente. Las variables categóricas se expresaron como números y porcentajes.

Para comparar las variables numéricas entre el grupo de escolares con obesidad grave y el grupo con obesidad no grave se utilizó el test de Student para muestras independientes, y para comparar las frecuencias de FRCV en ambos grupos se usaron el test del chi^2 y/o el de Fisher. Se describió la agregación de FRCV y se calcularon las odds ratios de prevalencia (OR) con intervalo de confianza del 95 %. Se consideró como significativo todo valor de $p \leq 0,05$. Se utilizó el programa SSPS-17.

ASPECTOS ÉTICOS

El estudio original recibió la aprobación "Resolución No.11/98 de 30/04/1998". Este estudio secundario cumplió con la Declaración de Helsinki. Se actualizó y presentó al Comité Ético Científico de la Universidad, con una solicitud de dispensa del consentimiento informado debido a que este análisis secundario no utilizó datos sensibles identificables, no produjo cambios, ni hizo necesario contactar con los participantes del estudio original para obtener información adicional. La base de datos se manejó de modo codificado y anónimo, resguardando los datos, que fueron solamente manejados por dos de los investigadores.

RESULTADOS

Del universo de 3325 escolares estudiados, el 53,6 % presentaban un estado nutricional normal, el 28,6 % sobrepeso, el 15,7 % obesidad y el 2,1 % obesidad severa. La muestra para el presente análisis estuvo constituida por 589 sujetos con obesidad, de los cuales 521 (88,5 %) tenían obesidad no grave y 68 (11,5 %) obesidad grave. Todos fueron representativos del universo, sin diferencias en cuanto a edad, sexo o maduración puberal. La descripción de los FRCV y el síndrome metabólico ya se ha publicado para el total de la muestra del estudio original (13), por lo que limitándonos a nuestro objetivo, se hizo el presente análisis a los sujetos con obesidad según la magnitud de esta.

Los 589 escolares tenían una edad de 11,4 ± 0,98 años, sin diferencias de acuerdo con el género o el grado de obesidad. De ellos, 245 (41,6 %) correspondían al género femenino y 344 (58,4 %) al masculino. En la tabla I se describen los datos generales y los antecedentes obtenidos en las encuestas en cuanto a enfermedades crónicas familiares, educación parental y actividad física simplificada, reportada por el alumno, para la muestra total y para cada grupo según gravedad de la obesidad. Se observa que no hubo diferencias entre los niños con obesidad y aquellos con obesidad grave.

En la tabla II se describen las mediciones antropométricas y las variables de interés analizadas para el grupo total y según el grado de obesidad. Destaca que los niños con obesidad grave tenían mayor IMC e zIMC (por definición), además de mayor estatura y una significativamente mayor obesidad abdominal y adiposidad troncal. Con respecto a los marcadores de riesgo cardiometabólico, los niños con obesidad grave presentaron mayores valores de todos los factores evaluados excepto los de CT, C-LDL y glicemia.

Al analizar los componentes del SM utilizando los puntos de corte de la clasificación de Cook y cols. (27), en la tabla III se observa que los más prevalentes en la muestra total fueron la obesidad central (85 %), la hipertrigliceridemia (49,1 %) y la RI (38 %), seguidos por el C-HDL bajo (27 %). El SM tuvo una frecuencia del 27 %. Se verifica además que los niños con obesidad grave presentaron una frecuencia aun mayor de obesidad central, PAS o PAD, RI y SM que aquellos con obesidad no grave.

Tabla I. Características de 589 escolares con obesidad, según su magnitud

	Total	Obesidad no grave	Obesidad grave	p (Chi²)	
Número (%)	589 (100)	521 (87,1)	68 (11,5)	-	
Género	Femenino Masculino	245 (41,6) 344 (58,4)	221 (42,4) 300 (57,6)	24 (35,3) 44 (64,7)	0,26
Maduración puberal (Tanner)	I-II III-V	333 (56,5) 256 (43,5)	299 (57,4) 222 (42,6)	34 (50,0) 34 (50,0)	0,25
Antecedentes ECNT en los padres	Obesidad DM HTA Dislipidemia IM AVE Trombosis	263 (59,8) 75 (21,4) 126 (34,7) 109 (30) 22 (6,1) 7 (1,9) 18 (5,1)	228 (58,9) 64 (20,6) 111 (34,4) 95 (29,3) 17 (5,3) 7 (2,14) 16 (5,1)	35 (66,4) 11 (27,5) 15 (37,5) 14 (35,9) 5 (13,5) 0 (0) 2 (5,6)	0,3 0,3 0,7 0,4 0,08 1 0,9
Actividad física*	Sí No	184 (31,1) 405 (68,8)	167 (32,5) 354 (67,9)	17 (25) 51 (75)	0,23
Escolaridad del jefe del hogar†	Primaria Secundaria Universitaria	152 (32,8) 277 (59,8) 34 (7,3)	130 (31,0) 247 (60,7) 30 (7,4)	22 (39,3) 30 (53,6) 4 (7,3)	0,59

Obesidad: no grave (zIMC ≥ +2 a < +3) y grave (zIMC ≥ +3), según curvas de la OMS de 2007. ECNT: enfermedades crónicas no transmisibles; DM: diabetes mellitus; *HTA: hipertensión arterial; IM: infarto miocárdico; AVE: accidente vascular encefálico. *Actividad física: respuesta dicotómica a la pregunta: "El día de ayer: ¿anduviste en bicicleta o caminaste al menos durante una hora?". †Dato disponible en 463 encuestas respondidas.*

Tabla II. Mediciones antropométricas y variables cardiometabólicas en 589 escolares con obesidad, según su magnitud

	Total (n = 589)	Obesidad no grave (n = 521)	Obesidad grave (n = 68)	Valor p (t de Student)
IMC	26,3 ± 3,0	25,6 ± 2,0	31,8 ± 1,0	< 0,001
zIMC	2,5 ± 0,4	2,4 ± 0,26	3,4 ± 0,4	< 0,001
zT/E	0,3 ± 0,9	0,3 ± 0,9	0,7 ± 0,9	0,001
Perímetro de cintura (cm)	88,7 ± 8,1	87,1 ± 6,2	101,4 ± 10,0	< 0,001
Razón cintura/estatura	0,6 ± 0,04	0,59 ± 0,03	0,67 ± 0,04	< 0,001
Razón PSE/PTC	1,3 ± 0,3	1,3 ± 0,3	1,4 ± 0,3	< 0,001
CT (mg/dL)	169,7 ± 31,7	169,6 ± 32,5	170,4 ± 24,6	0,8
C-HDL (mg/dL)	46,9 ± 10,1	47,2 ± 10,0	44,5 ± 10,2	0,042
C-LDL (mg/dL)	97,1 ± 27,5	97,3 ± 28,2	95,4 ± 21,0	0,50
TG (mg/dL)	128,9 ± 78,9	125,7 ± 76,1	153,2 ± 94,5	0,024
Glicemia (mg/dL)	90,4 ± 6,3	90,4 ± 6,4	89,9 ± 5,8	0,54
Insulinemia (µUI/mL)	22,8 ± 13,0	22,1 ± 12,7	28,5 ± 13,9	0,001
Índice HOMA	5,1 ± 3,1	5,0 ± 3,0	6,4 ± 3,3	0,001
PAS (mm Hg)	113,8 ± 7,0	113,3 ± 6,9	117,3 ± 6,8	< 0,001
PAD (mm Hg)	57,4 ± 6,8	57,1 ± 6,8	59,3 ± 6,6	0,014

Obesidad: no grave (zIMC ≥ +2 a < +3) y grave (zIMC ≥ +3), según curvas de la OMS de 2007. IMC: índice de masa corporal; zIMC: puntaje z del IMC; zT/E: puntaje z del índice talla/edad; PSE: pliegue cutáneo subescapular; PTC: pliegue cutáneo tricipital; CT: colesterol total; C-HDL: colesterol de lipoproteínas de alta densidad; C-LDL: ccolesterol de lipoproteínas de baja densidad; TG: triglicéridos. Índice HOMA = [(glicemia / 18) x insulinemia] / 22,5]. PAS: presión arterial sistólica; PAD: presión arterial diastólica.

Tabla III. Frecuencia de factores de riesgo cardiometabólico, síndrome metabólico e insulinorresistencia en 589 escolares de acuerdo con la magnitud de la obesidad (n, %)

	Total (n = 589)	Obesidad no grave (n = 521)	Obesidad grave (n = 68)	Valor p (Chi²)
Perímetro de cintura ≥ p90	504 (85,6)	437 (83,9)	67 (98,5)	< 0,001
Hipertrigliceridemia (≥ 110 mg/dL)	289 (49,1)	249 (47,8)	40 (58,8)	0,08
Hipercolesterolemia (≥ 200 mg/dL)	90 (15,3)	85 (16,3)	5 (7,3)	0,09
C-LDL alto (≥ 130 mg/dL)	62 (10,5)	59 (11,3)	3 (4,41)	0,13
C-HDL bajo (< 40 mg/dL)	164 (27,8)	141 (27,1)	23 (33,8)	0,25
Glicemia ≥ 100 mg/dL	48 (8,1)	44 (8,4)	4 (5,9)	0,45
PAS ≥ p95 o PAD ≥ p95	41 (7,0)	33 (6,3)	8 (11,8)	0,001
Insulinemia ≥ p90	237 (40,2)	193 (37,1)	44 (64,7)	< 0,001
RI (HOMA ≥ p90)	224 (38,1)	181 (34,7)	43 (63,2)	< 0,001
Síndrome metabólico	160 (27,2)	133 (25,5)	27 (39,7)	0,017

Obesidad: no grave (zIMC ≥ +2 a < +3) y grave (zIMC ≥ +3), según curvas de la OMS de 2007. C-LDL: colesterol de lipoproteínas de baja densidad; C-HDL: colesterol de lipoproteínas de alta densidad; PAS: presión arterial sistólica; PAD: presión arterial diastólica; índice HOMA = [(glicemia / 18) x insulinemia] / 22,5]; RI: resistencia insulínica. Síndrome metabólico: presencia de ≥ 3 criterios (obesidad central, hipertrigliceridemia, C-HDL bajo, hipertensión arterial sistólica o diastólica y/o glicemia elevada en ayunas) (27).

No alcanzaron la significación: la mayor frecuencia de hiperTG, el bajo C-HDL y la glicemia elevada en ayunas.

En cuanto a la agregación de los componentes del SM, la figura 1 destaca que, de forma significativa, los niños con obesidad grave congregaron con mayor frecuencia 2 criterios y, especialmente, 3 o más criterios en comparación con aquellos con obesidad no grave. Se destaca que solamente un niño de los 68 con obesidad grave tuvo ausencia de criterios (1,5 %), mientras que en el grupo de obesidad no grave, estos fueron 34/521 (6,5 %).

Por último, la tabla IV muestra de forma decreciente los OR de los factores cardiometabólicos de los niños con obesidad grave, por encima de los de aquellos con obesidad no grave.

Tabla IV. Riesgo de presentar diferentes factores de riesgo cardiometabólicos y síndrome metabólico en 589 escolares con obesidad, según la magnitud de esta

	Obesidad no grave (n = 521)	Obesidad grave (n = 68)	Total (n = 589)	OR (IC 95 %)
Obesidad central (+)	437	67	504	12,9 (1,8-94,1)
Obesidad central (-)	84	1	85	
Resistencia insulínica (+)	181	43	224	3,23 (1,91-5,46)
Resistencia insulínica (-)	340	25	365	
Hiperinsulinemia (+)	193	44	237	3,11 (1,84-5,28)
Hiperinsulinemia (-)	328	24	352	
HTA sistólica (+)	79	22	101	2,67 (1,53-4,69)
HTA sistólica (-)	442	46	488	

(Continúa en la página siguiente)

Tabla IV (Cont.). Riesgo de presentar diferentes factores de riesgo cardiometabólicos y síndrome metabólico en 589 escolares con obesidad, según la magnitud de esta

	Obesidad no grave (n = 521)	Obesidad grave (n = 68)	Total (n = 589)	OR (IC 95 %)
Síndrome metabólico (+)	133	27	160	1,92 (1,14-3,24)
Síndrome metabólico (-)	388	41	429	
Hipertrigliceridemia (+)	249	40	289	1,56 (0,93-2,61)
Hipertrigliceridemia (-)	272	28	300	
C-HDL bajo (+)	141	23	68	1,38 (0,80-2,36)
C-HDL bajo (-)	380	45	521	
Hipercolesterolemia (+)	240	30	270	0,92 (0,56-1,54)
Hipercolesterolemia (-)	281	38	319	
C-LDL alto (+)	150	18	168	0,89 (0,50-1,58)
C-LDL alto (-)	371	50	421	
Hiperglicemia (+)	44	4	48	0,68 (0,24-1,95)
Hiperglicemia (-)	477	64	541	

Obesidad: no grave (zIMC ≥ +2 a < +3) y grave (zIMC ≥ +3), según curvas de la OMS de 2007. HTA: hipertensión arterial; C-HDL: colesterol de lipoproteínas de alta densidad; C-LDL: colesterol de lipoproteínas de baja densidad.

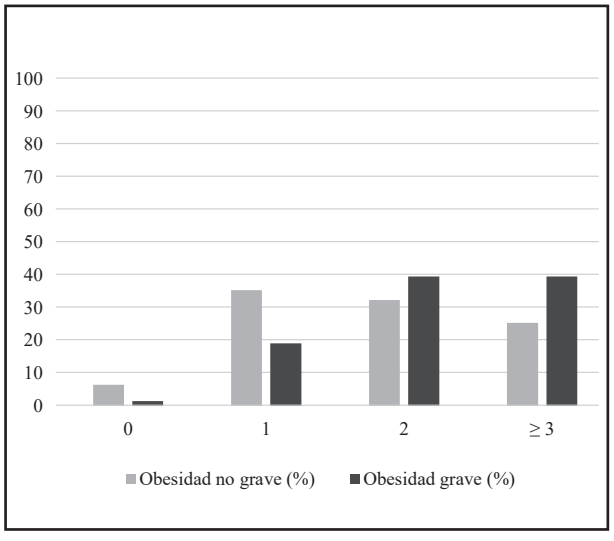

Figura 1. Agregación de componentes del síndrome metabólico en 589 escolares, según la gravedad de la obesidad (chi^2 p = 0,003) (0, 1, 2, ≥ 3: número de componentes del síndrome metabólico presentes de forma simultánea. Obesidad no grave: zIMC ≥ +2 a < +3. Obesidad grave: z-IMC ≥ +3 [OMS 2007]).

DISCUSIÓN

Este estudio evaluó el riesgo cardiometabólico de 589 niños y adolescentes con obesidad, según la magnitud de esta, utilizando los puntos de corte recomendados por el Ministerio de Salud de Chile en 2017. Estos definen la obesidad como un puntaje zIMC ≥ +2 y < +3, y la obesidad grave como un zIMC ≥ +3, según la referencia de la OMS de 2007. Se demuestra que este punto de corte se asocia a un mayor riesgo de obesidad central, dislipidemias, HTA, RI y síndrome metabólico. Según nuestro conocimiento, es el primer estudio en nuestro país que explora esta asociación.

La prevalencia de la obesidad grave en la muestra analizada fue de 11,5 % y representó un 2 % de la totalidad del estudio original (n = 3325), realizado entre 2009 y 2012. La prevalencia en la población escolar chilena de 2019 fue del 6 %, es decir, tres veces más alta que la encontrada en nuestra muestra, habiendo aumentado la obesidad global desde un 17 % hasta un 24 % en este período de tiempo (4). Este incremento de la obesidad grave en la niñez se ha reportado en otros países y es preocupante, por la mayor carga de enfermedad que la acompaña y su presentación en todos los rangos de edad de la infancia (6,18).

Los tres FRCV más prevalentes en la muestra fueron la obesidad central o abdominal, la hipertrigliceridemia y la RI, destacando que la frecuencia de casi todos los factores fue mayor en los niños con obesidad grave. En este subgrupo, la obesidad central o abdominal estaba presente en casi todos (98 %), alrededor del 60 % tenían TG altos o RI y el 40 % cumplían los criterios del SM. Algunos de estos hallazgos pueden compararse a los reportados por Skinner en niños y adolescentes con obesidad grave en Estados Unidos, habiendo incluido un subgrupo de 12 a 19 años, edad inicial que se asemeja a la de nuestra muestra. Skinner definió la obesidad grave o de tipo III como aquella mayor de 140 % del percentil 95 según las curvas de los CDC, y reportó prevalencias mayores que en la de tipo I, con un C-HDL bajo del 23 % y el 19,7 % ($p \leq 0,001$) e hipertrigliceridemia del 28,9 % y el 19,9 %, respectivamente (7,18).

Es llamativa la alta presencia de trastornos del metabolismo de la glucosa observada en nuestra muestra, con hiperinsulinemia en el 37 % y RI en el 34,7 % de los niños con obesidad no grave, cifras que alcanzan el 64 % y el 63,2 %, respectivamente, en aquellos con obesidad grave. La hiperglicemia tuvo menor prevalencia, del 6 y 8 %, sin diferencia entre grupos. Estos hallazgos son comparables a lo descrito en Brasil (28) en un estudio que evaluó a 90 sujetos con obesidad de 8 a 18 años, categorizados también por el grado de obesidad según las curvas de la OMS de 2007. Se describió una glicemia elevada en el 10 % de los sujetos, hiperinsulinemia en el 27,8 % y RI según el HOMA en el 52,2 %, aumentando este último valor hasta el 65,4 % en aquellos con obesidad grave. Otro estudio realizado en Bolivia (29), encontró una prevalencia de la RI del 39,4 % en 61 niños y adolescentes obesos de 5 a 18 años, sin categorizar la muestra según la gravedad de la obesidad.

En esta muestra, la prevalencia del síndrome metabólico en el grupo con obesidad no grave fue del 25,5 % y en el de obesidad grave, del 39,7 %. Otros autores de Latinoamérica (29) han descrito una prevalencia del SM del 36 % en un grupo de 61 niños y adolescentes con obesidad, sin discriminar por el grado de esta. En Europa (30), por otra parte, se reportó la presencia de SM en el 41,8 % de 352 niños y adolescentes con obesidad de 2 a 19 años; al categorizarlos por gravedad, este valor fue del 27,6 % para la obesidad y del 60,7 % para la obesidad grave, indicando que el riesgo de presentar SM había sido 2,6 veces mayor en los sujetos con zIMC mayor de +3.

En nuestra muestra, el OR de presentar FRCV en los sujetos con obesidad grave frente a los sujetos con obesidad no grave fue variable: muy alto para la obesidad central (OR: 12), intermedio para la hiperTG o la RI (alrededor de 3) y de 2 para el SM. Es necesario precisar que la definición de SM varía en los diferentes estudios y que es importante la edad de los sujetos participantes, ya que la asociación a comorbilidades tiende a ser directamente proporcional a la edad y los estudios que incluyen una mayor proporción de niños mayores tenderán a presentar mayores prevalencias.

Nos parece importante destacar que, en esta muestra, los antecedentes de obesidad o enfermedades crónicas en las madres o padres no mostraron diferencias entre el grupo con obesidad grave y el de obesidad no grave, así como tampoco hubo relación con el nivel educacional de los padres. Lo primero sugiere que las alteraciones reportadas se relacionan con la magnitud de la adiposidad más que con la herencia, que es de tipo poligénico en la mayoría de las comorbilidades. Sin embargo, se necesita resaltar la naturaleza multifactorial de estas y que los padres de los niños con edades alrededor de los 10 años pueden ser aún jóvenes para expresar estas morbilidades o incluso desconocerlas por su naturaleza oligosintomática. El nivel socioeconómico fue similar en ambos grupos y la actividad física del niño fue igualmente baja en ambos grupos, reportando solo un 30 % haber realizado actividad física el día precedente.

Como fortalezas de nuestro estudio destacamos que la muestra analizada proviene de la muestra de un estudio poblacional de 3325 sujetos, homogénea en su distribución y metodología en cuanto a la evaluación clínica y de laboratorio. También, que tiene uniformidad en la distribución en cuanto a maduración sexual, con representación equilibrada de prepúberes, púberes iniciales y niños con pubertad avanzada. Ello es importante ya que influye notoriamente en la expresión de la comorbilidad por los cambios en la composición corporal que la acompañan. Como debilidad podemos identificar el tiempo transcurrido desde el estudio original y la fecha actual, pero, dado el incremento de la obesidad en niños y adolescentes en nuestro país, y específicamente el de la obesidad grave, los resultados encontrados en nuestro análisis solamente podrían tener una mayor magnitud en el momento actual, sin que hubiera diferencia en la dirección de las asociaciones.

A la vista de los resultados obtenidos, podemos plantear que la categorización por gravedad de los niños y adolescentes con obesidad, utilizando el punto de corte del zIMC $\geq +3$ con las curvas OMS-2007, tiene importancia pronóstica y terapéutica ya que permite identificar a un grupo de pacientes con mayor riesgo cardiometabólico que debe ser derivado al nivel secundario de la atención sanitaria para estudiar dichas complicaciones y recibir un tratamiento integral y optimizado.

Estos resultados también respaldan la necesidad urgente de desarrollar nuevos estudios que incluyan intervenciones médicas más efectivas sobre los hábitos de alimentación y estilos de vida, y que nos permitan evidenciar cuáles de nuestras recomendaciones tienen mayor impacto en prevenir, revertir o mejorar el riesgo cardiometabólico en la población pediátrica.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Nutrición anciano

Estudio en vida real para evaluar la adherencia y el sabor de un suplemento oral nutricional hipercalórico e hiperproteico en pacientes con desnutrición en un hospital

A real-world study to evaluate adherence and flavor of a high-protein hypercaloric oral nutritional supplement in patients with malnutrition in a hospital

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Resumen

Objetivo: el objetivo de nuestro estudio en vida real fue evaluar en pacientes ingresados desnutridos la adherencia y las preferencias de sabor de un suplemento oral nutricional (SON) hipercalórico e hiperproteico.

Métodos: se incluyeron en este estudio en vida real un total de 34 pacientes ingresados con pérdida de peso reciente. Se administró un sabor (café, vainilla o fresa) cada día de forma aleatoria a cada paciente durante tres días consecutivos. En los primeros tres días se pidió a los pacientes que completaran dos cuestionarios destinados a reflejar la tolerancia y aceptación del SON (Renutryl®). La adherencia del SON fue evaluada durante el ingreso hospitalario.

Resultados: el sabor dulce fue más elevado para el sabor fresa (4,54 ± 0,2 puntos) que para el sabor vainilla (3,13 ± 0,1 puntos; $p < 0,03$) y el sabor café (3,03 ± 0,1 puntos; $p < 0,02$). Al analizar a los pacientes que tomaron suplementos después de elegir el sabor, los pacientes que eligieron café tomaron un total de 13,3 ± 1,1 envases de promedio durante la hospitalización (0,91 ± 0,2 por día), los pacientes que eligieron fresa tomaron 13,4 ± 1,3 envases (0,92 ± 0,1 por día) y, finalmente, los pacientes que eligieron envases de vainilla tomaron 8,3 ± 0,9 envases durante el ingreso (0,61 ± 0,1 por día), con diferencias significativas a favor de los sabores de fresa y café frente al sabor de vainilla. Por otra parte, el SON elegido mayoritariamente por los pacientes al alta hospitalaria fue el pack multisabor (n = 20; 50 %).

Conclusiones: las preferencias de sabor de los SON de tres sabores son similares, aunque la adherencia fue más elevada durante el ingreso con respecto a los SON con sabor a café y fresa. La dulzura puede haber influido en este hallazgo, sobre todo con el sabor fresa, con una buena tolerancia de los 3 sabores.

Palabras clave:

Adherencia. Aceptación. Suplemento oral nutricional. Tolerancia. Sabor.

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Abstract

Aim: the objective of our real-life study was to evaluate adherence and taste preferences of a hypercaloric and hyperprotein oral nutritional supplement (ONS) in malnourished hospitalized patients.

Methods: a total of 34 in patients with recent weight loss were included in this study. One flavor (coffe, vanilla or strawberry) was administered each day in a random way to each patient during three consecutive days. In the first three days, patients were asked to fulfill two questionnaires intended to reflect ONS (Renutryl®) tolerance and acceptance. Adherence to the ONS was measured during hospital stay.

Results: the sweet flavor was higher for strawberry (4.54 ± 0.2 points) than for the vanilla flavor (3.13 ± 0.1 points; $p < 0.03$) and coffee flavor (3.03 ± 0.1 points; $p < 0.02$). When analyzing the total number of patients who took supplements after choosing the flavor, the patients who chose coffee took a total of 13.3 ± 1.1 packages on average during hospitalization (0.91 ± 0.2 per day), the patients who chose strawberry took 13.4 ± 1.3 packages (0.92 ± 0.1 per day), and finally the patients who chose vanilla packages took 8.3 ± 0, 9 packages during admission (0.61 ± 0.1 per day), with significant differences in favor of the strawberry and coffee flavors versus vanilla. The ONS chosen mostly by the patients at hospital discharge was the multiflavor pack (n = 20; 50 %).

Conclusions: taste preferences for the three flavored ONSs are similar, although adherence was higher during admission to the coffee- and strawberry-flavored ONS. Sweetness may have influenced this finding, especially with the strawberry flavor, with a good tolerance of all three flavors

Keywords:

Adherence. Acceptance. Oral nutritional supplement. Tolerance. Flavor.

INTRODUCCIÓN

En los países de la Unión Europea (UE), más de 20 millones de pacientes se ven afectados por la desnutrición relacionada con la enfermedad (DRE), lo que supone un coste económico para los gobiernos de la UE de hasta 120 mil millones anuales (1). En los Estados Unidos, aproximadamente del 33 % al 54 % de los pacientes hospitalizados presentan DRE. Estas altas cifras de prevalencia de la DRE se ven todavía más elevadas cuando analizamos poblaciones de ancianos institucionalizados, situándose entre el 23 % y el 85 %, y hasta el 65 % de los residentes tienen pérdida de peso y desnutrición no intencionales (2). En nuestro medio, la prevalencia se sitúa en el 23 % entre los pacientes hospitalizados de nuestra comunidad autónoma (3), evidenciándose este problema tanto en las áreas de hospitalización médicas (4) como en las áreas quirúrgicas (5).

Aunque, en algunos casos, la intervención sobre la calidad o la cantidad de los alimentos que proporciona la dieta oral puede mejorar el problema, en muchos casos el paciente en cuestión simplemente no puede o no quiere consumir suficientes alimentos naturales para alcanzar sus necesidades en presencia de una DRE. En este caso, es vital considerar otras opciones para mejorar la ingesta nutricional, como los suplementos nutricionales orales (SNO). Un creciente cuerpo de evidencia sugiere que los SNO, que suministran macronutrientes y micronutrientes para fines médicos especiales de manera adicional a la dieta oral, podrían mejorar la situacion clínica de los pacientes hospitalizados desnutridos. Se han publicado una gran cantidad de beneficios con el uso de los SON, incluidos la reducción de la duración de la estancia hospitalaria (6), la disminuncion del coste del episodio de hospitalización (7), el porcentaje de complicaciones (8), los síntomas depresivos (9) y las tasas de readmisión hospitalaria (10), con mejoría de la masa magra (11) y, lo que es más importante, de la mortalidad (12). Sin embargo, la aceptabilidad y la ingesta de estos SON son frecuentemente subóptimas, sobre todo entre los pacientes hospitalizados (13), probablemente en relación con un bajo nivel de apetito pero también porque a estos no les gustan el sabor, la textura y el olor de algunos SON (14). Ante esta situación se ha intentado optimizar la ingesta con un número reducido de envases al día de SON enriquecidos, como son los suplementos hipercalóricos y hiperproteicos que en muchas ocasiones se prescriben en una única toma diaria. Los estudios de intervención con SON que evalúan estos aspectos son escasos debido a problemas logísticos en su realizacion y éticos en su diseño. Por tanto, los estudios en vida real nos pueden proporcionar información en un área con tan poca evidencia científica. Estos estudios generan datos obtenidos fuera del contexto de los ensayos controlados aleatorios y resultantes de la práctica clínica habitual (9). Sin duda, para evaluar los resultados de los pacientes y garantizar que los pacientes reciban el tratamiento adecuado para ellos, es necesario utilizar datos del mundo real.

El objetivo de nuestro estudio en vida real fue evaluar en pacientes ingresados desnutridos la adherencia y las preferencias de sabor de un suplemento oral nutricional hipercalórico e hiperproteico

MATERIAL Y MÉTODOS

PROCEDIMIENTO

Para realizar el estudio se utilizó un SON hipercalórico e hiperproteico (Renutryl®), de 300 ml el envase, con tres sabores diferentes (vainilla, fresa y café). La tabla I resume la composición de este SON. Un total de 34 pacientes con pérdida de peso reciente (> 5 % durante los 3 meses anteriores o > 10 % durante los 6 meses anteriores) o menos del 70 % de la ingesta estimada de necesidades calóricas durante un período superior a 7 días, se incluyeron en este estudio. Todos los pacientes recibieron 1 envase al día de este SON. Los criterios de exclusión fueron: infecciones en curso, enfermedad gastrointestinal grave, enfermedad cancerosa con tratamiento activo, función hepática gravemente alterada (concentración de bilirrubina total > 3,5 mg/dl) y/o función renal gravemente alterada (concentración de creatinina sérica > 3 mg/dl), disfagia, tratamiento con esteroides actual, toma de medicación que modifique el peso y hábito alcohólico activo.

Este estudio se realizó de acuerdo con las pautas establecidas en la Declaración de Helsinki y todos los procedimientos en los que participaron pacientes fueron aprobados por el comité de

Tabla I. Composición nutricional de Renutryl®

		100 ml	300 ml
Valor energético	**kcal**	**200**	**600**
	kJ	**840**	**2520**
Proteínas	**g**	**10**	**30**
Carbohidratos	**g**	**24,3**	**73**
Azúcares	g	7	21
Grasas	**g**	**7**	**21**
AGS	g	0,9	2,7
AGM	g	4	12
AGP	g	1,3	3,9
Fibra	**g**	**0**	**0**
Minerales			
Calcio	mg	229	687
Fósforo	mg	153	459
Magnesio	mg	50	150
Sodio	mg	95	285
Potasio	mg	240	720
Cloro	mg	85	255
Hierro	mg	1,7	5,1
Zinc	mg	2,5	7,5
Yodo	mcg	25	75
Cobre	mcg	0,25	0,75
Manganeso	mg	0,17	0,51
Selenio	mcg	13,3	40
Cromo	mcg	21	63
Molibdeno	mcg	7	21
Vitaminas			
A (retinol)	mcg	117	351
D_3 (colecalciferol)	mcg	1,7	5,1
E (d-α-tocoferol)	mg	3,3	9,9
K_1	mcg	11,7	35
C	mg	20	60
B_1	mg	0,20	0,60
B_2	mg	0,27	0,81
B_6	mg	0,37	1,11
B_{12}	mcg	0,8	2,4
Niacina	mgNE	2,3	6,9
Ác. pantoténico	mg	0,83	2,5
Ác. fólico	mcg	67	201
Biotina	mcg	10	30
Colina	mg		

(Continúa en la columna siguiente)

ética del HCUVA (14-137). Estos pacientes se reclutaron en el hospital, y todos los participantes firmaron un consentimiento informado. A todos ellos se les facilitó un envase de un sabor diferente cada día (café, vainilla o fresa) de forma aleatoria durante tres días consecutivos de ingreso. Después del cuarto día y con el sabor elegido por el paciente, se registró el número de SON tomados durante la estancia hospitalaria. Un dietista verificó la ingesta diaria de SON.

El estudio finalmente incluyó a 34 pacientes que requirieron soporte nutricional oral (pacientes cardíacos, n = 13; pacientes oncologicos, n = 8; enfermedad digestiva, n = 7; pacientes neurológicos, n = 3; pacientes traumatizados, n = 3).

PREFERENCIAS DE SABOR

Se pidió a los pacientes que consumieran los tres sabores distintos de este SON en tres días consecutivos (1 SON por día de 300 ml) y que eligieran el sabor que hubieran preferido el cuarto día y registraran el consumo de este sabor durante la estancia en el hospital. En los primeros tres días se pidió a los pacientes que completaran dos cuestionarios diarios destinados a reflejar la tolerancia y la aceptación del SON. Ambos cuestionarios se basaron en una escala analógica visual de 10 puntos que se relacionaba con parámetros tales como el regusto, el sabor, el gusto, la preferencia de sabores, el impacto en la tolerancia digestiva y el apetito (16) (Tabla II). También se les preguntó el último día del ingreso el sabor que elegirían para continuar tomando el SON en el domicilio durante el siguiente trimestre (café, vainilla, fresa o caja multisabor).

DETERMINACIONES

A todos los pacientes se les realizó una anamnesis completa y un examen físico. La evaluación general del estado nutricional incluyó una determinación del peso corporal, la altura y el índice de masa corporal (kg/m^2). Se midieron las siguientes determinaciones bioquímicas: glucosa, creatinina, sodio, potasio, albúmina, prealbúmina y transferrina.

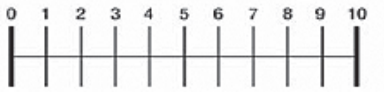
Tabla II. El cuestionario de escala analógica visual de 10 puntos utilizado en el estudio

A. Aceptación

¿Te gustó esta bebida? Nada (0) - Mucho (10)
¿La encontraste dulce? Nada (0) - Mucho (10)
¿La encontraste salada? Nada (0) - Mucho (10)
¿La encontraste amarga? Nada (0) - Mucho (10)
¿La encontraste ácida? Nada (0) - Mucho (10)
¿Tuvo regusto? Nada (0) - Mucho (10)
¿Tuviste náuseas después de beberla? Nada (0)- Mucho (10)
¿Tenías hambre en la siguiente comida después de beberla? Nada (0) - Mucho (10)
¿Cómo te sentiste después de beberla? Muy mal (0) - Muy bien (10)

B. Tolerancia

¿Cómo te sentiste hoy? Muy mal (0) - Muy bien (10)
¿Tuviste náuseas? Nada (0) - Constantemente (10)
¿Tuviste vómitos? Nada (0) - Constantemente (10)
¿Tuviste reflujo de acidez en la boca? Nada (0) - Constantemente (10)
¿Tuviste dolor de abdomen? Nada (0) - Constantemente (10)
¿Sentiste el abdomen inflado? Nada (0) - Constantemente (10)
¿Tuviste dolor de estómago? Nada (0) - Constantemente (10)
¿Tuviste flatulencia? Nada (0) - Constantemente (10)
¿Cuántas deposiciones has realizado hoy? Número
¿Cuál fue su consistencia? Muy líquida - Muy dura



La evaluación del peso corporal se midió con una precisión de 0,1 kg con una báscula digital (OMRON; LA, CA, EUA) y el índice de masa corporal se calculó como: peso corporal / altura^2. El primer día de ingreso se extrajeron muestras de sangre en ayunas para determinar la glucosa (70-110 mg/dl), la creatinina (0,6-1,1 mg/dl), el sodio (135-145 meq/L), el potasio (3,5-5 meql/L), la albúmina (3,5-4,5 g/dl), la prealbúmina (18-28 mg/dl) y la transferrina (250-350 mg/dl) (Hitachi, ATM, Manheim, Alemania) usando un autoanalizador automatico COBAS INTEGRA 400® (Roche Diagnostic, Montreal, Canadá).

ANÁLISIS ESTADÍSTICO

Se realizó un cálculo del tamaño muestral basado en la preferencia de sabor, siendo necesarios treinta pacientes para detectar una mejora de 1 punto en cualquier pregunta de la escala analógica visual, con un error de tipo I < 0,05 y una potencia estadística del 80 %. Los autores opinan que una mejora de 1 punto debe considerarse un cambio relevante porque representa un 10 % del total de puntos de la escala. Los resultados se expresaron como media ± desviación estándar. La distribución de variables se analizó con la prueba de Kolmogorov-Smirnov. Las calificaciones del SON se compararon mediante análisis de la varianza unidireccionales (ANOVA) seguidos de la prueba post-hoc de Scheffe, o la prueba de Student, según el caso. El paquete estadístico utilizado fue el SPSS, versión 23.0 (IL, EE. UU.).

RESULTADOS

La edad media fue de 60,4 +/- 13,5 años y la distribución por sexos fue de 18 mujeres y 16 hombres. El índice de masa corporal promedio fue de 21,1 +/- 4,2 kg/m^2) y el peso de 57,8 +/- 12,6 kg. Todos los pacientes que participaron en el estudio valoraron los tres sabores del SON y respondieron a la escala analógica visual (Tabla II). Tras finalizar los 3 días de la prueba de sabor, el 55,8 % (n = 19) de los pacientes prefirieron el café, el 47,0 % (n = 18) la

Tabla III. Evaluación de la aceptación con el cuestionario de escala analógica visual de 10 puntos utilizado en el estudio

Sabor	Vainilla	Café	Fresa
¿Te gustó esta bebida?	6,41 ± 1,4	6,46 ± 1,7	6,41 ± 1,3
¿La encontraste dulce?	3,13 ± 0,1	3,03 ± 0,1	4,54 ± 0,2*
¿La encontraste salada?	0,27 ± 0,2	0,06 ± 0,1	0,03 ± 0,1
¿La encontraste amarga?	0,36 ± 0,1	0,27 ± 0,2	0,19 ± 0,3
¿La encontraste ácida?	0,18 ± 0,1	0,16 ± 0,1	0,09 ± 0,2
¿Tuvo regusto?	3,21 ± 0,4	3,20 ± 0,3	3,21 ± 0,2
¿Tuviste náuseas despues de beberla?	1,00 ± 0,9	0,66 ± 0,7	0,38 ± 0,3
¿Tenías hambre en la siguiente comida después de beberla?	4,91 ± 1,4	5,01 ± 1,2	4,58 ± 1,1
¿Cómo te sentiste después de beberla?	5,87 ± 1,8	5,73 ± 1,2	5,83 ± 0,9
Sumatorio	25,51 ± 5,6	24,8 ± 4,33	25,2 ± 2,9

**p < 0,05 con otros sabores. Fresa frente a vainilla (p = 0,03) y fresa frente a café (p = 0,03).*

fresa y el 26,2 % (n = 9) la vainilla (p = 0,03). Entre las diferencias significativas en la aceptación de los pacientes (Tabla III) —en el cuestionario con escala analógica visual el 1 significa "nada" y el 10 significa "mucho"—, el dulce fue superior para el sabor a fresa (4,54 +/- 0,2 puntos) que para el sabor a vainilla (3,13 +/- 0,1 puntos; p < 0,03) y el sabor a café (3,03 +/- 0,1 puntos; p < 0,03) (Tabla III). No existió ningún otro parámetro que mostrara diferencias en la escala de aceptación entre los 3 sabores del producto y tampoco hubo diferencias significativas en términos de aceptación en el sumatorio total de los tres sabores (Tabla III).

Por otra parte, no hubo diferencias significativas en la tolerancia entre los sabores de los SON (Tabla IV). El número de deposiciones y la consistencia también fueron similares con los tres sabores (Tabla IV). Al analizar la adherencia del número total de pacientes que tomaron suplementos después de elegir el sabor, los pacientes que eligieron el sabor café tomaron un total de 13,3 +/- 1,1 envases de promedio durante la hospitalización (0,91 +/- 0,2 por día), los pacientes que eligieron la fresa tomaron 13,4 +/- 1,3 envases (0,92 +/- 0,1 por día) y, finalmente, los pacientes que eligieron los envases de vainilla tomaron 8,3 +/- 0,9 envases durante el ingreso (0,61 +/- 0,1 por día), con diferencias significativas a favor de los sabores de fresa y café frente al de vainilla (Tabla V). Por otra parte, el SON elegido mayoritariamente por los pacientes al alta hospitalaria fue la caja multisabor (n = 20, 50 %). Eligieron el café el 15,0 % (n = 6), la fresa el 12,5 % (n = 5) y la vainilla el 7,5 % (n = 3).

Tabla IV. Evaluación de la tolerancia con el cuestionario de escala analógica visual de 10 puntos utilizado en el estudio

Sabor	Vanilla	Café	Fresa
¿Cómo te sentiste hoy?	6,03 ± 2,2	6,06 ± 1,9	6,12 ± 1,1
¿Tuviste náuseas?	0,63 ± 0,9	0,90 ± 0,4	0,96 ± 0,6
¿Tuviste vómitos?	0,21 ± 0,1	0,43 ± 0,3	0,22 ± 0,2
¿Tuviste reflujo de acidez en la boca?	0,69 ± 0,1	0,86 ± 0,3	0,61 ± 0,2
¿Tuviste dolor de abdomen?	0,93 ± 0,2	1,20 ± 0,4	1,16 ± 0,2
¿Tuviste el abdomen inflado?	1,09 ± 0,3	1,33 ± 0,4	0,96 ± 0,2
¿Tuviste dolor de estómago?	0,88 ± 0,1	0,90 ± 0,2	0,99 ± 0,4
¿Tuviste flatulencia?	1,78 ± 0,3	1,30 ± 0,4	1,25 ± 0,3
¿Cuántas deposiciones has realizado hoy?	1,41 ± 0,3	1,53 ± 0,4	1,55 ± 0,4
¿Cuál fue su consistencia?	1,34 ± 0,6	1,33 ± 0,2	1,05 ± 0,3

No existieron diferencias significativas entre los 3 sabores.

Tabla V. Características de los tres grupos de pacientes durante el ingreso tras la elección del sabor

Sabor	Vanilla	Café	Fresa
Edad (años)	59,3 ± 13,1	64,3 ± 11,6	62,3 ± 10,7
Peso (kg)	60,2 ± 11,9	62,1 ± 10,4	59,1 ± 9,6
IMC (kg/m^2)	20,6 ± 3,0	21,6 ± 4,2	21,1 ± 3,0
Glucosa (mg/dl)	94,4 ± 8,9	93,6 ± 7,7	92,3 ± 8,2
Creatinina (mg/dl)	0,7 ± 0,2	0,6 ± 1,1	0,8 ± 0,3
Sodio (meq/L)	138,1 ± 10,9	137,7 ± 9,7	139,1 ± 8,4
Potasio (meq/L)	4,0 ± 0,9	4,1 ± 1,0	4,2 ± 0,9
Albúmina (g/l)	3,6 ± 0,4	3,4 ± 1,1	3,7 ± 0,4
Prealbúmina (mg/dl)	17,1 ± 7,1	18,1 ± 3,4	17,4 ± 3,6
Transferrina (mg/dl)	163,1 ± 41,6	165,9 ± 29,4	162,4 ± 41,6
Promedio de envases en ingreso	8,3 ± 0,9	13,3 ± 1,1*	13,4 ± 1,3*
Envases diarios	0,61 ± 0,1	0,91 ± 0,2*	0,92 ± 0,1*
Días de ingreso	13,6 ± 0,7	14,7 ± 0,2	14,5 ± 0,3

**p < 0,05; diferencias significativas en promedio de envases durante el ingreso entre el sabor café (p = 0,02) y fresa (p = 0,02) frente al sabor vainilla. Diferencias significativas en promedio de envases diarios de sabor café (p = 0,03) y fresa (p = 0,03) frente a vainilla.*

Los niveles promedios de los parámetros bioquímicos fueron: glucosa, 94,0 +/- 24,0 mg/dl; creatinina, 0,7 +/- 0,3 mg/dl; sodio, 138,5 +/- 3,4 meq/L; potasio, 4,2 +/- 0,5 meql/L; albúmina, 3,6 +/- 0,3 g/dl; prealbúmina, 17,7 +/- 6,1 mg/dl; y transferrina, 164,8 +/- 59,1 mg/dl. No existieron diferencias estadísticas entre los datos bioquímicos y epidemiológicos de estos tres grupos de sabor (Tabla V).

DISCUSIÓN

El principal resultado de nuestro trabajo es la mejor adherencia a los SON hipercalóricos e hiperproteicos con sabor a café y fresa en los pacientes ingresados en el hospital con criterios de suplementación. El sabor a fresa fue calificado como más dulce que los sabores a vainilla y café, con una buena tolerancia de los 3 sabores.

Los suplementos nutricionales orales (SON) representan una forma de suplementación nutricional mínimente invasiva frente a la nutrición enteral por sonda, gastrostomía, etc. Estos preparados se han mostrado útiles para suplementar la dieta oral en pacientes con desnutrición relacionada con la enfermedad (DRE) (17). Es necesario recordar que estos suplementos presentan en su composición vitaminas y minerales en cantidades

inferiores a las recomendadas y que, por tanto, no pueden utilizarse como único y exclusivo aporte nutricional durante un período prolongado (18). La dispensación y prescripción de los SON es muy común en nuestro medio ya que están disponibles en múltiples formatos (envase listo para tomar, polvo para reconstituir, botella, bric, etc.), con diferentes texturas (líquida, yogur líquido y pudin), con diferentes sabores e incluso con la posibilidad de añadir aromas, pudiéndose muchos de ellos prescribir a través de receta médica y estando financiados con unas indicaciones muy precisas por el sistema público de salud. A pesar de ello, una de las debilidades de esta variante de suplementación nutricional son los problemas de cumplimiento por parte de los pacientes (13). La baja palatabilidad, los efectos de la monotonía y los sabores existentes podrían explicar en parte esta baja adherencia. Por tanto, parece crucial asegurarse de que a los pacientes se les ofrezcan los sabores que les gustan, para poder mejorar la adherencia, la aceptación y la tolerancia.

Existen pocos trabajos en la literatura que se hayan centrado en las preferencias de los sabores de los SON. Por ejemplo, dos estudios han demostrado que los pacientes prefieren el sabor del SON con base láctea frente al SON con base de zumo de fruta (19-20). Sin duda, una prescripción de una única toma diaria nos puede ayudar a mejorar el cumplimiento y por ello decidimos evaluar esta fórmula hipercalórica e hiperproteica en formato de 300 ml y con base de proteínas de origen lácteo. Previamente, Darmon y cols. (21) demostraron que los suplementos con base láctea, ya fueran hiperenergéticos, hiperproteicos o ambas cosas a la vez, eran mejor calificados por los pacientes hospitalizados desnutridos que los SON con base de zumo de fruta. En este estudio (24), los SON del tipo del zumo de fruta, que a menudo se consideran más fácilmente aceptables por los pacientes, obtuvieron puntuaciones bajas y nunca se eligió por parte del paciente un SON no saborizado durante más de 5 días. Otro trabajo previo (14) mostró que un SON hiperenergético con base láctea era mejor valorado y consumido durante el ingreso hospitalario con sabor a chocolate, frente a los sabores a vainilla o fresa. En otras publicaciones, la dulzura parece ser uno de los factores más relevantes que contribuyen a la palatabilidad del SON (22). No obsatnte, otros factores organolépticos deben estar implicados en la adherencia, como hemos detectado en nuestro trabajo, en el que los sabores a café y a fresa son los de mejor cumplimiento, a pesar de que el dulzor solo fue significativamente más valorado en el sabor fresa. Incluso en algún trabajo, los SON oligoméricos, con un característico registo amargo, se han valorado mejor que los SON poliméricos en pacientes con patología maligna a nivel pélvico (23). Si bien el número de estudios en esta área es bajo, algunos grupos han investigado este tema en niños. Sí que parece claramente demostrado que los SON comerciales presentan una mayor adherencia y cumplimiento que los suplementos elaborados de manera artesanal en el hospital, como han demostrado Cohen y cols. (24) en una cohorte de pacientes de oncología pediátrica. Por último, en algunos trabajos se ha demostrado (25) que los pacientes modifican sus preferencias, mostrando que casi la cuarta parte de los pacientes (23 %) sacrificarían el sabor de su SON si este produjera beneficios nutricionales sobre su enfermedad crónica.

Nuestro estudio piloto sienta las bases para que se diseñen más trabajos en vida real con SON para evaluar las preferencias de sabor, la adherencia y el cumplimiento en pacientes desnutridos, ya que pueden tener una repercusión sobre el número de envases ingeridos y, de manera secundaria, sobre la situación nutricional. Por ejemplo, la cantidad de envases que los pacientes tomaron al ingreso también fue mayor con los sabores a café y a fresa. Sin embargo, estos resultados no pueden extrapolarse al cumplimiento a largo plazo después del alta, ya que los pacientes eligieron la caja multisabor, formato que la mayoría de las compañías han comercializado para sus SON. Por tanto, se necesitan nuevos estudios a largo plazo y la evaluación de las preferencias de los sujetos desnutridos en diferentes momentos durante el tratamiento.

Nuestro estudio tiene limitaciones: en primer lugar, es un estudio de muy corta duración con un promedio de días de ingreso inferior a dos semanas; en segundo lugar, la patología que presentaron los pacientes era heterogénea, incluyédose pacientes de diferentes edades y enfermedades. Algunas variables no se han controlado, como el hábito de fumar, los diferentes estados de cada enfermedad y la medicación, que podrían influir en la percepción del gusto. Por útlimo, si la intervención nutricional hubiera durado más tiempo, podríamos haber medido el efecto sobre la situación nutricional del cumplimiento con estos SON. La fortaleza de nuestro trabajo es su desarrollo en vida real, obteniéndose datos que son fácilmente utilizables en cualquier entorno de hospitalización de nuestro medio, así como la utilización de un SON hipercalorico e hiperproteico en toma única diaria que ha demostrado su utilidad en la práctica clínica (26). Independientemente del tipo de SON, parece claro que el sabor y la consistencia se calificaron en otros estudios como más relevantes que otras características hedónicas (apariencia, olor, regusto) (27).

En conclusión, las preferencias de sabor de este SON con tres sabores son similares, aunque la adherencia y el cumplimiento son más elevados durante el ingreso con los SON con sabor a café y a fresa. La dulzura puede haber influido en este hallazgo, sobre todo con el sabor a fresa, con una buena tolerancia de los 3 sabores. Se necesitan más estudios con diferentes SON, con diferentes tipos de pacientes y con mayor duración de la intervención para valorar el efecto del sabor y otras variables sobre el cumplimiento y la adherencia en unos productos donde tanto los minerales como los aminoácidos y las grasas han demostrado tener efecto sobre el sabor (28).

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Obesidad y síndrome metabólico

Effect of bariatric surgery on neurocognitive function after 6 months of follow-up: a pilot study

Efectos de la cirugía bariátrica sobre la función neurocognitiva después de 6 meses de seguimiento: un estudio piloto

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Abstract

Background: reduced cognitive performance has been observed in patients with severe obesity. Bariatric surgery and subsequent adipose tissue loss seem to affect cognitive functioning positively; however, improvement predictors are not well established.

Aim: to evaluate the cognitive performance and the nutritional status of patients with severe obesity 6-month after bariatric surgery.

Methods: we assessed the neuropsychological performance of 22 patients with obesity (body mass index: ~ 42.9 kg/m²). The nutritional evaluation consisted of the routine tests performed in the baseline and postoperative periods. Lastly, we calculated the correlation between neuropsychological assessment results and blood biomarkers.

Results: the patients did not present cognitive impairment in the preoperative assessment, but performed below the standard range. The patients underwent significant weight loss after 6 months from surgery (~ 22 kg), with a change in obesity class III to I. Also, the patients presented a significant improvement in attention, mental flexibility, inhibitory control, and processing speed. Additionally, we observed a significant improvement in serum folic acid (108 %), gamma-glutamyl transferase (-41 %), uric acid (-32 %), ferritin (-28 %), triglycerides (-19 %), and high-density lipoprotein (9 %). Lastly, we found a moderate positive correlation between processing speed and body weight ($r = 0.46$), gamma-glutamyl transferase ($r = 0.54$), and total protein and mental flexibility ($r = 0.75$).

Conclusion: bariatric surgery promoted significant weight loss and improved attention, mental flexibility, processing speed, and several nutritional biomarkers. Nevertheless, the surgery had limited effects on other cognitive functions such as short- and long-term memory and language.

Keywords:

Obesity. Bariatric surgery. Neuropsychological tests. Nutritional status.

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Ethical approval: the Ethics Committee of the institution approved all procedures performed in the present study (process number 8763/2009). Additionally, all procedures performed in studies involving human participants are in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards.

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Resumen

Introducción: se ha observado una disminución del rendimiento cognitivo en los pacientes con obesidad grave. La cirugía bariátrica y la pérdida de tejido adiposo parecen mejorar el funcionamiento cognitivo; sin embargo, los predictores de mejora no están bien establecidos.

Objetivos: evaluar el rendimiento cognitivo y el estado nutricional de pacientes con obesidad severa después de 6 meses de una cirugía bariátrica.

Métodos: evaluamos el desempeño neuropsicológico de 22 pacientes con un índice de masa corporal ~ 42,9 kg/m². Se analizaron las pruebas de rutina realizadas al inicio y después de la cirugía. Calculamos la correlación con la evaluación neuropsicológica y los biomarcadores sanguíneos.

Resultados: los pacientes no mostraron deterioro cognitivo en la evaluación preoperatoria, pero sí un rendimiento por debajo del estándar. Los pacientes mostraron una pérdida de peso significativa 6 meses después de la cirugía (~ 22 kg), con un cambio de la clasificación de obesidad de III a I. Además, los pacientes mostraron una mejora significativa de la atención, la flexibilidad mental, el control inhibitorio y la velocidad de procesamiento. Además, observamos una mejora significativa del ácido fólico sérico (108 %), la gamma-glutamil-transferasa (-41 %), el ácido úrico (-32 %), la ferritina (-28 %), los triglicéridos (-19 %) y las lipoproteínas de alta densidad (9 %). Finalmente, encontramos una correlación positiva moderada entre la velocidad de procesamiento y el peso corporal (r = 0,46) y la gamma-glutamil-transferasa (r = 0,54), y entre la proteína total y la flexibilidad mental (r = 0,75).

Conclusiones: la cirugía bariátrica promovió una pérdida de peso significativa y mejoró la atención, la flexibilidad mental, la velocidad de procesamiento y varios biomarcadores nutricionales. Sin embargo, tuvo efectos limitados sobre otras funciones cognitivas, como la memoria y el lenguaje a corto y largo plazo.

Palabras clave:

Obesidad. Cirugía bariátrica. Pruebas neuropsicológicas. Estados nutricionales.

INTRODUCTION

Obesity has reached epidemic proportions representing a public health problem worldwide, with approximately 38 % of the adult world population estimated to be overweight by 2030, and severe obesity (when body mass index or BMI ≥ 40 kg/m^2) is associated with chronic diseases and comorbidities (1). In obesity, elevated inflammatory markers such as C-reactive protein (CRP) (2), gamma-glutamyl transferase (GGT), and alanine aminotransferase (ALT) (3), are observed together with nonalcoholic fatty liver disease (NAFLD) (4). Additionally, adiposity reportedly affects the brain and reduces cognitive abilities (5), being associated with a higher risk of developing neurological disorders such as cerebral gray matter atrophy and Alzheimer's disease (6). Obese persons also score lower in cognitive testing and tasks of attention, memory, and executive function (7).

Bariatric surgery is an effective and increasingly popular method for weight loss among severely obese people. However, up to one third of patients either fail to lose weight or experience significant weight gains at follow-up (8). Nevertheless, bariatric surgery is associated with cognitive improvement – particularly memory and psychological health – 12 weeks and 24 months after surgery (9). However, cognitive impairment may also contribute to suboptimal weight loss after bariatric surgery. Patients with obesity frequently display deficient attention, executive functioning skills, and memory when compared to eutrophic individuals (10). Additionally, higher BMI is associated with worst performances on response inhibition, working memory, planning, and cognitive flexibility (10).

The long-term effects of bariatric surgery on cognitive function remain poorly understood. Additionally, until this moment we did not observe previous studies that have investigated the association between blood biomarker changes, neuropsychological deficit, and postoperative nutritional status. We hypothesized that, after bariatric surgery, patients with obesity would exhibit enhanced cognitive function, which could be dependent on biomarker improvements. Thus, the present study aimed to assess the neuropsychological function of patients with severe obesity 6 months after bariatric surgery. Moreover, we analyzed if neuropsychological function improvement was associated with changes in the patients' nutritional profiles.

MATERIALS AND METHODS

STUDY DESIGN AND PARTICIPANTS

This was a longitudinal prospective study. The sample comprised 22 patients with severe obesity (BMI ≥ 40 kg/m^2) aged 18 years or older, recruited according to the number of patients treated at the Bariatric Surgery Clinic. The chosen sample included patients who had data available for all the variables investigated at preoperative baseline and 6 months after surgery. All participants underwent a Roux-en-Y gastric bypass (RYGB) (11), and all surgeries were performed by the same surgeons without postoperative complications. Inclusion criteria were BMI ≥ 40 kg/m^2 and 18 years of age or older. Exclusion criteria were smoking, excessive alcohol consumption, pregnancy, malignant neoplasms, unresolved psychiatric illnesses, neurological damage, having no formal education, and impossibility to follow-up. All participants signed informed consent forms, and all procedures were approved by the Ethics Committee (process number 8763/2009) and started only after obtaining an informed consent.

ANTHROPOMETRICS AND BIOCHEMICAL MEASUREMENTS

Anthropometric data were analyzed at baseline and 6 months after surgery. The variables weight (kg), height (m), BMI (kg/m^2), change in BMI (kg/m^2), and total weight loss (%TWL; kg and %) were obtained through standardized protocols. Blood and urine samples were collected from all subjects, at baseline and at 6 months after surgery, for chemistry and hematology testing.

NEUROPSYCHOLOGICAL TESTS

Neuropsychological tests were applied to all volunteers at baseline and 6 months after surgery by the same investigator. The battery of tests demonstrated a high sensitivity to the altered cognitive performance of obese individuals (10) and bariatric surgery patients (12). The tests also assessed performance in multiple cognitive domains and were completed in approximately 60 minutes. The specific tests comprised the following we expose.

Semi-structured interview and mental state

The 30-item Mini-Mental State Examination (MMSE) screening test assessed temporal and spatial orientation, registration, memory, attention, calculation, language, recall, and constructive skills (13).

Beck's Anxiety Inventory (BAI)

Assessed the presence and severity of anxiety. The items described the emotional, physiological, and cognitive symptoms of anxiety, but not of depression (14).

Stroop Color and Word Test (SCWT)

This tool assessed mental flexibility, selective visual attention, and inhibitory control. The subjects performed color (SCWT 1) and color-word trials (SCWT 2); with the scores from the two trials, the number of correct responses to each set were obtained (SCWT 3) (15).

Concentrated Attention Test (TEACO-FF)

The scores were obtained by the result of the stimuli that the person should mark and actually scored, subtracted from errors (stimuli that should not be marked and were) and omissions, that is, the target stimuli that were not marked by the person (16).

Rey-Osterrieth Complex Figure (ROCF)

It is a qualitative test that assesses the skills of visuospatial organization, planning, and strategy development skills, as well as visuospatial, immediate (short-term), and late (long-term) memory. This analysis included copy accuracy and delayed recall accuracy (17).

Rey Auditory-Verbal Learning Test (RAVLT)

This instrument measured episodic declarative memory, immediate memory, new verbal learning, retention of information, and memory recognition (18).

Wechsler Adult Intelligence Scale-Third Revision (WAIS-III)

This scale assessed verbal understanding, perceptual organization, working memory, and processing speed. It provided the executive intelligence quotient (EIQ) and processing speed index (PSI) (19).

STATISTICAL ANALYSIS

All the data were described as median, minimum, maximum, or interquartile range. All neuropsychological, anthropometric, and biochemical analyses were performed through the Wilcoxon rank-sum non-parametric test for paired samples. Spearman's rank correlation coefficient test was used to assess the relationship between neuropsychological tests and biochemical data that reached statistically significant differences. For this analysis, the difference between post-test and baseline was obtained. The margin of error used in the statistical tests was 5 %.

RESULTS

Table I describes the demographic and medical characteristics of subjects.

Table I. Baseline data in the screening of demographic and medical characteristics (n = 22)

Age (yrs) median [minimum; maximum]	42.5 [24; 61]
Gender, male/female (n)	2/20
Married/single (n)	15/7
Psychological support (n)	5
Use of psychiatric medication (n)	5
Obesity in the family (n)	19
Start of weight gain	
After pregnancy (n)	13
During childhood/puberty (n)	9
Grade education	
Incomplete basic school (n)	4
Complete basic school (n)	7
Complete high school (n)	9
Complete higher education (n)	2
Comorbidities	
Hypertension (n)	15
Orthopedic problems (n)	7
Others	
Alcohol consumption (n)	5
Employed (n)*	19
Difficulties at work (n)†	20

**Maid job, kitchen porter, receptionist, teacher, truck driver, retired employee, dentistry assistant and manicure. †Due to pain, tiredness, and/or discrimination.*

Consistent with clinical interpretation, anxiety symptoms were absent during the assessment period (raw score of ~ 1 on BAI). The MMSE screening verified that no patients presented incapacitating neurocognitive disorders (median z-score = -0.15).

Six months after the surgery, TWL and BMI decreased significantly (by approximately 22 % and 21 %, respectively). Additionally, the mean BMI values of the participants fell within moderate obesity (BMI = obese class I). Approximately, 31 % of participants exhibited a TWL greater than 25 %; only one participant presented a TWL of less than 10 % (Table II).

In most of the neuropsychological tests, the patients performed within the low-average range considered standard for their age, and no participant presented cognitive domain impairments. Attention, mental flexibility, and inhibitory control improved significantly (by approximately 12 %) on the SCWT 2. The other attention domains presented no statistical differences (Fig. 1).

Visuospatial organization, planning, visual, short- and long-term memory, and language presented no statistical differences at the 6-month postoperative assessment (Fig. 2A and 2B).

Table II. Anthropometric data of obese patients before RYGB and 6 months after RYGB (n = 22)

Measure	Median [minimum; maximum]	
	Baseline	6 months after RYGB
Body weight (kg)	111.7 [84; 155]	84 [69.7; 129]*
BMI (kg/m²)	42.9 [34.7; 53]	33.7 [26.1; 44.2]*
Change BMI (kg/m²)		-9.1 [-14.6; -3]
TWL (kg)		-21.9 [-40; -7]
TWL (%)		-19.6 [-34.4; -8.3]

*BMI: body mass index; RYGB: Roux-en-Y gastric bypass; %TWL: total weight loss. *Different from baseline for the Wilcoxon Rank-Sum Test ($p < 0.05$).*

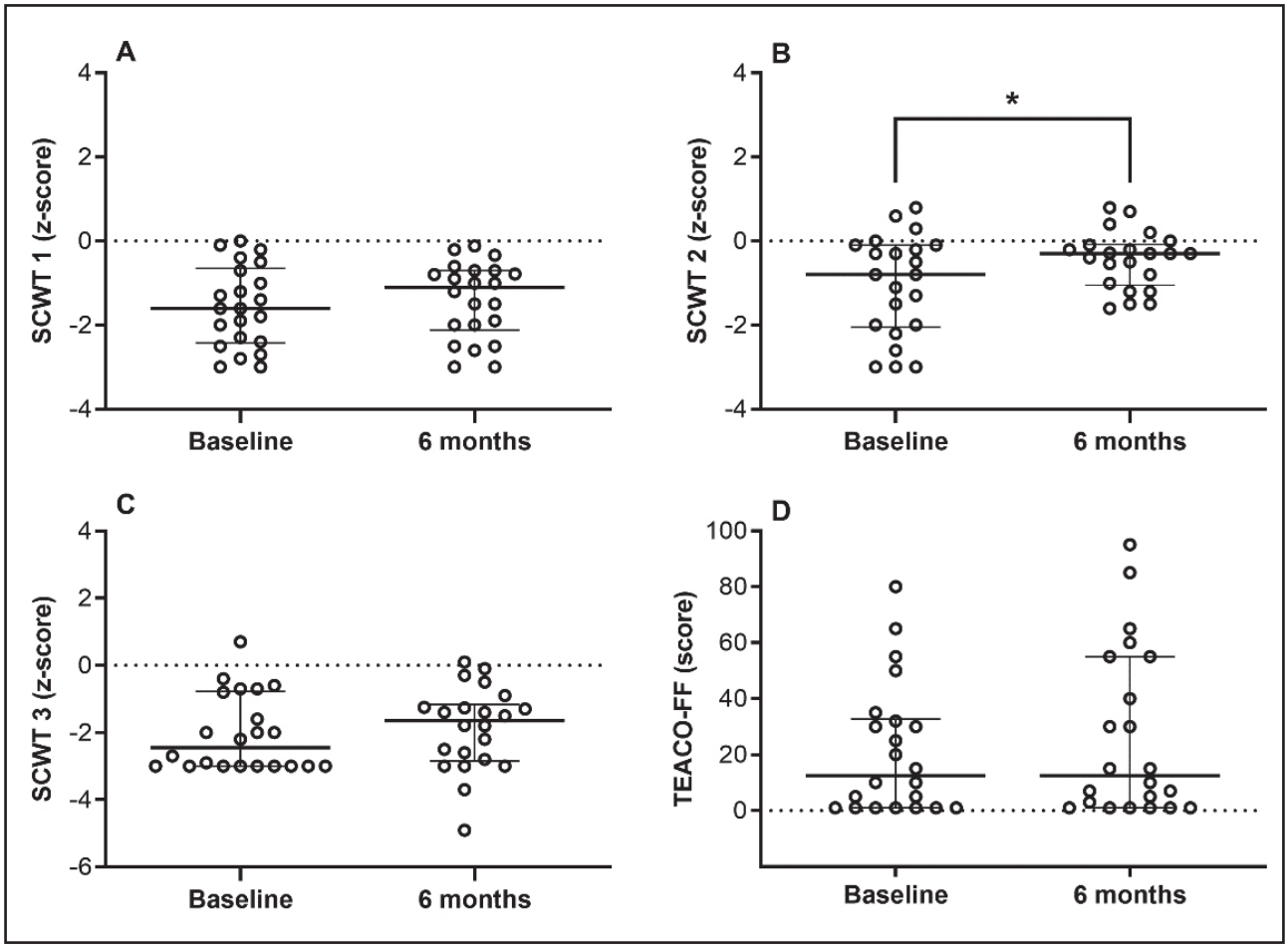

Figure 1.

Attention, mental flexibility, and inhibitory control (SCWT: Stroop color and word test (panels A, B and C); TEACO-FF: concentrated attention test (panel D). *Different from baseline for the Wilcoxon Rank-Sum Test ($p < 0.05$). Data are median and interquartile range, n = 22.

Similar results were obtained for episodic memory, verbal learning, retention of information, memory recognition, and executive functions (Fig. 2C, 2D, and 2E). However, the PSI presented a lower variability and increased significantly by approximately 12 % at the 6-month postoperative cutoff (Fig. 2F).

The biomarkers decreased significantly (~ 41 % in GGT, 28 % in ferritin, 32 % in uric acid, 19 % in triglycerides, and 5.5 % in total protein). Moreover, we found a significant increase of folic acid (~ 108 %), high-density lipoprotein (HDL; ~ 9 %), and mean corpuscular volume (4 %) (Table III).

A moderate positive correlation was observed between SCWT 2 and total protein (r = 0.75), and between PSI and body weight (r = 0.46) and GGT (r = 0.54, respectively) (Table IV).

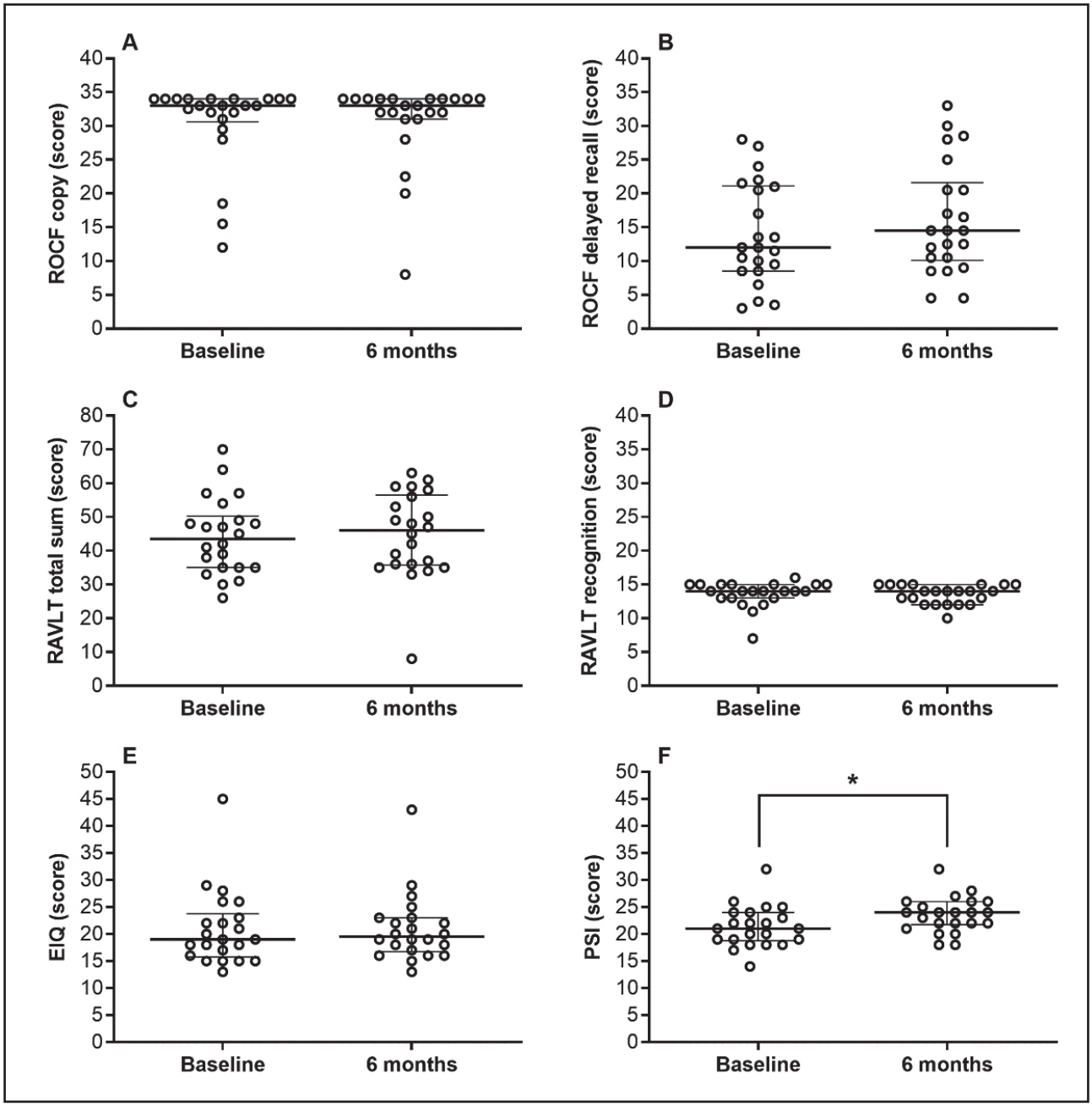

Figure 2.

Visuospatial organization, planning, visual, short-term, long-term and episodic memory, verbal learning, retention of information, memory recognition. ROCF:: Rey-Osterrieth complex figure (panels A and B); RAVLT: Rey auditory-verbal learning test (panels C and D); EIQ: execution intelligence quotient (panel E); PSI: processing speed index (panel F). *Different from baseline for the Wilcoxon Rank-Sum test ($p < 0.05$). Data are median and interquartile range, n = 22.

Table III. Biochemical and hematological data of obese patients before RYGB and 6 months after RYGB (n = 22)

Measure	Median [minimum; maximum]	
	Baseline	6 months after RYGB
Glucose (mg/dL)	92 [74; 105]	83.6 [70.4; 110.7]
TC (mg/dL)	192 [112; 236]	168 [139; 224]
TG (mg/dL)	109 [38; 205]	77.1 [44; 145]*
HDL (mg/dL)	48 [32.7; 99]	52 [33; 89.6]*
LDL (mg/dL)	117 [53; 175]	103 [72; 140]
Folic acid (ng/mL)	6.7 [4.2; 24]	21.3 [4.3; 24]*
Iron (µg/dL)	76 [37; 119]	78.4 [26; 106.9]
Ferritin (µg/L)	157.5 [14.9; 363]	112.5 [4; 259]*
LIBC (µg/dL)	232 [85; 374]	231.7 [124; 379]
Hemoglobin (g/dL)	13.4 [11.4; 15.7]	13 [11.3; 15]
Hematocrit (%)	39 [34; 47]	40 [35; 45]
MCV (fL)	88 [78; 94]	90 [74; 100]*
Vitamin A (mg/L)	0.42 [0.22; 0.59]	0.42 [0.27; 0.62]
Vitamin B_{12} (ng/L)	356.5 [151; 1000]	381 [150; 657]
Vitamin E (mg/L)	5.6 [3.8; 8.4]	5.7 [3.8; 9]
ALT (U/L)	24.7 [11.6; 59]	21.4 [10.8; 43.7]
GGT (U/L)	29 [14; 298]	20.3 [6.7; 112]*
Urea (mg/dL)	26 [10; 49]	25 [18.8; 41.2]
Uric acid (mg/dL)	5.1 [3.5; 7.1]	3.3 [2.1; 5.9]*
Creatinine (mg/dL)	0.8 [0.6; 1]	0.7 [0.6; 0.9]
Total protein (g/dL)	7 [6.6; 9.8]	6.5 [5.9; 7.4]*
Albumin (g/dL)	4.2 [3.7; 4.7]	4.1 [3.6; 4.5]

*ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LIBC: latent iron-binding capacity; MCV: mean corpuscular volume; RYGB: Roux-en-Y gastric bypass; TC: total cholesterol; TG: triglycerides. *Different from baseline for the Wilcoxon Rank-Sum Test ($p < 0.05$).*

Table IV. Correlations of biomarker changes with neuropsychological test changes achieving significant statistical differences at 6 months after RYGB

	Correlation coefficient (p-value)	
	SCWT 2	PSI
Body weight, kg	-0.27 (0.905)	0.46 (0.033)*
TG, mg/dL	0.26 (0.348)	-0,15 (0.583)
HDL, mg/dL	0.24 (0.394)	0.08 (0.765)
Folic acid, ng/mL	0.10 (0.777)	-0.16 (0.663)
Ferritin, ng/mL	-0.42 (0.106)	0.09 (0.740)
MCV, fL	-0.15 (0.556)	-0.1 (0.700)
GGT, U/L	0.06 (0.823)	0.54 (0.045)*
Uric acid, mg/dL	0.72 (0.071)	-0.25 (0.589)
Total protein, g/dL	0.75 (0.033)*	0.02 (0.965)

*GGT: gamma-glutamyl transferase; HDL: high-density lipoprotein; MCV: mean corpuscular volume; PSI: processing speed index; RYGB: Roux-en-Y gastric bypass; SCWT: Stroop color and word test; TG: triglycerides. *Different for Spearman's correlation test ($p < 0.05$).*

DISCUSSION

According to the applied neuropsychological tests, the participants of this study did not present cognitive impairments but performed poorly within the standard range in the preoperative assessments. The weight loss achieved in the 6-month postoperative period was accompanied by a slight increase in attention, mental flexibility, inhibitory control, and processing speed. Additionally, we observed a significant positive correlation between SCWT 2 and total protein, and between PSI and body weight, and PSI and GGT.

Unlike previous studies, our results did not indicate a cognitive deficit in bariatric surgery candidates (20). Regardless, the significant improvement in SCWT 2 in our study is in accordance with the improvements in attention switching 12 weeks after surgery (12). A previous study showed that the enhanced attention and mental flexibility persist for up to 24 months after bariatric surgery (9,21). The cognition prejudice in obesity is attributed to lower metabolic activity and a smaller gray matter volume in the prefrontal cortex, hypothalamus, and cingulate gyrus (22). Although the data are inconsistent, inflammatory cytokines released from visceral fat such as interleukin 6, tumor necrosis factor-alpha, and CRP lead to changes in both gray and white matter volumes (22).

It has also been shown that long-term obesity may lead to hippocampal damage, microvascular remodeling, and reduced frontal lobe volume, and interferes in brain maturation during adolescence (23). Our results did not show changes in short- or long-term, episodic, work, or visuospatial memory. Although our sample included nine patients who developed obesity in childhood or adolescence, it is possible that we did not observe cognitive deficiencies due to our insufficient sample size.

Improvement in processing speed was moderately associated with body weight and GGT. Although the mechanisms involved are not fully understood, GGT is a strong independent predictor of obesity (odds ratio of 4.8) (24). Similarly, the specific mechanism

involving processing speed and GGT has not been described; however, GGT has recently been associated with cognitive decline risk in middle-aged and elderly persons (25). GGT was also proposed to trigger pro-oxidant and pro-inflammatory properties, which might affect the vascular structure (26).

Our GGT and ALT results were similar to those of a previous study regarding patients with obesity submitted to RYGB (27). Additionally, lower GGT levels may indicate reduced NAFLD inflammation (3). Although the mechanisms involved in NAFLD improvement after bariatric surgery are not fully understood, reduction in insulin resistance and dyslipidemia may contribute to it (27).

Uric acid (UA) reduction is consistent with other study that reported UA decrease in patients with obesity who underwent RYGB (28). The decrease in UA is proportional to the degree of weight loss (assessed by change in BMI). This relationship may be due to reduced urate production and increased renal urate clearance following weight loss (29). Further research is needed to clarify the origin and relationship between UA and adiposity. We also found a significant increase in HDL at the 6-month follow-up visit, and it is suggested that after RYGB, the subsequent hepatic expression of the paraoxonase-1 gene contributes to antioxidative and antiatherogenic HDL activity (30).

Our study's primary limitation was its small sample size, which restricted our understanding of the impact of postoperative weight loss on cognitive function. A secondary limitation was the lack of a control group, given we recruited the patients by convenience without randomization, which diminished the study's power. Thus, we were unable to determine causality for the observed cognitive changes induced by weight loss.

Additionally, a third limitation was the significant variability in our sample. The hospital environment, the researcher-participant relationships, and the patients' emotional aspects may have negatively influenced the collection of cognitive function data. In our study, the leading investigator was a psychologist who observed qualitative changes in the patients' affective, marital, familiar, and self-image domains. A fourth limitation we did not anticipate was modifiable risk factors such as low serum iron, folic acid, and vitamins. Thus, we are unsure whether nutrient supplementation prior to bariatric surgery could affect neurocognitive function. Lastly, the 6-month follow-up limited the substantiation of greater cognitive function improvements, such as those found in studies with 24 or 36 months after surgery (9,21).

To our knowledge, our study was the first one to analyze the association between cognitive function and nutritional biomarkers. However, we were unable to validate if an improvement in nutritional profile directly affects cognitive function. Further clinical studies, with a larger sample size, are necessary to understand the influences of nutritional status and massive weight loss over the cognitive function of bariatric patients. Additionally, bariatric patient difficulties must be considered when adapting the multidisciplinary approach, positively changing sedentary behavior and eating patterns.

As a practical application of the present results, this study could help guide the psychologist during follow-up of a bariatric patient. It is worth paying attention to the results of the cognitive analysis, as changes in it could signal nutritional deficiencies and, therefore, the patient should be referred for nutritional care, which reinforces the importance of a multidisciplinary team in the care of these patients.

In conclusion, after bariatric surgery the patients presented a slight improvement in attention, mental flexibility, speed processing, and several nutritional biomarkers. Nevertheless, bariatric surgery marginally impacted other cognitive domains, such as short- and long-term memory and language.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Obesidad y síndrome metabólico

Relation of serum IL-32 levels and gene polymorphism rs45499297 with obesity in Mexican patients: a laboratory and *in silico* analysis

Relación de los niveles séricos de IL-32 y del polimorfismo rs45499297 con la obesidad en pacientes mexicanos: un análisis de laboratorio e in silico

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Abstract

Background: many genes have been involved in the development of obesity. Interleukin 32 (IL-32) is a proinflammatory cytokine; rs45499297 is a T/C promoter, single-nucleotide polymorphism of the *IL-32* gene.

Objectives: this study aimed to evaluate the rs45499297 polymorphism and its association with obesity. Another objective of this study was to carry out an *in silico* analysis.

Methods: this study was cross-sectional, and included 333 subjects classified by body mass index and fat percentage. The plasma glucose and lipid profile were measured. We measured serum IL-32 protein by ELISA and the rs45499297 polymorphism by PCR-RFLP. We used several databases to build the *IL-32* gene network and infer transcription factors that bind to this polymorphic site.

Results: subjects underweight and with low fat percentages had lower levels of IL-32. CT genotype and allele C were less frequent in the overweight/obesity group than in the normal-weight group. Interestingly, this result remained only in the male gender. We found that the transcription factors Hepatocyte Nuclear Factor and Specificity Protein 1 bind to this polymorphic site. In addition, we infer that *IL-32* is involved in metabolic pathways related to viral infections.

Conclusion: the TC genotype is associated with overweight/obesity. The decrease in levels of IL-32 observed in underweight and low fat percentage groups could be due to an impaired inflammatory profile. The *in silico* analysis showed that several transcriptional factors bind at this polymorphic site, and that the enrichment of the metabolic pathways is diverse.

Keywords:

Obesity. Interleukin 32. BMI. Fat percentage. Polymorphism. *In silico.*

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Resumen

Introducción: la interleucina 32 es una citocina proinflamatoria. El rs45499297 es un polimorfismo de nucleótido simple del gen de *IL-32,* situado en la región promotora y caracterizado por un cambio de T/C.

Objetivo: evaluar el polimorfismo rs45499297 y su asociación con la obesidad, y realizar un análisis *in silico.*

Métodos: el estudio fue transversal e incluyó 333 sujetos clasificados por índice de masa corporal y porcentaje de grasa. Se midieron la glucosa y el perfil lipídico, así como los niveles séricos de IL-32 mediante ELISA y el genotipo del polimorfismo rs45499297 mediante PCR-RFLP. Para el análisis *in silico* se utilizaron varias bases de datos para hacer la red de genes de *IL-32* e inferir factores de transcripción unidos al sitio polimórfico.

Resultados: los sujetos con bajo peso y bajo porcentaje de grasa tienen niveles más bajos de IL-32. El genotipo TC y el alelo C se encontraron con menos frecuencia en los sujetos con sobrepeso/obesidad que en los normopeso, resultado que permaneció solo en el género masculino. Se encontró que el factor nuclear de los hepatocitos y la proteína de especificidad 1 se unen a este sitio polimórfico. Se infiere que *IL-32* está involucrado en vías metabólicas relacionadas con las infecciones virales.

Palabras clave:

Obesidad. Interleucina 32. IMC. Porcentaje de grasa. Polimorfismo. *In silico.*

Conclusión: el genotipo TC está asociado al sobrepeso/la obesidad. La disminución de los niveles de IL-32 observada en los sujetos con bajo peso y bajo porcentaje de grasa podría ser por un perfil inflamatorio alterado. El análisis *in silico* mostró que varios factores de transcripción se unen al sitio polimórfico y que el enriquecimiento de las vías metabólicas es diverso.

INTRODUCTION

The incidence of obesity is rapidly increasing in the entire world. In 2016, the World Health Organization (WHO) estimated that more than 1.9 billion adults aged 18 and older were overweight (1). In Mexico, data showed that the prevalence of being overweight between 20 and 29 years old was 29.5 % for men and 25.3 % for women for obesity (2).

Obesity results from a disruption of energy balance that leads to weight gain and metabolic disturbances that cause tissue stress, inflammation, and endothelial dysfunction (3) involving various environmental and genetic factors (4). Gene-association studies have identified several genes that affect obesity-related traits (5) and have suggested that single nucleotide polymorphisms (SNP) account for around 30 % of BMI (body mass index) variance (6).

Chronic low-grade inflammation contributes to obesity-associated comorbidities, and adipose tissue is a major immunologically active organ contributing to this inflammation (8,9). Adipose tissue is metabolically active that can secrete a variety of adipokines and proinflammatory cytokines such TNFα and IL-1β in addition to anti-inflammatory cytokines like IL-10 (7).

Interleukin 32 (IL-32) is a proinflammatory cytokine that performs essential immune regulation. It is expressed by human peripheral blood mononuclear cells upon activation, induced in human epithelial cells by IFN-γ, and in natural killer cells by IL-12 plus IL-18 (9). IL-32 participates in inflammatory disorders such as rheumatoid arthritis, ulcerative colitis, multiple sclerosis, and cancer (10). Despite this characterization, the specific role of this protein in obesity remains to be determined.

The gene encoding IL-32 protein is located on chromosome 16p13.3 and contains six exons. Several SNPs have been studied in various diseases (5,11-13). The polymorphism rs45499297 is located in the promoter region of the *IL-32* gene, characterized by a change from T to C. However, the association between this polymorphism and BMI, fat percentage, and lipid profile has not been reported. This study aimed to evaluate the role of IL-32 serum levels and the rs45499297 polymorphism in obese subjects. Another objective was to carry out an *in silico* analysis to investigate the interaction of this gene with factors that regulate its expression and analyze the network of this gene.

SUBJECTS, MATERIALS AND METHODS

STUDY PARTICIPANTS

This study was cross-sectional and included 333 subjects – 245 females and 88 males – all between 18 and 69 years of age. The participants were classified into the following groups: 22 underweight (BMI < 18.5 kg/m^2), 188 normal-weight (BMI = 18.5-24.9 kg/m^2), and 122 overweight/obese (BMI > 25 kg/m^2) subjects. Additionally, we also classified them by percentage of fat. This interpretation was made considering gender and age as follows: for men, low (F% < 8), standard (F% = 8-19.9) and high/obese (F% ≥ 20); in women, low (F% < 21), standard (F% = 21-32.9), and high/obese (F% ≥ 33) (14). These guidelines yielded 16 low-fat, 153 standard-fat, and 164 high-fat/obese subjects.

Subjects were recruited from September 2017 to August 2019. The demographic and clinical characteristics of the studied population were recorded in an appropriate questionnaire. The exclusion criteria were based on subjects taking anti-inflammatory medications, having a history of autoimmune diseases, chronic alcohol usage, pregnancy, or women in lactation. All study subjects signed an informed consent form. The local ethics committee approved the study (6/2017-2018).

BIOCHEMICAL ANALYSIS

Blood samples were taken after eight hours of fasting and obtained from the antecubital vein in test tubes without anticoagulants. The serum was obtained by centrifuging at 3500 rpm for 20 minutes. An Abbott Aero Set autoanalyzer with the original kit was used to measure plasma glucose, total cholesterol, triglycerides, and HDL levels. The Friedewald equation was used to calculate LDL levels.

MEASUREMENT OF IL-32 LEVELS

We quantified serum levels of IL-32 by ELISA DuoSet (R&D Systems, USA). Briefly, plates were coated by 100 µL per well with Capture Antibody, then 100 µL of standard or sample was added per well, and the procedure was performed according to the manufacturer's instructions. The absorption was determined at 450 nm.

GENETIC ANALYSIS

DNA extraction was carried out from peripheral blood leukocytes using the Purelink Genomic DNA mini kit, following manufacturer's instructions. IL-32 SNP rs45499297 (T/C) was genotyped by the restriction fragment length polymorphism-based method, as previously described (12). Forward 5'–GATTGCTGAGACCAGTGA-3' and reverse 5'–TCTCTGAGCCCAGGAATG-3' primers were used to obtain a fragment of 445 bp. Amplification was performed with PCR conditions in a gradient thermocycler. The thermal profile was as follows: an initial denaturation step at 95 °C for 3 min, followed by 35 cycles of denaturation at 94 °C for 30 s, annealing at 62 °C for 30 s, and an extension at 72 °C for 45 s, with a final extension step at 72 °C for 5 min. Amplified products were visualized by 6 % acrylamide gel electrophoresis.

We treated amplified products with the enzyme *BamHI*. The outputs obtained were as follows: the TT genotype presented two fragments, 306 bp and 139 bp. The TC genotype showed 445 bp, 306 bp, and 139 bp fragments. The CC genotype is a fragment of 445 bp. Amplified products were visualized by 6 % acrylamide gel electrophoresis and stained with silver nitrate.

STATISTICAL ANALYSIS

The characteristics of subjects were described using simple frequency, percentages, mean and standard deviation. After applying the corresponding normality tests, the association between study variables was performed using the chi-square test, Kruskal-Wallis test, or ANOVA. A $p < 0.05$ was considered statistically significant.

IN SILICO ANALYSIS

The investigation of the factors that regulate transcription of the *IL-32* gene due to the effect of the rs45499297 polymorphism was carried out using the HaploReg (15), PROMO (16), rVarBase (17), and AliBaba (18) software.

To analyze the *IL-32* gene network we used the COXPRESdb database (19) to obtain the genes coexpressed with *IL-32*. We used the first 50 genes and then constructed these genes' protein interaction network using STRING (20). KEGG pathway enrichment analyses of these coexpressed genes were carried out in the Database DAVID (21) and WebGestalt (22).

RESULTS

The demographic and biochemical characteristics of the study population classified according to their BMI and body fat percentage are shown in table I. As expected, the overweight/obesity group presented elevated glucose, total cholesterol, triglycerides, LDL-C, and VLDL-C levels. Overweight/obese subjects also presented lower HDL-C levels ($p < 0.001$). When separating subjects by body fat percentage, the high-fat/obesity group presented higher glucose, total cholesterol, triglycerides, LDL-C, and VLDL-C levels.

Table I. Demographic and biochemical characterization of the study population classified by BMI and fat percentage

BMI			
Variables	**Underweight**	**Normal weight**	**Overweight/ obesity**
Gender (male/female)	6/16	41/147	41/81
Age (years)	20.7 ± 4.45	21.6 ± 5.27	26.7 ± 11.20*,†
Glucose (mg/dL)	85.24 ± 12.74	85.30 ± 17.79	92.24 ± 19.37†
Total cholesterol (mg/dL)	139.78 ± 39.39	156.14 ± 38.43	172.58 ± 54.15*,†
Triglycerides (mg/dL)	72.03 ± 45.63	89.83 ± 46.35*	115.59 ± 63.83*,†
HDL-C (mg/dL)	70.08 ± 50.40	57.56 ± 25.26	44.04 ± 17.21*,†
LDL-C (mg/dL)	58.47 ± 53.12	84.44 ± 45.85	107.71 ± 55.29*,†
VLDL-C (mg/dL)	14.40 ± 9.12	17.96 ± 9.27*	23.11 ± 12.76*,†
Fat percentage			
Variables	**Low**	**Standard**	**High/obesity**
Gender (male/female)	3/13	29/124	56/108
Age (years)	21.3 ± 5.14	21.1 ± 5.37	25.8 ± 10.04†
Glucose (mg/dL)	79.90 ± 13.80	84.14 ± 14.22	92.04 ± 21.03*,†
Total cholesterol (mg/dL)	136.79 ± 22.84	156.87 ± 45.54	167.29 ± 46.74*,†
Triglycerides (mg/dL)	59.27 ± 18.18	89.56 ± 47.66*	109.83 ± 60.58*,†
HDL-C (mg/dL)	64.62 ± 37.30	57.19 ± 28.30	48.50 ± 21.91†
LDL-C (mg/dL)	55.54 ± 37.92	83.67 ± 52.93*	101.80 ± 49.36*,†
VLDL-C (mg/dL)	11.85 ± 3.63	17.91 ± 9.53*	21.96 ± 12.11*,†

**p < 0.05 compared with the underweight group or low-fat group; †p < 0.05 compared with the normal-weight group or standard group.*

Figure 1 shows the analysis of serum IL-32 levels. Underweight subjects had lower levels of IL-32 when compared to normal-weight subjects (p = 0.035). Besides, IL-32 was lower in subjects with low fat than in those with a standard fat percentage (p = 0.025) and high/obesity groups (p = 0.026).

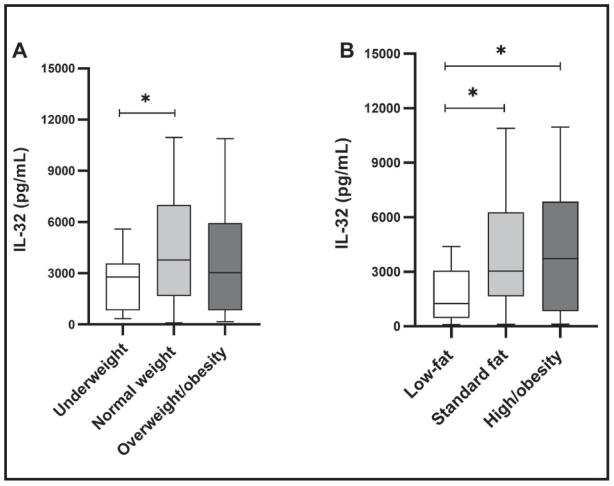

Figure 1.

Analysis of serum IL-32 levels. A. Analysis according to BMI. The underweight group presented lower levels of IL-32 than the normal weight group. B. Analysis according to percentage of fat. The low-fat group presented lower levels of IL-32 than the standard-fat group and a high percentage of the high-fat/obesity group.

Later, we genotyped the *IL-32* rs45499297 polymorphism. As shown in table II, the CC genotype is not associated with obesity, according to BMI. However, the TC genotype showed a statistical difference between the three study groups (p = 0.009); specifically, this difference was between the normal-weight and overweight/obesity groups (p = 0.003). We obtained similar results for allele C (p = 0.048); and, like in the genotype analysis, the difference was between the normal-weight and overweight/obesity groups (p = 0.024). The rs45499297 polymorphism analysis showed no significant differences between the different fat percentage groups for both genotypes and alleles (Table II). Also, the rs45499297 polymorphism did not affect biochemical parameters or IL-32 protein levels (data not shown).

We also analyzed the association between obesity and gender. Men have a higher frequency of obesity by percentage of fat (p = 0.007) and a trend towards higher BMI (p = 0.067) than women (data not shown). However, when we included genotype in this analysis (we omitted the CC genotype for statistical reasons), we found a statistical difference between the three groups (p = 0.026). Interestingly. it was observed that the TC genotype is less frequent in the male overweight/obesity group (p = 0.016). This suggests that the TC genotype may have a protective effect against obesity in young men. Data are shown in table II.

For the *in silico* analysis, we examined the potential functional effect of this polymorphism in various databases. As seen in table III, we found several transcription factors that overlap in the position of the rs45499297 polymorphism. It is noteworthy that two

Table II. Association of the IL-32 polymorphism by BMI and fat percentage and by gender

	BMI				Fat percentage			
	Underweight % (n = 22)	Normal weight % (n = 189)	Overweight/ obesity % (n = 122)	p-value	Low % (n = 16)	Standard % (n = 153)	High/ obesity % (n = 164)	p-value
Genotype/Allele								
TT	86.4 (19)	70.4 (133)	84.5 (103)	Ref.	75.0 (12)	75.2 (115)	76.6 (128)	Ref.
TC	13.6 (3)	29.1 (55)	13.9 (17)*	0.009	18.7 (3)	24.8 (38)	22.5 (34)	0.790
CC	0	0.5 (1)	1.6 (2)	0.809	6.3 (1)	0	0.9 (2)	0.510
T	93.2 (41)	84.9 (321)	91.4 (223)	Ref.	93.7 (30)	87.6 (268)	88.4 (290)	Ref.
C	6.8 (3)	15.1 (57)	8.6 (21)*	0.048	6.3 (2)	12.4 (38)	11.6 (38)	0.756
Male								
TT	80.0 (5)	68.3 (28)	92.3 (36)	0.026	66.7 (2)	72.4 (21)	85.2 (46)	0.316
TC	20.0 (1)	31.7 (13)	7.7 (3)*		33.3 (1)	27.6 (8)	14.8 (8)	
Female								
TT	87.5 (14)	71.4 (105)	82.7 (67)	0.087	83.3 (10)	75.8 (94)	75.9 (82)	0.839
TC	12.5 (2)	28.6 (42)	17.3 (14)		16.7 (2)	24.2 (30)	24.1 (26)	

**p < 0.05 compared with the normal-weight group.*

Table III. Transcription factors and motifs overlapping the rs45499297 *IL-32* polymorphism according to different databases

SNP	Alleles	Location	HaploReg	PROMO	rVarBase	AliBaba
rs45499297	T/C	chr16:3115272-3115273	ATF3_disc2, ERalpha-a_ disc2, Glis2, HNF4_known1, LRH1, Nkx2_9, Pax-5_disc1, RXR::LXR, RXRA_known1	HNF-3alpha, RXR-alpha	JUND, HNF4G, TCF12, POU2F2, FOS, FOSL2, MAX, HNF4A, STAT3, STAT1, HEY1, MAFK, ATF2, BCL3, HSF1, SP1, HDAC2, BCL3	SP1, NF-1

of them were inferred in three databases — Hepatocyte Nuclear Factor (HNF), with its variants. In addition, the transcriptional factor Specificity Protein 1 (SP1) was inferred in two databases. Therefore, this polymorphism appears to be a binding site for different transcription factors.

Based on the fact that IL-32 levels were decreased in the underweight group, we carried out the analysis of the IL-32 network (Fig. 2). We found that the 50 genes co-expressed with *IL-32* were interconnected with 327 interactions. The top 5 of the KEGG metabolic pathways are shown in figure 2A, along with the number of genes involved in each metabolic pathway. Figure 2B shows the network of genes co-expressed with *IL-32*. It should be noted that *IL-32* does not participate in any of the enriched routes of the top 5.

DISCUSSION

IL-32 is a proinflammatory cytokine that is important for immune regulation and implicated in inflammatory disorders (11,23,24). We found significantly decreased levels of IL-32 in subjects who were underweight and low-fat when compared to normal-weight and standard-fat subjects. Fadaei et al. also performed IL-32 measurements and found higher levels in patients with type 2 diabetes *mellitus* versus controls, which supports the results from this study; in the diabetes group, they also found a positive correlation between BMI and IL-32 (25).

IL-32 production is predominantly induced by IL-1β, TNFα, IL-2, or INF-γ in monocytes and epithelial cells (23, 26). Interestingly, malnutrition presents alterations of IL-1β, TNFα, IL-2, and IFN-γ (27-30). Therefore, these cytokines may be regulating the production of IL-32 protein levels in underweight subjects. Rytter et al. found several levels of cytokines in children with malnutrition (27). Th1-cytokines IL-1, IL-2, IL-12, and INF-γ were lower in malnourished than in well-nourished children, while Th2-cytokines IL-10 and IL-14 were higher in those who were malnourished compared to those well-nourished. The authors conclude that malnourished children have an anti-inflammatory

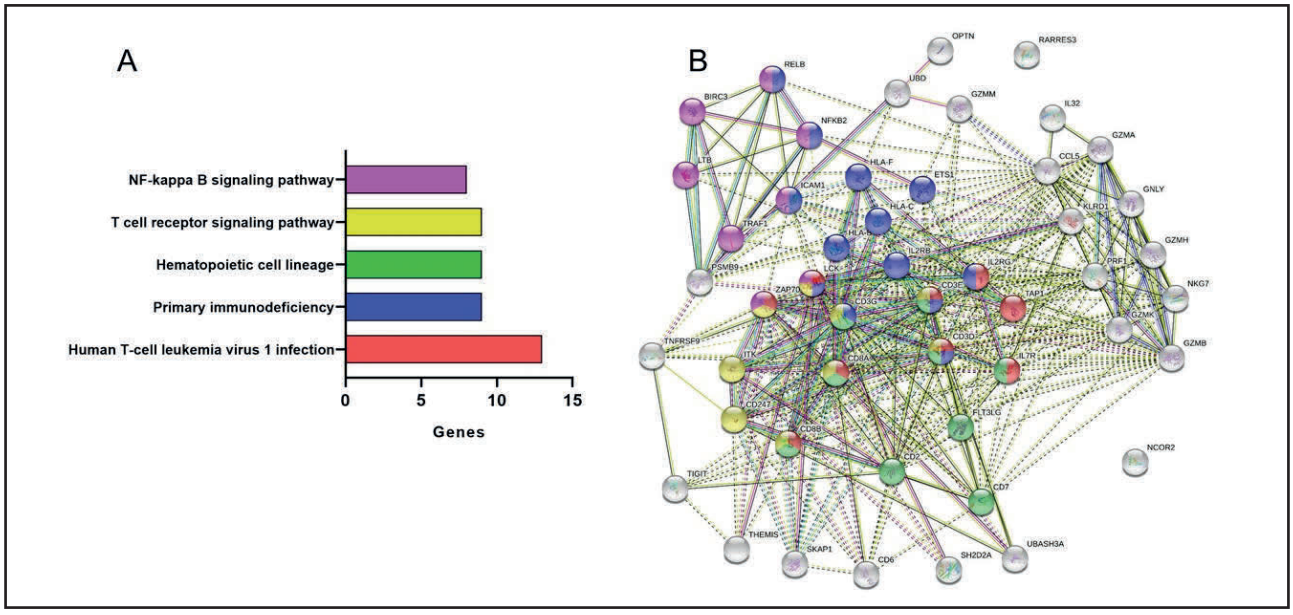

Figure 2.

Enriched metabolic pathways and *IL-32* interaction network. A. Top 5 of the enriched metabolic pathways and the number of genes that participate in each of them. B. *IL-32* network — the genes of the enriched metabolic pathways match the color of the genes involved.

profile. Therefore, other altered cytokines in malnutrition may be affecting serum IL-32 levels in our study group.

We analyzed the rs45499297 polymorphism and its relationship with obesity for the first time in a Mexican population. We found that allele C and genotype TC of the IL-32 polymorphism are less frequent in the overweight/obesity group. Because so far there are no reports of this polymorphism in obesity or metabolic diseases, we cannot compare our results. However, Morsaljahan et al. analyzed this polymorphism in people from Iran with multiple sclerosis. They found that allele C was more frequent in patients than controls (11), so these results could indicate that this polymorphism is associated with another inflammatory disease.

We found that this polymorphism did not modify the biochemical parameters or serum levels of IL-32. There are also no reports of the rs45499297 polymorphism compared to biochemical parameters. However, in a study reported by Damen et al., which analyzed *IL-32* promoter rs4786370 in patients with rheumatoid arthritis, the lipid profile was affected (12); this may be because IL-32 is an essential regulator of cholesterol transporters ABCA1 and ABCG1 (31). Therefore, other polymorphisms of IL-32 may be capable of affecting biochemical parameters, although it is advisable to look for new factors associated with the phenotype of obesity, as in this case the rs45499297 polymorphism.

The high/obesity group was comprised of more men than women. Other studies have reported results similar to ours, where young men have a higher percentage of obesity than women (32,33). However, our results appear to show that the TC genotype acts as a protective factor in men. This result could be due to the different hormonal profiles existing between both genders, as it is well known that people with obesity have high levels of leptin (34,35). Leptin is present in higher amounts in females than in males (36,37). Therefore, the TC genotype may confer protection against being overweight and obese in men more than women due to hormonal reasons.

Since it is known that transcription factors regulate gene expression by binding to the promoter region of the gene, it is presumed that the polymorphisms present in these regions affect gene expression. Hepatocyte Nuclear Factor 4 alpha (HNF4α), or its variants, and the transcriptional factor Specificity Protein 1 (SP1) were inferred in different databases. Previous studies reported that the *IL-32* gene has a binding site for these transcriptional factors (39,40). However, we have inferred that the binding site overlaps with the rs45499297 polymorphism.

Our network analysis also showed the interconnectivity between signaling pathways such as human T-cell leukemia virus 1 infection (HTLV1), primary immunodeficiency, hematopoietic cell lineage, T-cell receptor signaling pathway, and NF-kappa B signaling pathway. Malnutrition has been associated with HIV and HTLV1 (39,40), so it is inferred that genes co-expressed with *IL-32* are involved with these metabolic pathways, in addition to the fact that this cytokine is modified in malnourished states. This information is essential to understand disease mechanisms, especially in diseases with a high degree of complexity, such as obesity, in which several metabolic pathways are involved in the pathogenesis of the disease.

One limitation of the current study is the mean age of the participants, as the findings cannot be generalized to middle-aged or mature adults. So more research is needed with a greater range of ages. In addition, the results of the *in silico* analysis must be corroborated by experimental work.

CONCLUSION

Until now, there is little information on IL-32 and obesity. This study found an association of the rs45499297 polymorphism with overweight/obesity. However, there was no association of the polymorphism with lipid profile and serum IL-32 protein levels. The level of IL-32 was lower in underweight and low-fat subjects. On the other hand, the *in silico* analysis showed that this polymorphism is found in the binding site of several transcriptional factors. In addition to that, the enrichment of the metabolic pathways is diverse.

The results presented in this work could stimulate future research to clarify the pathophysiology of obesity, which has become a global problem that increases over time. Moreover, it is possible to better understand this pathology from a nutritional perspective and the genetic and immunology points of view.

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ARÁN

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Trabajo Original

Obesidad y síndrome metabólico

Autonomic function and its relationship with central obesity and hemodynamic variables in obese and overweight adults

Función autonómica y su relación con la obesidad central y las variables hemodinámicas en adultos obesos y con sobrepeso

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Abstract

Introduction: central obesity is associated with an autonomic dysfunction characterized by an increase in sympathetic activity and a reduction in vagal tone, leading to a decrease in heart rate variability.

Objective: we aimed to analyze the relationship between the time and frequency domains of heart rate variability with central obesity, and its hemodynamic variables in normal-weight, overweight and obese adults.

Methods: a total of 65 adults were evaluated (25.4 ± 3.2 years old) and distributed in 3 groups: normal weight group (NW group), overweight group (OW group) and obese group (OB group). Heart rate variability parameters at rest and both anthropometric and hemodynamic variables were recorded.

Results: the results showed a positive correlation between waist circunference and LF/HF ratio in the OW ($p = 0.0008$; $r = 0.6607$; $r^2 = 0.4365$) and OB ($p = 0.0001$; $r = 0.8286$; $r^2 = 0.6866$) groups. The waist-to-height ratio showed significant differences with HF in the NW, OW, and OB groups. The variables related to the parasympathetic system (SDNN, RMSSD, pNN50, HF) in the OB and OW groups showed a decrease in values when compared to the NW group. Likewise, the variable related to the sympathetic system (LF) in the OB and OW groups increased its values when compared with the NW group. The LF/HF ratio increased from the NW group to the OW and OB groups (1.6 ± 0.7; 2.5 ± 1.8 and 3.3 ± 0.7).

Conclusion: overweight and obese adults present a modulation of sympathetic activity predominance at rest. This increased activity is represented by the time and frequency domains of heart rate variability, having an important correlation with waist circumference and waist-to-height ratio.

Keywords:

Autonomic nervous system. Heart rate variability. Central obesity. Hemodynamic variables. Waist circumference.

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Resumen

Introducción: la obesidad central se asocia con una disfunción autonómica caracterizada por una mayor actividad simpática y reducción del tono vagal, conduciendo a una disminución de la variabilidad de la frecuencia cardíaca (VFC).

Objetivo: analizar la relación entre los dominios de tiempo y frecuencia de la VFC con la obesidad central y sus variables hemodinámicas en adultos con peso normal, sobrepeso y obesidad.

Metodología: participaron 65 adultos (25,4 ± 3,2 años) distribuidos en 3 grupos: peso normal (grupo NW), sobrepeso (grupo OW) y obesidad (grupo OB). Se registraron los parámetros de la VFC y las variables antropométricas y hemodinámicas.

Resultados: se observó una correlación positiva entre la circunferencia de la cintura y la relación LF/HF en el grupo OW ($p = 0,0008$; $r = 0,6607$; $r^2 = 0,4365$) y OB ($p = 0,0001$; $r = 0,8286$; $r^2 = 0,6866$). La relacion cintura/altura mostró una diferencia significativa con la HF en los grupos NW, OW y OB. La actividad parasimpática (SDNN, RMSSD, pNN50, HF) de los grupos OB y OW evidenció una disminución de los valores en comparación con el grupo NW. La actividad simpática (LF) en el grupo OB y OW presentó mayores valores que en el grupo NW. La relación LF/HF aumentó del grupo NW hacia el OW y el OB (1,6 ± 0,7; 2,5 ± 1,8 y 3,3 ± 0,7).

Conclusiones: el sobrepeso y la obesidad presentan una predominancia de la actividad simpática en reposo. Este aumento de la actividad está representado en el dominio de tiempo y frecuencia de la VFC y, además, presenta una correlación importante con la circunferencia de la cintura y la relación cintura/altura.

Palabras clave:

Sistema nervioso autónomo. Variabilidad de la frecuencia cardiaca. Obesidad central. Variables hemodinámicas. Circunferencia de la cintura.

INTRODUCTION

Obesity is well known as a metabolic disorder of multifactorial origin with an increased incidence in developed and developing countries (1). It has led to non-communicable diseases such as arterial hypertension, hypercholesterolemia, insulin resistance and type-2 diabetes *mellitus* (2). Worldwide, according to the World Health Organization (WHO) in 2016, 39 % of adults ≥ 18 years (39 % of men and 40 % of women) are overweight, and 13 % of them (11 % of men and 15 % of women) are obese, the prevalence being a serious health problem (3). Obesity starts with an increase of free fatty acids in the organism. They accumulate initially in the subcutaneous adipose tissue and when this tissue is no longer able to store it, excess adiposity drains into the visceral fat deposits around the organs in the abdominal area (4), inducing an increase in inflammatory mediators from the fatty tissue. This inflammatory process establishes changes in both structure and function in the obese subjects (5).

Thus, scientific evidence indicates changes in autonomic function in overweight and obese people (6), since there is a deterioration of balance in autonomic nervous system (ANS) functioning. This unbalance is represented by an increase in sympathetic activity and a decrease in vagal tone leading to a reduction in heart rate variability (HRV) (7), which refers to the intervals between heartbeats in a specific time, and are a reflection of the balance between ANS, blood pressure (BP), and gut, heart, and vascular tone (8). In order to know if a person has overweight or obesity, we need to use the variables of BMI and WC. We define BMI as an indicator of the relationship between weight and height (9), and we understand WC as the amount of visceral adipose tissue in the abdominal region, measured in centimetres (10), which is considered an important cardiovascular risk factor (11).

Therefore, obese and overweight people have an imbalance in their ANS because of their visceral adipose tissue, expressed in their BP and their sympathetic function predominance (12). This imbalance in the ANS has been frequently mentioned related to an unhealthy lifestyle, sedentarism, and metabolic abnormalities (13). However, few studies have established a relationship between the time and frequency domain of HRV associated with central obesity. It is necessary to acknowledge that central obesity is a factor related to cardiovascular diseases, arrhythmias, hypertension, and cardiac death (14) because of the physiological and metabolic changes associated with cardiac function (15). The aim of this study was to analyze the relationship between the time and frequency domains of HRV and central obesity with its hemodynamic variables in obese and overweight people. We hypothesized that central obesity is associated with changes in the time and frequency domains of HRV that can negatively affect cardiac function.

MATERIAL AND METHODS

This study presents a non-experimental, cross-sectional correlation-causal design.

PARTICIPANTS

The present study considers 65 men adults, all sedentary college students aged from 20 to 30 years (25.4 ± 3.18 years). Participants were recruited through public announcement and social networks. Exclusion criteria were as follows: habit of physical exercises expressed as at least 3 times a week, smoking, subjects with hypertension, cardiopulmonary and morbid diseases, use of drugs or medicines that affect ANS. Before the evaluation, the participants were asked not to have consumed any alcoholic and/or stimulant drinks during 24 hours prior to the measurements, not to have carried out any physical activity of moderate or high intensity the previous day, and to have completed a 12-hour fasting period, in addition to signing the informed consent. All participants signed a written informed consent before undergoing research, and this study was evaluated and approved by the ethics committee of the university involved (CEC UST Nº52/2019).

PROCEDURE

The study was conducted at the exercise physiology laboratory. The room was air-conditioned, controlling temperature to range between 22 °C and 24 °C, relative humidity between 50 % and 60 %, and dim lighting. All 65 participants were distributed into three groups — the first group consisted of 24 adults, identified as NW group (BMI = 21.78 ± 1.38 kg/m^2), the second group was composed of 20 adults classified as overweight (OW group) (BMI = 27.4 ± 4.08 kg/m^2), and the last group included 21 adults classified as obese (OB group) (BMI = 33.79 ± 2.74 kg/m^2).

AUTONOMIC FUNCTION EVALUATION

Before the HRV evaluation the participants remained at rest in the supine position and the cardiac band (Polar brand, model H7) evaluated autonomic functions. The Cardiomood software recorded the R-R intervals of the QRS complex during a 10-minute period for data extraction and analysis. The analysis of the spectral method is based on fast Fourier transforms (FFT). We analyzed the frequency domain components such as high frequency (HF), range from 0.15 to 0.4 Hertz (Hz), and low frequency (LF), range from 0.04 to 0.15 Hertz. The LF component reflects a sympathetic modulation, while the HF component of vagal modulation and the LF/HF ratio are an indirect index of the vagal-sympathetic balance (16). All frequency domain parameters are expressed in normalized units (nu). Also, we analyzed the time-domain components such as SDNN (standard deviation for all R-R intervals), which describes short or long variations in the R-R intervals, NN50 (number of adjacent intervals varying by more than 50 ms, expressed in %), which is a variable derived from the difference in R-R intervals, and RMSSD (square of the mean root of the junction of the adjacent R-R intervals), which provides an indicator of the wandering cardiac control (8).

HEMODYNAMIC AND ANTHROPOMETRIC VARIABLE EVALUATION

After recording HRV, specialists using cardiac auscultation with the Omrom m6/comfort equipment measured blindly BP, systolic blood pressure (SBP), and diastolic blood pressure (DBP), in the seated position. In the same context, they evaluated heart rate (HR) by the heart band used before. With the information recorded they calculated the double product (DP) as HR (bpm) x SBP (mmHg), and the mean arterial pressure (MAP), which is the perfusion pressure for the body organs (16). On two occasions they measured SBP and HR at the same time at three-minute intervals.

In order to determine the BMI and categorize their level of obesity we measured and weighed the participants. With anthropometric tape (SECA – 203; accuracy, 0.1 cm) they recorded twice the WC using as midpoint the anatomical reference between the anterior superior iliac crest and the tenth rib and averaging both measures for the analysis (17). Also, we calculated the waist-to-height ratio (WHtR), which considers a better indicator of cardiometabolic risk than BMI and WC among adults, with a cut-off point at 0.5 cm, meaning that a value higher than 0.5 represents a higher risk of obesity-related diseases regardless of age, sex or ethnicity (18). We took into account these 3 anthropometric measurements and their averages for the analysis.

STATISTICAL ANALYSIS

For the statistics we used the GraphPad Prism 5 for Windows® software. The population profile data were described using descriptive statistics, and the results were presented as mean, standard deviation, coefficient of variation, and absolute number values. In the inferential analysis the Shapiro-Wilk normality test was performed to establish the distribution of the data. The comparison between groups was performed using a single-factor ANOVA and post hoc comparison with Bonferroni's test, depending on the normality and homoscedasticity tests. Pearson's or Spearman's correlation test was conducted, depending on normality and homoscedasticity. Differences in these tests were considered statistically significant when $p < 0.05$. In addition, a linear regression analysis was performed to model the relationship between the WC and ratio of LF-to-HF variables under study.

RESULTS

All participants completed the study and table I shows the anthropometric, hemodynamic and autonomic function characteristics of all groups. Of the 65 participants studied, 24 were women (63.09 %) and 41 men (36.9 %), with an average age of 25.4 ± 3.18 years (20 to 29 years), distributed as follows: 36.9 % in the NW group, 30.7 % in the OW group, and 32.3 % in the OB group. In relation to the anthropometric characteristics the average BMI was 27.22 ± 5.17 kg/m^2 for the entire studied group. The mean WC was 98.35 ± 20.57 cm for the individuals, distributed as 78.46 ± 7.22 cm in the NW group, 102.21 ± 11.14 cm in the OW group, and 120.83 ± 14.39 cm in the OB group. Hemodynamic results are presented in table I.

Regarding the HRV analysis, figure 1 shows the different HRV parameters in the frequency domains according to nutritional status. It is observed that there are significant differences in (A) LF, (B) HF and (C) LF/HF frequencies according to nutritional status. When analyzed, it is evident that people with NW have significantly less LF than the OW group ($p \leq 0.001$) and the OB group ($p \leq 0.001$). In addition, it was observed that people with NW have significantly higher HF than the OW group ($p = 0.002$) and OB group ($p \leq 0.001$). Additionally, figure 1 presents the highest predominance of autonomous sympathetic modulation (LF 81.61 ± 10.84 nu) in the OB group, as well as the lowest parasympathetic modulation (HF 25.50 ± 4.56 nu). Likewise, the LF/HF ratio increases from the NW and OW groups towards the OB group, with values of 1.57 ± 0.74 nu, 2.45 ± 1.79 nu, and 3.28 ± 0.86 nu, respectively.

Table I. Anthropometric, hemodynamic and autonomic function characteristics of the study groups

Parameters	Variables	NW Group (n = 24)	OW Group (n = 20)	OB Group (n = 21)
Anthropometric	Age (years)	22 ± 2.29	23 ± 2.07	22 ± 1.87
	Weight (kg)	60.75 ± 8.28	77.54 ± 17.54	93.57 ± 15.39
	Height (mts)	1.67 ± 0.09	1.67 ± 0.10	1.66 ± 0.10
	BMI (kg/m^2)	21.78 ± 1.38	27.40 ± 4.08	33.79 ± 2.74
	WC (cm)	78.46 ± 7.22	102.21 ± 11.14	120.83 ± 14.39
	WHtR	0.47 ± 0.03	0.59 ± 0.07	0.73 ± 0.10
Hemodynamic	SBP (mm Hg)	105.00 ± 13.51	113.14 ± 11.23	117.86 ± 11.02
	DBP (mm Hg)	60.42 ± 6.9	66.28 ± 8.9	77.38 ± 13.10
	MAP (mm Hg)	75.28 ± 7.73	80.33 ± 898	90.87 ± 10.82
	HR	75.67 ± 20.94	72.23 ± 10.54	74.76 ± 10.39
	DP	8015.00 ± 2851.85	8195.50 ± 1472.95	8811.9 ± 1472.53
Autonomic function	LF (nu)	56.04 ± 12.87	72.78 ± 22.45	81.61 ± 10.84
	HF (nu)	41.04 ± 13.23	30.56 ± 19.41	25.50 ± 4.56
	LF/HF (nu)	1.57 ± 0.74	2.45 ± 1.79	3.28 ± 0.68
	SDNN (ms)	65.00 ± 19.34	84,65 ± 36,90	74,97 ± 36,58
	RMSSD (ms)	55.16 ± 27.22	61.96 ± 48.03	64.22 ± 24.97
	PNN50 (%)	31.47 ± 17.99	31.28 ± 24.41	32.47 ± 20.85

Values expressed as mean ± standard deviation. NW: normal weight group; OW: overweight group; OB: obese group; BMI: body mass index; WC: waist circumference; WHtR: waist-to-height ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; DP: double product; LF: low frequency; HF: high frequency; SDNN: standard deviation of NN intervals; RMSSD: root mean square of successive RR interval differences; PNN50: percentage of successive RR intervals that differ by more than 50 ms.

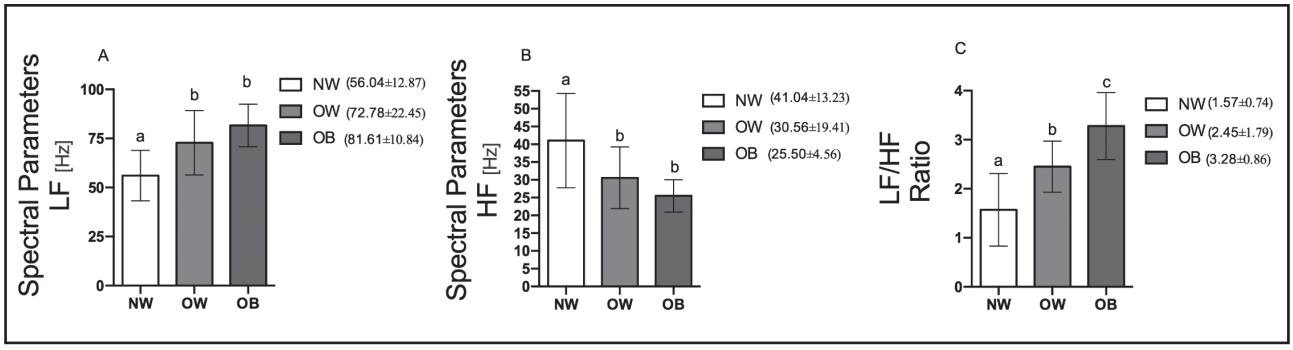

Figure 1.

Descriptive graph showing HRV parameters in the frequency domain across the NW, OW and OB groups: A. LF (low frequency); B. HF (high frequency); and C. LF/HF (LF-to-HF ratio). The statistical analysis was performed with a one-factor ANOVA (NW: normal weight group; OW: overweight group; OB: obese group; a,b,c within a column with a different letter indicates significant differences between groups [one-factor ANOVA and post hoc comparison with Bonferroni's test]. A p-value < 0.05 was considered for all analyses).

From the simple correlation analysis, the largest number of associations are found in the OB group, observing a positive correlation between WC, WHtR, HR and DP with LF and the LF/HF ratio ($p \leq 0.05$), and negative correlation between WC and WHtR with HF values ($p \leq 0.05$). Similarly, in the OW group a positive correlation is shown between the variables WC, WHtR and MAP and the LF/HF ratio ($p \leq 0.05$), and negative correlation between the values of WC and WHtR with HF ($p \leq 0.05$). Finally, a negative correlation is shown in the NW group between WC and WHtR with HF ($p \leq 0.05$), as shown in table II.

The time-domain component only exhibits a significant difference in the OB and OW group. The first group reveals a negative correlation between the variables SBP and DP with SDNN, also adding a negative correlation between SBP and RMSSD ($p \leq 0.05$), as shown in table IV. Likewise, for the OW group, a negative correlation is observed in the variables HR and DP with PNN50 ($p \leq 0.05$), as shown in table III.

Finally, a strong positive correlation is observed between WC and the LF/HF ratio in the OW group ($p = 0.0008$, $r = 0.6607$; $r^2 = 0.4365$) (Table III) and OB group ($p = 0.0001$, $r = 0.8286$; $r^2 = 0.6866$) (Table IV).

DISCUSSION

Central obesity is an important precursor of different metabolic diseases (5) and, for that reason, this study assessed the relationship between the time and frequency domains of HRV with central obesity and its hemodynamic variables, emphasizing an important sympathetic activity at resting conditions in obese and overweight adults compared to those of normal weight.

Table II. Correlation between HRV time and frequency domain measures with WC, SBP, DBP, HR and DP in the NW group

Variables NW Group (n = 24)									
Variables	**Frequency-domain measures**								
	LF (Hz)			**HF (Hz)**			**LF/HF (%)**		
	p	**r**	**r^2**	**p**	**r**	**r^2**	**p**	**r**	**r^2**
WC (cm)	0.3418	0.08774	0.007	*0.0175	-0.4320	0.1866	0.0734	0.305	0.093
WHtR (cm)	0.2754	0.1281	0.01642	*0.0428	-0.3583	0.1284	0.1093	0.2607	0.0679
SBP (mm Hg)	0.280	0.124	0,027	0.2416	-0.150	0.0187	0.2917	0.1179	0.02156
DBP (mm Hg)	0.349	-0.0831	0.0043	0.2428	0.1495	0.02818	0.2535	-0.1423	0.02153
MAP (mm Hg)	0.4431	0.0308	0.0032	0.407	0.0506	0.00039	0.4158	-0.0458	0.0951
HR (bpm)	0.322	0.0992	0.0325	0.305	0.1093	0.0177	0.4690	-0.01676	0.00958
DP	0.3065	0.108	0.00308	0.420	0.0435	0.00395	0.4795	0.0110	0.00084
Variables	**Time-domain measures**								
	SDNN (ms)			**RMSSD (ms)**			**PNN50 (%)**		
	p	**r**	**r^2**	**P**	**r**	**r^2**	**p**	**r**	**r^2**
WC (cm)	0.2605	0.1377	0.01896	0.4219	-0.0424	0.00180	0.2881	-0.1201	0.01442
WHtR (cm)	0.3100	0.1066	0.00113	0.3212	-0.0998	0.00997	0.1342	-0.2353	0.05535
SBP (mm Hg)	0.1608	-0.2113	0.1141	0.0858	-0.2885	0,1181	0.0710	-0.3088	0.0746
DBP (mm Hg)	0.3381	-0.0899	0.0053	0.410	0.0490	0,00024	0.2910	0.1183	0.01154
MAP (mm Hg)	0.1545	-0.2167	0.0575	0.2563	-0.1405	0.0363	0.3625	-0.0757	0.00905
HR (bpm)	0.4422	0.0313	0.00450	0.2103	0.1724	0.00466	0.0511	0.4179	0.1254
DP	0.3108	-0.1061	0.00117	0.4928	0.00391	0.0147	0.1913	0.1866	0.0406

*NW: normal-weight group; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; DP: double product; LF: low frequency; HF: high frequency; LF/HF: LF-to-HF ratio; SDNN: standard deviation of NN intervals; RMSSD: root mean square of successive RR interval differences; PNN50: percentage of successive RR intervals that differ by more than 50 ms. *Value with statistical difference in HRV frequency and time domain measures of the NW group with anthropometrics and hemodynamics variables (Pearson´s test; $p < 0.05$).*

Table III. Correlation between HRV time and frequency domain measures with WC, SBP, DBP, HR and DP in the OW group

OW Group (n = 20)									
Variables	**Frequency-domain measures**								
	LF (Hz)			**HF (Hz)**			**LF/HF (%)**		
	p	**r**	**r^2**	**p**	**r**	**r^2**	**p**	**r**	**r^2**
WC (cm)	0.4643	-0.0214	0.0004	*0.0416	-0.3968	0.1574	*0.0008	0.6607	0.4365
WHtR (cm)	0.4423	-0.0346	0.0012	*0.0436	-0.3711	0.1377	*0.0061	0.5487	0.3010
SBP (mm Hg)	0.1717	0.2236	0.0500	0.1364	0.2576	0.01853	0.2121	0.1893	0.03582
DBP (mm Hg)	0.0738	0.3359	0.1291	0.2888	0.1325	0.01756	0.2924	0.1301	0.1643
MAP (mm Hg)	0.0648	0.3506	0.1229	0.2617	0.1517	0.0230	*0.0538	0.3708	0.1375
HR (bpm)	0.2045	0.1954	0.7145	0.3221	0.1100	0.0214	0.2374	0.1695	0.0287
DP	0.1164	0.3506	0.0780	0.2687	0.1466	0.02149	0.1246	0.2702	0.0730
Variables	**Time-domain measures**								
	SDNN (ms)			**RMSSD (ms)**			**PNN50 (%)**		
	p	**r**	**r^2**	**P**	**r**	**r^2**	**p**	**r**	**r^2**
WC (cm)	0.2344	-0.1718	0.02952	0.2015	-0.1979	0.0391	0.3790	-0.0735	0.0054
WHtR (cm)	0.3912	0.0659	0.00435	0.4074	0.05593	0.00312	0.3008	0.1243	0.01545
SBP (mm Hg)	0.4936	0.00384	0.00589	0.3215	-0.1105	0.01220	0.2440	-0.1646	0.0270
DBP (mm Hg)	0.1186	0.2770	0.0020	0.3791	0.0734	0.0033	0.2085	-.0.1922	0.0430
MAP (mm Hg)	0.3282	0.1060	0.01124	0.3600	-0.0855	0.0073	0.1798	-0.2164	0.0468
HR (bpm)	0.4401	-0.0360	0.0012	0.2761	-0.1414	0.01998	*0.0163	-0.4791	0.2296
DP	0.4620	-0.0228	0.0005	0.2344	-0.1718	0.02952	*0.0166	-0.4774	0.2279

*OW: overweight group; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; DP: double product; LF: low frequency; HF: high frequency; LF/HF: LF-to-HF ratio; SDNN: standard deviation of NN intervals; RMSSD: root mean square of successive RR interval differences; PNN50: percentage of successive RR intervals that differ by more than 50 ms. *Value with statistical difference in HRV frequency and time domain measures of the OW group with anthropometrics and hemodynamics variables (Pearson´s test; $p < 0.05$).*

Table IV. Correlation between HRV time and frequency domain measures with WC, SBP, DBP, HR and DP in the OB group

OB Group (n = 21)									
Variables	**Frequency-domain measures**								
	LF (Hz)			**HF (Hz)**			**LF/HF (%)**		
	p	**r**	**r^2**	**p**	**r**	**r^2**	**p**	**r**	**r^2**
WC (cm)	*0.0033	0.5737	0.3291	*0.0093	-0.5084	0.2585	*0.0001	0.8286	0.6866
WHtR (cm)	*0.0014	0.6195	0.3838	*0.0326	-0.4096	0.1677	*0.0001	0.7981	0.6369
SBP (mm Hg)	0.3329	0.1001	0.01003	0.4647	-0.0206	0.00042	0.3897	0.0650	0.00422
DBP (mm Hg)	0.0926	0.3008	0.0904	0.4114	-0.0520	0.00270	0.1579	0.2300	0.0529

(Continues on next page)

Table IV (Cont.). Correlation between HRV time and frequency domain measures with WC, SBP, DBP, HR and DP in the OB group

OB Group (n = 21)									
Variables	**Frequency-domain measures**								
	LF (Hz)			**HF (Hz)**			**LF/HF (%)**		
	p	**r**	**r^2**	**p**	**r**	**r^2**	**p**	**r**	**r^2**
MAP (mm Hg)	0.1124	0.2766	0.0765	0.4165	-0.0489	0.00239	0.1832	0.2076	0.04311
HR (bpm)	*0.0035	0.5696	0.3245	0.4462	0.03146	0.00098	*0.0340	0.4057	0.1646
DP	*0.0059	0.5379	0.2894	0.4889	0.00644	0.00785	*0.0410	0.4057	0.1646
Variables	**Time-domain measures**								
	SDNN (ms)			**RMSSD (ms)**			**PNN50 (%)**		
	p	**r**	**r^2**	**P**	**r**	**r^2**	**p**	**r**	**r^2**
WC (cm)	0.2178	-0.1797	0.03230	0.2617	0.1475	0.02176	0.2319	-0.1690	0.00285
WHtR (cm)	0.2759	-0.1376	0.01894	0.1265	0.2611	0.06816	0.3510	-0.0887	0.00787
SBP (mm Hg)	*0.0029	-0.5799	0.3363	*0.0042	-0.3902	0.1523	0.3227	-0.1067	0.01138
DBP (mm Hg)	0.2041	-0.1905	0.03628	0.1983	0.1952	0.03809	0.4806	0.01130	0.00012
MAP (mm Hg)	0.0597	-0.3505	0.1228	0.4572	0.02496	0.00062	0.4535	-0.0271	0.00073
HR (bpm)	0.1226	-0.2652	0.0703	0.2750	0.1383	0.01912	0.3471	-0.0912	0.00831
DP	*0.0054	-0.5444	0.2964	0.3591	-0.0837	0.00701	0.3203	-0.1082	0.01171

*OB: obese group; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; DP: double product; LF: low frequency; HF: high frequency; LF/HF: LF-to-HF ratio; SDNN: standard deviation of NN intervals; RMSSD: root mean square of successive RR interval differences; PNN50: percentage of successive RR intervals that differ by more than 50 ms. *Value with statistical difference in HRV frequency and time domain measures of the OB group with anthropometrics and hemodynamics variables (Pearson´s test; $p < 0.05$).*

Our main results showed that adults with obesity and overweight present a higher sympathetic modulation at rest through the time and frequency domains of HRV, and also present an important correlation with WC and waist-to-height ratio. Research protocols that measure health indicators that are easy to monitor, as HRV, are important because these people showed a delay in their recovery period because of arrhythmia and acute coronary pathology caused by their hypercoagulability state and their autonomic dysfunction as given by obesity and diabetes (19). Thus, such indicators can be used for the prevention and screening of cardiovascular diseases.

The evaluation of HRV in its frequency and time domains has been acknowledged as a non-invasive and low-cost method diagnostic tool for different cardiovascular diseases and dysautonomia in the ANS (20). In this regard, low levels of HRV are an important predictor for cardiovascular disorders and morbid diseases (21,22), but above all they are a predictor for mortality — people with autonomic unbalance are 5.3 times more likely to suffer sudden death (22).

The relationship between hyperactivity of the sympathetic system and underactivity of the parasympathetic system expresses the autonomic unbalance reflected in the results of this study, evidenced by the frequency domain behavior of the population studied (23,24) (Fig. 1). In this context, the time domain described in this study (Table I) presents a tendency towards a decrease of these values from the NW group to the OB group, as is described in the following scientific evidence (6) — comparing obese individuals with normal weight individuals the former present a decrease in vagal parameters (SDNN = 35.55 ms, RMSSD = 28.75 ms, pNN50 = 6.4 %), with a normal value in the NW group (SDNN = 46.15, RMSSD = 41.55, pNN50 = 25.65 %) (6). Likewise, Sant Anna Junior et al. (2015), also confirm the results found in our study, which evaluated 80 morbidly obese subjects and 30 normal weight subjects. The results showed low levels of HRV variables in morbidly obese subjects (SDNN = 40.0 ± 18.0 ms, RMSSD = 23.7 ± 13.0 ms, pNN50 = 14.8 ± 10.4%) compared to the NW group (SDNN = 70.0 ± 27.8 ms, RMSSD = 40.3 ± 22.4 ms, pNN50 = 25.9 ± 7.2 %) (24).

The frequency domain behavior observed in this work evidences that LF levels and the LF/HF ratio (Fig. 1) describe an important modulation on sympathetic predominance in the OB and OW groups, unlike the NW group where a vagal modulation predominance is observed and described in the HF levels, it being in autonomic equilibrium. Similar findings were described by Rossi et al. (2015), who evaluated 92 subjects divided into the NW and OB groups. The autonomic function of the OB group had a sympathetic nervous system predominance given by their frequency domain values (LF = 58.50 ± 12.93 Hz; HF = 41.49 ± 12.93 Hz), while in the NW group predominance was for parasympathetic function (LF = 48.65 ± 12.59 Hz; HF = 51.53 ± 12.56 Hz) (25). Similarly, in the study by Sant Ann Junior et al. (2015), the LF/HF ratio variable presented a sympathetic autonomic function predominance in the morbidly OB group (5.0 ± 2.8 nu/Hz) and sympathetic-vagal equilibrium in the control group (1.0 ± 0.9 nu/Hz) (24).

Also, a positive correlation was observed between sympathetic activity and the anthropometric variables, especially WC as represented in the OB group, while the NW group shows a vagal behavior (Table I). In this context, our findings are supported by Oliveira et al. (2020), who analyzed 64 obese subjects with elevated WC (118.83 ± 10.66 cm). The HRV variables showed a strong predominance sympathetic modulation (LF 56.44 ± 20.31 Hz) in contrast to a decrease in parasympathetic modulation (HF 42.52 ± 19.18 Hz) (26). Rastovi et al. (2017) obtained the same results in their study with 63 obese women, where the frequency domain variables of HRV (LF 55.09 ± 13.77 Hz / HF 44.91 ± 13.77 Hz) presented an imbalance in their ANS more favourable to the sympathetic function, corroborating the relationship between visceral adipose tissue and HRV parameters (27).

In the same way, the WHtR is a variable that quantifies more precisely central obesity due to its independence of age, sex and gender (18). Values greater than 0.5 cm are considered an indicator of cardiovascular diseases, and indicate a close relationship with sympathetic activity and an inverse relationship with vagal activity (28). In this sense, the OB and OW groups present values greater than 0.5 cm, showing a probability of suffering a cardiovascular disease whereas the NW group remains under 0.5 cm, showing that they have less probabilities of having a cardiovascular disease (Table I). Furthermore, scientific evidence shows that anthropometric variables such as body weight, body fat percentage, BMI, WC and waist-to-hip ratio have a close relationship with ANS unbalance. Accordingly, Grassi et al. (2019) in their meta-analysis, which included 45 studies and involved 1438 people, showed that the increase in sympathetic activity is detectable in obese and overweight people as related to body composition factors (29). Similarly, Pontiroli et al. (2013) observed and followed 24 obese people who reduced their body weight in 6 months, some through gastric banding surgery and others through diet-based caloric reduction, showing that both groups demonstrated significant changes in their frequency and time HRV variables (30). According to the results presented in this paper, it is possible to observe that by reducing central obesity there is a modification in ANS function.

Considering hemodynamic variables, we observed in our study that the parameters of SBP, DBP, MAP and DP have higher values in the OB and OW group than in the NW group (Table I). In fact, scientific evidence indicates that an increase in sympathetic activity is linked to an increment in BP, due to the modulation of autonomic control over arteriovenous vasomotor tone (7); and an increased sympathetic expression also could lead to early cardiac autonomic neuropathy in diabetics, which can lead to a therapeutic intervention with early-stage angiotensin 2 receptor antagonists (31). In this context, Indumathy et al. (2015) compared a group of obese people (n = 45) with a normal-weight group (n = 43), which showed that the variables SBP, DBP, MAP and DP were significantly high (114.53 ± 9.28 mm Hg, 76.67 ± 7.26 mm Hg, 89.29 ± 6.01 mm Hg, and 88.14 ± 13.11 mm Hg/min) when compared to the control group (108.05 ± 8.60 mm Hg, 67.88 ± 6.78 mm Hg, 81.27 ± 6.81 mm Hg, 76.29 ± 12.09 mm Hg/min), and at the same time all these variables were significantly correlated with the frequency domain of LF/HF ratio (7). Likewise, Oliveira et al. (2020), in their study, analyzed 64 obese subjects at rest who presented high BP (PAS 126.66 ± 17.02 mm Hg and PAD 84.33 ± 10.05 mm Hg) and an increase in the frequency domain variable related to the sympathetic system LF (56.44 ± 20.31 Hz), and a decreased value in the parasympathetic system component HF (42.52 ± 19.18 Hz) (26). This phenomenon could be explained by the relationship between high BP and increased free fatty acids, leading to a state of hyperinsulinemia and hyperleptinemia, caused by the sensitivity of the α1-adrenoceptor-mediated response, which increases BP by activation of the sympathetic nervous system, of the kidneys and of skeletal muscles (7,26).

The results and conclusions of this study on the HRV parameters with central obesity could be explained by the excess of energy that accumulates in the visceral fat deposits, establishing an increase of the adipocyte by a hypertrophy mechanism. This accumulation of inflammatory mediators from the fatty tissue induces an inflammatory process which is related to changes in structure and function (5). In this context, a higher energy balance generates greater activity of macrophages with pro-inflammatory characteristics (5), which are responsible for the secretion of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α). This cytokine participation represents a fundamental role in insulin resistance, affecting the sensitivity of insulin in adipocytes through inhibitors in the signalling pathway of this hormone, establishing a state of hyperinsulinemia and hyperleptinemia (32). Also, we have tried to explain that the peripheral signals transmitted by insulin to the hypothalamus are related to the activation of the proopiomelanocortin (POMC) pathway, which in the same way activates melanocortin receptors (MC4). In fact, the activation of the MC4 receptor modulates peripheral sympathetic activation, presumably by direct and indirect signaling processes. However, current evidence suggests that an increase in circulating TNF-α would produce a failure of intracellular signaling in sympathetic and parasympathetic efferent neurons in the brain stem, increasing cardiac and renal sympathetic discharge without improving thermogenesis (33).

There are some limitations to our study. The participants selected for this study were a generally healthy group of adults. Therefore, our findings may not be generalizable to the whole population in this age range, and this should be considered when examining HRV in people with certain illnesses or diseases such as metabolic syndrome. HRV is not an appropriate measure to assess sympathetic activity; further studies may use more precise methods.

CONCLUSION

The study reveals that adults with obesity and overweight present greater sympathetic modulation at rest through the time and frequency domains of HRV, and also present an important correlation with WC and the waist-to-height ratio. The findings of this study could be considered for a probable line of research oriented to delay the cardiovascular complications caused by an unbalanced sympathetic response in the long term.

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ARÁN

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Trabajo Original

Obesidad y síndrome metabólico

No effect of combined tele-exercises and nutritional coaching on anthropometric, body composition or exercise capacity outcomes in overweight and obese women: a randomized clinical trial

Ningún efecto de la combinación de ejercicios a distancia y entrenamiento nutricional sobre los resultados antropométricos, de composición corporal o de capacidad de ejercicio en mujeres con sobrepeso y obesidad: un ensayo clínico aleatorizado

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Abstract

Background: we aimed to investigate the isolated effect of tele-exercises (TE) and their combined effect with nutritional coaching (NC) on health-related parameters of overweight and obese individuals.

Methods: forty-one overweight (body mass index ≥ 25 kg/m^2) and obese (body mass index ≥ 30 kg/m^2) women were randomly assigned to the experimental groups: TE (n = 20) or TE+NC (n = 21). TE was applied 3 days/week in both groups, while TE+NC also received NC 1 day/week. Anthropometric, body composition, and exercise capacity-related outcomes, quality of life, and eating behavior were assessed before and after 8 weeks of the intervention.

Results: a significant main time effect ($p < 0.01$) was detected for flexibility, isometric muscle strength and dynamic muscle endurance, but no main group effect was noted ($p > 0.05$). On the other hand, neither a significant main time nor group effect ($p > 0.05$) was detected in the anthropometric and body composition measures, quality of life, or eating behavior. Similarly, no significant between-group difference was observed in the absolute or relative change analysis (all comparisons, $p > 0.05$).

Conclusions: an 8-week TE program enhanced exercise capacity, but did not impact anthropometric or body composition-related outcomes. The combination of NC+TE did not have a clinical advantage in the management of overweight and obesity.

Keywords:

Obesity. Exercise training. Nutrition. Health promotion.

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Resumen

Introducción: nuestro objetivo fue investigar el efecto aislado de los tele-ejercicios (TE) y su efecto combinado con el *coaching* nutricional (CN) sobre los parámetros relacionados con la salud de las personas con sobrepeso y obesidad.

Métodos: cuarenta y una mujeres con sobrepeso (índice de masa corporal ≥ 25 kg/m^2) y obesas (índice de masa corporal ≥ 30 kg/m^2) fueron asignadas aleatoriamente a los grupos experimentales: TE (n = 20) o TE+CN (n = 21). La TE se aplicó 3 días/semana en ambos grupos, mientras que el grupo TE+CN también recibió NC 1 día/semana. Se evaluaron los resultados antropométricos, la composición corporal y la capacidad de ejercicio, la calidad de vida y la conducta alimentaria antes y después de 8 semanas de intervención.

Resultados: se detectó un efecto de tiempo principal significativo ($p < 0,01$) para la flexibilidad, la fuerza muscular isométrica y la resistencia muscular dinámica, pero no se observó ningún efecto de grupo principal ($p > 0,05$). Por otro lado, no se detectó ningún efecto de tiempo principal ni de grupo significativo ($p > 0,05$) en las medidas antropométricas y de composición corporal, calidad de vida o conducta alimentaria. De manera similar, no se observaron diferencias significativas entre los grupos en el análisis del cambio absoluto o relativo (todas las comparaciones, $p > 0,05$).

Conclusiones: un programa de TE de 8 semanas mejoró la capacidad de ejercicio pero no afectó los resultados antropométricos o relacionados con la composición corporal. La combinación de CN + TE no obtuvo ninguna ventaja clínica en el manejo del sobrepeso y la obesidad.

Palabras clave:

Obesidad. Entrenamiento de ejercicio. Nutrición. Promoción de la salud.

INTRODUCTION

Updated data from the World Health Organization (WHO) have shown that more than 39 % of adults are overweight (body mass index [BMI] ≥ 25 kg/m^2), and 13 % are obese (BMI ≥ 30 kg/m^2) (1). Since 1980, the prevalence of these conditions has doubled (2). Overweight and obesity impair muscle strength, flexibility, and peak oxygen consumption (3,4), negatively affecting quality of life. Furthermore, overweight and obesity are major risk factors for cardiovascular and metabolic disorders (5), and all-cause mortality (6). Despite some diseases, medications and genetics may account for fat accumulation (7), the leading cause of overweight and obesity is the imbalance between calories consumed and expended, and hence, dieting, physical activity, and cognitive behavioral therapy play essential roles in the treatment of these conditions (8). Women are impacted by body image and beauty as imposed by society (9), which results in impairments in physical health as well as in quality of life. Given this, specific intervention programs to combat obesity in women are recommended to maintain homogeneity groups (discussions, themes, and, consequently, adherence) (9).

In March 2020, WHO declared the coronavirus disease-2019 (COVID-19) a pandemic. Due to COVID-19 lethality and consequent crisis, lockdown measures to mitigate the disease progress have brought to all countries the need to implement social distancing and impede economic activities across a broad spectrum of nonessential occupations (10). These adjustments caused changes in food consumption and physical activity patterns that may exacerbate the current trends in the prevalence of overweight/obesity (11), strengthening the need for strategies to promote increased caloric expenditure and reduced caloric intake, while respecting the COVID-19-associated social distancing policies. Among them, home-based tele-exercises (TE) (12) and online nutritional coaching (NC) (13) have emerged as potential supporting tools for health professionals to overcome the behavioral barriers associated with overweight and obesity while still maintaining social distancing.

TE is based on video conferencing, which involves simultaneous and real-time two-way video and audio transmission. This allows both the exercise instructor and the participant to undergo supervised training in their own homes while seeing and hearing each other. Although the employment of TE is a relatively new methodology, emerging evidence has demonstrated its efficacy in improving exercise adherence in children with cystic fibrosis (14) and free-fat mass and flexibility in older adults (12). However, the efficacy of TE in improving exercise capacity, body composition, and quality of life in overweight/obese individuals has not yet been investigated. In parallel, NC is a derivative of the health and wellness coaching behavioral strategy that promotes eating habits and may be employed in person or remotely (15). The NC professional supports the clients by helping them achieve self-directed goals aligned with their identified personal values. Hence, NC is a patient-centered process based on behavior change theory that encourages self-discovery and active learning processes during weight and fat loss, on a process of enlightenment and empowerment of the client by looking to the future and not the past (16). While emerging studies (17-19) have highlighted NC as a promising and far more effective intervention than energy-restricted diets, most studies examining NC efficacy were limited by short duration, small sample sizes, and the lack of control groups. Furthermore, the potential additive effect of NC combined with other interventions also aimed at promoting weight loss still requires clarification.

Therefore, the present study aimed to investigate the combined effect of TE and NC and compare it with the isolated effect of TE on the quality of life and exercise capacity, as well as anthropometric and body composition measures in overweight and obese women. Based on the previous findings of studies employing TE (12,20), we hypothesized that TE would positively affect all health-related outcomes. We also hypothesized that the combination of TE and NC would promote an even greater enhancement of these outcomes since previous studies have demonstrated that strategies targeting anthropometric and body composition improvements also led to an improved exercise capacity (21).

MATERIALS AND METHODS

EXPERIMENTAL DESIGN

According to the guidelines of the CONSORT Statement, an 8-week randomized, parallel-group clinical trial was conducted

between August 2020 and October 2020 in Maringa (Brazil). Using a computer-generated randomization code, participants were randomly assigned (1:1) to receive either tele-exercises (TE) or tele-exercises + nutritional coaching (TE+NC). Both experimental groups underwent a TE program for 8 weeks, while the TE+NC group received NC once a week. The participants were assessed at baseline (PRE) and 8 weeks after the intervention (POST). The assessments were conducted at the same time of the day to avoid circadian variation-derived influence and at 2 hrs after the last meal. Throughout the study, participants in the TE group were asked to maintain their food habits, which was confirmed by food recalls. Quality of life, anthropometric, body composition, and exercise capacity measures were obtained at PRE and POST. Adverse events and adherence towards the protocols were recorded throughout the trial.

PARTICIPANTS

A convenience sample of women was recruited from the basic health units near the university through a local community extended project. The inclusion criteria were as follows: being overweight (BMI ≥ 25 kg/m^2) or obese (BMI ≥ 30 kg/m^2), 18-60 years of age, and not engaged in an exercise training program for at least one year before the study. Exclusion criteria included cancer in the past five years, use of psychotropic or glucocorticoid medication, acute myocardial infarction ≤ 6 months, current engagement in dieting programs, and any cardiovascular, neurological or musculoskeletal disorders that would contraindicate exercise practice.

Eighty-four women were initially screened, and 72 patients met the inclusion criteria and were randomly assigned to the TE or TE+NC groups. Due to lack of motivation and difficulty accessing electronic media, 16 and 15 participants from the TE+NC and TE groups, respectively, declined to proceed in the study after the PRE assessments. Figure 1 depicts a flowchart of the participants throughout the study. The participants' characteristics at the PRE are presented in table I.

All procedures were performed according to the ethical standards of the local research committee (approval number: 4.001.666/2019) and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients also provided a written informed consent. This trial was registered at the Brazilian Registry of Clinical Trials (REBEC) as RBR-98mbrw.

ANTHROPOMETRIC MEASUREMENTS AND BODY COMPOSITION ASSESSMENT

Bodyweight was measured using a digital scale (W200, Welmy, Santa Bárbara do Oeste, Brazil) with a maximum capacity of 200 kg and 100 g divisions (22), while height was measured using a stadiometer coupled to the scale with 0.1 cm divisions. BMI calculation and cut-off points were based on the values established by the WHO (23). Abdominal and waist circumferences were measured using a flexible non-stretchable tape measure (T87-2®, Wiso, Florianopolis, SC, Brazil) and analyzed using pre-determined standards (24). Body composition was measured using the tetrapolar bioimpedance method (*InBody* 570, *Biospace* Co Ltd., Seoul, Korea) according to the manufacturer's instructions, following recommendations to improve validity (25) and reliability (26).

CARDIORESPIRATORY EVALUATION

Peak oxygen consumption (VO_{2peak}) was evaluated through the six-minute walking test, where participants were instructed to walk as fast as possible to reach the greatest distance within 6 min. According to the American Association of Cardiovascular and Pulmonary Rehabilitation guidelines, the test was performed on a circular track with a length of 30 m, without verbal encouragement. Participants only received standardized information every minute about the remaining time until the end of the test. VO_{2peak} was calculated according to the previous studies (27).

FLEXIBILITY ASSESSMENT

Using a Wells Bench, the sit-and-reach test was employed to evaluate the flexibility of the posterior chain (paravertebral muscles, maximal glutes, hamstrings, and sural triceps). The testing procedures have been described elsewhere (28). Participants were instructed to repeat the test three times, with a 60-second interval between attempts. The highest value obtained was recorded and expressed in cm.

ISOMETRIC MUSCLE STRENGTH AND DYNAMIC MUSCLE ENDURANCE ASSESSMENT

Following previous recommendations (29), isometric muscle strength was assessed using handgrip (TKK 5101, Takei Physical Fitness Test®, Tokyo, Japan) and lumbar (TKK 5002, Takei Physical Fitness Test®, Tokyo, Japan) dynamometers, with capacities of 100 and 300 kgf, respectively. Three attempts lasting 3-5 sec each was allowed, with 1 min of passive recovery between each other. The highest values were recorded.

Abdominal and push-up resistance tests were performed according to procedures described elsewhere (30,31) to assess dynamic muscle endurance. For both tests, the maximum number of repetitions achieved in 60 sec was recorded.

QUALITY OF LIFE

Quality of life was evaluated using the short form-12 (SF-12), a 12-item questionnaire created as a short but valid version of the SF-36. This tool aims to detect clinical and socially relevant differences in health status over time in the general population and all patients (30).

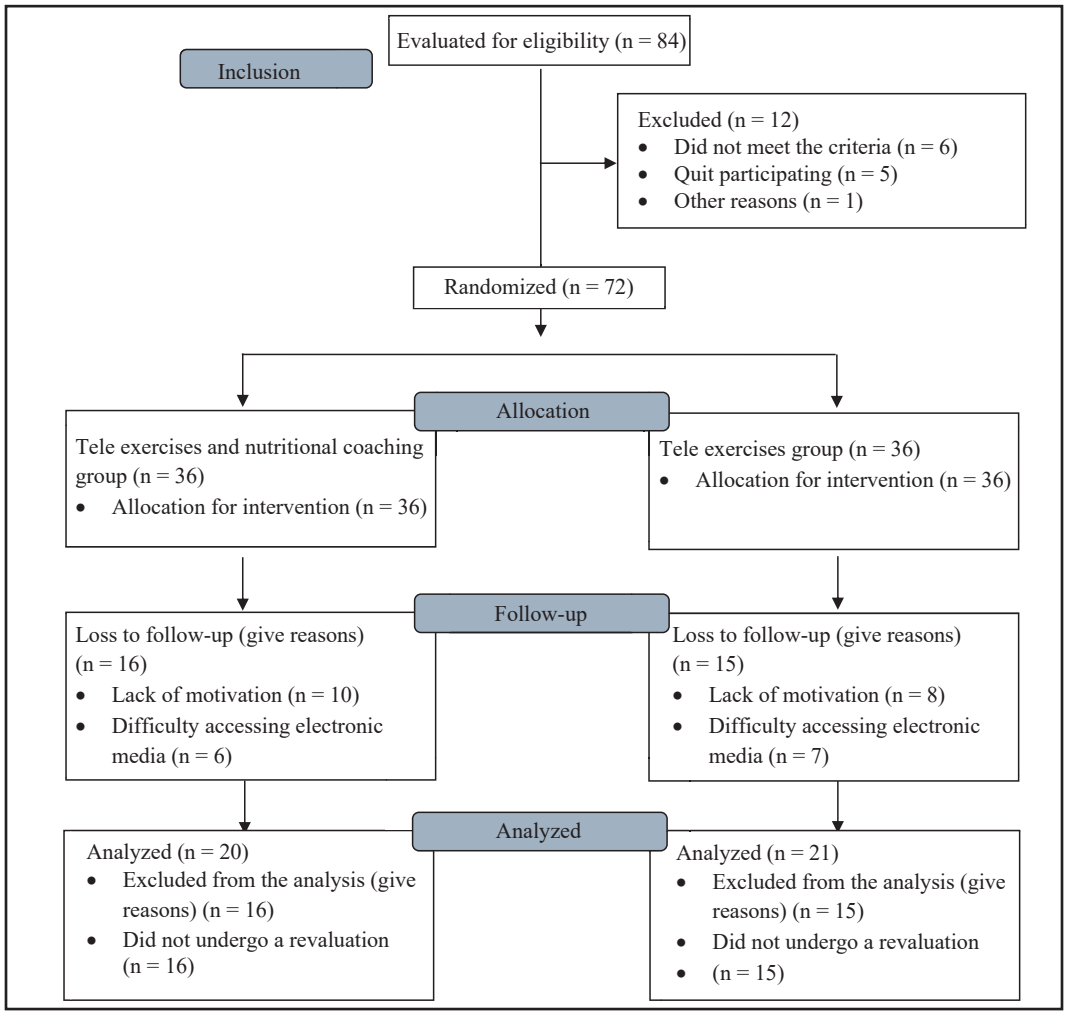

Figure 1.

Flowchart of the participants throughout the study.

Table I. Anthropometric and body composition outcomes

Outcomes	TE+NC					TE				
	PRE	POST	*ES*	Δabs	Δ%	PRE	POST	*ES*	Δabs	Δ%
Body weight (kg)	89.7 ± 18.0	89.2 ± 18.5	0.03	-0.54	-0.56	87.2 ± 19.4	86.6 ± 18.8	0.03	-0.59	-0.69
Height (cm)	164.0 ± 0.7	164.0 ± 0.7	0.00	0.00	0.00	161.4 ± 8.1	161.4 ± 8.1	0.00	0.00	0.00
BMI (kg/m²)	33.3 ± 5.3	33.1 ± 5.4	0.04	-0.20	-0.62	33.4 ± 6.3	33.2 ± 6.2	0.03	-0.22	-0.59
WC (cm)	95.8 ± 12.7	95.9 ± 12.9	0.01	0.15	0.18	95.5 ± 12.6	94.9 ± 12.5	0.05	-0.63	-0.60
AC (cm)	106.2 ± 12.8	105.3 ± 12.7	0.04	-0.87	0.71	106.3 ± 14.0	105.2 ± 13.2	0.08	-1.08	-0.89
Absolute free-fat mass (kg)	50.1 ± 9.2	49.5 ± 9.7	0.06	-0.61	-1.26	48.4 ± 8.0	48.7 ± 7.9	0.04	0.32	0.71
Absolute fat mass (kg)	39.7 ± 11.2	39.2 ± 11.4	0.04	-0.46	-1.17	38.5 ± 13.4	37.9 ± 12.7	0.04	-0.59	-0.73
Body fat percentage (%)	44.8 ± 4.1	44.4 ± 4.2	0.06	-0.34	---	44.0 ± 5.9	43.3 ± 5.8	0.12	-0.72	---

Data are expressed as mean ± standard deviation. BMI: body mass index; WC: waist circumference; AC: abdominal circumference; Δ: absolute and relative changes; ES: effect size; TE: tele-exercises group; TE+NC: tele-exercises + nutritional coaching group.

TE PROGRAM

TE was carried out online by a certified personal trainer three times a week, with participants staying at their own houses. Exercises during the sessions included body weight as well as the adaptation of materials from the daily routine (e.g., broom, shopping bags, water bottles). The instructor interacted to correct gesture, and to promote exercise progression, dynamism and empathy, aiming at participant adherence. The classes were transmitted on YouTube through a private link. Possible doubts regarding the materials and adequate clothes were solved through a private WhatsApp group message between the researchers, the personal trainers, and the participants. All the TE sessions started with a general warm-up consisting of a 3-min walk, followed by a 3-min stretching period for both the upper and lower body. Afterward, the main exercises followed, which remained the same during the 8-week intervention. Most TE was performed using the participants' body weight as resistance, and all exercises were performed with three sets. The TE sessions included three exercises for the lower body (i.e., squat, lunge, hip thrust), four exercises for the upper body (i.e., lateral shoulder raise [using water bottles], chest press on the wall, push-ups, triceps bench dip), one exercise for abdominal muscles (i.e., plank), and one exercise for cardiorespiratory fitness (i.e., rope jumping). Exercise sets consisted of 30 sec of active movement interspersed with 30 sec of rest in the first 4 weeks, and these should be performed with a rating of perceived exertion (RPE) of 4-6 a.u., based on the modified RPE scale (30). In the last 4 weeks of training, participants performed 40 seconds of active movement in each set interspersed by 20 seconds of rest, while maintaining the RPE between 7-9 a.u. (31). The TE sessions were completed with a cool-down, consisting of a 3-min walk followed by a 3-min stretching period for the upper and lower body.

NC APPROACH

The NC approach was carried out by two dietitians certified by the Brazilian Coaching Association. The NC sessions were conducted online, once a week, and are detailed elsewhere (19). Briefly, the sessions included general coaching strategies and tools, such as motivational interviewing, decisional balance, positive psychology, ambivalence, nonviolent communication, mindfulness, setting of short-term goals, and strategies to change habits. No diet was prescribed by the dietitians, and they were not involved in any other procedure related to the current investigation. The size and quantity of food portions, the amount of fat in the diet, and the consumption of fruits and vegetables were analyzed by the dietitians through three 24-h dietary recalls.

STATISTICAL ANALYSIS

Data are presented as mean ± standard deviation. The presence of outliers was visually inspected, while the sphericity and normality of the data were checked using the Mauchly test and Shapiro-Wilk test, respectively. A two-way mixed model with "Group" (TE and TE+NC) and "Time" (PRE and POST) as fixed factors was used to analyze the intervention effect. Participants were then random factors in all the comparisons. A Tukey post-hoc test was performed whenever a significant F-value was obtained. An unpaired t-test was employed to compare potential between-group differences at the PRE and the between-group absolute (i.e., POST-PRE) and relative changes. Cohen's *d* was calculated to estimate the difference of effect size between two means (32), with the following qualitative descriptors: < 0.2, negligible effect; 0.2-0.39, small effect; 0.40-0.75, moderate effect; and > 0.75, large effect. Data were analyzed using the SAS statistical software (v.9.3; SAS Institute, North Carolina, USA), with statistical significance set at $p \leq 0.05$.

RESULTS

ANTHROPOMETRIC AND BODY COMPOSITIONS OUTCOMES

No between-group differences were observed at PRE for all the anthropometric and body composition outcomes (Table I) (all $p > 0.05$). Similarly, no significant main time or group effect (all $p > 0.05$) was observed (Table I). No significant between-group differences were detected for the absolute or relative changes in the anthropometric and body composition outcomes.

EXERCISE CAPACITY

No between-group differences were observed at PRE for the exercise capacity outcomes (Table II) (all $p > 0.05$). A significant main time, but no group, effect was detected for isometric grip strength in both the right ($p = 0.0006$ and $p = 0.901$, respectively) and left hand ($p = 0.0006$ and $p = 0.659$, respectively), lumbar isometric strength ($p = 0.006$ and $p = 0.369$, respectively), flexibility ($p < 0.0001$ and $p = 0.285$, respectively), and total number of repetitions performed during the abdominal ($p < 0.0001$ and $p = 0.872$, respectively) and push-up resistance tests ($p = 0.004$ and $p = 0.261$, respectively). A significant main time ($p = 0.003$), but no group, effect ($p = 0.596$) was also shown for VO_{2peak}, wherein a significant decrease was detected in the TE+NC group ($p = 0.007$) but not in the TE group ($p = 0.801$) (Table II). No significant between-group differences were detected for the absolute or relative changes in any of the exercise capacity outcomes.

SF-12, EATING BEHAVIOR, INTERVENTION ADHERENCE, AND ADVERSE EVENTS

The SF-12 score did not significantly differ between the groups across the study (all comparisons, $p > 0.05$). Similar-

Table II. Exercise capacity outcomes

Outcomes	TE+NC					TE				
	PRE	POST	ES	Δabs	Δ%	PRE	POST	ES	Δabs	Δ%
Sit-and-reach (cm)	21.3 ± 8.9	24.5 ± 7.8*	0.38	3.24	25.18	24.3 ± 9.1	27.2 ± 7.8*	0.34	2.88	24.23
Right handgrip (kg)	28.9 ± 5.7	31.0 ± 6.8*	0.25	1.76	5.73	28.8 ± 6.0	30.6 ± 7.4*	0.31	1.79	7.02
Left handgrip (kg)	28.3 ± 6.3	30.1 ± 7.5*	0.27	2.07	7.04	27.5 ± 5.4	29.3 ± 6.2*	0.28	1.88	6.74
Lumbar traction (kg)	69.7 ± 18.7	74.3 ± 19.7*	0.17	4.68	8.42	73.9 ± 21.9	81.8 ± 23.4*	0.35	8.90	12.76
Abdominal resistance (reps)	14.8 ± 7.9	19.5 ± 9.1*	0.55	4.74	36.55	14.9 ± 8.2	20.2 ± 6.9*	0.69	5.29	51.41
Push-up resistance (reps)	17.8 ± 6.7	20.2 ± 9.9*	0.28	2.37	23.63	19.1 ± 7.2	23.6 ± 5.5*	0.71	4.57	40.65
VO_{2peak} ($mL \cdot kg \cdot min^{-1}$)	18.9 ± 3.1	17.5 ± 2.7*	0.36	-1.38	-6.95	17.9 ± 2.4	17.6 ± 3.1	0.12	-0.35	-1.92

*Data are expressed as mean ± standard deviation. *Denotes a significant within-group difference ($p < 0.05$). Δ: absolute and relative changes; ES: effect size; TE: tele-exercises group; TE+NC: tele-exercises + nutritional coaching group.*

ly, the size and quantity of food portions, the amount of fat in the diet, and the consumption of fruits and vegetables did not significantly differ between the groups throughout the study (all comparisons, $p > 0.05$). Adherence to the TE program was 71 ± 11 % and 69 ± 13 % in the TE and TE+NC groups, respectively. No adverse events were reported.

DISCUSSION

Obesity is a significant and rapidly increasing global health issue. It is concomitantly accompanied by an increase in multimorbidity (33), burdening many healthcare systems. Due to the COVID-19 pandemic, it is essential to develop strategies for treating overweight and obesity that observe the imposed social isolation policies. Among the emerging strategies, TE and NC have been receiving attention given their capability to be conducted online and their potential to increase energy expenditure and decrease energy consumption. To the best of the authors' knowledge, no other study had investigated the isolated effects of TE or the combined effects of TE and NC on health-related parameters of overweight/obese individuals. Our results showed that most exercise capacity outcomes improved after TE. Conversely, quality of life, body composition, and anthropometric measures TE were not affected by TE, and NC did not have any additional effect on these measures.

Using information and communication technologies to provide cost-effective and flexible healthcare services across geographic, time, and economic barriers (12), TE has emerged as an alternative to conventional, face-to-face, and hands-on exercise services for increasing energy expenditure during the COVID-19-induced social isolation. While this tool has been receiving increasing attention among fragile populations (12,20), little is known about its therapeutic efficacy in overweight/obese individuals. The most evident finding in our study (i.e., improved flexibility, isometric muscle strength, and dynamic muscle endurance) might have resulted from the greater amount of time spent on exercise volume for the resistance (~ 25 min per session) and stretching (~ 6 min per session) exercises in our TE program. On the other hand, the lack of improvement in VO_{2peak} may have been due to the small amount of time spent on the cardiorespiratory aspect (~ 6 min per session), the difficulty associated with the lack of space to do the cardiorespiratory exercises at home, or the non-specificity of the test used to assess the VO_{2peak}. Intriguingly, the improvement in most exercise capacity outcomes did not translate into improvements in the participants' perceived quality of life. It is possible that SF-12 may not have enough sensitivity to detect small effects on this outcome resulting from online exercise interventions, although this remains elusive. Finally, TE did not affect the anthropometric and body composition outcomes. This might be explained by the employed training intensity, that despite having been progressively increased throughout the intervention, may not have been sufficiently high to promote large energy expenditures, and consequently, substantial anthropometric and/or body composition changes. The adequate progression of intensity and volume in TE programs remains unelucidated. Despite of the lack of reduction in body weight and fat in the current study, it must be borne in mind that such variables did not increase. In this direction, recent evidence has shown a natural tendency to weight gain during the lockdown (34), which is supported by epidemiological studies reporting weight increases in 48.6 % of their sample (3,533 participants) during the lockdown period (35). Thus, although the present design did not include a control group (i.e., without any intervention) to confirm this hypothesis, the weigh maintenance could be seen as a positive outcome considering the context of the COVID-19 pandemic.

Despite being a promising strategy, it should be noted that TE interventions have varying acceptability among different populations and regions worldwide. In this sense, less emphasis has been laid on reporting its feasibility, such as the specific reasons for withdrawal from the intervention and adverse events (36). In our study, despite the absence of adverse events, some participants withdrew from the study due to difficulty in accessing and operating the electronic media, while others withdrew due to lack of motivation to continue. Therefore, identifying the factors affecting adherence to remote exercise interventions and using easier/more accessible tools to participants seems to be a key point for improving engagement in TE programs and achieving greater benefits in health-related parameters.

The use of health coaching, from which NC is derived, is widespread and appears to be ever-increasing. Supporting this notion, a study commissioned by the International Coaching Federation reported that the total number of professional coach practitioners worldwide was ~ 53,300, most of these located in higher-income regions. In addition, the US estimated market value for personal coaching was $1.02 billions (37). In the present investigation, we showed that eating behaviors did not significantly change in the TE+NC group, contradicting the emerging evidence on NC's efficacy for treating overweight/obesity (16-19). While one could argue against the short duration of the NC approach in our study, our findings are in line with recent meta-analytic data showing a trivial effect of self-reported health coaching strategies for weight loss (38). It is noteworthy that the quality of evidence supporting weight loss in this recent meta-analysis was very low, and studies were deemed to have a high risk of bias, highlighting the need for higher quality research in this area before making any kind of recommendation (38). Therefore, based on our findings and available evidence, health coaching interventions still do not have scientific support for their practice as healthcare interventions.

Our study has limitations. First, recent systematic reviews concluded that interventions provided exclusively online aimed at changing behavior, such as those included in the present examination, led to clinically small benefits when performed in a short period (39). Hence, the lack of benefits on the anthropometric and body composition measures and the small magnitude of effect size on the exercise capacity outcomes in the present study may be due to the short duration of the interventions, reinforcing the need for more extended duration studies for the therapeutic potential of online interventions. Second, all tests included in this research were chosen for their clinical applicability in larger populations and their ability to simulate the real-world conduct of dietitians and fitness/personal trainers. However, despite the methodological precautions adopted in each of the tests, we recognize that some were the gold standard, making them partially susceptible to measurement errors/variations. Therefore, future studies examining the therapeutic efficacy of online interventions should employ gold-standard methods to verify small but clinically meaningful effects. Finally, it was not possible to perform blood collections and laboratory analyses of metabolic and cardiovascular health outcomes, such as fasting blood glucose, insulin, and lipid profiles, which are generally altered in overweight/obese individuals. Future studies must employ these analyses to widely explore the therapeutic effects of TE programs in overweight/obese individuals.

CONCLUSION

In conclusion, 8 weeks of TE for overweight and obese women effectively improved exercise capacity but did not impact quality of life and anthropometric or body composition-related outcomes. Nonetheless, before recommending TE for overweight/obese individuals, our results call the need for more studies examining the long-term efficacy of TE, how the modulation of its prescription-related variables may influence its therapeutic effects, and the real effect of TE on gold-standard body composition methods. Moreover, no additive effect was detected when NC was combined with TE. As such, the current results do not support the use of NC strategies for improving health-related parameters.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Obesidad y síndrome metabólico

Estudio en vida real de una plataforma «online» para la prescripción de ejercicio físico a pacientes obesos: efecto sobre los parámetros antropométricos y bioquímicos, y sobre la calidad de vida

Real-world study of an online platform for the prescription of physical exercise to obese patients — Effect on anthropometric, biochemical parameters and quality of life

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Resumen

Introducción: uno de los factores de riesgo relacionados con la obesidad es el sedentarismo. La realización de ejercicio físico produce beneficios metabólicos; no obstante, su prescripción mediante herramientas *online* se ha evaluado escasamente.

Objetivo: el objetivo de nuestro trabajo fue valorar el efecto de la prescripción de ejercicio físico mediante una plataforma *online* sobre los parámetros antropométricos, los factores de riesgo cardiovascular y la calidad de vida de pacientes obesos sedentarios.

Material y métodos: en un total de 35 pacientes obesos se recogieron de manera basal y a las 12 semanas datos antropométricos, la masa muscular por ecografía a nivel del cuádriceps, una determinación analítica, la presión arterial y la calidad de vida con el test SF-36. Durante 12 semanas se prescribió un programa de ejercicio físico estructurado a través de una plataforma *online* (www.vibraup.com).

Resultados: tras el programa de ejercicio físico se produjo una mejoría significativa del índice de masa corporal (-1,51 ± 0,1 kg/m^2; p = 0,01), el peso (-3,7 ± 0,6 kg; p = 0,01), la circunferencia de la cintura (-6,9 ± 0,3 cm; p = 0,01), la masa grasa (-3,9 ± 0,2 kg; p = 0,01), la masa muscular (5,5 ± 1,6 kg; p = 0,01), la tensión arterial diastólica (-4,5 ± 0,4 mm Hg; p = 0,01), la insulina (-2,8 ± 0,1 UI/L; p = 0,04) y la resistencia a la insulina (HOMA-IR) (-0,9 ± 0,1 unidades; p = 0,03) . Los diferentes parámetros ecográficos del recto anterior del cuádriceps mejoraron significativamente. La prevalencia del síndrome metabólico disminuyó del 27,3 % al 12,1 % (p = 0,03). En el test de calidad de vida SF36 se obtuvo una mejoría significativa en las dimensiones de salud general (20,9 ± 4,1 puntos; p = 0,001), rol físico (6,9 ± 0,9 puntos; p = 0,01) y salud mental (14,0 ± 1,3 puntos; p = 0,01).

Conclusión: la prescripción de ejercicio físico con una plataforma *online* a pacientes obesos mejora el peso y la masa grasa corporal, y aumenta la masa muscular, con disminución de la resistencia a la insulina y mejora de la calidad de vida.

Palabras clave:

Estudio vida real. Ejercicio físico. Obesidad. Plataforma *online*.

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Abstract

Introduction: one of the risk factors related to obesity is a sedentary lifestyle. Physical exercise produces metabolic benefits. Its prescription through online tools has been poorly evaluated, though.

Objective: the objective of our study was to assess the effect of the prescription of physical exercise through an online platform on anthropometric parameters, cardiovascular risk factors, and quality of life in sedentary obese patients.

Material and methods: in a total of 35 obese patients, anthropometric data, muscle mass by ultrasound at the quadriceps level, laboratory parameters, blood pressure, and quality of life using the SF36 tool were collected at baseline and at 12 weeks. For 12 weeks, a structured physical exercise program was prescribed through an online platform — www.vibraup.com.

Results: after the physical exercise program with the online platform, there was a significant improvement in body mass index (-1.51 ± 0.1 kg/m^2; p = 0.01), weight (-3.7 ± 0.6 kg; p = 0.01), waist circumference (-6.9 ± 0.3 cm; p = 0.01), fat mass (-3.9 ± 0.2 kg ; p = 0.01), muscle mass (5.5 ± 1.6 kg; p = 0.01), diastolic blood pressure (-4.5 ± 0.4 mm Hg; p = 0.01), insulin (-2.8 ± 0.1 IU/L; p = 0.04), and insulin resistance (HOMA-IR) (-0.9 ± 0.1 units; p = 0.03). The ultrasound parameters of the anterior rectus muscle also improved significantly. The prevalence of metabolic syndrome decreased from 27.3 % to 12.1 % (p = 0.03). The SF36 quality of life test showed a significant improvement in general health (20.9 ± 4.1 points; p = 0.001), physical role (6.9 ± 0.9 points; p = 0 .01), and mental health (14.0 ± 1.3 points; p = 0.01).

Conclusion: the prescription of physical exercise with an online platform to obese patients improves weight, decreases body fat mass and increases muscle mass, with a decrease in insulin resistance and an improvement in quality of life.

Keywords:

Real world study. Physical exercise. Obesity. Online platform.

INTRODUCCIÓN

La prevalencia de la obesidad a nivel mundial ha aumentado considerablemente en los últimos años. Se estima que el 13 % de los adultos son obesos (11 % de hombres y 15 % de mujeres) y que hasta el 39 % de los adultos presentan sobrepeso (39 % de hombres y 40 % de mujeres) (1). La obesidad es un factor de riesgo de desarrollar hipertensión arterial, dislipemia, hipertensión arterial, eventos cardiovasculares, osteoartropatía, cáncer y un largo etcétera de comorbilidades (2). Por otra parte, es frecuente encontrar en el paciente obeso una disminución de la masa muscular, lo que denominamos sarcopenia. La unión de estas dos entidades es lo que denominamos obesidad sarcopénica (3). Los pacientes que presentan estas dos situaciones tienen aun un mayor riesgo de sufrir trastornos metabólicos, una mayor prevalencia de enfermedades cardiovasculares, elevadas tasas de mortalidad y un menor rendimiento físico (4).

Uno de los factores de riesgo relacionados con este aumento de la obesidad es el sedentarismo. El aumento de las jornadas laborales, la implantación de tiempos de ocio con perfil sedentario, así como la utilización de medios de transporte para cualquier desplazamiento ha incrementado la inactividad física. Todo esto ha llevado a que casi un tercio de la población adulta mundial pueda considerarse sedentaria (2). Existen diversas estrategias para abordar la obesidad, entre ellas el abordaje nutricional, la terapia conductual, los tratamientos farmacológicos, los procedimientos quirúrgicos bariátricos y, sin duda, el incremento del ejercicio físico (5). En cuanto al abordaje de la obesidad mediante el ejercicio físico, la Organización Mundial de la Salud (OMS) recomienda que los adultos de 18 a 64 años deben realizar al menos 150 minutos de actividad física aeróbica de intensidad moderada durante la semana o al menos 75 minutos de actividad física aeróbica de intensidad vigorosa durante la semana (6). Por otra parte, no debemos olvidar que el entrenamiento de fuerza tiene un papel fundamental en la pérdida de peso, así como en el mantenimiento y la ganancia de la masa muscular (7).

En las situaciones en que se logra una pérdida significativa de peso mediante un programa de ejercicio físico se han demostrado beneficios importantes para las personas con obesidad. Entre estos beneficios destacan un menor riesgo de desarrollar hipertensión, enfermedades cardiovasculares, diabetes, cáncer de mama y depresión, así como un incremento de los niveles de colesterol HDL y mejoras en el sistema inmunológico (8-10). Sin embargo, está por determinarse la prescripción de ejercicio físico que permitiría alcanzar los mejores beneficios para la salud (11). Existen varios métodos eficaces para prescribir ejercicio físico en el tratamiento de la obesidad, como puede ser el entrenamiento en circuito, el entrenamiento concurrente y el entrenamiento interválico de alta intensidad (HIIT). El entrenamiento en circuito ha demostrado mejorar la fuerza muscular y la capacidad cardiorrespiratoria en el paciente obeso (12). En cuanto a los entrenamientos concurrente y HIIT, estos han demostrado ser capaces de disminuir la grasa corporal y la circunferencia de la cintura en adultos con sobrepeso y obesidad, teniendo efectos similares a los del entrenamiento continuo de intensidad moderada pero con un 40 % menos de tiempo invertido a la semana (13). No obstante, una de las barreras detectadas para realizar ejercicio físico es la inversión de tiempo por parte del sujeto (14). Por ello, la utilización de plataformas *online* que permitan realizar ejercicio físico en el entorno del propio paciente están demostrando una buena aceptación por parte del usuario (15).

El objetivo de nuestro trabajo es valorar el efecto de la prescripción de ejercicio físico en la consulta médica, mediante una plataforma *online,* sobre los parámetros antropométricos, los factores de riesgo cardiovascular y la calidad de vida de pacientes obesos sedentarios.

MATERIAL Y MÉTODOS

En el estudio se reclutaron pacientes obesos con hábitos sedentarios que acudían a las consultas de nuestro hospital para evaluar su obesidad (índice de masa corporal ≥ 30 kg/m^2). Un

total de 35 pacientes obesos aceptaron participar en el estudio y todos firmaron un consentimiento informado para su inclusión antes de participar en el estudio. El trabajo científico se realizó de acuerdo con la Declaración de Helsinki y el protocolo fue aprobado por el Comité de Ética del HCUVa (PI20/2062).

Los criterios de inclusión de los pacientes fueron la presencia de obesidad diagnosticada con un índice de masa corporal ≥ 30 kg/m^2, así como la utilización habitual por parte del paciente de un ordenador, una tableta o un móvil para el acceso a la información. Los criterios de exclusión fueron los siguientes: antecedentes de eventos cardiovasculares, hábito enólico, proceso oncológico activo, limitación funcional grave para realizar ejercicio físico de manera habitual, toma durante los 6 meses anteriores al estudio de fármacos que influyeran en los niveles de lípidos o glucosa y haber realizado una dieta hipocalórica durante ese periodo.

Durante la visita basal se recogieron datos antropométricos (peso, talla, índice de masa corporal (IMC), masa grasa por impedancia y circunferencia de la cintura), la masa muscular por ecografía a nivel del cuádriceps, la presión arterial y la calidad de vida con el test SF-36. Para determinar los parámetros bioquímicos se alicuotaron 5 ml de sangre venosa en tubos recubiertos con ácido etilendiaminotetraacético (EDTA) después de un ayuno nocturno de 10 horas. Se midieron los siguientes parámetros; insulina, colesterol total, colesterol LDL, colesterol HDL, triglicéridos y proteína C-reactiva. También se registró la ingesta dietética mediante una encuesta de 3 días. La presencia de síndrome metabólico (SM) se definió de acuerdo con los criterios establecidos por el Panel de Tratamiento de Adultos III (ATP III) (16). Los pacientes debían cumplir al menos 3 de los siguientes criterios para ser diagnosticados de SM; glucosa en ayunas elevada o tratamiento para la diabetes, triglicéridos elevados (≥ 150 mg/dl) o tratamiento para la dislipemia, colesterol HDL bajo ≤ 40 mg/dl (hombres) o ≤ 50 mg/dl (mujeres), presión arterial sistólica o diastólica elevada (≥ 130/85 mm Hg o tratamiento antihipertensivo) y aumento de la circunferencia de la cintura (≥ 94 cm [hombres] o ≥ 80 cm [mujeres]). Los pacientes recibieron el mes anterior a la inclusión en el programa de ejercicio físico instrucciones para seguir unas recomendaciones dietéticas estándar con 1600 calorías al día, 80 gramos de proteínas, 70 gramos de lípidos con un 50 % de grasas monoinsaturadas, y 160 gramos de hidratos de carbono y 15 gramos de fibra, para evitar modificaciones dietéticas a lo largo del programa de ejercicio físico.

PROGRAMA DE EJERCICIO FÍSICO A TRAVÉS DE UNA PLATAFORMA *ONLINE*

El programa de ejercicio físico llevado a cabo por los sujetos se realiza mediante registro en la plataforma web (www.vibraup.com), ya sea en dispositivo móvil, tableta u ordenador. Los pacientes realizaron este registro mediante un código de acceso facilitado por su endocrinólogo a través de la propia plataforma web (correo electrónico) o bien en papel. El programa de entrenamiento tuvo una duración de 12 semanas. Cada sujeto realizaba 3 niveles de 4 semanas de duración y con una frecuencia semanal de 2 días de entrenamiento dirigidos por la plataforma web; los entrenamientos tenían una duración de entre 10 y 30 minutos aproximadamente, variando en función del nivel del paciente. La tabla I refleja a modo de ejemplo 4 semanas de un nivel de este programa de entrenamiento, que consistió en la realización de una serie de ejercicios multiarticulares que combinaban trabajo de fuerza con trabajo cardiovascular, lo que se denomina entrenamiento concurrente. En la programación se plantea una progresión lineal ascendente tanto del volumen como de la intensidad.

Tabla I. Nivel 1 con 4 semanas de ejercicio programado por la plataforma www.vibraup.com

Semana 1									
Autoevaluación					Fuerza 2				
Tiempo total sesión: 10 minutos	**Nombre ejercicio**	**N.º series**	**Tiempo**	**Descanso**	**Tiempo total sesión: 10 minutos**	**Nombre ejercicio**	**N.º series**	**Tiempo**	**Descanso**
Calentamiento	Círculos hombros				Calentamiento	Círculos rodillas			
	Rotaciones de tronco					Dorsiflexión de tobillo en el aire			
	Círculos cadera					Círculos cadera			

(Continúa en la página siguiente)

Tabla I (Cont.). Nivel 1 con 4 semanas de ejercicio programado por la plataforma www.vibraup.com

Semana 1									
Autoevaluación					**Fuerza 2**				
Tiempo total sesión: 10 minutos	**Nombre ejercicio**	**N.º series**	**Tiempo**	**Descanso**	**Tiempo total sesión: 10 minutos**	**Nombre ejercicio**	**N.º series**	**Tiempo**	**Descanso**
Parte principal	Sentarse y levantarse	1	15”	30”	Parte principal	*Bracing*	3	15”	15”
	Sentarse y levantarse	1	30” máximo número de repes	30”					
	Fondos de rodillas en banco	1	15”	30”		Sentadilla	3	20”	30”
	Fondos de rodillas en banco	1	30” máximo número de repes	30”		Bisagra de cadera	3	20”	30”
Vuelta a la calma	Estiramiento de hombro				Vuelta a la calma	Estiramiento isquiotibiales			
	Estiramiento escápulas					Estiramiento aductores			
						Liberación con pelota			
Actividad semanal									
Autoevaluación actividad física		**Tiempo de actividad**	**Número de pasos/ pisos**		**Intensidad**			**Distancia**	
Caminar		Menor posible			Alta			1500 metros	
Actividad semanal		**Objetivo**	**Recomendación**		**Actividad semanal**	**Objetivo**		**Recomendación**	
Caminar		18000 pasos	2500 pasos diarios		Subir escaleras	20 pisos		2-3 pisos diarios	
Semana 2									
Fuerza 1					**Fuerza 2**				
Tiempo total sesión: 10 minutos	**Nombre ejercicio**	**N.º series**	**Tiempo**	**Descanso**	**Tiempo total sesión: 10 minutos**	**Nombre ejercicio**	**N.º series**	**Tiempo**	**Descanso**
Calentamiento	Círculos hombros				Calentamiento	Círculos rodillas			
	Rotaciones de tronco					Dorsiflexión de tobillo en el aire			
	Círculos cadera					Círculos cadera			

(Continúa en la página siguiente)

Tabla I (Cont.). Nivel 1 con 4 semanas de ejercicio programado por la plataforma www.vibraup.com

Semana 2									
Fuerza 1					**Fuerza 2**				
Tiempo total sesión: 10 minutos	**Nombre ejercicio**	**N.º series**	**Tiempo**	**Descanso**	**Tiempo total sesión: 10 minutos**	**Nombre ejercicio**	**N.º series**	**Tiempo**	**Descanso**
Parte principal	*Bracing*	3	15”	15”	Parte principal	*Bracing*	3	15”	15”
	Movilidad de hombro con toalla	3	20”	30”		Sentadilla	3	25”	30”
	Fondos de rodillas en banco	3	20”	30”		Bisagra de cadera	3	25”	30”
Vuelta a la calma	Estiramiento pectoral				Vuelta a la calma	Estiramiento isquiotibiales			
	Estiramiento dorsal					Estiramiento aductores			
						Liberación con pelota			
Actividad semanal									
Actividad semanal		**Objetivo**	**Recomendación**		**Actividad semanal**	**Objetivo**		**Recomendación**	
Caminar		21000 pasos	3000 pasos diarios		Subir escaleras	25 pisos		3-4 pisos diarios	
Semana 3									
Fuerza 1					**Fuerza 2**				
Tiempo total sesión: 12 minutos	**Nombre ejercicio**	**N.º series**	**Tiempo**	**Descanso**	**Tiempo total sesión: 10 minutos**	**Nombre ejercicio**	**N.º series**	**Tiempo**	**Descanso**
Calentamiento	Círculos hombros				Calentamiento	Círculos rodillas			
	Rotaciones de tronco					Dorsiflexión de tobillo en el aire			
	Círculos cadera					Círculos cadera			
Parte principal	*Bracing*	3	20”	20”	Parte principal	*Bracing*	3	20”	20”
	Movilidad de hombro con toalla	3	25”	30”		Sentadilla	3	30”	30”
	Fondos de rodillas en banco	3	25”	30”		Bisagra de cadera	3	30”	30”

(Continúa en la página siguiente)

Tabla I (Cont.). Nivel 1 con 4 semanas de ejercicio programado por la plataforma www.vibraup.com

Semana 3									
Fuerza 1					**Fuerza 2**				
Tiempo total sesión: 12 minutos	**Nombre ejercicio**	**N.º series**	**Tiempo**	**Descanso**	**Tiempo total sesión: 10 minutos**	**Nombre ejercicio**	**N.º series**	**Tiempo**	**Descanso**
Vuelta a la calma	Estiramiento de hombro				Vuelta a la calma	Estiramiento isquiotibiales			
	Estiramiento dorsal					Estiramiento aductores			
						Liberación con pelota			
Actividad semanal									
Actividad semanal		**Objetivo**	**Recomendación**		**Actividad semanal**		**Objetivo**	**Recomendación**	
Caminar		24500 pasos	3500 pasos diarios		Subir escaleras		28 pisos	4 pisos diarios	
Semana 4									
Fuerza 1					**Fuerza 2**				
Tiempo total sesión: 14 minutos	**Nombre ejercicio**	**N.º series**	**Tiempo**	**Descanso**	**Tiempo total sesión: 10 minutos**	**Nombre ejercicio**	**N.º series**	**Tiempo**	**Descanso**
Calentamiento	Círculos hombros				Calentamiento	Círculos rodillas			
	Rotaciones de tronco					Dorsiflexión de tobillo en el aire			
	Círculos cadera					Círculos cadera			
Parte principal	*Bracing*	3	20”	20”	Parte principal	*Bracing*	3	20”	20”
	Movilidad de hombro con toalla	3	30”	30”		Sentadilla	3	30”	20”
	Fondos de rodillas en banco	3	30”	30”		Bisagra de cadera	3	30”	20”
Vuelta a la calma	Estiramiento pectoral				Vuelta a la calma	Estiramiento isquiotibiales			
	Estiramiento escápulas					Estiramiento aductores			
	Estiramiento dorsal					Liberación con pelota			
Actividad semanal									
Actividad semanal		**Objetivo**	**Recomendación**		**Actividad semanal**		**Objetivo**	**Recomendación**	
Caminar		28000 pasos	4000 pasos diarios		Subir escaleras		30 pisos	4-5 pisos diarios	

Los ejercicios llevados a cabo se han planteado sobre la base de una organización tradicional en los primeros niveles, progresando hacia un formato en circuito en los niveles posteriores, donde se alternan ejercicios con diferentes objetivos (fuerza, estabilización, cardiovasculares). De manera adicional, los sujetos tuvieron una tarea basada en incrementar su actividad física, concretamente subir escaleras y caminar. También se les pidió a los sujetos que registrasen de forma diaria su actividad física en la propia plataforma (pisos subidos, medidos por el propio sujeto, y pasos realizados, medidos mediante la aplicación móvil G-Step [Green Health Care, LA, CA, EE. UU.]). Los sujetos fueron asignados a un nivel concreto bajo un algoritmo ejecutado con parámetros y datos introducidos por el sujeto como: edad, estado físico y de entrenamiento, índice de masa corporal y presencia de problemas articulares. Una vez asignado, el sujeto comenzaba su periodo de entrenamiento. Tanto el médico como el paciente tenían acceso a una pestaña de seguimiento en la propia plataforma web, donde podían consultar sus progresos y registros de datos diarios y así conocer la evolución y posible adherencia al programa de ejercicio.

PARÁMETROS ANTROPOMÉTRICOS, ECOGRAFÍA MUSCULAR Y PRESIÓN ARTERIAL

La altura (cm) y la circunferencia de la cintura (cm) se midieron con una cinta métrica no elástica (Omrom, LA, CA, EE. UU.). El peso corporal se determinó con los sujetos sin ropa, utilizando una báscula digital (Omrom, LA, CA, EE. UU.). Utilizando estos parámetros se calculó el índice de masa corporal (IMC) (peso corporal (kg) dividido por el cuadrado de la altura (m)). La masa grasa se determinó por bioimpedancia, con una precisión de 5 g (17) (EFG BIA 101 Anniversary, Akern, Italia), utilizando la siguiente ecuación para su cálculo:

$$(0{,}756\ \text{Altura}^2 / \text{Resistencia}) + (0{,}110 \times \text{Masa corporal}) + (0{,}107 \times \text{Reactancia}) - 5{,}463$$

A todos los sujetos se les hizo una ecografía muscular del recto anterior del cuádriceps de las extremidades inferiores izquierda y derecha con una sonda de 10 a 12 MHz y una matriz lineal multifrecuencia (Mindray Z60, Madrid, España). La sonda se alineó perpendicularmente al eje longitudinal y transversal del recto anterior del cuádriceps, y la evaluación se realizó sin comprensión a nivel del tercio inferior desde el polo superior de la rótula y la espina ilíaca anterosuperior, midiendo el área, la circunferencia y los diámetros anteroposterior y trasversal.

Las presiones arteriales sistólica y diastólica medias se calcularon promediando tres mediciones consecutivas (Omrom, LA, CA, EE. UU.) después de que los sujetos se sentaran durante 10 minutos.

TEST DE CALIDAD DE VIDA SF-36 Y VALORACIÓN PERSONAL

También se realizó el test de calidad de vida SF-36 con 11 ítems, que evalúa 8 dimensiones, antes de iniciar el programa y a las 12 semanas. Por último, se realizó una pregunta directa antes y después de realizar el programa de ejercicio físico con una escala Likert («¿Cómo te encuentras antes de realizar este programa de ejercicio físico?» y «¿Cómo te encuentras tras realizar este programa de ejercicio físico de 12 semanas?») con las siguientes respuestas: 0 = me cuesta moverme, 1 = me muevo bien pero me fatigo, 2 = me muevo perfectamente y 3 = me encuentro al 100 %).

EVALUACIÓN DE LA CONDICIÓN FÍSICA

Se indicó a los participantes que autoevaluasen dos pruebas de fuerza dirigidas por la plataforma web, de modo que en la semana 1, día 1 (que coincidía con un inicio de nivel), el sujeto hiciera una medición de los siguientes parámetros: fuerza del tren superior (máximo número de flexiones en 30 segundos), fuerza del tren inferior (máximo número de sentadillas en 30 segundos) y caminar 1500 metros en el menor tiempo posible. La primera medición fue supervisada y realizada por el paciente junto con uno de los profesionales investigadores, asegurando la comprensión, correcta ejecución y el modo de registrar los resultados obtenidos para posteriores meses.

PARÁMETROS BIOQUÍMICOS

Para evaluar el perfil lipídico determinamos los niveles de colesterol total, colesterol HDL y triglicéridos utilizando el analizador COBAS INTEGRA 400 (Roche Diagnostic, Montreal, Canadá). El colesterol LDL se calculó mediante la fórmula de Friedewald (colesterol LDL = colesterol total - colesterol HDL - triglicéridos / 5) (18). Los niveles de glucosa se determinaron mediante un método automatizado de hexoquinasa-oxidasa y la insulina se midió mediante un ensayo de electroquimioluminiscencia con el analizador COBAS INTEGRA 400 (Roche Diagnostic, Montreal, Canadá). Para el cálculo de la resistencia a la insulina se utilizó el *Homeostasis Model Assessment* (HOMA-IR), que se calculó utilizando estos valores: glucosa × insulina / 22,5 (19). La proteína C-reactiva (PCR) se midió por inmunoturbimetría (Roche Diagnostics GmbH, Mannheim, Alemania).

ANÁLISIS ESTADÍSTICO

El análisis estadístico se realizó con el software estadístico SPSS para Windows, versión 23.0 (SPSS Inc. Chicago, IL, EE. UU.). Los valores de p por debajo de 0,05 se consideraron estadísticamente significativos. El tamaño de la muestra se determinó para detectar diferencias de 3 kg de peso corporal tras la intervención con un 90 % de potencia y un 5 % de significación. La prueba de Bonferroni se aplicó para pruebas múltiples para reducir el error de tipo I en el análisis de asociación. Las estadísticas descriptivas de todos los valores de las variables se presentan como media y desviación estándar para las variables

continuas y como porcentaje para las variables categóricas. Las variables se analizaron con la prueba ANOVA más la prueba *post hoc* de Bonferroni y la prueba de la t de Student (para la variable de distribución normal) o la prueba de Kruskal-Wallis (para la variable de distribución no normal). El test del chi cuadrado se utilizó para valorar las variables cualitativas.

RESULTADOS

En total, se incluyeron 35 pacientes obesos (25 mujeres y 10 varones) con una edad media 46,4 ± 6,4 años. El índice de masa corporal medio fue de 34,1 ± 5,7 kg/m^2 con un peso medio de 93,7 ± 12,1 kg.

La tabla II muestra la evolución de las variables antropométricas y la bioimpedanciometría tras la intervención con ejercicio físico. Con respecto a las variables antropométricas clásicas, existió una disminución significativa del IMC (-1,51 ± 0,1 kg/m^2; p = 0,01), el peso (-3,7 ± 0,6 kg; p = 0,01) y la circunferencia de la cintura (-6,9 ± 0,3 cm; p = 0,01). Con respecto a las variables de la bioimpedanciometría, existió una disminución significativa de la masa grasa (-3,9 ± 0,2 kg; p = 0,01) y un aumento de la masa muscular (5,5 ± 1,6 kg; p = 0,01). La tensión arterial diastólica también disminuyó significativamente (-4,5 ± 0,4 mm Hg; p = 0,01).

En la tabla III se muestra la evolución de los diferentes parámetros ecográficos del recto anterior del cuádriceps, con un incremento significativo del área muscular, de la circunferencia muscular y del eje Y de este músculo tanto en la extremidad inferior derecha como en la izquierda.

Con respecto a las variables bioquímicas, en la tabla IV se muestra una disminución significativa de los niveles de insulina (-2,8 ± 0,1 UI/L; p = 0,04) y de la resistencia a la insulina (HOMA-IR) (-0,9 ± 0,1 unidades; p = 0,03). El resto de parámetros no se modificaron significativamente.

Tabla II. Parámetros antropométricos, bioimpedanciometríaa y tensión arterial

	Basal	12 semanas	p
Peso (kg)	93,7 ± 12,1	90,0 ± 13,1*	0,01
IMC (kg/m^2)	34,1 ± 5,7	31,6 ± 7,9*	0,01
Circunferencia de cintura	110,3 ± 15,6	103,7 ± 9,6*	0,01
Angulo de fase (°)	6,2 ± 0,9	6,3 ± 0,7	0,61
Masa grasa (kg)	36,8 ± 10,2	32,9 ± 9,6*	0,01
Masa muscular (kg)	25,7 ± 7,4	31,2 ± 9,5*	0,01
TAS (mm Hg)	129,0 ± 19,6	126,4 ± 18,7	0,32
TAD (mm Hg)	83,4 ± 9,7	78,9 ± 9,3*	0,01

*TAS: tensión arterial sistólica; TAD: tensión arterial diastólica. *p < 0,05.*

Tabla III. Parámetros de ecografía muscular del recto anterior del cuádriceps derecho e izquierdo

	Basal	12 semanas	p
Área muscular derecha (cm^2)	3,9 ± 1,3	4,8 ± 1,6*	0,002
Área muscular izquierda (cm^2)	4,1 ± 1,6	5,0 ± 1,9*	0,01
Circunferencia muscular derecha (cm)	8,4 ± 1,3	9,0 ± 1,3*	0,02
Circunferencia muscular izquierda (cm)	8,6 ± 1,5	9,4 ± 1,5*	0,02
Eje X muscular derecho (cm)	3,2 ± 0,5	3,4 ± 0,5	0,11
Eje X muscular izquierdo (cm)	3,3 ± 0,5	3,7 ± 0,6*	0,03
Eje Y muscular derecho (cm)	1,3 ± 0,3	1,6 ± 0,4*	0,01
Eje Y muscular izquierdo (cm)	1,3 ± 0,4	1,6 ± 0,4*	0,01

**p < 0,05.*

Tabla IV. Parámetros bioquímicos

	Basal	12 semanas	p
Glucosa (mg/dl)	93,4 ± 8,9	93,9 ± 8,5	0,74
Creatinina (mg/dl)	0,76 ± 0,1	0,77 ± 0,1	0,71
Colesterol total (mg/dl)	197,1 ± 41,2	186,1 ± 32,6	0,26
LDL-colesterol (mg/dl)	117,7 ± 33,6	117,4 ± 27,4	0,91
HDL-colesterol (mg/dl)	54,1 ± 15,6	51,1 ± 12,7	0,21
Triglicéridos (mg/dl)	113,4 ± 41,7	119,5 ± 59,3	0,01
Insulina (UI/L)	17,4 ± 9,1	14,6 ± 8,2*	0,04
HOMA-IR	4,3 ± 1,2	3,4 ± 1,9*	0,03
PCR (mg/dl)	4,1 ± 2,2	4,6 ± 1,9	0,33

*PCR: proteína C-reactiva. *p < 0,05.*

Tras el análisis de las variables antropométricas y bioquímicas, los pacientes se clasificaron en función de la presencia de síndrome metabólico (SM), presentando SM antes del inicio del programa de ejercicio físico un 27,3 % de los pacientes, porcentaje que, tras la realización del programa, descendió al 12,1 % (p = 0,03). El 100 % de los pacientes, antes de iniciar el programa de ejercicio físico, presentaban al menos un criterio de SM del ATP III, mientras que un 33,4 % tenían 2 o más criterios de SM. Tras las 12 semanas de ejercicio físico, solo el 93,7 % de los pacientes presentaba uno o más criterios de SM y solo un 28,2 % dos o más criterios (p = 0,03), con un 6,3 % de los pacientes sin ningún criterio de SM..

La tabla V muestra la evolución de las diferentes dimensiones del test de calidad de vida SF-36. Se obtuvo una mejoría significativa en las dimensiones de salud general (20,9 ± 4,1 puntos; p = 0,001), rol físico (6,9 ± 0,9 puntos; p = 0,01) y salud mental (14,0 ± 1,3 puntos; p = 0,01). A la pregunta «¿Cómo te encuentras antes y tras realizar este programa de ejercicio físico?», un 8,6 % respondieron que, antes de realizar el programa de ejercicio físico, les costaba moverse, un 34,3 % que se movían bien pero fatigándose y el resto que se movían perfectamente o al 100 % (57,1 %). Tras la realización del programa de ejercicio, las puntuaciones mejoraron, con tan solo un 2,9 % de pacientes respondiendo que les costaba moverse y un 11,4 % que se movían bien pero con fatiga, respondiendo el resto de pacientes que se movían perfectamente o al 100 % (85,7 %) (p = 0,01).

En el autorregistro de 3 actividades se detectó que, tras el programa de ejercicio físico, mejoraron significativamente las sentadillas en 30 segundos (17,2 ± 5,9 *vs.* 21,8 ± 6,2; p = 0,01), los fondos en 30 segundos (16,2 ± 3,5 *vs.* 19,6 ± 4,1; p = 0,01) y el tiempo en segundos necesario para recorrer 1,5 km (971,7 ± 192,9 *vs.* 828,4 ± 169,2; p = 0,01) después del programa de 12 semanas de ejercicio físico.

Tabla V. Test de calidad de vida SF-36

	Basal	12 semanas	p
Salud general	51,4 ± 426,9	72,1 ± 22,2*	0,001
Actividad física	80,0 ± 19,0	85,7 ± 16,3	0,09
Rol físico	80,6 ± 22,8	87,5 ± 20,3*	0,01
Rol emocional	90,1 ± 23,1	91,6 ± 22,6	0,31
Función social	94,8 ± 10,6	94,1 ± 8,6	0,12
Dolor	72,5 ± 28,7	75,3 ± 27,6	0,53
Vitalidad	71,7 ± 13,9	74,6 ± 16,2	0,51
Salud mental	59,3 ± 22,2	73,7 ± 21,1*	0,01

**p < 0,05.*

DISCUSIÓN

En nuestro estudio en vida real, la prescripción de ejercicio físico con una plataforma *online* durante 12 semanas a pacientes obesos sedentarios mejoró el peso, disminuyendo la masa grasa y aumentando la masa muscular. Por otra parte, mejoraron la resistencia a la insulina y la presencia del síndrome metabólico, con una mejoría significativa de la calidad de vida y de la condición física de los pacientes obesos.

La intervención con ejercicio físico a través de plataformas *online* puede ser una metodología de trabajo interesante para disminuir el sedentarismo y mejorar la salud de los pacientes obesos. Algunos trabajos ya han mostrado la buena aceptación de este tipo de herramientas en obesos (14,15); no obstante, su efecto sobre las variables antropométricas, bioquímicas y de calidad de vida no se ha evaluado en este colectivo. Esta ausencia de estudios se debe a múltiples factores: la dificultad de diseñar herramientas de este tipo, la baja adherencia del paciente obeso al ejercicio y los problemas de diseño de los estudios en forma de ensayo clínico aleatorizado capaces de evaluar la eficacia de estas intervenciones *online*. Por todo ello, en nuestro caso hemos realizado un trabajo en vida real. Estos estudios en vida real en medicina generan datos obtenidos del mundo real, es decir, fuera del contexto de los ensayos controlados aleatorios, y generados durante la práctica clínica habitual (20).

La mejoría del peso y del índice de masa corporal (IMC) (-3,8 %) observada en nuestro trabajo es similar a la mostrada en otros estudios con intervenciones presenciales de ejercicio físico (21) y muy similar a la de las intervenciones de ejercicio físico presencial combinado con una ingesta calórica controlada (5,8 % del IMC) (22). En otros estudios también se ha demostrado una disminución de otros parámetros de adiposidad con el ejercicio físico, como la circunferencia de la cintura (23). Por otra parte, otros trabajos han demostrado una mejoría de la presión arterial en torno al 4 o 5 % (24); en nuestro estudio, esta mejoría se situó alrededor del 6 %. Los programas de ejercicio físico basados en la fuerza han demostrado mayores disminuciones (24). Estos resultados pueden deberse a la adecuada combinación de los protocolos de entrenamiento, pues el entrenamiento en formato circuito ha mostrado tener una gran capacidad para generar un gasto energético mayor con un esfuerzo percibido menor (25). Es necesario tener en cuenta que la estimulación del músculo esquelético produce como respuesta el proceso de angiogénesis (26), con formación de nuevos vasos sanguíneos a partir de los preexistentes, produciendo una disminución de la resistencia vascular periférica (27), lo que podría explicar la disminución de la tensión arterial junto al ejercicio cardiovascular. También podría estar asociado a una mejor función endotelial por una mayor producción de óxido nítrico (28).

Con respecto a las mejorías metabólicas observadas en nuestro grupo de obesos con un programa de ejercicio físico a través de una plataforma *online*, estas son similares a las encontradas en la literatura con la prescripción de ejercicio de manera presencial (29-31). La disminución de la resistencia a la insulina en los pacientes obesos, junto a la disminución del número de

criterios que forman parte del síndrome metabólico, es un hallazgo relevante. En un trabajo realizado con mujeres sedentarias prediabéticas con obesidad, de una duración de 12 semanas, los niveles de glucemia postintervención disminuyeron significativamente (29). En otro estudio con un programa de 8 semanas de sesiones de ejercicio físico, disminuyó significativamente la resistencia a la insulina de los sujetos hiperglicémicos y hiperlipémicos (30), mejorando en otros trabajos también el consumo máximo de oxigeno (VO_{2max}) en los pacientes con intolerancia a la glucosa tras la realización de un programa de ejercicio físico (31). Si bien es cierto que un adecuado entrenamiento concurrente contribuye a la mejora del metabolismo de la glucosa en sangre, en algunos trabajos, la metodología HIIT ha demostrado tener más potencia para lograr este objetivo (32). Por sus características metodológicas, los sustratos energéticos de los esfuerzos de alta intensidad son fundamentalmente la glucosa y los fosfágenos, lo que podría explicar esa mejoría de la glucosa basal.

Además de todos estos beneficios sobre el peso, la masa grasa y los parámetros bioquímicos, demostrados también en otros trabajos previamente mencionados (21-33), es necesario reseñar el aumento de la masa muscular observado en nuestro estudio. Sánchez y cols. (34), en un estudio de intervención con 10 pacientes obesos candidatos a cirugía bariátrica, demostraron mediante impedanciometría un incremento a los 2 meses de la masa magra. En nuestro caso, el aumento de la masa magra se detectó no solo por impedanciometría sino que también la ecografía del recto anterior del cuádriceps mostró una mejoría significativa. Sin duda, este aumento de la masa muscular mejorará la capacidad funcional de estos pacientes y mejorará la sarcopenia existente en muchos pacientes obesos (3,4). Por ejemplo, se ha demostrado que los programas de 12 semanas de ejercicio físico mejoran significativamente la fuerza funcional y la fuerza dinámica de los pacientes obesos sometidos a cirugía bariátrica, aumentando la capacidad de realizar las actividades de la vida diaria (35).

Un último punto de interés en los pacientes con la patología crónica e incapacitante que es la obesidad, y que requiere la colaboración del paciente, es la calidad de vida. En nuestro trabajo, al analizar el test SF36 mejoraron los campos de salud general, actividad física y salud mental. Este apartado se ha evaluado escasamente. Por ejemplo, en el trabajo de Sánchez y cols. (34) no se encontraron mejorías significativas de la calidad de vida tras el programa de ejercicio; tal vez el bajo tamaño muestral y la utilización de un test con un menor número de preguntas (EuroQol-5D) no permitió detectar la mejoría. No obstante, este trabajo (34) también demostró un alto grado de satisfacción por parte de los pacientes obesos con el programa de ejercicio físico, como también sucedió en nuestro diseño. El entorno *online* ya ha demostrado una alta aceptación en este colectivo y un aumento de la actividad física a 3 y 6 meses (15) pero sin evaluar las modificaciones antropométricas y metabólicas, siendo por tanto relevantes nuestros resultados.

Dentro de las limitaciones del estudio podemos destacar el pequeño tamaño muestral, así como la duración limitada de la intervención. Otra limitación es la ausencia de un grupo de control, realizándose la comparación de cada paciente consigo mismo en el tiempo basal. No obstante, estas deficiencias se contrarrestan con fortalezas como es la utilización de una plataforma *online* de prescripción de ejercicio, que permitió que el paciente obeso pudiera desarrollar los ejercicios físicos en su entorno habitual. La mayor parte de los trabajos de intervención con ejercicio físico en el paciente obeso se han realizado con programas presenciales, incluso acompañados de dietas hipocalóricas simultáneas, como muestra la revisión de Cuadri y cols. (36). Sin embargo, en la era digital en la que estamos inmersos, las aplicaciones móviles sencillas han conseguido demostrar un aumento de la adherencia al ejercicio físico (37). Por tanto, es necesario evaluar la posibilidad de prescribir ejercicio físico con un programa estructurado a través de aplicaciones móviles.

En conclusión, la prescripción de ejercicio físico con una plataforma *online* a pacientes obesos mejora el peso, disminuye la masa grasa corporal y aumenta la masa muscular, con una disminución de la resistencia a la insulina y una mejoría de la calidad de vida. Esta herramienta es un método de bajo coste económico que facilita la labor de prescripción del ejercicio físico. Esto permite que el paciente tenga una pauta de ejercicio físico adaptada a sus características individuales. Así mismo, la aplicación permite al personal sanitario tener control sobre la evolución de este paciente, teniendo acceso a todos los parámetros necesarios para realizar un adecuado seguimiento. Las herramientas de prescripción de ejercicio *online*, como la evaluada en este caso (Vibraup), supone un área de conocimiento que aún necesita investigación y evidencia para poder establecer las bases de su uso. Se deben plantear futuras líneas de investigación evaluando periodos mayores de entrenamiento, distintas poblaciones y la aplicación en el tratamiento de otro tipo de patologías donde el ejercicio físico sea de utilidad terapéutica.

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Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Assessment of the fat mass index in women recently diagnosed with gynecological tumors

Evaluación del índice de masa grasa en mujeres diagnosticadas recientemente de tumores ginecológicos

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Abstract

Objectives: to evaluate the nutritional status and body composition of women with gynecological tumors and evaluate the fat mass index (FMI) as a complementary indicator for addressing the nutrition status.

Methods: a cross-sectional study with women recently diagnosed with gynecological tumors. Nutritional status was assessed using conventional anthropometry and the Patient-Generated Subjective Global Assessment. For body composition, bioelectrical impedance was used.

Results: a total of 158 women participated, most of them with excess weight and high body fat. The FMI showed a positive and significant correlation with body mass index, arm circumference, tricipital skinfold, and arm muscle circumference.

Conclusion: women recently diagnosed with gynecological tumors had excess weight and high body fat. The FMI may be a potentially useful indicator to complement the assessment of nutritional status and help the multidisciplinary team to perform early clinical and nutritional interventions.

Keywords:

Nutritional status. Body composition. Gynecologic neoplasms.

Resumen

Objetivos: evaluar el estado nutricional y la composición corporal de mujeres con tumores ginecológicos, y evaluar el índice de masa grasa (IMG) como indicador nutricional complementario.

Métodos: estudio transversal con mujeres diagnosticadas recientemente de tumores ginecológicos. El estado nutricional se evaluó mediante la antropometría convencional y la Evaluación Global Subjetiva Generada por el Paciente. Para la composición corporal se utilizó la impedancia bioeléctrica.

Resultados: participaron 158 mujeres, la mayoría con exceso de peso y grasa corporal alta. El IMG mostró una correlación positiva y significativa con el índice de masa corporal, la circunferencia del brazo, el pliegue cutáneo tricipital y la circunferencia de los músculos del brazo.

Conclusión: las mujeres diagnosticadas recientemente con tumores ginecológicos presentaron exceso de peso y grasa corporal alta. El IMG puede ser un indicador potencialmente útil para complementar la evaluación del estado nutricional y ayudar al equipo multidisciplinario a realizar intervenciones clínicas y nutricionales tempranas.

Palabras clave:

Estado nutricional. Composición corporal. Neoplasias ginecológicas.

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INTRODUCTION

The global cancer burden has grown significantly. Gynecological cancer is most prevalent among obese women living in developing countries and having low socioeconomic status. In Brazil, the expected number of new cases of this neoplasm for each year of the 2020-2022 triennium will be 16,710, with an estimated risk of 16.35 cases per 100,000 women (1).

Among risk factors for cancer inadequate lifestyles stand out, including smoking, high alcohol consumption, inadequate diet, obesity, and body fat, among other environmental factors (2-4). Obesity, a major global epidemic, is considered the most significant preventable risk factor for several types of malignant tumors among adult women; therefore, maintaining a healthy weight is a primary recommendation among cancer prevention entities (5). A study on the proportion of cancer cases attributed to lifestyle in Brazil found that 36.5 % of cervical cancers and 5.7 % of ovarian cancers in Brazil are attributed to an elevated body mass index (BMI) (6).

There are few studies in the literature assessing the nutritional status and body composition of women with gynecological tumors, especially before antineoplastic therapy. Gold-standard methods to estimate body composition in this population, such as magnetic resonance imaging, computed tomography, and DEXA, could be high-cost (12). Therefore, in the context of limited resources, the adoption of complementary indicators in determining nutritional status can be very useful.

Thus, the objectives of this study were: 1) to evaluate the nutritional status and body composition of women with gynecological tumors before starting cancer treatment; 2) to evaluate the fat mass index (FMI) as a complementary indicator for addressing the nutrition status.

MATERIALS AND METHODS

STUDY AND SAMPLE CHARACTERIZATION

This is a cross-sectional study with women recently diagnosed with gynecological tumors, between January and September 2017, at a public hospital in Brazil. The study included women with positive pathology for gynecological cancer (ICD 10 - C52, ICD 10 - C53, ICD 10 - C56, and other correspondents) (7,8), without any previous antineoplastic treatments, aged 20 years or more. Women with mental or cognitive deficits were excluded.

For the sociodemographic characterization we used the economic class according to the Brazilian Economic Classification criteria of the Brazilian Association of Research Companies (ABEP) (9). Clinical stage was classified according to the AJCC 8th edition (10). We collected self-reported diabetes *mellitus* (type 2) and arterial hypertension (11-13).

ASSESSMENT OF NUTRITIONAL STATUS AND BODY COMPOSITION

The following measures were considered: current weight (kg), height (m), body mass index (BMI, kg/m^2) (14), arm circumference (AC, cm), tricipital skinfold (TS, mm), and arm muscle circumference (AMC, cm).

AC and TS measurements were determined according to the criteria established by Lohman et al. (15). We adopted the cutoff points proposed by Blackburn and Thornton (16). Nutritional status was also assessed using the Patient-Generated Subjective Global Assessment (PG-SGA), culturally adapted to Portuguese (Brazilian) by Campos and Prado (17), and classified according to Ottery (A: well-nourished; B: mildly/moderately malnourished; C: severely malnourished) (18).

We used the multi-frequency segmented bioimpedance analysis (InBody® model 230 equipment) to evaluate body composition. The fat mass index (FMI) was determined using the equation: FMI (kg/m^2) = fat mass (kg) / height^2 (m), and classified according to the cutoff points for women proposed by Kyle et al. (19). Of the 171 women who agreed to participated in the survey, 158 (92.4 %) underwent a bioelectrical impedance test.

We conducted a descriptive analysis of the data. Pearson's correlation coefficient (r) was used to estimate the correlation between FMI and conventional anthropometric variables. We considered a strong correlation for values higher than 0.70 (20). We adopted the significance level of $p < 0.05$. The analyses were conducted with the aid of the SPSS sotware, version 22.

This study followed the rules and guidelines of Good Clinical Practice according to Resolution 466/2012, and was approved by the Research Ethics Committee of the Hospital under the protocol number: 2.042.767. We have no conflicts of interest to declare.

RESULTS

A total of 158 women recently diagnosed predominantly with cervical neoplasia (56.9 %) in a non-advanced stage (I and II, 59.2 %) participated in the study. The average age of the participants was 52.2 ± 15.3 years. Most were married (53.2 %), economic class C (52.6 %) (low economic level), non-smokers (72.8 %), non-alcoholic (68.4 %), and unemployed (62.0 %) (Table I).

Regarding nutritional status, 45.9 % (n = 72) were adequate according to AMC, and well nourished (A) (86.1 %, n = 136) when assessed by the PG-SGA. As for BMI, most were overweight (71.5 %, n = 113) (Table I). The sample was composed, on average, by women with excess weight and high body fat (Table II).

The FMI showed a positive and significant correlation with BMI (r = 0.934), AC (r = 0.812), TS (r = 0.562) and AMC (r = 0.747), $p < 0.001$ (Fig. 1).

We identified that women with a very high FMI belonged to the groups with illiterate/incomplete elementary schooling (52.4 %), no work activity (73.0 %), a low economic class (C, 57.4 %), obesity (BMI) (85.7 %) and well nourished (95.2 %) (Table III).

Table I. Sociodemographic, clinical and nutritional status characterization of the participants

Characteristics	n	%
Sociodemographic		
Education		
Illiterate/Incomplete elementary school	73	46.2
Complete elementary school and incomplete middle school	31	19.6
Complete high school and incomplete higher education	40	25.3
Higher education or more	14	8.9
Total	158	100.0
Marital status		
Single	31	19.6
Married	84	53.2
Widowed	26	16.5
Divorced	17	10.8
Total	158	100.0
Work activity		
No	98	62.0
Yes	60	38.0
Total	158	100.0
*Economic class**		
A	1	0.6
B	30	19.2
C	82	52.6
D and E	43	27.6
Total	156	100.0
Smoker		
No	115	72.8
Yes	18	11.4
Former smoker	25	15.8
Total	158	100.0
Drinker		
No	108	68.4
Yes	30	19.0
Former drinker	20	12.7
Total	158	100.0
Clinical		
Tumor site†		
Cervix	87	56.9
Endometrium	39	25.5
Ovary	23	15.0
Vagina	3	2.0
Vulva	1	0.7
Total	153	100.0
Staging‡		
I	45	33.3
II	35	25.9
III	40	29.6
IV	15	11.1
Total	135	100.0
Diabetes (type 2)		
No	135	85.4
Yes	23	14.6
Total	158	100.0
Hypertension		
No	96	60.8
Yes	62	39.2
Total	158	100.0
BMI		
Underweight	6	3.8
Adequate	39	24.7
Overweight	57	36.1
Obesity	56	35.4
Total	158	100.0
AMC§		
Severe malnutrition	4	2.5
Moderate malnutrition	11	7.0
Mild malnutrition	26	16.6
Adequate	72	45.9
Overweight	25	15.9
Obesity	19	12.1
Total	157	100.0
PG-SGA		
Well nourished (A)	136	86.1
Moderate malnutrition (B)	21	13.3
Severely malnourished (C)	1	0.6
Total	158	100.0

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Table I (Cont.). Sociodemographic, clinical and nutritional status characterization of the participants

*BMI: body mass index; AMC: arm muscle circumference; PG-SGA: Patient-Generated Subjective Global Assessment. *2 missing values; †5 missing values; ‡23 missing values; §1 missing value.*

Table II. Summary measures of the participants' anthropometric variables and body composition

Variables	Mean ± standard deviation
Conventional anthropometry	
Weight (kg)	70.5 ± 17.2
Height (m)	1.6 ± 0.1
Body mass index (kg/m^2)	28.7 ± 6.5
Arm circumference (cm)	30.4 ± 5.2
Tricipital skinfold (mm)	24.8 ± 6.7
Arm muscle circumference (cm)	22.5 ± 4.1
Bioelectrical impedance	
Muscle mass (%)	33.5 ± 5.3
Muscle mass (kg)	22.9 ± 4.3
Fat mass (%)	38.1 ± 9.9
Fat mass (kg)	27.7 ± 12.0

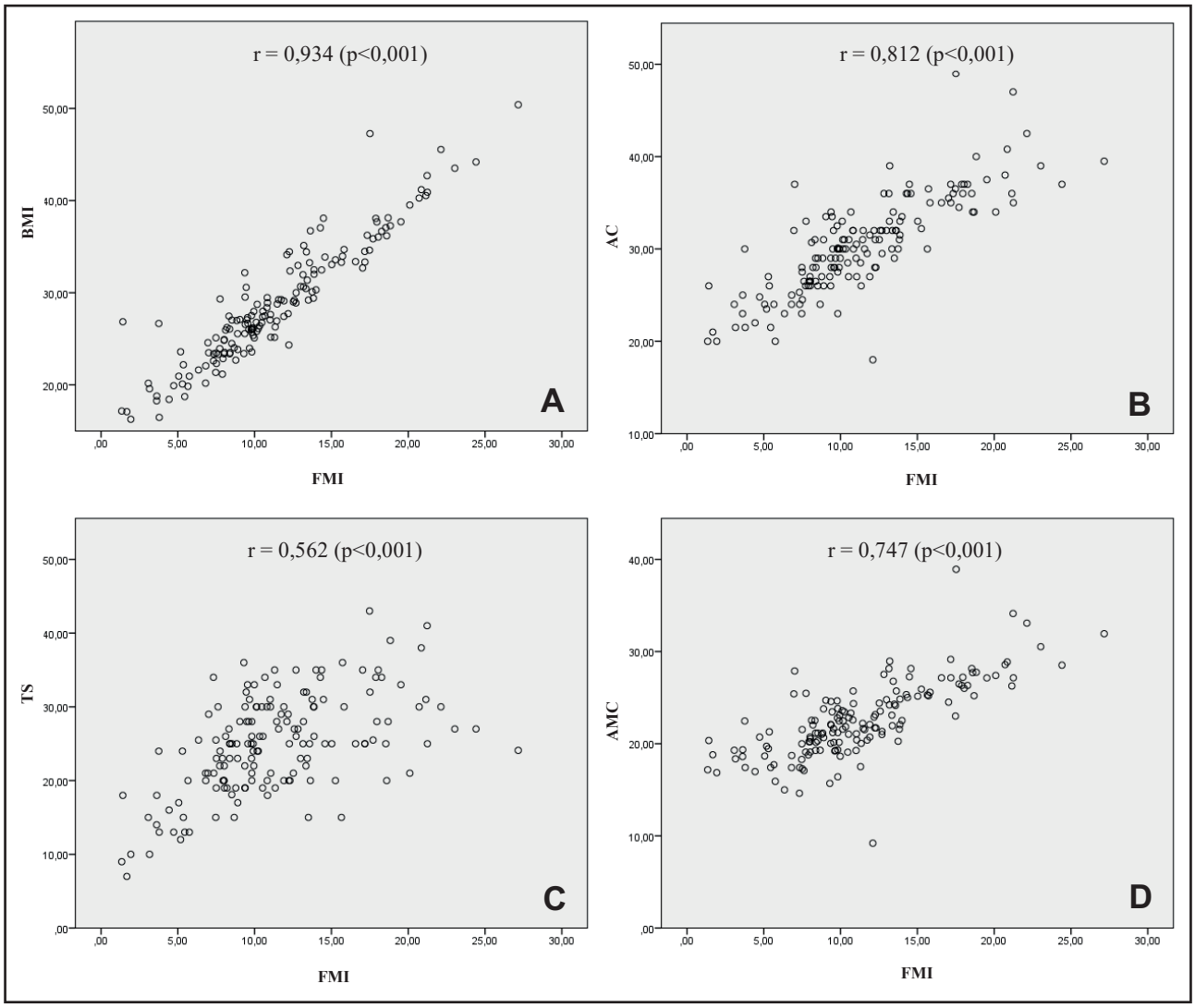

Figure 1.

Correlation between fat mass index (FMI) and conventional anthropometric variables (FMI: fat mass index; BMI: body mass index; AC: arm circumference; TS: triceps skinfold; AMC: arm muscle circumference).

Table III. Classification of the Fat Mass Index (FMI) of the participants considering the sociodemographic, clinical, and nutritional status characteristics

	Fat Mass Index (FMI), n (%) (95 % CI)			
Characteristics	**Low**	**Normal**	**High**	**Very high**
Sociodemographic				
Education				
Illiterate/Incomplete elementary school	9 (90.0) (70.0-100.0)	10 (33.3) (16.7-50.0)	21 (38.2) (25.5-50.9)	33 (52.4) (41.3-63.5)
Complete elementary school and incomplete middle school	1 (10.0) (0-30.0)	5 (16.7) (6.7-30.0)	5 (9.1) (1.9-18.2)	20 (31.7) (20.6-42.9)
Complete high school and incomplete higher education	-	9 (30.0) (13.3-46.7)	21 (38.2) (25.5-50.9)	10 (15.9) (7.9-25.4)
Higher education or more	-	6 (20.0) (6.7-36.6)	8 (14.5) (5.5-23.6)	-

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Table III (Cont.). Classification of the Fat Mass Index (FMI) of the participants considering the sociodemographic, clinical, and nutritional status characteristics

	Fat Mass Index (FMI), n (%) (95 % CI)			
Characteristics	**Low**	**Normal**	**High**	**Very high**
Sociodemographic				
Marital status				
Single	2 (20.0) (0-50.0)	4 (13.3) (3.3-26.7)	16 (29.1) (18.2-41.8)	9 (14.3) (6.3-23.8)
Married	4 (40.0) (10.0-70.0)	20 (66.7) (50.0-83.3)	30 (54.5) (41.8-67.3)	30 (47.6) (34.9-60.3)
Widow	2 (20.0) (0-50.0)	3 (10.0) (0-23.3)	8 (14.5) (5.5-23.6)	13 (20.6) (11.1-31.7)
Divorced	2 (20.0) (0-50.0)	3 (10.0) (0-20.0)	1 (1.8) (0-5.5)	11 (17.5) (7.9-27.0)
Work activity				
No	5 (50.0) (20.0-80.0)	19 (63.3) (46.7-80.0)	28 (50.9) (38.2-65.5)	46 (73.0) (61.9-84.1)
Yes	5 (50.0) (20.0-80.0)	11 (36.7) (20.0-53.3)	27 (49.1) (34.5-61.8)	17 (27.0) (15.9-38.1)
*Economic class**				
A	-	-	-	1 (1.6) (0-4.9)
B	-	7 (23.3) (10.0-40.0)	15 (27.3) (14.5-38.2)	8 (13.1) (4.9-23.0)
C	3 (30.0) (0-60.0)	15 (50.0) (30.0-66.7)	29 (52.7) (40.0-67.3)	35 (57.4) (44.3-70.5)
D and E	7 (70.0) (40.0-100.0)	8 (26.7) (10.0-43.3)	11 (20.0) (9.1-30.9)	17 (27.9) (16.4-39.3)
Smoker				
No	8 (80.0) (50.0-100.0)	24 (80.0) (63.3-93.3)	40 (72.7) (60.0-83.6)	43 (68.3) (55.6-79.4)
Yes	1 (10.0) (0-30.0)	2 (6.7) (0-16.7)	7 (12.7) (5.5-21.8)	8 (12.7) (4.8-22.2)
Former smoker	1 (10.0) (0-30.0)	4 (13.3) (3.3-26.7)	8 (14.5) (5.5-25.4)	12 (19.0) (9.5-28.6)
Drinker				
No	9 (90.0) (70.0-100.0)	21 (70.0) (53.3-86.7)	36 (65.5) (52.7-76.4)	42 (66.7) (55.6-77.8)
Yes	-	8 (26.7) (10.0-43.3)	11 (20.0) (10.9-30.9)	11 (17.5) (9.5-28.6)
Former drinker	1 (10.0) (0-30.0)	1 (3.3) (0-10.0)	8 (14.5) (5.5-23.6)	10 (15.9) (7.9-25.4)
Clinical				
Tumor site†				
Cervix	5 (55.6) (22.2-88.9)	20 (69.0) (51.7-86.2)	34 (63.0) (50.0-75.9)	28 (45.9) (32.8-59.0)
Endometrium	2 (22.2) (0-55.6)	3 (10.3) (0-20.7)	7 (13.0) (5.6-22.2)	27 (44.3) (31.1-57.4)
Ovary	1 (11.1) (0-33.3)	5 (17.2) (3.4-31.0)	12 (22.2) (11.1-33.3)	5 (8.2) (1.6-16.4)
Vagina	1 (11.1) (0-33.3)	-	1 (1.9) (0-5.6)	1 (1.6) (0-4.9)
Vulva	-	1 (3.4) (0-10.3)	-	-
Staging‡				
I	2 (20.0) (0-50.0)	5 (20.0) (4.1-36.0)	16 (32.7) (20.4-46.9)	22 (43.1) (29.4-56.9)
II	2 (20.0) (0-50.0)	8 (32.0) (16.0-52.0)	14 (28.6) (16.3-40.8)	11 (21.6) (9.8-33.3)
III	2 (20.0) (0-50.0)	8 (32.0) (16.0-48.0)	16 (32.7) (20.4-46.9)	14 (27.5) (15.7-41.1)
IV	4 (40.0) (10.0-70.0	4 (16.0) (4.0-32.0)	3 (6.1) (0-14.3)	4 (7.8) (2.0-15.7)
Diabetes (type 2)				
No	10 (100.0)	28 (93.3) (83.3-100.0)	51 (92.7) (83.6-98.2)	46 (73.0) (61.9-82.5)
Yes	-	2 (6.7) (0-16.7)	4 (7.3) (1.8-16.4)	17 (27.0) (17.5-38.1)
Hypertension				
No	7 (70.0) (40.0-90.0)	20 (66.7) (50.0-83.3)	42 (76.4) (63.6-87.3)	27 (42.9) (31.7-55.6)
Yes	3 (30.0) (10.0-60.0)	10 (33.3) (16.7-50.0)	13 (23.6) (12.7-36.4)	36 (57.1) (44.4-68.3)
BMI				
Underweight	6 (60.0) (30.0-90.0)	-	-	-
Adequate	2 (20.0) (0-50.0)	27 (90.0) (80.0-100.0)	9 (16.4) (7.3-27.3)	1 (1.6) (0-4.8)
Overweight	2 (20.0) (0-50.0)	3 (10.0) (0-20.0)	44 (80.0) (67.3-90.9)	8 (12.7) (4.8-20.6)
Obesity	-	-	2 (3.6) (0-9.1)	54 (85.7) (76.2-93.7)

(Continues on next page)

Table III (Cont.). Classification of the Fat Mass Index (FMI) of the participants considering the sociodemographic, clinical, and nutritional status characteristics

	Fat Mass Index (FMI), n (%) (95 % CI)			
Characteristics	**Low**	**Normal**	**High**	**Very high**
Clinical				
AMC[§]				
Severe malnutrition	-	2 (6.7) (0-16.7)	1 (1.8) (0-5.5)	1 (1.6) (0-4.8)
Moderate malnutrition	5 (50.0) (20.0-80.0)	5 (16.7) (3.3-30.0)	1 (1.8) (0-7.3)	-
Mild malnutrition	3 (30.0) (0-60.0)	12 (40.0) (23.3-56.7)	10 (18.2) (9.1-29.1)	1 (1.6) (0-4.8)
Adequate	2 (20.0) (0-50.0)	9 (30.0) (13.3-46.7)	39 (70.9) (58.2-81.8)	22 (35.5) (24.2-48.3)
Overweight	-	1 (3.3) (0-10.0)	3 (5.5) (0-12.7)	21 (33.9) (22.6-45.2)
Obesity	-	1 (3.3) (0-10.0)	1 (1.8) (0-5.5)	17 (27.4) (17.7-38.7)
PG-SGA				
Well nourished (A)	3 (30.0) (10.0-60.0)	25 (83.3) (70.0-96.7)	48 (87.3) (78.2-94.5)	60 (95.2) (88.9-100.0)
Moderate malnutrition (B)	6 (60.0) (30.0-90.0)	5 (16.7) (3.3-30.0)	7 (12.7) (5.5-21.8)	3 (4.8) (0-11.1)
Severely malnourished (C)	1 (10.0) (0-30.0)	-	-	-

*BMI: body mass index; AMC: arm muscle circumference; PG-SGA: Patient-Generated Subjective Global Assessment. *2 missing values; †5 missing values; ‡23 missing values; §1 missing value.*

DISCUSSION

This study investigated the nutritional status and body composition of women diagnosed with gynecological tumors without previous antineoplastic treatment, and evaluated their FMI as a complementary indicator for addressing the nutrition status.

In this study, cervical cancer was predominant, corroborating both national and international statistics pointing at it as the most frequent gynecological tumor in the female population (1).

The women in this study were overweight and had high body fat at diagnosis. Although excess body fat and lifelong weight gain can influence the development of some gynecological cancers through inflammatory, metabolic, and hormonal mechanisms (21), its influence on cervical cancer risk has been poorly understood.

Excess body fat can negatively influence treatment and patient quality of life. Patients with morbid obesity and endometrial cancer or ovarian cancer submitted to surgery had a higher number of surgical complications than patients with a BMI < 40.0 kg/m^2 (22,23). Similarly, a study on the impact of obesity on complications and survival in 2,500 patients with endometrial cancer found that obese women had a higher risk of all-cause mortality (24).

In addition to the impact on performing an adequate and safe surgery, excess body fat can compromise a safe and effective administration of cytotoxic agents. There are limited data on the evaluation of the relationship between obesity and the pharmacokinetics of chemotherapy, specifically regarding volume, in obese patients. The issue of reassessing chemotherapy doses based on body composition in this population should be discussed (25).

The FMI showed a strong and positive correlation with conventional anthropometric measurements such as BMI, AC, and AMC, and a moderate and positive correlation with TS; thus, it can be considered a good indicator for assessing body composition at diagnosis, besides using the lean body mass index. The isolated use of BMI does not reflect body composition in a cancer patient and, therefore, should always be used with other body composition measures (26).

In the present study, most women with a very high FMI were obese (BMI > 30 kg/m^2) and had a low economic and educational level. Similarly, in a study that estimated the frequency and sociodemographic distribution of risk and protective factors for chronic diseases in Brazil (27), the frequency of overweight and obesity among women decreased notably with increased education.

This study has some limitations. The study was developed in only one oncology hospital, and its cross-sectional design limits the evaluation of causal relationships. We did not evaluate weight loss or weight gain before the assessment, which could influence body composition. In addition, no data were collected that could validate the FMI measurement as a predictor of complications and other clinical outcomes since that was not the objective of the present study. It is important to point out that it would be interesting to evaluate whether the patients were menopausal or premenopausal, since fat mass is associated with an increased risk of uterine corpus cancer in postmenopausal women (28). We believe that our results may arouse interest in conducting new studies with prospective follow-up, given the importance of nutritional intervention at diagnosis and the implications of overweight in cancer treatment.

CONCLUSION

Women recently diagnosed with malignant gynecological tumors without previous antineoplastic treatments were admitted with overweight and increased FMI.

Besides, FMI showed a good correlation with conventional measures of BMI, AC, and AMC. Thus, FMI may be a good indicator of body composition and a potentially useful tool to complement the assessment of nutritional status. In clinical practice, FMI can help multidisciplinary teams to perform early clinical and nutritional interventions.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Is there a relationship between oral hygiene and nutritional status in peritoneal dialysis patients?

¿Existe alguna relación entre la higiene bucal y el estado nutricional de los pacientes en diálisis peritoneal?

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Abstract

Brackground: in the early stages of kidney disease, oral manifestations (gingivitis and periodontitis) may cause premature tooth loss and limit food intake. There is scarce evidence of the relationship of oral hygiene and nutritional status in patients on Peritoneal Dialysis (PD).

Objective: we aimed to assess the relationship of oral hygiene with nutritional, clinical, and physical performance parameters in PD patients.

Methods: this cross-sectional study included outpatients aged 34-69 years. Oral health questionnaire, nutritional, functional, and clinical assessment tools such as Malnutrition Inflammation Score (MIS), Subjective Global Assessment (SGA), handgrip strength, and Gastrointestinal Symptoms Questionnaire (GSQ) were applied. Patients were divided according to debris, calculus, and Simplified Oral Hygiene Index (OHI-S) in two groups: "clean-slightly dirty" and "dirty-very dirty".

Results: in total, 41 patients were included, those in the "dirty-very dirty" group had a worse nutritional status with higher scores on the MIS tool and worse nutritional diagnosis with SGA as compared to the "clean-slightly dirty" group. The handgrip strength was higher in patients in the best category of oral hygiene, and those with the worst hygiene presented greater severity of gastrointestinal symptoms. The risks of malnutrition in the three indices of oral hygiene with the worst category were statistically significant.

Conclusion: poor oral hygiene was associated with poorer nutritional status, lower handgrip, and worse GSQ. Poor oral hygiene might be related to persistent inflammation status and catabolism that favored protein-energy wasting.

Keywords:

Oral hygiene. Peritoneal dialysis. Protein-energy wasting. Periodontitis. Probiotics.

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Consent to participate: all participants were provided with a consent form to participate.

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Resumen

Introducción: en las primeras etapas de la enfermedad renal, las manifestaciones orales (gingivitis y periodontitis) pueden causar la pérdida de dientes prematura y limitar la ingestión de los alimentos. Existe poca evidencia de la relación entre la higiene bucal y el estado de nutrición en los pacientes con Diálisis Peritoneal (PD).

Objetivos: evaluar la relación de la higiene bucal con los parámetros nutricionales, clínicos y de funcionalidad física en pacientes con DP.

Métodos: este es un estudio transversal que incluyó a pacientes ambulatorios de 34 a 69 años. Se aplicó un cuestionario de salud bucal, herramientas de evaluación nutricional, pruebas de funcionalidad y un cuestionario de síntomas gastrointestinales, con las herramientas MIS *(Malnutrition Inflammation Score),* SGA *(Subjective Global Assessment);* fuerza de prensión de mano y el cuestionario de síntomas gastrointestinales GSQ *(Gastrointestinal Score Questionnaire).* Los pacientes fueron agrupados de acuerdo con los índices de placa, cálculo y OHI-S *(Simplified Oral Hygiene Index)* en dos grupos: "limpio-ligeramente sucio" y "sucio-muy sucio".

Resultados: se incluyeron 41 pacientes en total, aquellos en el grupo "sucio-muy sucio" presentaron un peor estado nutricional con mayores puntajes de la herramienta MIS y peor diagnóstico nutricional con la SGA comparado con el grupo "limpio-ligeramente sucio". La fuerza de prensión de mano fue mayor en los pacientes con la mejor categoría de higiene bucal, y aquellos con peor higiene presentaron mayor gravedad de síntomas gastrointestinales. El riesgo de desnutrición en los tres índices de higiene bucal con la peor categoría fueron estadísticamente significativos.

Conclusiones: la mala higiene bucal se asoció con un peor estado nutricional, menor fuerza de prensión de la mano y peor GSQ. Una higiene bucal deficiente podría estar relacionada con un estado de inflamación y catabolismo persistentes favoreciendo el desgaste proteínico energético en pacientes en diálisis peritoneal.

Palabras clave:

Higiene oral. Diálisis peritoneal. Desgaste energético proteico. Periodontitis. Probióticos.

INTRODUCTION

The deterioration of oral health in patients with chronic kidney disease (CKD) begins from early stages, and is related to the increase in serum urea and creatinine, mineral-bone imbalance, decreased salivary flow, and excessive growth of pathogenic bacteria in the mouth (1).

Several changes in the oral cavity occur in most patients with CKD, such as changes in salivary composition, modifications in the oral mucosa, and development of gingivitis and periodontitis, the latter being responsible for premature loss of teeth. These oral disorders persist even when patients receive renal replacement therapy (RRT), such as Peritoneal Dialysis (PD) (1-3).

Observational studies have described that the quality of oral hygiene decreases as CKD progresses, although patients at any stage of the disease brush their teeth once or several times a day; however, the implementation of other oral hygiene techniques is infrequent (4).

Patients on dialysis have limited access to subsequent dental services; around 10 %-20 % of these patients have attended dental clinics at least once a year (5,6), and those, who have other pathologies had more frequently visited various medical specialties due to their chronicity and complications. In a cohort study, patients with CKD and diabetes *mellitus* visited an ophthalmologist more frequently (n = 696, 58.8 %) than a dentist (n = 139, 11.8 %) (7). Conversely, the information available regarding attendance at a nutrition service is scarce (8); however, reports have described that the time that a patient spends in an individualized nutritional consultation correlates with improvement in serum glucose levels and blood pressure (9).

The evidence that associates oral health with nutritional status in patients with CKD is limited. Some authors described malnutrition as a severe problem and, it could be worse by the use of prostheses that do not fit or may cause injuries, local infection, cavities, or lack of teeth (6), limiting chewing capacity, and reducing energy and protein intake as well as nutritional biomarkers such as albumin, total iron-binding capacity, or serum transferrin (10).

CKD patients with fewer teeth eat less energy and protein compared to those with more teeth (10). Previous studies showed that those with moderate-severe periodontitis had a higher percentage of malnutrition (with serum albumin < 3.5 g/dL) and inflammation (11). Other events that could interfere with nutritional status are the presence of gastrointestinal symptoms and the evaluation of physical function by handgrip strength, which has been scarcely explored in patients on PD with oral cavity alterations.

Different links between the manifestations of poor oral health and the systemic alterations of CKD were established, such as protein-energy wasting (PEW), infection, and atherosclerotic complications (2). However, the assessment of oral hygiene habits and their possible relationship with the nutritional status in patients who had undergone renal replacement therapy had not been described in our population. This study aimed to assess the relationship of oral hygiene with nutritional, clinical, and physical function (handgrip strength) parameters in patients on PD.

METHODS

This cross-sectional study was part of a clinical trial related to the use of adjuvant therapies in the treatment of periodontitis in patients with CKD performed in our institution, from September 2019 to March 2020. It included a total of 41 outpatients on PD for more than 3 months, aged 34-69 years, and who signed the informed consent form. Kidney transplant patients with no natural teeth present and CKD secondary to autoimmune processes were excluded. The study was performed under the ethical principles of the good clinical practice guidelines and was registered and approved by our Institutional Research and Ethics Committee.

DEMOGRAPHIC DATA

Demographic data such as age, sex, education, the primary cause of CKD, etiology, comorbidities, time of diagnosis of CKD, and dialysis vintage were collected from the patients' clinical records and corroborated with the patient by a member of the research staff.

ORAL HYGIENE INDICES

Oral hygiene was assessed by a dentist who used the scoring system proposed by Greene-Vermillion (12), which consists of three components: the debris, the calculus, and the Simplified Oral Hygiene Index (OHI-S); it is based on numerical determinations according to the dental fraction with debris and/or calculus found in the previously selected dental surfaces, to later estimate the OHI-S. The preselected teeth were examined, considering the scores described in figure 1.

The OHI-S quantitatively evaluates the oral hygiene of a group of subjects, and it is composed of the combined average of the debris and calculus scores (12).

When the data were collected, the debris and calculus indices were calculated by adding the scores and dividing them between the analyzed dental surfaces, which could have a range of 0-3 points. For the estimation of the OHI-S, the debris and calculus indices were added and averaged, obtaining a range of 0-6 points, considering that the lower the score, the better the dental hygiene (12).

The following scores were considered for debris and calculus indices: 0-1 point, "clean-slightly dirty", and 2-3 points, "dirty-very dirty" (Fig. 1); and for OHI-S: 0-2 points, "clean-slightly dirty" and 3-6 points, "dirty-very dirty".

ORAL HYGIENE QUESTIONNAIRE

Oral hygiene habits were evaluated with a seven-item questionnaire that has been previously applied in various populations with CKD (13,14). The frequency of brushing, flossing, and mouthwashing, and the last visit to a dental service were some of the questions included in this questionnaire.

NUTRITIONAL ASSESSMENT

Different tools and nutritional indices were used, such as the "Malnutrition Inflammation Score" (MIS) (15), which are validated in our population (16) and subjeccts were classified after the sum of scores: a normal nutritional status (< 3 points), mild malnutrition (3-5 points), moderate malnutrition (6-8 points), and severe malnutrition (> 8 points). For this research, we considered the total MIS score (0-30 points), and we established two categories for the nutritional diagnoses: "normal-mild" and "moderate-severe." The Subjective Global Assessment (SGA) (17), which involves a clinical history and a physical examination, states a classification of: well-nourished "A", mild-moderate malnutrition "B", and severe malnutrition "C". For the description of the results, we categorized the data as "normal-mild malnutrition" and "moderate-severe malnutrition." Finally, we use the Bilbrey nutritional composite index (18) that evaluates the nutritional status in dialysis patients and include anthropometric and biochemical parameters, these parameters were stratified and scored with 3, 4, 5, and 6 points according to the normal, slight decrease, moderate decrease, and severe decrease values respectively; then, the score was added and was established as normal nutritional status (< 25 points), mild malnutrition (26-28 points), moderate malnutrition (29-31 points), and severe malnutrition (> 32 points). The total score was considered and sustained the classifications described above.

The anthropometric measurements of weight and height were performed with a scale using a stadiometer SECA® Model 700 (Hamburg, Germany), and then the body mass index (BMI) was calculated. Skinfolds were measured with a Lange® skinfold caliper (California, USA), elbow breadth with an anthropometer, and body circumferences with a fiberglass measuring tape to

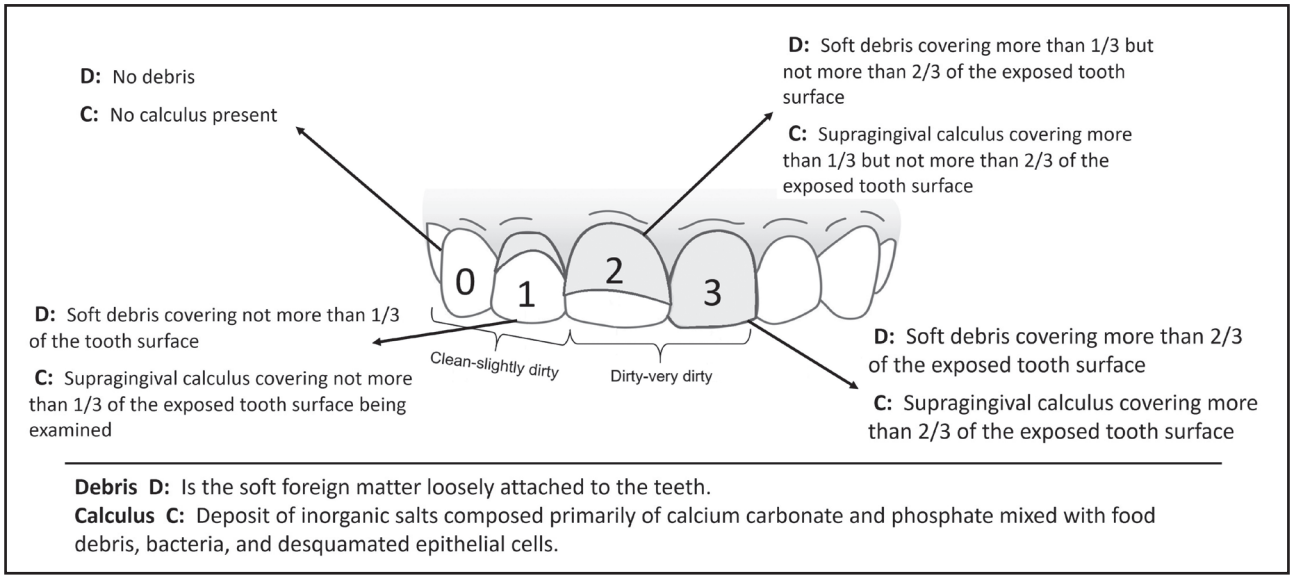

Figure 1.

Definition and scores for debris and calculus indices.

estimate the percentage of fat mass and the Mid-Arm Muscle Circumference (MAMC). All measures were taken by a trained and standardized nutritionist (19,20). The bioelectrical impedance analysis (BIA) measurements were performed with Bodystat® equipment (QuadScan 4000 model, Isle of Man, UK).

Physical function was measured by the handgrip strength while the patient was standing and holding the dynamometer with the dominant hand, they make a single strong pressure; this measurement was performed in triplicate, the average of the measurements was reported, a Takei® dynamometer (model Smedley III T-18A, Japan) was used.

To assess the severity of gastrointestinal symptoms we used the short version of the Gastrointestinal Symptoms Questionnaire (GSQ) (21), and considered the total score of the original questionnaire: mild (9-10 points), moderate (11-13 points), and severe gastrointestinal symptoms (> 14 points).

LABORATORY TESTS

The laboratory studies of the electronic file were recorded in a period not exceeding one month before the date of the patient's visit: urea, creatinine, potassium, phosphorus, albumin, sodium, Parathyroid Hormone (PTH), and transferrin.

STATISTICAL ANALYSIS

The distribution analysis was performed through skewness and kurtosis; the description of quantitative data was expressed with means and standard deviations, or medians with interquartile ranges. Categorical variables were described as frequencies and percentages.

For the description and the analysis of the population, we established three groups according to the oral hygiene indices, the comparison between groups was performed with the Student's t-test or the Mann-Whitney U-test according to the data distribution, while the comparison of the categorical variables was performed with the Chi-squared test or Fisher's exact test. Spearman correlations and logistic regression models were carried out, reporting odds ratios (OR) to evaluate the association of oral hygiene with nutritional status. A $p < 0.05$ was considered statistically significant. The data were analyzed using the software STATA 14.1.

RESULTS

A total of 41 patients were included, and the population was grouped according to oral hygiene indices. Most (78 % [debris], 83 % [calculus], and 81 % [OHI-S]) presented adequate oral hygiene, and were thus included in the classification as "clean-slightly dirty." Table I describes the characteristics of the population according to their oral indices.

ORAL HYGIENE

It was observed that the number of natural teeth present in patients was constant in all the groups; considering the items of the oral hygiene questionnaire, the patients in any category of "clean-slightly dirty" attended a dental service more frequently in a < 6-month period, brushed their teeth more frequently, and had undergone a dental scaling. In all these categories, the patients reported a poor use of dental floss and mouthwash ($p \geq 0.05$) (Table I).

NUTRITIONAL STATUS, LABORATORY PARAMETERS, AND ORAL HYGIENE

After the evaluation of the anthropometric parameters, no significant differences were observed; however, the patients in all the groups were slightly overweight and had an increase in the reserve of adipose tissue according to the BMI, the percentage of body fat mass, and triceps skinfold (Table II).

Regarding the results of BIA, the groups with better oral hygiene ("clean-slightly dirty") presented a higher resistance/height (R/H), reactance/height (Xc/H), and phase angle; these results could translate into a greater fat reserve and even greater cellularity; however, compared to the groups with poorer oral hygiene, these differences were not found to be statistically significant.

The patients with better oral hygiene ("clean-slightly dirty") presented better scores with the different nutritional assessment tools compared with the "dirty-very dirty" category; when the results of the MIS were analyzed, the former obtained lower scores indicating a better nutritional status ($p < 0.05$). More than 75 % of the patients with poorer oral hygiene obtained an SGA classification of "B-C" (moderate-severe malnutrition) reflecting a worse nutritional status. When the score of the Bilbrey nutritional composite index was analyzed, no significant differences were observed between the oral hygiene groups (Table II).

When the laboratory studies were analyzed, a tendency was observed to have a better nutritional status in the "clean-slightly dirty" debris group evaluated with serum albumin when compared with the worst oral hygiene group ($p = 0.071$).

A trend was observed, having a greater strength on the group of debris on the "clean-slightly dirty" category compared with the category with worse oral hygiene: 24.6 ± 7.4 vs. 17.7 ± 4.5 and $p = 0.054$, respectively; similar findings were observed in the rest of the oral hygiene indices. Finally, there was a tendency to present greater GSQ in those with poorer oral hygiene in the OHI-S group ($p = 0.078$; Table II).

To identify a possible association between poorer oral hygiene and nutritional status, a Spearman correlation was performed; debris and OHI-S indices reported a negative correlation in weight, handgrip, phase angle, and albumin ($p < 0.05$), indicating that with higher scores of these oral indices, the nutritional markers decreased. Also, positive correlations were reported in the three oral indices with the tools of MIS and Bilbrey, indicating that higher was the oral indices, the worse the nutritional status (Table III).

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Table I. Basal characteristics of patients

Variables	Debris		Calculus		OHI-S		p-value		
	Clean-slightly dirty 32 (78.1%)	Dirty-very dirty 9 (21.9%)	Clean-slightly dirty 34 (82.9%)	Dirty-very dirty 7 (17.1%)	Clean-slightly dirty 33 (80.5%)	Dirty-very dirty 8 (19.5 %)	Debris	Calculus	OHI-S
Age (years)	53 (42-59)	60 (39-60)	54 (43-60)	55 (37-60)	54 (43-59)	57 (38-60)	0.613*	0.741*	0.973*
Sex (n, %)									
Male	19 (59.3)	7 (77.8)	21 (61.8)	5 (71.4)	20 (60.6)	6 (75)	0.445†	1.000†	0.687†
Female	13 (40.7)	2 (22.2)	13 (38.2)	2 (28.6)	13 (39.4)	2 (25)			
Educational level (n, %)									
Elementary-Junior	15 (46.9)	3 (33.3)	15 (44.1)	3 (42.9)	15 (45.5)	3 (37.5)	0.706†	1.000†	1.000†
High school	17 (53.1)	6 (66.7)	19 (55.9)	4 (57.1)	18 (54.5)	5 (62.5)			
University and higher									
Etiology (n, %)									
DM	14 (43.8)	5 (55.6)	15 (44.1)	4 (57.1)	14 (42.4)	5 (62.5)	0.744†	0.872†	0.760†
Hypertension	5 (15.6)	--	5 (14.7)	--	5 (15.2)	--			
Unknown	5 (15.6)	2 (22.2)	6 (17.7)	1 (14.3)	6 (18.2)	1 (12.5)			
Other	8 (25)	2 (22.2)	8 (23.5)	2 (28.6)	8 (24.2)	2 (25.0)			
Time with CKD diagnosis (months)	48 (30-90)	48 (24-60)	54 (24-84)	36 (24-60)	48 (24-84)	42 (30-60)	0.545*	0.462*	0.594*
Dialysis vintage (months)	24 (12-36)	24 (24-60)	24 (12-36)	24 (24-60)	24 (12-36)	24 (18-48)	0.446*	0.476*	0.799*
Total of natural teeth (n, %)	25 (24-28)	26 (16-29)	25 (23-28)	27 (16-29)	25 (23-28)	26.5 (18-29)	0.962*	0.916*	0.855*
Frequency of dental visits (n, %)									
< 6 months	20 (62.5)	5 (55.6)	20 (58.8)	5 (71.4)	19 (57.6)	6 (75.0)	0.717*	0.685*	0.448*
> 6 months	12 (37.5)	4 (44.4)	14 (41.2)	2 (28.6)	14 (42.4)	2 (25.0)			
Brushing frequency (n, %)									
Less than once a day	5 (15.6)	1 (11.1)	4 (11.8)	2 (28.6)	29 (87.9)	6 (75.0)	1.000†	0.268†	0.578†
More than two times a day	27 (84.4)	8 (88.9)	30 (88.2)	5 (71.4)	4 (12.1)	2 (25.0)			
Uses mouthwash (n, %)									
Yes	7 (21.9)	1 (11.1)	7 (20.6)	1 (14.3)	7 (21.2)	1 (12.5)	0.659†	1.000†	1.000†
No	25 (78.1)	8 (88.9)	27 (79.4)	8 (85.7)	26 (78.8)	7 (87.5)			
Uses dental floss (n, %)									
Yes	8 (25)	3 (33.3)	7 (20.6)	4 (57.1)	7 (21.2)	4 (50.0)	0.178†	0.680†	0.069†
No	24 (75)	6 (66.7)	27 (79.4)	3 (42.9)	26 (78.8)	4 (50.0)			
Previous dental scaling (n, %)									
Yes	24 (75.0)	5 (55.6)	26 (76.5)	3 (42.9)	25 (75.8)	4 (50.0)	0.202†	0.408†	0.165†
No	8 (25.0)	4 (44.4)	8 (23.5)	4 (57.1)	8 (24.2)	4 (50.0)			

**Mann-Whitney U-test; †Fisher's exact test. DM: diabetes* mellitus.

Table II. Nutritional status and physical function by oral hygiene indices

Variable	Debris		Calculus		OHI-S		p-value		
	Clean-slightly dirty 32 (78.1 %)	Dirty-very dirty 9 (21.9 %)	Clean-slightly dirty 34 (82.9 %)	Dirty-very dirty 7 (17.1 %)	Clean-slightly dirty 33 (80.5 %)	Dirty-very dirty 8 (19.5 %)	Debris	Calculus	OHI-S
Weight (kg)	71.2 ± 12.6	70.6 ± 11.6	70.2 ± 12.3	75.2 ± 12.2	70.5 ± 12.4	73.4 ± 12.4	0.898†	0.333†	0.552†
BMI (kg/m^2)	26.3 (24.4-29.3)	25.5(24.8-27.0)	26.2 (24.1-28.8)	27.0 (25.5-27.7)	26.3 (24.1-28.8)	26.8 (25.4-27.6)	0.403*	0.405*	0.553*
Fat mass (%)	31.4 ± 6.7	29.8 ± 2.9	31.2 ± 6.6	30.9 ± 4.0	31.2 ± 6.7	30.6 ± 3.7	0.530†	0.928†	0.831†
MAC (cm)	25.2 ± 3.7	25.0 ± 4.2	25.6 ± 4.0	24.3 ± 2.6	25.1 ± 3.8	25.5 ± 3.9	0.891†	0.553†	0.787†
MAMC (cm)	30.4 ± 4.2	29.2 ± 3.7	30.5 ± 4.3	28.5 ± 2.1	30.2 ± 4.2	29.7 ± 3.5	0.495†	0.311†	0.759†
TSF (mm)	16.4 ± 7.4	13.3 ± 3.8	16.2 ± 7.3	13.5 ± 4.1	16.4 ± 7.4	13.3 ± 3.8	0.295†	0.385†	0.295†
R/H (Ω/m)	281.2 ± 51.6	268.6 ± 41.4	284.7 ± 50.2	250.6 ± 35.3	284.4 ± 51.4	257.3 ± 35.7	0.590†	0.164†	0.240†
Xc/H (Ω/m)	29.5 (19.5-34.2)	19.0 (15.9-19.8)	29.4 (17.4-34.2)	19.8 (19.0-20.8)	29.5 (18.6-34.2)	19.4 (19.0-20.8)	0.199*	0.851*	0.381*
PA°	5.7 (4.8-6.8)	3.9 (2.9-5.3)	5.7 (4.4-6.8)	4.8 (4.1-5.3)	5.7 (4.4-6.8)	4.5 (3.7-5.3)	0.129*	0.662*	0.267*
MIS score	3.3 ± 1.9	6.1 ± 1.9	3.5 ± 1.9	5.7 ± 2.6	3.4 ± 1.9	5.7 ± 2.4	*0.003*†	*0.014*†	*0.006*†
MIS classification, (n, %)									
Normal-mild	29 (90.6)	3 (33.3)	29 (85.3)	3 (42.9)	29 (87.9)	3 (37.5)	*0.001*‡	*0.031*‡	*0.007*‡
Moderate-severe	3 (9.4)	6 (66.8)	5 (14.7)	4 (57.1)	4 (12.1)	5 (62.5)			
SGA classification, (n, %)									
Normal-mild malnutrition	24 (75.0)	2 (22.2)	24 (72.7)	2 (25.0)	24 (72.7)	2 (25.0)	*0.006*‡	*0.035*‡	*0.035*‡
Moderate-severe malnutrition	8 (25.0)	7 (77.8)	9 (27.3)	6 (75.0)	9 (27.3)	6 (75.0)			
Bilbrey nutritional composite index score	27 (26-28)	27 (27-32)	27 (26-28)	27 (27-31)	27 (26-28)	27 (27-32)	0.181*	0.458*	0.181*
Bilbrey nutritional composite index, (n, %)									
Normal	5 (17.2)	---	5 (16.7)	---	5 (17.2)	--	0.559‡	0.564‡	0.559‡
Any degree of malnutrition	24 (82.8)	7 (100)	25 (83.3)	6 (100)	24 (82.8)	7 (100)			
Urea (mg/dL)	133.2 ± 39.4	139.2 ± 43.1	132.2 ± 38.7	145.9 ± 45.8	132.1 ± 39.3	144.4 ± 42.6	0.693†	0.410†	0.439†
Creatinine (mg/dL)	12.8 ± 4.4	13.2 ± 4.5	12.5 ± 4.4	14.7 ± 4.3	12.6 ± 4.4	14.2 ± 4.3	0.808†	0.225†	0.366†
Albumin (g/dL)	3.7 ± 0.4	3.4 ± 0.4	3.6 ± 0.4	3.4 ± 0.5	3.6 ± 0.4	3.4 ± 0.4	0.071†	0.257†	0.176†
Transferrin (mg/dL)	226.2 ± 39.1	208.7 ± 42.2	220.2 ± 41.4	236.3 ± 28.8	221.8 ± 41.0	226.5 ± 36.8	0.272†	0.369†	0.781†
Sodium (mmol/L)	139 (137-141.5)	139 (139-140)	139.5 (138-141)	139 (137-144)	139 (138-141)	139 (138-142)	0.899*	0.875*	0.765*
PTH (pg/mL)	490.9 (267.4-620.2)	316.8 (100.2-415.1)	471.0 (222.6-609.5)	364.2 (89.2-415.1)	479.3 (239.6- 609.5)	342.8 (93.8-415.1)	0.054*	0.145*	0.093*
Phosphorous (mg/dL)	5.9 (4.8-6.9)	6.2 (4.1-7.9)	5.7 (4.7-6.9)	6.5 (4.1-9.1)	5.7 (4.7-6.8)	6.3 (5.0-8.5)	0.899*	0.405*	0.392*
Potassium (mg/dL)	4.7 (4.5-5.2)	5.1 (4.8-5.5)	4.7 (4.5-5.1)	5.4 (3.9-6.5)	4.7 (4.5-5.1)	5.3 (4.4-6.0)	0.191*	0.290*	0.205*
Handgrip strength (kg)	24.6 ± 7.4	17.7 ± 4.5	23.9 ± 7.8	21.2 ± 4.7	24.1 ± 7.8	20.4 ± 4.4	0.054†	0.510†	0.316†
GSQ score	11.5 (9-13)	13 (10-17)	11.5 (9-13)	13 (10-17)	11 (9-13)	14 (10.5-17)	0.273*	0.178*	0.078*

**Mann-Whitney U-test. †Student's t-test; ‡Fisher's exact test. BMI: body mass index; MAC: mid-arm circumference; MAMC: mid-arm muscle circumference; TSF: tricipital skinfold; PA: phase angle; MIS: malnutrition inflammation score; SGA: subjective global assessment; PTH: parathyroid hormone; GSQ: gastrointestinal symptoms questionnaire.*

Table III. Correlation coefficient* of oral hygiene indices with nutritional and functionality parameters

	Debris	*p*-value	Calculus	*p*-value	OHI-S	*p*-value
Weight (kg)	-0.379	*0.067*	-0.045	0.832	-0.129	0.547
BMI (kg/m^2)	-0.121	0.572	0.172	0.419	0.145	0.497
MIS scores	0.476	*0.018*	0.185	0.386	0.303	0.148
Bilbrey nutritional composite index score	0.390	*0.059*	0.262	0.215	0.390	*0.059*
SGA classification	0.242	0.253	0.182	0.394	0.242	0.253
Handgrip strength (kg)	-0. 419	*0. 041*	-0. 045	0. 833	-0. 145	0. 497
PA (°)	-0.517	*0.009*	-0.264	0.212	-0.404	*0.050*
Albumin (g/dL)	-0.405	*0.049*	-0.246	0.245	-0.356	*0.087*
Transferrin (mg/dL)	-0.210	0.324	0.172	0.419	0.016	0.940
PTH (pg/mL)	-0.081	0.707	0.009	0.966	-0.097	0.652

**Spearman correlations. BMI: body mass index; MIS: malnutrition inflammation score; SGA: subjective global assessment; PA: phase angle; PTH: parathyroid hormone.*

FACTORS ASSOCIATED WITH ORAL HYGIENE IN PATIENTS ON PERITONEAL DIALYSIS

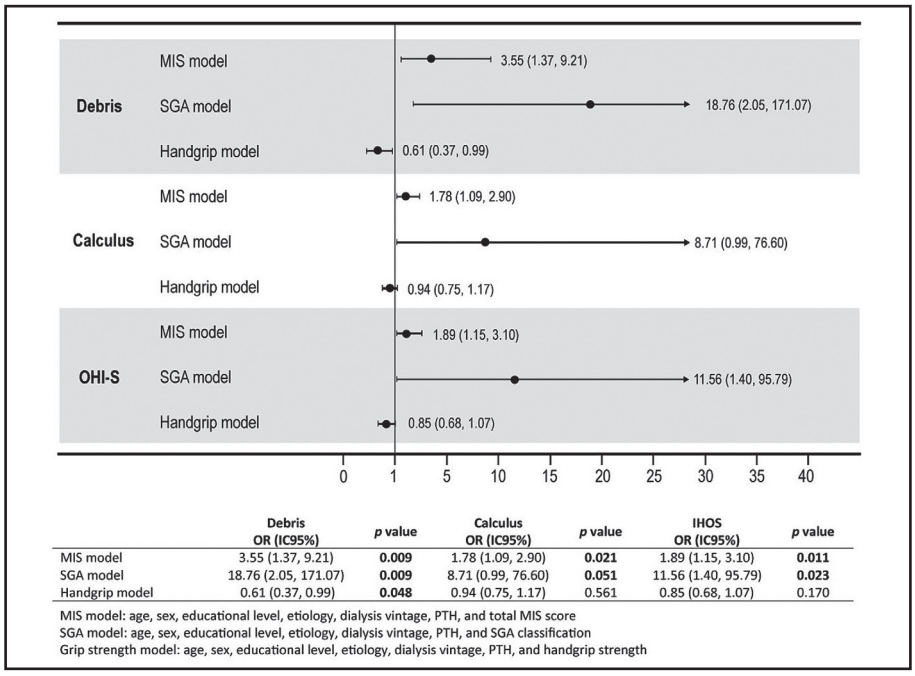
When the univariate analysis was performed, the total score of the MIS tool was associated with the three hygiene oral indices, the SGA classification with debris and calculus indices, and finally the handgrip with the debris index. Parathyroid hormone showed lower and non-significant correlations; nevertheless, due to the biological plausibility of this variable, we considered its inclusion in the regression models (Table IV).

After adjusting for different variables, three logistic regression models were performed, considering the total MIS score, SGA category, and grip strength (kg) as a dependent variable. In the three models, an association was observed between the risk of increasing the MIS score by one unit and having a category of moderate-severe malnutrition by SGA classification due to scores of ≥ 2 in all oral indices. In the handgrip strength model, those with a higher value had a protective effect owing to a worse debris index (OR = 0.61 and $p = 0.048$; Fig. 2).

Table IV. Univariate logistic regression analysis by oral hygiene indices

	Debris OR (95 % CI)	*p*-value	Calculus OR (95 % CI)	*p*-value	OHI-S OR (95 % CI)	*p*-value
Age (years)	1.01 (0.94-1.08)	0.761	0.98 (0.90-1.06)	0.660	0.99 (0.92-1.07)	0.929
Sex (male)	0.41 (0.74-2.33)	0.320	0.63 (0.10-3.83)	0.631	0.51 (0.08-2.93)	0.453
Weight (kg)	0.99 (0.93-1.05)	0.895	1.03 (0.96-1.10)	0.329	1.01 (0.95-1.08)	0.543
MIS score	2.00 (1.24-3.22)	*0.004*	1.58 (1.05-2.37)	*0.027*	1.64 (1.09-2.47)	*0.016*
Bilbrey nutritional composite index score	1.22 (0.90-1.67)	0.188	1.11 (0.81-1.54)	0.495	1.22 (0.90-1.67)	0.188
SGA classification	6.03 (1.30-27.87)	*0.021*	5.68 (1.15-28.08)	*0.033*	5.81 (1.22-27.5)	0.026
Handgrip strength (kg)	0.81 (0.65-1.01)	*0.066*	0.94 (0.80-1.11)	0.449	0.92 (0.78-1.08)	0.312
PA°	1.06 (0.82-1.36)	0.625	1.16 (0.89-1.52)	0.251	1.09 (0.85-1.40)	0.461
Albumin (g/dL)	0.17 (0.23-1.33)	0.093	0.32 (0.04-2.27)	0.259	0.27 (0.40-1.86)	0.186
PTH (pg/mL)	0.99 (0.99-1.00)	0.232	0.99 (0.99-1.00)	0.497	0.99 (0.99-1.00)	0.364

BMI: body mass index; MIS: malnutrition inflammation score; SGA: subjective global assessment; PA: phase angle; PTH: parathyroid hormone.



	Debris OR (IC95%)	*p* value	Calculus OR (IC95%)	*p* value	IHOS OR (IC95%)	*p* value
MIS model	3.55 (1.37, 9.21)	**0.009**	1.78 (1.09, 2.90)	**0.021**	1.89 (1.15, 3.10)	**0.011**
SGA model	18.76 (2.05, 171.07)	**0.009**	8.71 (0.99, 76.60)	**0.051**	11.56 (1.40, 95.79)	**0.023**
Handgrip model	0.61 (0.37, 0.99)	**0.048**	0.94 (0.75, 1.17)	0.561	0.85 (0.68, 1.07)	0.170

MIS model: age, sex, educational level, etiology, dialysis vintage, PTH, and total MIS score
SGA model: age, sex, educational level, etiology, dialysis vintage, PTH, and SGA classification
Grip strength model: age, sex, educational level, etiology, dialysis vintage, PTH, and handgrip strength

Figure 2.

Association of nutritional status and functionality with worse oral hygiene categories.

DISCUSSION

Protein energy wasting is a highly prevalent condition in dialysis patients; recently it has been reported that the global prevalence of PEW in the dialysis population was up to 50 % (22), PEW is characterized by an insufficient intake of nutrients, retention of uremic toxins, an increase in inflammatory processes, and an increase in protein catabolism, which led to decreased body fat and muscle reserves (23). Recently, the interest and search for possible associations between oral health and the different pathophysiological mechanisms of CKD were increased (11,24); this article was one of the first to assess the relationship of oral hygiene with nutritional, clinical, and handgrip strength parameters in patients on PD.

Patients with poor oral hygiene might present alterations associated with PEW and frailty (25): decreased serum albumin (11), increased inflammatory markers, and decreased energy and protein intake (10,26). We found that oral hygiene indices were associated with PEW as evaluated with different tools and with handgrip strength. All oral hygiene groups with the category "clean-slightly dirty" showed slightly high serum albumin levels, while the debris group showed a tendency between their groups (3.7 ± 0.4 vs. 3.4 ± 0.4, $p = 0.071$); while there is no data related to dietary intake in our study, it was observed that patients with lesser oral hygiene had a poorer nutritional status with higher scores from the MIS tool (debris: 6.1 ± 1.9, calculus: 5.7 ± 2.6, and OHI-S: 5.7 ± 2.4; $p < 0.05$), and moderate-severe malnutrition with the SGA classification (debris: 77.8 %, calculus: 75 %, and OHI-S: 75 %; $p < 0.05$). Those with the worst nutritional status, regardless of sex, had a decrease in handgrip strength in the category "dirty-very dirty" versus "clean-slightly dirty" (debris: 17.7 ± 4.5 vs. 24.6 ± 7.4 and $p = 0.054$; calculus: 21.2 ± 4.7 vs. 23.9 ± 7.8 and $p > 0.05$; and OHI-S: 20.4 ± 4.4 vs. 24.1 ± 7.8 and $p > 0.05$). Diminished handgrip strength was a predictor of poor outcomes, such as increased length of hospital stay, greater functional limitations, poorer quality of life, and increased mortality (27).

A relationship was observed between oral health and kidney function where patients with lower glomerular filtration rate had poor oral health and a higher proportion of moderate and severe periodontitis (28), which is a persistent state of infection and inflammation of the gingiva and dental supporting tissues that can cause tooth loss (29). Several authors have described that patients with any renal replacement therapy attend the dental service sporadically because they considered these visits unnecessary (29), the interdisciplinary staff sometimes lacked general knowledge on this topic (30), and the oral hygiene habits is deficient in the dialysis population (6). We identified that most of the patients used additional items in a limited way to maintain their oral hygiene; around 50 % of those who presented poorer oral hygiene did not use dental floss and more than 80 % did not use mouthwash ($p > 0.05$), similar to the report by Klassen et al., who assessed the oral health of 147 patients in both dialysis treatments, and found that the majority brushed their teeth one or more times a day (79 %) and that 73 % of patients did not use dental floss (6).

One of the main complications reported in dialysis patients was peritonitis; the presence of oral streptococci has been identified in cultures of dialysis fluid in patients with peritonitis re-

lated to previous dental procedures without having performed antibiotic prophylaxis procedures (31). There was a relationship between malnutrition and infectious processes that could lead to peritonitis, patients with PEW (evaluated by SGA) had a greater number of peritonitis events (RR = 5.6; 95 % CI, 2.2-14.3; p = 0.001) (32).

Although the relationship between peritonitis and oral health was theoretically presumed, evidence is limited. Oka et al. identified that patients who dedicated more time to daily oral hygiene and replaced their toothbrushes more frequently had a longer peritonitis-free time (33). In our study, those with better oral hygiene who attended a dental service more frequently (< 6 months) and brushed their teeth > 2 times a day showed no significant differences. Approaching a dental service by all patients would provide more information about useful brushing techniques and the use of other oral hygiene tools, as well as an early identification of oral alterations that might impact their nutritional status.

The presence of oral disorders, such as periodontitis, could lead to premature tooth loss, limiting the ability to chew, reducing nutrient intake, and compromising nutritional status. In our study, it was not possible to evaluate the association between number of teeth and nutritional intake, considering that the total number of teeth remained stable in all categories of oral hygiene. Ioannidou et al. identified that tooth loss was a significant predictor in reducing energy and protein intake, and that the inflammatory response could also cause protein catabolism, contributing to malnutrition (10).

The oral health problems in patients with CKD were recognized as causes of persistent inflammation (2,34), are associated with an increased mortality risk from cardiovascular disease (24), and may compromise nutritional status (10,35-37). It was observed in this study that the risks were statistically significant for a worse nutritional status for both MIS and SGA tools on all oral hygiene indices in the category "dirty-very dirty." Therefore, we believe that oral hygiene could be considered within the etiology of PEW and be approached in a multidisciplinary way. So far, the association between parathyroid hormone and oral hygiene indexes has been scarcely examined; nevertheless, it was reported that this and other parameters of mineral and bone metabolism, and inflammatory markers are increased in patients with moderate-severe periodontitis in comparison with those with a healthy periodontium and gingivitis without statistical significance (35); on the contrary, we identify that patients with better oral hygiene present higher PTH concentrations. Further studies are required to explore the relationship between mineral and bone metabolism biomarkers with oral hygiene indices in these patients.

Although our population was free of periodontal disease, it has been reported that poor oral hygiene had multiple local and systemic consequences. Periodontitis was one of the pathologies that had the most negative effects on health, whch is related to the presence of inflammation and constant infectious processes. For this reason, a novel strategy with the use of certain probiotics has been recently suggested as an additional treatment to conventional ones in healthy subjects (38). Renal patients with periodontitis have been shown to have an oral microbiota primarily composed of gram-negative bacteria and cocci, compared with healthy controls, suggesting an association with poor oral hygiene (39), and that their presence could generate endothelial damage in the kidney due to dissemination of pro-inflammatory antigens, endotoxins, and cytokines (40).

One of the limitations of our study was the nature of its design (cross-sectional), the small sample size, and the lack of dietary intake records. Furthermore, a bioimpedance vector analysis (to assess hydration) was not possible because some patients came with fluid in the peritoneal cavity, thus limiting the validity of the results. This study was one of the first to describe the relationship of oral hygiene with nutritional and clinical status, and physical function by handgrip strength in patients on PD. It is necessary to develop new research lines with larger sample sizes and dentists specialists in periodontics, one that may assess the application of adjuvant treatments such as probiotics on the oral health and nutritional status of the population with CKD in its different stages.

CONCLUSIONS

In this population of patients on PD, the risk of having a worse nutritional status was associated with poorer indices of oral hygiene, specifically regarding debris and OHI-S, regardless of age, sex, education, etiology, and time on dialysis. Additionally, patients with better physical functionality (by handgrip strength) had greater protection against the development of debris, which was why a nutritional and dental intervention was recommended to evaluate and address the treatment of these patients. More studies were required to evaluate the synergistic effect of nutritional intervention and conventional treatment of oral health, in addition to the use of probiotics in CKD patients on PD.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Valoración del estado nutricional en enfermos mentales institucionalizados

Assessing nutritional status in institutionalized mental patients

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Resumen

Introducción y objetivos: la malnutrición continúa siendo un problema no reconocido en los centros psiquiátricos. El objetivo del presente estudio fue conocer la prevalencia de la malnutrición y reconocer la importancia de la dieta en la alimentación de los enfermos mentales.

Métodos: se evaluó el estado nutricional de 65 pacientes mediante medidas antropométricas (peso, talla, índice de masa corporal, pliegue cutáneo tricipital, pliegue cutáneo bicipital, pliegue cutáneo subescapular, pliegue cutáneo suprailíaco, pliegue cutáneo tibial, pliegue cutáneo abdominal, índice cintura-cadera, circunferencia de la cadera y circunferencia de la cintura), analíticas (ferritina, triglicéridos, albúmina, colesterol, glucosa), otras variables (presión arterial), el cuestionario MNA-2009 y el menú de una semana. De cada paciente, además, se registraron datos personales, sexo, hábito tabáquico, edad, tipo de enfermedad, actividad física, visitas familiares y las variables enmarcadas en el cuestionario MNA-2009.

Resultados: la muestra estuvo formada por 13 mujeres y 52 hombres, todos ellos enfermos mentales de una institución psiquiátrica. El 43,1 % presentaban sobrepeso y el 21,5 % obesidad, siendo estos índices superiores en las mujeres que en los hombres. Respecto a los valores bioquímicos, se observó que los niveles de triglicéridos y colesterol eran superiores a los valores recomendados. Además, los sujetos presentaron un gran desequilibrio en macronutrientes y micronutrientes en la valoración nutricional diaria.

Conclusión: en este estudio se ha demostrado la gran prevalencia de la malnutrición en los pacientes psiquiátricos, en concreto de la obesidad por el gran exceso que presentan cada uno de los macronutrientes y micronutrientes repartidos en el menú durante el día de los pacientes psiquiátricos.

Palabras clave:

Malnutrición. MNA. Sobrepeso. Obesidad. Paciente psiquiátrico. Salud mental.

Abstract

Introduction and objectives: malnutrition remains an unrecognised problem in psychiatric centers. The aim of the present study was to find out the prevalence of malnutrition and to recognize the importance of diet in the nutrition of the mentally ill.

Methods: the nutritional status of 65 patients was assessed by anthropometric measurements (weight, height, body mass index, tricipital skin fold, bicipital skin fold, subscapular skin fold, suprailiac skin fold, tibial skin fold, abdominal skin fold, waist-hip index, hip circumference and waist circumference), blood tests (ferritin, triglycerides, albumin, cholesterol, glucose), other variables (blood pressure), the MNA-2009 questionnaire, and the one-week menu. Personal data, sex, smoking habits, age, type of disease, physical activity, family visits and the variables included in the MNA-2009 questionnaire were also recorded for each patient.

Results: the sample consisted of 13 women and 52 men, all of whom were mentally ill patients in a psychiatric institution. A total of 43.1 % were overweight and 21.5 % obese, with more women than men in each category. Regarding biochemical values, it was observed that triglyceride and cholesterol levels were higher than recommended values. In addition, they presented a great imbalance in macronutrients and micronutrients in the daily nutritional assessment.

Conclusion: this study has demonstrated the high prevalence of malnutrition in psychiatric patients, in particular obesity, due to the large excess of each of the macronutrients and micronutrients in the daily menu of psychiatric patients.

Keywords:

Malnutrition. MNA. Overweight. Obesity. Psychiatric patient. Mental health.

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INTRODUCCIÓN

En contra del típico mito popular, la malnutrición no solo afecta a los pacientes hospitalarios sino que también aparece de forma muy especial y concreta afectando gravemente la salud de las personas con enfermedad mental.

La Asociación Europea de Nutrición Enteral y Parenteral (ESPEN, por sus siglas en inglés) define la malnutrición como "un estado de nutrición en que una deficiencia, exceso o desequilibrio de energía, proteínas y otros nutrientes causa efectos adversos medibles en los tejidos, el cuerpo (la forma del cuerpo, el tamaño y la composición) y los análisis clínicos" (1). La malnutrición, por tanto, incluye tanto la sobrenutrición (sobrepeso y obesidad) como la desnutrición (nutrición insuficiente).

La desnutrición es el déficit de ingesta de nutrientes que se observa o se diagnostica mediante pruebas antropométricas o bioquímicas o métodos de *screening*. Por el contrario, la obesidad es el exceso de ingesta de nutrientes según los requerimientos de cada individuo, que conduce a un estado de obesidad o sobrepeso, siendo este un factor de riesgo para numerosas enfermedades crónicas. La obesidad es multifactorial y este término se ha empleado para denominar a distintos tipos de personas a lo largo de los años pero que, al final, científicamente hablando, se denomina, en el ámbito de la salud, acumulación anormal o excesiva de grasa (2).

La obesidad es una de las enfermedades que más afectan a los países desarrollados, pero la desnutrición está más relacionada con los países subdesarrollos y la realidad es que también está muy presente en los hospitales psiquiátricos (3). De hecho, en los últimos años ha sido un tema de gran interés y gran cauce. Para prevenir el gran porcentaje de prevalencia de la obesidad en la población, se ha recurrido a educarla nutricionalmente, incentivándola a consumir alimentos sanos con campañas publicitarias y elaborando charlas para dar información sobre cómo afectaría a la salud el exceso de peso y las implicaciones que tiene esta enfermedad para otras patologías: conduciendo a otras enfermedades crónicas como la diabetes *mellitus* (DM), la dislipidemia y otros cambios relacionados con el síndrome metabólico, y aumentando el riesgo de desarrollar enfermedades cardiovasculares, que son una causa importante de muerte en los individuos con esquizofrenia (4). La obesidad es la nueva epidemia de nuestra sociedad, puesto que las cifras van aumentando cada año (5).

Los enfermos mentales o con trastornos mentales tienen un riesgo elevado de padecer alteraciones nutricionales. A pesar de que algunos estudios realizados sobre este aspecto aportan resultados contradictorios (6,7), la gran mayoría coinciden en señalar situaciones deficitarias en los principales parámetros nutricionales, ya sean antropométricos o bioquímicos, como es el caso de las alteraciones vitamínicas (vitaminas D y del grupo B, especialmente B_6, B_9 y B_{12}), minerales (Mg, Mn, Zn y Se) y de aminoácidos esenciales (triptófano), comúnmente producidas en este tipo de pacientes (8,9), aunque otros estudios han podido encontrar que la mayoría de los pacientes estaban por encima de los parámetros normales (10).

Para un estado nutricional correcto se recomienda el siguiente reparto de macronutrientes: proteínas entre un 10 y un 15 % de las calorías totales; lípidos, menos del 30-35 %; hidratos de carbono, al menos el 50-60 % restante, tratándose mayoritariamente de hidratos de carbono complejos. Los mono y disacáridos (excepto los de lácteos, frutas y verduras) no deben aportar más del 10 % de la energía total. Además, se recomienda hacer entre 4 y 5 comidas diarias, prestando más importancia al desayuno y la comida, ya que son las ingestas alimentarias más importantes del día, y aligerando la cena (11).

Con todo, el objetivo general de este estudio es determinar el estado nutricional de pacientes que residen en un centro institucionalizado de enfermos mentales situado en Murcia. Sobre este objetivo general se plantearon varios objetivos secundarios: conocer la prevalencia de la malnutrición calórico-proteica y total mediante parámetros antropométricos y bioquímicos, identificar la prevalencia de la malnutrición mediante el método de cribado MNA y valorar las ingestas diarias de los pacientes para comprobar el déficit o exceso de macronutrientes o micronutrientes.

MATERIAL Y MÉTODOS

POBLACIÓN OBJETO DEL ESTUDIO Y DISEÑO EXPERIMENTAL

Al comienzo del estudio, la muestra poblacional estaba formada por 70 pacientes del centro de enfermos mentales situado en Murcia, con un rango de edades desde los 23 a los 65 años. Se excluyeron 5 pacientes por no cumplir los criterios de inclusión: pacientes con movilidad reducida o que no tenían recogidos en sus análisis clínicos algunos de los datos evaluados. También se excluyeron los pacientes que presentaban un estado de ánimo negativo, actitud violenta o que habían permanecido menos de un año ingresados. La recogida de datos se realizó durante 2 meses (de marzo a mayo). Durante dicho periodo, se llevaron a cabo las diferentes actividades para el desarrollo del estudio:

- Evaluación de la ingesta de nutrientes de los pacientes, valorando la composición nutricional del menú semanal completo (Tabla I) aportado por la directora del centro.
- Evaluación antropométrica de los pacientes.
- Evaluación nutricional de los pacientes utilizando el MNA.
- Análisis de los parámetros bióquimicos de los pacientes. Resultados aportados por la directora del centro.

Los datos y medidas de los pacientes se recogieron con la autorización y supervisión de la directora del centro y cuentan con la aprobación del Comité de Bioética.

VALORACIÓN NUTRICIONAL COMPLETA DE LOS PACIENTES INSTITUCIONALIZADOS

La valoración nutricional de estos pacientes se hizo mediante el cribado MNA 2009 (Mini Nutritional Assessment 2009) (Fig. 1). A continuación se registraron los siguientes datos de cada pa-

Tabla I. Menú semanal

	Lunes	Martes	Miércoles	Jueves	Viernes	Sábado	Domingo
Desayuno	Zumo de piña						
	Tostadas con aceite y sal						
	Leche (330 ml)						
Comida	Ensalada de tomate	Ensalada mixta	Ensalada de tomate	Ensalada mixta	Caldo con pelotas	Ensalada de tomate	Ensalada mixta
	Arroz y costillejas	Albóndigas en salsa y patatas fritas	Fabada	Pollo al ajillo	Merluza con patatas y alioli	Estofado de ternera	Arroz y marisco
	Naranja	Mousse de mocca	Plátano	Naranja	Fresas	Mandarina	Naranja
Merienda	Leche						
	Magdalena (27 g) o galletas (30 g)						
Cena	Sopa de pollo	Crema de calabacín	Salteado campestre	Crema de zanahoria	Menestra	Champiñón relleno	Ensalada de tomate
	Fiambre (pechuga de pavo, queso, chorizo)	Bocadillo de jamón	Lenguado rebozado al horno	Lomo adobado	Salchicha de Frankfurt, Jamón de York	Barritas de merluza	Tortilla de patatas
	Pera	Piña	Manzana	Piña	Pera	Manzana	Yogur

ciente, que se recogieron de la historia clínica con la aprobación del Comité de Bioética, la directora del centro y los propios pacientes (o tutores, en su caso):

- Sexo.
- Edad.
- Hábito tabáquico.
- Tipo de dieta.
- Parámetros bioquímicos en sangre: colesterol, glucosa, ferritina, albumina, triglicéridos y presión arterial.

Por último se llevó a cabo el estudio antropométrico de cada uno de los pacientes tomando las siguientes medidas:

- Peso (kg).
- Talla (m).
- Circunferencia de la cadera (CCadera) (cm).
- Circunferencia de la cintura (CCintura) (cm).
- Pliegue cutáneo tricipital (PCT) (mm).
- Pliegue cutáneo bicipital (PCB) (mm).
- Pliegue cutáneo subescapular (PCSB) (mm).
- Pliegue cutáneo suprailíaco (PCSP) (mm).
- Pliegue cutáneo abdominal (PCA) (mm).
- Pliegue cutáneo cuadricipital (PCC) (mm).
- Pliegue cutáneo tibial (PCtibial) (mm).

Para pesar a los pacientes se empleó una báscula electrónica EB-9003 Discover (Santiago de Cali, Colombia); para medirlos, un tallímetro SECA 217 (Hamburgo, Alemania). Las circunferencias de cintura y cadera se midieron con una cinta métrica flexible milimetrada SECA 201 (Hamburgo, Alemania), siguiendo lo establecido por la Sociedad Española para el Estudio de la Obesidad (SEEDO) (12). Los pliegues se midieron con un Plicómetro Holtain mecánico (HOL-98610ND) (Gales, Reino Unido).

A partir de las medidas antropométricas se calcularon el índice de masa corporal (IMC = kg/m^2), el índice cintura-cadera (ICC = circunferencia de la cintura (cm)/circunferencia de la cadera (cm)) y la grasa corporal total (GCT = [(4,95/D) – 4,5] × 100). Con los valores del IMC se clasificaron los sujetos de acuerdo con la clasificación de la OMS: < 18,5 kg/m^2: bajo peso; 18,5-24,9 kg/m^2: normopeso; 25-29,9 kg/m^2: sobrepeso; 30-34,9 kg/m^2: obesidad de grado I; 35-39,9 kg/m^2: obesidad de grado II; > 40 kg/m^2: obesidad de grado III.

Los valores de la CCintura que se usaron de referencia para medir el riesgo cardiovascular fueron: 95 cm para los hombres y 82 cm para las mujeres (12).

La SEEDO establece unos niveles normales aproximados de 0,8 en mujeres y 1 en hombres para el ICC. Valores superiores indican obesidad abdominovisceral, lo que se asocia con un riesgo cardiovascular aumentado y un incremento de la probabilidad de sufrir enfermedades como la diabetes de tipo II, la hipertensión y la hiperlipidemia (12).

Para los valores de glucosa se utilizaron como referencia unos valores normales en sangre de 55-100 mg/dL; para el colesterol, de 131-201 mg/dL; para los triglicéridos, de 35-201 mg/dL; para la albumina, de 3,5-5 g/dL; para la presión sistólica, de 120-129 mm Hg; para la diastólica, de 80-84 mm Hg, y para la ferritina, de 20-300 µg/L (13).

Mini Nutritional Assessment

MNA®

Nestlé Nutrition Institute

Apellidos: Nombre:

Sexo: Edad: Peso, kg: Altura, cm: Fecha:

Responda a la primera parte del cuestionario indicando la puntuación adecuada para cada pregunta. Sume los puntos correspondientes al cribaje y si la suma es igual o inferior a 11, complete el cuestionario para obtener una apreciación precisa del estado nutritional.

Cribaje

A Ha perdido el apetito? Ha comido menos por faltade apetito, problemas digestivos, dificultades de masticacióno deglución en los últimos 3 meses?
0 = ha comido mucho menos
1 = ha comido menos
2 = ha comido igual ☐

B Pérdida reciente de peso (<3 meses)
0 = pérdida de peso > 3 kg
1 = no lo sabe
2 = pérdida de peso entre 1 y 3 kg
3 = no ha habido pérdida de peso ☐

C Movilidad
0 = de la cama al sillón
1 = autonomía en el interior
2 = sale del domicilio ☐

D Ha tenido una enfermedad aguda o situación de estrés psicológico en los últimos 3 meses?
0 = sí 2 = no ☐

E Problemas neuropsicológicos
0 = demencia o depresión grave
1 = demencia leve
2 = sin problemas psicológicos ☐

F Índice de masa corporal (IMC) = peso en kg / (talla en m)²
0 = IMC <19
1 = 19 ≤ IMC < 21
2 = 21 ≤ IMC < 23
3 = IMC ≥ 23 ☐

Evaluación del cribaje ☐☐
(subtotal máx. 14 puntos)

12-14 puntos: estado nutricional normal
8-11 puntos: riesgo de malnutrición
0-7 puntos: malnutrición

Para una evaluación más detallada, continúe con las preguntas G-R

Evaluación

G El paciente vive independiente en su domicilio?
1 = sí 0 = no ☐

H Toma más de 3 medicamentos al día?
0 = sí 1 = no ☐

I Úlceras o lesiones cutáneas?
0 = sí 1 = no ☐

J. Cuántas comidas completas toma al día?
0 = 1 comida
1 = 2 comidas
2 = 3 comidas ☐

K Consume el patiente
- productos lácteos al menos una vez al día? sí ☐ no ☐
- huevos o legumbres 1 o 2 veces a la semana? sí ☐ no ☐
- carne, pescado o aves, diariamente? sí ☐ no ☐

0.0 = 0 o 1 síes
0.5 = 2 síes
1.0 = 3 síes ☐.☐

L Consume frutas o verduras al menos 2 veces al día?
0 = no 1 = sí ☐

M Cuántos vasos de agua u otros líquidos toma al día? (agua, zumo, café, té, leche, vino, cerveza…)
0.0 = menos de 3 vasos
0.5 = de 3 a 5 vasos
1.0 = más de 5 vasos ☐.☐

N Forma de alimentarse
0 = necesita ayuda
1 = se alimenta solo con dificultad
2 = se alimenta solo sin dificultad ☐

O Se considera el paciente que está bien nutrido?
0 = malnutrición grave
1 = no lo sabe o malnutrición moderada
2 = sin problemas de nutrición ☐

P En comparación con las personas de su edad, cómo encuentra el paciente su estado de salud?
0.0 = peor
0.5 = no lo sabe
1.0 = igual
2.0 = mejor ☐.☐

Q Circunferencia braquial (CB en cm)
0.0 = CB < 21
0.5 = 21 ≤ CB ≤ 22
1.0 = CB > 22 ☐.☐

R Circunferencia de la pantorrilla (CP en cm)
0 = CP < 31
1 = CP ≥ 31 ☐

Evaluación (máx. 16 puntos) ☐☐.☐
Cribaje ☐☐.☐
Evaluación global (máx. 30 puntos) ☐☐☐

Evaluación del estado nutricional

De 24 a 30 puntos ☐ estado nutricional normal
De 17 a 23.5 puntos ☐ riesgo de malnutrición
Menos de 17 puntos ☐ malnutrición

Ref Vellas B, Villars H, Abellan G, et al. *Overview of the MNA® - Its History and Challenges*. J Nut Health Aging 2006 ; 10 : 456-465.
Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B. *Screening for Undernutrition in Geriatric Practice : Developing the Short-Form Mini Nutritional Assessment (MNA-SF)*. J. Geront 2001 ; 56A : M366-377.
Guigoz Y. *The Mini-Nutritional Assessment (MNA®) Review of the Literature - What does it tell us?* J Nutr Health Aging 2006 ; 10 : 466-487.

Para más información: www.mna-elderly.com

Figura 1.
Cuestionario MNA (fuente: De Luis y cols., 2001).

ANÁLISIS ESTADÍSTICO

Para el análisis estadístico de los datos se utilizó el software Statistical Package for Social Sciences (SPSS) versión 15.0 (SPSS Inc.; Chicago, Illinois, EUA). Se realizó un análisis descriptivo de los datos, expresándose las variables cuantitativas como medias y desviaciones típicas, y las variables cualitativas mediante frecuencias. Se realizó un análisis de la varianza de tipo ANOVA de una vía, con un nivel de significación del 95 %. Las relaciones entre variables se examinaron utilizando el coeficiente de correlación de Pearson. La significación estadística se asumió cuando el valor *p* era inferior a 0,05 (IC del 95 %).

RESULTADOS

La muestra poblacional estuvo constituida por 13 mujeres (20 %) y 52 hombres (80 %), con edades comprendidas entre 23 y 61 años, y una media de edad de 45,91 ± 10,08. En relación con el consumo de tabaco, el 75,39 % de la población son fumadores, de los cuales el 18,37 % son mujeres y el 81,63 % son hombres.

En la tabla II se muestran los datos descriptivos de los parámetros antropométricos de los pacientes de este estudio por sexos.

El valor medio del IMC en las mujeres fue significativamente superior ($p < 0,001$) al de los hombres. También se encontraron diferencias significativas en el valor medio de la talla, mayor en los hombres que en las mujeres ($p < 0,001$), y en el valor medio del pliegue cutáneo suprailíaco ($p < 0,001$) y la circunferencia de la cadera ($p < 0,001$), superiores en las mujeres con respecto a los hombres. El 75,38 % de los pacientes son fumadores, de los cuales el 13,85 % son mujeres y el 61,54 % son hombres. No se encontraron diferencias estadísticamente significativas entre hombres y mujeres en términos de PCT, PCB, PCSB, PCA, PCC, PCtibial, Ccintura, ICC y GCT. Sin embargo, según la circunferencia de la cintura, el 40 % de los pacientes presentaban un alto riesgo cardiovascular (RCV).

En la tabla III se muestra la distribución del IMC separado por sexos. Se encontró que el 33,8 % de los pacientes psiquiátricos presentaban normopeso (el 40,4 % eran hombres y el 7,7 % mujeres), existiendo diferencias significativas entre ambos sexos ($p < 0,001$). Se detectaron problemas de sobrepeso en el 43,1 %, existiendo diferencias significativas entre hombres y mujeres ($p < 0,001$). Se encontró que el 16,9 % de los pacientes presentaban obesidad y el 4,6 %, obesidad mórbida; en ambos casos se encontraron diferencias significativas entre hombres y mujeres ($p < 0,001$). Cabe destacar una baja tendencia a la obesidad, siendo esta superior en las mujeres que en los hombres, mientras que solo en un 1,5 % de los casos se detectó bajo peso, siendo todos los casos hombres. Se observó, tras pasar el cribado del MNA para la valoración nutricional, que todos los pacientes se encontraban en situación de malnutrición, ya fuera

Tabla II. Demografía y características antropométricas de los pacientes psiquiátricos (media ± DE)

	Población total	Hombres	Mujeres
Peso (kg)	75,46 ± 13,73	75,74 ± 12,42	74,31 ± 18,63
Talla (m)*	1,67 ± 0,09	1,71 ± 0,06	1,54 ± 0,04
IMC (kg/m^2)*	27,06 ± 5,1	26,04 ± 3,97	31,13 ± 6,91
PCT (mm)	11,48 ± 11,23	11,71 ± 11,41	10,59 ± 10,85
PCB (mm)	7,69 ± 4,91	7,26 ± 4,22	9,44 ± 6,97
PCSB (mm)	6,59 ± 4,75	6,43 ± 4,43	7,24 ± 6,05
PCSP (mm)*	5,26 ± 3,76	4,49 ± 2,54	8,33 ± 5,92
PCA (mm)	8,27 ± 3,73	7,86 ± 2,92	9,85 ± 5,90
PCC (mm)	7,39 ± 3,73	7,02 ± 3,52	8,85 ± 4,33
PCtibial (mm)	5,67 ± 2,78	5,53 ± 2,62	6,24 ± 3,41
CCintura (cm)	95,02 ± 16,01	93,82 ± 15,41	99,8 ± 18,07
CCadera (cm)*	99,53 ± 12,59	96,90 ± 9,09	119,68 ± 23,3
ICC (cm)	0,96 ± 0,16	0,97 ± 0,17	0,9 ± 0,11
GCT (Kg)	16,27 ± 8,01	15,76 ± 7,00	18,32 ± 11,34
Porcentaje de fumadores (*n*)	75,38 % (9)	61,54 % (40)	13,85 % (49)

**p < 0,01. IMC: índice de masa corporal; PCT: pliegue cutáneo tricipital; PCB: pliegue cutáneo bicipital; PCSB: pliegue cutáneo subescapular; PCSP: pliegue cutáneo suprailíaco; PCA: pliegue cutáneo abdominal; PCC: pliegue cutáneo cuadricipital; PCtibial: pliegue cutáneo tibial; CCintura: circunferencia de la cintura; CCadera: circunferencia de la cadera; ICC: índice cintura/cadera; GCT: grasa corporal total.*

Tabla III. Distribución por índice de masa corporal (IMC) y sexo (*n* (%))

IMC		Total	Hombres	Mujeres
< 18,5 kg/m^2	Bajo peso	1 (1,5 %)	1 (1,9 %)	0
18,5-24,9 kg/m^2*	Normopeso	22 (33,8 %)	21 (40,4 %)	1 (7,7 %)
25-29,9 kg/m^2*	Sobrepeso	28 (43,1 %)	22 (42,3 %)	6 (46,2 %)
30-34,9 kg/m^2*	Obesidad de grado I	11 (16,9 %)	8 (15,4 %)	3 (23,1 %)
35-39,9 kg/m^2	Obesidad de grado II	0	0	0
> 40 kg/m^2*	Obesidad mórbida	3 (4,6 %)	0	3 (23,1 %)

**p < 0,01.*

por bajo peso o por exceso de peso. Este resultado se debería estudiar en próximos estudios debido a que no existe ningún cribado de valoración nutricional adecuado para este tipo de pacientes. El utilizado es el idóneo para personas ancianas.

En la tabla IV se muestran los valores descriptivos de los parámetros bioquímicos diferenciados por categorías de IMC. Se observa que los valores de glucosa más altos los presentan los pacientes con bajo peso, con un IMC inferior a 18,5 kg/m^2, pero esto no es muy concluyente ya que, en la categoría de bajo peso, solo se encuentra una persona (por ello no tiene desviación típica), aunque se han encontrado diferencias significativas entre las categorías de IMC ($p < 0,05$). Respecto al colesterol, los triglicéridos y la presión sistólica, se observa que los valores más altos se presentan en los pacientes con obesidad mórbida, es decir, con un IMC superior a 40 kg/m^2. En la categoría de obesidad mórbida, los valores de glucosa son también altos. En cuanto a la albúmina y la presión diastólica, los valores más altos se encuentran en los pacientes con obesidad de grado I; en relación con la albúmina se han encontrado diferencias significativas entre las categorías de IMC ($p < 0,001$); también se han encontrado diferencias significativas en el colesterol con respecto a la clasificación del IMC ($p < 0,05$).

En la tabla V se muestra el coeficiente de correlación entre el IMC y los parámetros bioquímicos. Se ha encontrado una aso-

Tabla IV. Parámetros bioquímicos distribuidos según la clasificación del IMC (media ± DE)

IMC		Glucosa (mg/dL)*	Colesterol (mg/dL)†	Triglicéridos (mg/dL)	Albúmina (g/dL)†	Ferritina (µg/L)	Presión sistólica (mmHg)	Presión diastólica (mmHg)
< 18,5 kg/m^2	Bajo peso	131,00	148,00	112,00	3,90	3,30	95,00	52,00
18,5-24,9 kg/m^2	Normopeso	99,39 ± 21,40	181,41 ± 34,63	138,36 ± 72,86	3,90 ± 0,25	105,60 ± 59,60	108,36 ± 18,85	71,64 ± 9,60
25-29,9 kg/m^2	Sobrepeso	86,00 ± 21,86	153,93 ± 26,19	135,21 ± 63,73	4,13 ± 0,39	97,35 ± 68,64	110,00 ± 17,73	73,07 ± 9,99
30-34,9 kg/m^2	Obesidad de grado I	87,64 ± 17,83	170,91 ± 21,99	125,18 ± 93,48	4,58 ± 0,58	97,15 ± 54,61	120,55 ± 16,45	78,00 ± 10,90
35-39,9 kg/m^2	Obesidad de grado II	0	0	0	0	0	0	0
> 40 kg/m^2	Obesidad mórbida	117,67 ± 11,02	208,33 ± 31,75	164,67 ± 39,37	3,90 ± 0,75	107,00 ± 69,31	125,67 ± 26,58	76,00 ± 14,42
Total		92,99 ± 22,28	168,52 ± 32,08	135,58 ± 70,28	4,12 ± 0,46	99,11 ± 62,42	111,72 ± 17,09	73,23 ± 10,44

**p < 0,05; †p < 0,01.*

Tabla V. Coeficiente de correlación entre los parámetros bioquímicos, la presión arterial y el IMC de los pacientes evaluados

	Colesterol	Triglicéridos	Presión sistólica	Presión diastólica	Albúmina	Ferritinina	Glucosa
IMC (kg/m^2)	0,135	0,041	*0,337†*	*0,303**	*0,273**	0,046	-0,043
Colesterol		*0,406†*	0,045	0,038	-0,088	0,188	0,173
Triglicéridos			-0,015	0,024	-0,151	0,159	0,035
Presión sistólica				*0,761†*	0,013	0,054	-0,055
Presión diastólica					-0,021	0,098	*-0,247**
Albúmina						0,112	-0,164
Ferritinina							-0,072

**p < 0,05; †p < 0,01.*

ciación significativa positiva entre el IMC, la albumina, la presión sistólica y la diastólica; es decir, al aumentar el IMC aumentan los valores de albúmina, presión sistólica y diastólica. Se ha observado una asociación significativa positiva entre el colesterol y los triglicéridos; también se ha encontrado una asociación significativa negativa entre la glucosa y la presión diastólica: es decir, al aumentar la glucosa disminuye la presión diastólica y a la inversa.

En la tabla VI se muestra el análisis de las cuatro comidas de cada día (el desayuno, la comida, la merienda y la cena) de una semana. En ambas tablas aparecen un desayuno y una merienda, debido a que siempre se trata del mismo desayuno y la misma merienda. Hay dos tipos de meriendas dependiendo de si el paciente es diabético o no, con exceso de peso o normal; para los diabéticos/con sobrepeso: merienda con galletas; para los pacientes normales, merienda con magdalenas.

Tras analizar ambas tablas se puede observar que, en las proteínas, el valor más alto se sitúa en la comida del domingo, con una aportación de 153,2 g; también los hidratos de carbono están en una situación similar: la cantidad de hidratos de carbono más alta se aporta el domingo en la comida, con 125,6 g. Sin embargo, la ingesta con mayor aporte de ácidos grasos monoiinsaturados y saturados, fibra y sodio es la comida del miércoles, con 29,15 g de ácidos monoiinsaturados, 24,12 g de ácidos saturados, 18,64 g de fibra y 2980,82 mg de sodio (Na). La comida del martes es la ingesta con mayor aporte de ácidos poliinsaturados, vitamina B_{12} y energía, con 29,7 g de ácidos poliinsaturados, 9,19 µg de vitamina B_{12} y 1193,12 kcal. La ingesta con mayor aporte de hierro es la cena del lunes, con 18,53 mg. Por último, se ha podido observar que la ingesta con mayor aporte de ácido fólico es la comida del lunes, con 224,41 µg.

En la tabla VII se observa la distribución energética y se muestra que hay un exceso en el aporte de proteínas que se situó por encima del 15 %; el aporte de hidratos de carbono también se sitúa por encima del 55 % (valores recomendados). Entre los valores obtenidos para el consumo de lípidos con respecto a la ingesta energética (86,4 %), el de ácidos grasos saturados (126 %) fue incluso superior al 100 %, el de ácidos grasos monoinsaturados (59 %) superior a la recomendación y el de ácidos grados poliinsaturados (159 %) también superior al 100 %.

La fibra es ligeramente inferior a la recomendación, ya que se obtiene una adecuación de media entre todas las comidas de la semana de aproximadamente un 36 %. Los micronutrientes en general se encuentran por debajo de las recomendaciones, exceptuando alguna comida que supera la recomendación diaria, como el hierro (Fe) o la vitamina B_{12} en la comida del sábado.

DISCUSIÓN

Diversos países experimentan actualmente enfermedades relacionadas con el exceso de peso. España está inmersa en un proceso de transición epidemiológica donde la población presenta un gran aumento en el índice de masa corporal, evidenciado por sobrepeso y obesidad que afecta a todas las regiones de España y a la población de todas las edades (14).

Tabla VI. Valoración nutricional de las comidas y cenas + desayunos analizados durante la semana

Valoración nutricional	Lunes		Martes		Miércoles		Jueves		Viernes		Sábado		Domingo		Merienda	
	Desayuno	Comida	Cena	Comida	Cena	Comida	Cena	Comida	Cena	Comida	Cena	Comida	Cena	Comida	Cena	Con Magdalenas	Con Galletas
Tamaño de porción (g)	440	772,25	1109,7	630,7	480,2	658,25	451,5	600,8	407	586,7	580	979	448,7	1109,7	581,5	244	214
Proteínas (g)	10,84	31,52	73,2	53,64	19,8	39,25	13,6	37,66	37	28,0	21,2	76,4	28,2	153,2	22,7	9,0	1,5
Hidratos de carbono (g)	36,81	118,5	46,2	69,2	48,5	62,5	42,34	67,95	29,04	91,0	37,7	54,1	42,1	125,6	34,1	52,9	17,5
Ácidos monoinsaturados (g)	8,258	9,56	7,3	23,79	11,13	29,15	6,98	10,22	12,71	6,9	17,6	18,8	15,2	9,6	7,7	1,3	4,4
Ácidos poliinsaturados (g)	1,685	2,7	3,053	29,7	11,1	8,548	10,7	5,52	4,12	8,1	9,2	10,6	16,6	9,8	2,6	0,5	0,8
Ácidos saturados (g)	3,796	5,87	9,14	17,48	5,36	24,12	2,62	5,53	8,29	1,2	8,05	12,4	3,2	3,6	4,1	54	3,1
Grasa total (g)	14,06	18,38	23,32	69,01	35,44	63,63	19,83	22,78	37,42	25,8	45,1	43,2	38,6	22,8	16,9	12,6	5,5
Fibra (g)	2,6	10,6	12,75	10,85	7,36	18,64	11,45	13,30	5,36	17,2	9,5	11,5	5,3	13,0	5,3	0,4	0,4
Sodio (mg)	298,6	157,53	2523,7	2116,16	1475,2	2980,82	2772,3	1372	2098	643,6	1247	693,7	1042,9	104,6	775	100,9	118,3
Vitamina B_{12} (µg)	0,8	0,45	1,06	9,19	0,4	0,65	0,09	0,35	0,86	1,6	0,8	3,0	1,5	1	1,8	0,8	0,8
Ácido fólico (µg)	33,8	224,41	165,85	122,51	115,28	155,23	128	63,03	65,43	117,1	125,2	127,2	47,2	174,2	138,8	13,0	11,0
Hierro (mg)	1,42	3,92	18,53	7,54	3,6	15,55	1,74	8,90	4,2	15,2	1,7	46,1	2,6	3,0	3,9	0,5	0,3
Energía (kcal)	371,4	777,33	572,43	1193,12	527,9	984,32	847,3	655,74	510,81	666,7	651,4	886,5	471,1	833,9	394,4	254,3	149,5

Tabla VII. Adecuación de la ración de los menús a la recomendación del rango de edad de 23-62 años

Adecuación %	Proteínas	Hidratos de carbono	Ácidos monoinsaturados	Ácidos poliinsaturados	Ácidos saturados	Grasa total	Fibra	Na	Fe	Ácido fólico	Vitamina B_{12}	Energía
Desayuno	72,3	66,9	41,3	33,7	47,5	40,1	10,4	19,9	17,8	8,5	66,8	14,6
Comida lunes	210,1	215,6	47,8	54,0	73,4	52,5	42,4	10,5	49,0	56,1	37,6	30,9
Comida martes	357,6	125,8	119,0	594,0	218,5	197,2	43,4	141,1	94,3	30,6	765,8	47,4
Comida miércoles	261,7	113,6	145,8	171,0	301,5	181,1	74,6	198,7	194,4	38,8	54,2	39,1
Comida jueves	251,1	123,6	51,1	110,4	69,1	65,1	53,2	91,5	111,3	15,8	29,2	26,0
Comida viernes	186,3	165,4	34,5	161,8	14,9	73,7	68,8	42,9	189,5	29,3	129,2	26,5
Comida sábado	509,0	98,4	94,1	212,2	154,9	123,5	45,8	46,3	576,3	31,8	246,7	35,2
Comida domingo	1021,3	228,3	48,1	196,8	44,4	65,1	51,9	7,0	38,0	43,6	83,3	33,1
Merienda 1*	59,7	96,2	21,8	9,6	675,0	36,0	1,7	6,7	6,8	3,2	66,7	10,1
Merienda 2†	10,0	31,9	6,3	16,0	38,3	15,7	1,5	7,9	4,0	2,7	66,7	5,9
Cena lunes	488,0	84,0	36,5	61,1	114,3	66,6	51,0	168,3	231,6	41,5	88,3	22,7
Cena martes	132,0	88,2	55,7	222,0	67,0	101,3	29,4	98,4	45,0	28,8	33,3	21,0
Cena miércoles	90,7	77,0	34,9	214,0	32,8	56,7	45,8	184,8	21,6	32,0	7,5	33,7
Cena jueves	246,7	52,8	63,6	82,4	103,6	106,9	21,4	139,9	52,5	16,4	71,7	20,3
Cena viernes	141,3	68,6	88,2	184,8	100,6	128,9	38,0	83,1	21,6	31,3	63,3	25,9
Cena sábado	187,3	76,6	76,0	332,0	39,4	110,2	21,1	69,5	32,8	11,8	124,2	18,7
Cena domingo	151,5	61,9	38,6	51,0	51,8	48,1	21,0	51,7	48,5	34,7	147,5	15,7

**Merienda con magdalenas. †Merienda con galletas.*

En este estudio, la edad media de los pacientes es aproximadamente de 46 años. Existen muy pocos estudios para poder afirmar una edad exacta en la que exista riesgo de enfermedad mental, pero entre los pocos estudios que existen, la edad media es inferior a 45 años (15, 10, 3), aunque existe uno que coincide con el rango de edad de nuestro estudio (16).

En esta población de estudio existe gran porcentaje de fumadores. Esta gran prevalencia de fumadores entre los pacientes psiquiátricos también se confirma en otros estudios realizados con enfermos mentales (15,10) e incluso lo corrobora un estudio dirigido a este tipo de personas, comparándolo a nivel nacional (17).

Los resultados obtenidos para el IMC muestran que la mayoría de los pacientes tienen sobrepeso; los valores medios del IMC de este tipo de población no coinciden con los de otros estudios realizados en esta población; de hecho, sus resultados se encuentran en la normalidad, no se encuentran en riesgo de obesidad (15,3). Pero existe un estudio de la ENSANUT 2012 (18) con unos resultados muy similares a los del estudio actual, que encontró que la prevalencia del sobrepeso es mayor en las mujeres que en los hombres y la de la obesidad es más alta en el sexo femenino que en el masculino. Además, también se han encontrado otros estudios que confirman resultados de IMC similares a los resultados de este estudio (10). La población estudiada cumple con este patrón. Es importante recordar que son personas con una vulnerabilidad mayor a la ganancia de peso y sus complicaciones, debido al consumo de algunos fármacos usados para su tratamiento con efectos secundarios sobre el control del apetito (19).

Aunque el ICC puede suponer un buen indicador del reparto de la grasa visceral, en los últimos años ha prevalecido en la práctica clínica la medición de la CCintura, ya que se considera mejor indicador de la grasa abdominal. La CCintura es un parámetro muy útil para personas que tienen peso normal o sobrepeso (12), pues el IMC puede dar a veces una lectura engañosa, como, por ejemplo, en los deportistas con mucha masa muscular.

El porcentaje de riesgo de sufrir una enfermedad cardiovascular en la población del estudio, según el valor de la CCintura, no supera el 40 %. Se ha observado un mayor riesgo en mujeres que en hombres, aunque hay un mayor índice de sobrepeso y obesidad entre los hombres. Este hecho podría estar asociado con el mayor desarrollo muscular de los hombres. Sin embargo, no tenemos datos concretos, ya que no se hicieron mediciones de la composición corporal. La observación de este resultado se contradice con los resultados obtenidos por De Oliveira (16), quien observó unos valores elevados de circunferencia de la cintura pero en ambos sexos.

Las mujeres de este estudio obtuvieron valores medios de índice cintura/cadera más altos que los de las recomendaciones de la OMS. Con respecto a los hombres, estos se encuentran en valores normales. Esta diferencia que existe entre hombres y mujeres según el índice cintura/cadera no existe en otros estudios realizados en este tipo de población; de hecho, los valores de ambos sexos se encuentran en la normalidad (10).

En los pacientes con trastorno psiquiátrico evaluados en el presente estudio se identificaron resultados de indicadores que reflejan signos clínicos de mala alimentación: por exceso, reflejado en la presencia de sobrepeso y obesidad, y por el incremento evidenciado en sus niveles de albumina en sangre (superiores a 3.5 g/dL) (20). En esta población de estudio se ha encontrado que el colesterol, los triglicéridos, la presión sistólica y la diastólica tienen valores superiores a los de las recomendaciones de normalidad de cada parámetro. Existe poca evidencia respecto a indicadores bioquímicos y trastornos psiquiátricos. Se sabe que, en algunos trastornos psiquiátricos por consumo de sustancias psicoactivas como la heroína y el opio, existe una disminución de los parámetros bioquímicos de glucosa sanguínea en ayunas, colesterol, calcio y ácido úrico (21).

Respecto a los niveles de glucosa en sangre, existe un estudio previo que sugiere que el aumento de los niveles de glucosa está asociado con la depresión (22). En el presente estudio, los valores de glucosa son muy similares. Se han observado valores superiores a los recomendados para la población y estos resultados también coinciden con los de otro estudio (23). Resultaría conveniente implementar una valoración subsiguiente donde se tomen en cuenta los indicadores bioquímicos como medio de evaluación del impacto del tratamiento nutricio del paciente durante su hospitalización.

Algunas de las enfermedades que presentaban los individuos de este estudio se tratan principalmente con antipsicóticos atípicos, de los que existen estudios que evidencian aumentos de peso y alteraciones metabólicas que podrían reducir la expectativa de vida en los pacientes que consumen estos fármacos (24). En ese estudio se observó el predominio del uso de antipsicóticos atípicos como la risperidona, la olanzapina y la quetiapina, lo que permite considerar la posibilidad de que estos pacientes presenten un factor de riesgo para continuar con la ganancia de peso. Un estudio pone en evidencia la heterogeneidad de los resultados de ganancia de peso inducida por antipsicóticos, incluyendo interacciones fármaco-ambiente poco conocidas que se traducen en un cambio neto del balance entre péptidos y hormonas que regula los procesos anorexígenos (catabólicos), la ingesta de alimentos y la homeostasis de la energía a través de orexigénicos (anabólicos) (25,26). Es importante mencionar la necesidad de desarrollar protocolos de investigación que vayan enfocados a conocer e indagar en la ganancia de peso de los pacientes tratados con estos fármacos, procurando contemplar a la par otras variables que se involucran en la ganancia de peso, como el consumo dietético y la actividad física, así como descartar alteraciones endocrinas que pudiesen sesgar los resultados. Sin embargo, se sabe que las personas con trastornos psiquiátricos se involucran menos en la actividad física en comparación con la población general (27).

Debido a que el aumento de peso resulta también del desequilibrio entre el consumo de energía y el gasto energético (28), es importante conocer el consumo de energía de los pacientes durante su estancia, así como su consumo nutrimental.

El manejo integral de estos pacientes debe hacer hincapié en el control dietético una vez que egresen de la hospitalización, puesto que, al igual que el resto de la población española, el paciente está expuesto a todos los factores ambientales que están contribuyeron al cambio de patrón alimentario en la sociedad de consumo, al generar cambios de comportamiento que determinan la elección del tipo de alimentos que se decide o no consumir (29,30), siendo aún más vulnerables por el uso de fármacos que se ha demostrado que favorecen la ganancia de peso.

Aunque la extrapolación de estos resultados es limitada debido al tamaño de la muestra, los hallazgos permiten poner en evidencia algunas características de la alimentación que reciben estas personas. La población estudiada no cumple las recomendaciones nutricionales establecidas por la Sociedad Española de Nutrición Comunitaria (SENC). La ingesta de micronutrientes fue inadecuada en términos generales y un grupo importante de pacientes presentó un elevado riesgo de deficiencia de ácido fólico, aunque presenta valores altos de vitamina B_{12} y minerales hierro y sodio.

Otros estudios difieren con los resultados de este estudio debido a que se muestran ingestas deficitarias de hierro (31). En otros estudios el resultado es muy similar al de la población del estudio presente (7).

Con relación a la distribución energética del menú del hospital, se observó un exceso de desequilibrio en el balance energético. Estos resultados coinciden con los de un estudio realizado en pacientes psiquiátricos (3), aunque los resultados obtenidos de hidratos de carbono y de ácidos grasos totales, monoiinsaturados, poliinsaturados y saturados son superiores a los obtenidos en el estudio de Arroyo (3). Hay que tener en cuenta que, aunque sean enfermos, la residencia es diferente, por lo que consumirían otros tipos de alimentos, ya que en este estudio la alimentación que siguen la adaptan según los gustos de los pacientes.

Además, el consumo medio de fibra se sitúa por debajo de las recomendaciones, por lo que deberían aumentar el consumo de alimentos del grupo de los cereales y las verduras para alcanzar dicha recomendación con el objetivo de prevenir el estreñimiento, síntoma frecuente en los pacientes que consumen de forma habitual fármacos psicolépticos.

La influencia de los factores nutricionales en el metabolismo cerebral y en la evolución de los trastornos mentales está adquiriendo cada vez más relevancia. Así, se están considerando algunos elementos nutricionales, como el cambio de hábitos dietéticos con mayor aporte de verduras y pescado o el aporte de suplementos nutricionales, como herramientas terapéuticas que, añadidas a las utilizadas convencionalmente, pueden mejorar la evolución de las patologías mentales, especialmente de aquellas más graves (esquizofrenia, anorexia, trastornos bipolares) en las que el riesgo de malnutrición es muy alto (32).

Con todo, cabe destacar la necesidad de incorporar al centro un nutricionista titulado para la adaptación de los menús semanales a las necesidades de cada uno de los pacientes, así como a su enfermedad, al tratamiento farmacológico de la misma y a la evolución de su estado nutricional.

CONCLUSIÓN

Gran parte de los pacientes presentaron exceso de peso, circunferencia abdominal y porcentaje de grasa corporal, siendo mayor el problema en las mujeres que en hombres. Estos son importantes factores de riesgo de sufrir enfermedades cardiovasculares y síndrome metabólico. Respecto al análisis nutricional de las ingestas, se ha observado un gran desequilibrio en la valoración nutricional de la dieta de los enfermos mentales institucionalizados, ya que presenta un alto porcentaje de macronutrientes (lípidos, hidratos de carbono y proteínas), sodio y hierro, y un bajo porcentaje de ácido fólico, superando los límites de adecuación con respecto a la población general.

Por lo tanto, además de la clínica médica, psiquiátrica y psicológica, se sugiere que, adicionalmente, se incluyan la evaluación y el tratamiento nutricionales de los pacientes mentales institucionalizados. Todo ello con el fin de detectar precozmente las alteraciones asociadas a la exposición a los antipsicóticos, en especial la obesidad, y de efectuar el registro de los cambios a lo largo del curso de la enfermedad y de la exposición a diferentes presentaciones, tipos y dosis de antipsicóticos, para lograr un entendimiento más preciso de la ganancia de peso, buscando la prevención de las enfermedades asociadas a la obesidad.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Assessment of body composition in cystic fibrosis: agreement between skinfold measurement and densitometry

Evaluación de la composición corporal en adultos con fibrosis quística: concordancia entre la densitometría y la antropometría

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Abstract

Introduction: few studies have evaluated body composition (BC) through different techniques, and the degree of agreement between them in adults with cystic fibrosis (CF).

Objectives: to describe BC using techniques to assess nutritional status and to test their concordance in CF.

Methods: a cross-sectional study in CF patients in a clinically stable situation. Nutritional assessment was performed using skinfold measurement (SM) and densitometry (DXA). Fat-free mass index (FFMI) was also determined. The diagnosis of malnutrition was established if body mass index (BMI) < 18.5 kg/m^2. Fat-free mass (FFM) malnutrition was diagnosed when FFMI was < 17 kg/m^2 in males and < 15 kg/m^2 in females (FFMI: fat-free mass in kg/height in m^2).

Results: forty-one patients were studied (twenty-two females, 53.7 %); median age was 29.8 (interquartile range, 20.9-33.7); BMI was 21.6 (19.8-23.0). Only four (9.8 %) patients had a BMI < 18.5. By DXA, FFM (kg) results were: median, 52.8 (47.8-56.9) with FFMI of 17.9 (16.7-19.3) in males and 36.7 (33.1-38.9) in females, FFMI of 14.7 (14.2-15.8). Twenty (48.6 %) patients presented FFM malnutrition, with 16.7 % of males and 59.1 % of females being affected. By SM, the FFMI was 18.7 (17.2-20.0) in males and 14.9 (14.2-15.8) in females; moreover, sixteen (39.1 %) patients presented malnutrition of FFM, with 20.8 % of males and 61.8 % of females being affected.

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Cystic fibrosis. Malnutrition. Nutritional assessment. Dual energy X-ray densitometry (DXA). Skinfold measurement (SM).

For FFM (kg), high concordance was obtained between SM and DXA (intraclass correlation coefficient of 0.950); likewise when they were compared by applying the ESPEN criteria for FFM malnutrition. However, when the techniques were compared to classify malnutrition according to FFMI, the kappa coefficient was only moderate (k = 0.440). The mean difference between FFM by DXA and SM was +1.44 ± 0.62 kg in favor of SM, with greater dispersion as FFM increased.

Conclusions: the prevalence of FFM malnutrition is high in adult CF patients, despite a normal BMI, especially in females. Notwithstanding the good statistical agreement between SM and DXA, concordance was moderate. Therefore, DXA remains the technique of choice, and SM may be used when the former is not available.

Resumen

Introducción: pocos estudios han evaluado la composición corporal (BC) mediante diferentes técnicas y el grado de concordancia entre ellas en adultos con fibrosis quística (FQ).

Objetivos: describir la BC mediante técnicas de evaluación nutricional y comprobar su concordancia en la FQ.

Métodos: estudio transversal de adultos con FQ en situación de estabilidad clínica. La evaluación nutricional se realizó mediante medición de pliegues cutáneos (SM) y densitometría (DXA). También se determinó el índice de masa libre de grasa (FFMI). El diagnóstico de desnutrición se estableció si el índice de masa corporal (IMC) era < 18,5 kg/m^2. Se diagnosticó desnutrición por masa libre de grasa (FFM) cuando el FFMI era < 17 kg/m^2 en los hombres y < 15 kg/m^2 en las mujeres (FFMI: masa libre de grasa en kg/estatura en m^2).

Resultados: se estudiaron cuarenta y un pacientes (veintidós mujeres (53,7 %), con una edad media de 29,8 años (rango intercuartílico, 20,9-33,7) y un IMC de 21,6 (19,8-23,0). Solo cuatro (9,8 %) pacientes tenían un IMC < 18,5. Mediante DXA, los resultados de FFM (kg) fueron (mediana y RIC): 52,8 (47,8-56,9) con FFMI de 17,9 (16,7-19,3) en los varones y 36,7 (33,1-38,9) en las mujeres con FFMI de 14,7 (14,2-15,8). Veinte (48,6 %) pacientes presentaban desnutrición del FFM, con el 16,7 % de varones y el 59,1 % de mujeres afectados. Mediante el SM, el FFMI fue de 18,7 (17,2-20,0) en los varones y de 14,9 (14,2-15,8) en las mujeres; además, dieciséis (39,1 %) pacientes presentaban malnutrición del FFMI, con el 20,8 % de varones y el 61,8 % de mujeres afectados.

En el caso de la FFM (kg), se obtuvo una alta concordancia entre el SM y la DXA (coeficiente de correlación intraclase de 0,950); igualmente cuando se compararon las técnicas aplicando los criterios ESPEN para la desnutrición de la FFM. Sin embargo, cuando se compararon las técnicas para clasificar la malnutrición según el FFMI, el coeficiente kappa fue solo moderado (coeficiente kappa = 0,440). La diferencia media entre el FFM por DXA y el SM fue de +1,44 ± 0,62 kg a favor del SM, con mayor dispersión a medida que aumenta el FFM.

Conclusiones: la prevalencia de la malnutrición por FFM es elevada en los pacientes adultos con FQ, a pesar de presentar un IMC normal, especialmente en el caso de las mujeres. A pesar de existir una buena correlación estadística entre el SM y la DXA, la concordancia fue moderada. Por lo tanto, la DXA sigue siendo la técnica de elección y el SM puede ser una alternativa cuando la DXA no esté disponible.

Palabras clave:

Fibrosis quística. Desnutrición. Valoración nutricional. Densitometría de doble energía X (DXA). Antropometría (SM).

INTRODUCTION

Cystic fibrosis (CF) is an inherited multisystemic disease caused by the alteration of a gene located on chromosome 7 (CFTR: cystic fibrosis transmembrane conductance regulator) (1). Alterations in CFTR lead to an impaired transport of chloride, bicarbonate, and sodium ions across epithelial cell membranes (2). In healthy subjects, mucus is mainly composed of mucins and water. Hydration and pH regulate mucus viscosity, and both functions are controlled by CFTR on the apical surface of epithelial cells. Chloride movement dictates the degree to which mucus retains water, while CFTR-mediated bicarbonate efflux plays a key role in defining pH, which is critical for a healthy antibacterial response. When the CFTR protein is altered, thick mucus secretions are produced (1). These thickened secretions are produced predominantly in the pancreas and lungs. This disturbance at the pulmonary level may cause decreased pulmonary function. In addition, malabsorption and maldigestion of nutrients, particularly fat-soluble vitamins and fats, can lead to poor nutritional status. Until a few years ago, malnutrition was considered to be associated with CF because it was practically always present at the time of diagnosis and a vast majority of patients suffered from deterioration of their nutritional status and died deeply malnourished. The interaction between lung function and nutrition has a great importance, as a parallel worsening in both would affect prognosis and quality of life. Thus, malnutrition behaves as a risk factor predictor of morbidity and mortality in CF (1-6). Although the prevalence of malnutrition has decreased considerably, figures close to 25 % continue to be reported in both children and adults (7).

Guidelines on endocrine-nutrition care for patients with CF at different stages of life (infants, children, and adults) have been developed by the *ESPEN, ESPGHAN,* and *ECFS.* These guidelines recommend periodic nutritional assessments as a primary step to achieve the best therapeutic and prognostic outcomes as possible (4). At every visit, patient's weight, height, body mass index (BMI), and weight loss over time are recorded (8). BMI is used in the clinical setting to quantify the nutritional status of CF patients. BMI targets are used in clinical practice; however, although the relationship between BMI and lung function in CF patients is well established, the exclusive use of BMI as an indicator of nutritional status can be misleading (9). In clinical practice, individuals with the same BMI may have different distributions of fat (FM) and fat-free mass (FFM); besides, patients with normal BMI may lack of FFM. Measuring the proportion of FFM and lean body mass may help to describe better the nutritional status in CF. In CF, one of the most important determinants of morbidity and mortality related to malnutrition is the decrease in fat-free mass (FFM); therefore, it is important to measure it accurately (10). Different methods can be used to assess whole-body and segmental BC: dual energy X-ray

densitometry (DXA), bioimpedanciometry (BIA), skinfold measurement (SM), or deuterium dilution (DD). In addition, imaging methods such as computed tomography (CT) or magnetic resonance imaging (MRI) can also be used for evaluating nutritional status. However, there has been great variability among the studies that assess body composition (BC) by different methods in CF patients (11). Therefore, clear conclusions to propose an evidence-based algorithm to assist in the assessment of BC cannot be drawn. Currently, DXA represents the preferred option for assessing and monitoring BC changes in this population, and is the most frequently applied method (10). Furthermore, in clinical practice DXA is considered the technique of choice (12). Thus, it is necessary to know the degree of agreement between the values obtained by DXA and other techniques more easily implemented in routine care, such as SM, which is more accessible for health care teams. In addition, increasingly accurate equations are available for the assessment of BC, which would support the use of SM (13). However, few studies have assessed BC using different techniques and evaluated their agreement in adults with CF.

We hypothesize that SM has both an adequate correlation and concordance for measuring FFM with respect to DXA in adults with CF.

The objective of our study was to describe BC using different techniques to evaluate nutritional status (DXA vs SM), and to assess their concordance in adults with CF.

MATERIALS AND METHODS

This was a cross-sectional, observational study in patients with CF in situation of clinical stability. A sequential recruitment was carried out when patients attended the CF adult's outpatient consulting room for their annual examination.

ANTHROPOMETRIC AND BODY COMPOSITION PARAMETERS

Height was obtained by a stadiometer (Holtain limited, Crymuch, UK) and weight was assessed through a scale (SECA 665). With these two values, BMI was calculated. The diagnosis of malnutrition was established when BMI was < 18.5 kg/m^2.

Skinfold thickness measurement (SM)

The skinfolds assessed were the triceps, biceps, subscapularis, and supra-iliac. A Holtain constant pressure caliper (Holtain Limited) was used to assess skinfolds. The same investigator performed the measurements in triplicate for each of the skinfolds assessed and the mean was calculated according to the recommendations by the Spanish Society of Endocrinology and Nutrition (SEEN) (14). The values for the healthy Spanish population were taken as a reference for the estimation of percentiles (15). Percentages and kilograms of FM and FFM were estimated according to the formulas of Siri (16) and Durnin and Womersley (17). Age, sex, weight, and the sum of four skinfolds (triceps, biceps, supra-iliac, and subscapular) were taken into account in the formula.

Dual-energy X-ray absorptiometry (DXA)

A General Electric Healthcare Lunar Prodigy Advance densitometer was used to scan the patients and the software used was EnCore 12.3 (18). All the scans were performed according to the manufacturer's standard scan and positioning protocols. Weight, total and regional fat, and FFM were recorded.

In addition, FFM index (FFMI) was calculated (FFMI: fat-free mass in kg/height in m^2) and the prevalence of FFM malnutrition was determined according to the European Society for Clinical Nutrition and Metabolism (ESPEN) criteria: < 17 kg/m^2 (men) or < 15 kg/m^2 (women) (8).

ASSESSMENT OF RESPIRATORY STATUS

Recorded exacerbations were assessed at the annual review appointment. Exacerbations occurring in the year preceding the assessment were considered (19). In addition, following the recommendations of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR), respiratory function tests were performed using forced spirometry with a JAEGER pneumotachograph (Jaeger Oxycon Pro® Erich Jaeger, Würzburg, Germany), and forced vital capacity (FVC), maximal expiratory volume in the first second (FEV_1), and the ratio between both (FEV_1/FVC) were determined for all patients. The values obtained were expressed in absolute terms in ml and as a percentage of the theoretical value for subjects of age, weight and height, according to a reference population (20). Bronchorrhoea was defined as the amount of sputum produced per day and was expressed in milliliters. To assess bronchorrhea, the patient made an estimate during the last three days before the visit (19).

DATA ANALYSIS

The SPSS version 22.0 was used for the data analysis (21). The Kolmogorof-Smirnoff test was used to evaluate the distribution of quantitative variables. The paired-samples t-test (or Wilcoxon's test in the absence of normality) was used to compare quantitative variables. Statistical significance was set at $p < 0.05$ for all statistical analyses performed.

The intraclass correlation coefficient (ICC) (22) was used to study the degree of agreement between the BC using the different techniques, and Bland-Altman plots were used to analyze the individual differences. The kappa coefficient was calculated in order to assess the concordance between the different methods to classify individuals with a low FFMI.

ETHICS

All subjects gave their informed consent before being included in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Research Ethics Committee of the Malaga Province (27/04/2017).

RESULTS

Forty-one patients with CF were recruited. Of these patients, nineteen were males (46.3 %) and twenty-two (53.7 %) were females. Their median age was 29.8 (20.9-33.7) (Table I).

Only four (9.8 %) patients had a BMI lower than 18.5 kg/m^2. By DXA, FFM (kg) results were median: 52.8 (interquartile range, 47.8-56.9) kg with FFMI 17.9 (16.7-19.3) kg/m^2 in men, and 36.7 (33.1-38.9) kg in women with FFMI 14.7 (14.2-15.8) kg/m^2. Using this technique, twenty (48.6 %) patients presented FFM malnutrition, with 16.7 % of males and 59.1 % of females being affected. By SM, FFMI was 18.7 (17.2-20.0) kg/m^2 in males and 14.9 (14.2-15.8) kg/m^2 in females; moreover, sixteen (39.1 %) patients presented FFM malnutrition, with 20.8 % of males and 61.8 % of females being affected. The general characteristics of the patients are summarized in table I. All patients designated as malnourished by FFM according to SM were found to be malnourished according to DXA.

Figures 1A and B show body composition as assessed by DXA and SM. They show that the prevalence of FFM malnutrition is higher for DXA than for SM. In addition, the prevalence of malnutrition was higher in females than in males in the nutritional assessment by both techniques.

Concordance was high between SM and DXA for the FFM in kg (ICC of 0.950; $p < 0.001$) and also in % (Table II). Concordance was also high for FM as expressed both in kg and %. When the techniques were compared by applying the ESPEN criteria for FFMI malnutrition, concordance was moderate: kappa coefficient of 0.440 when comparing SM with DXA ($p = 0.006$).

By analyzing individual differences using the Bland-Altman plot analysis, the degree of agreement between baseline BC data obtained with DXA and SM was assessed (Fig. 2). The mean overestimation with respect to DXA was +1.44 ± 0,62 kg, with a tendency to greater dispersion in higher FFM.

Table I. General characteristics

	CF (41)
	Median (interquartile range)
Age	29.8 (20.9-33.7)
Sex, n (%)	n (%)
Female	22 (53.7)
Male	19 (46.3)
Respiratory	
Bronchorrhea (mL)	10.0 (10.0-20.0)
Annual exacerbation	2.0 (1.0-4.0)
FEV_1 (%)	60.6 (48.5-87.9)
FVC (%)	74.6 (67.2-96.2)
FEV_1/FVC (%)	65.6 (53.7-65.6)
Nutritional status	
BMI (kg/m^2)	21.6 (19.8-23.0)
BMI ≥ 18.5 kg/m^2, n (%)	37 (90.2)
BMI < 18.5 kg/m^2, n (%)	4 (9.8)
DXA	
FM (kg)	
Male	14.9 (11.8-17.9)
Female	14.8 (13.8-15.2)
FFM (kg)	
Male	52.8 (47.8-56.9)
Female	36.7 (33.1-38.9)
FFMI (kg/m^2)	
Male (Normal ≥ 17 kg/m^2)	17.9 (16.7-19.3)
Female (Normal ≥ 15 kg/m^2)	14.7 (14.2-15.8)
SM	
FM (kg)	
Male	11.6 (8.5-19.3)
Female	15.3 (11.5-17.9)
FFM (kg)	
Male	52.1 (47.5-59.1)
Women	36.9 (33.8-40.5)
FFMI (kg/m^2)	
Male (Normal ≥ 17 kg/m^2)	18.7 (17.2-20.0)
Female (Normal ≥ 15 kg/m^2)	14.9 (14.2-15.8)

BMI: body mass index; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; DXA: dual-energy X-ray absorptiometry; FM: fat mass; FFM: fat-free mass; FFMI: fat-free mass index; SM: skinfold measurement.

DISCUSSION

In our study we found a high prevalence of FFM malnutrition, especially in females, according to the different nutritional assessment techniques used. In addition, we found a high statistical agreement between DXA and SM for FM and FFM values. However, the concordance when we assessed malnutrition according to FFMI was moderate. It was observed that SM tends to overestimate FFM and to underestimate FM, compared to DXA.

According to the Cystic Fibrosis Foundation (CFF), a BMI ≥ 22 kg/m^2 in females and a BMI ≥ 23 kg/m^2 in males is recommended as a target for adults, as it is associated with improved lung function (23). However, despite the improvement in disease progression and nutritional status, according to the latest European Cystic Fibrosis Registry the prevalence of malnutrition determined by BMI (below 18.5 kg/m^2) is approximately 30 % of adults (23). In our study, the mean BMI is slightly higher than the one published in the 2014 European CF registry (22.2 vs 21 kg/m^2) for a similar mean age (24). In addition, the rate of malnutrition determined by BMI in our CF population was 9.8 %, lower than the one published in other series (24,25). However, BMI measurement alone

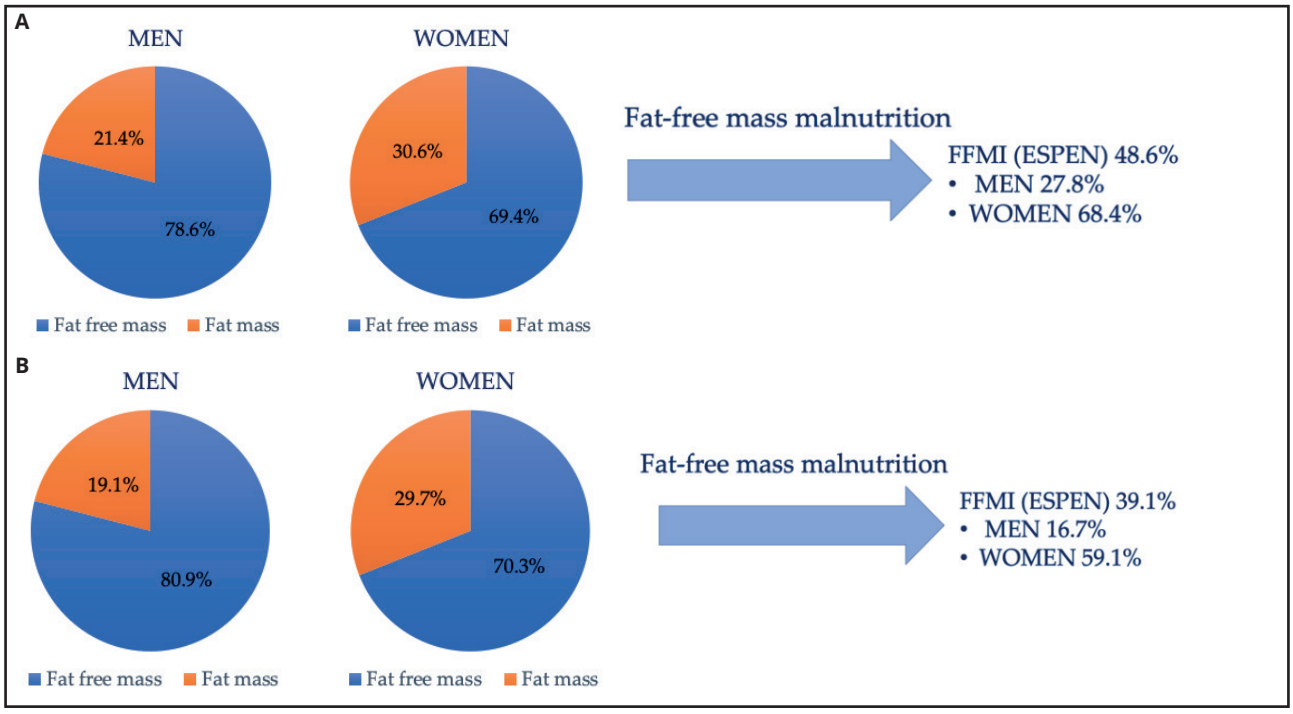

Figure 1.

A. Body composition according to sex by DXA (%). B. Body composition according to sex by SM (%).

Table II. Comparison of measurements and agreement between BC values by SM and DXA

	DXA medians (IQR values)	SM medians (IQR values)	p[1]	ICC	p[2]
FM (kg)	14.8 (9.6-18.9)	14.7 (10.3-17.9)	0.136	0.926	< 0.001
FFM (kg)	40.8 (36.0-52.5)	43.2 (36.6-52.5)	0.054	0.950	< 0.001
FM (%)	27.7 (18.6-33.5)	27.6 (17.9-33.7)	0.056	0.912	< 0.001
FFM (%)	72.3 (66.5-81.4)	72.4 (66.3-82.1)	0.057	0.912	< 0.001

Medians. IQR: interquartile range; ICC: intraclass correlation coefficient; DXA: dual-energy X-ray absorptiometry; SM: skinfold measurement; FM: fat mass; FFM: fat-free mass. p[1]: statistical significance of the comparison of DXA and SM measures; p[2]: statistical significance of CCI.

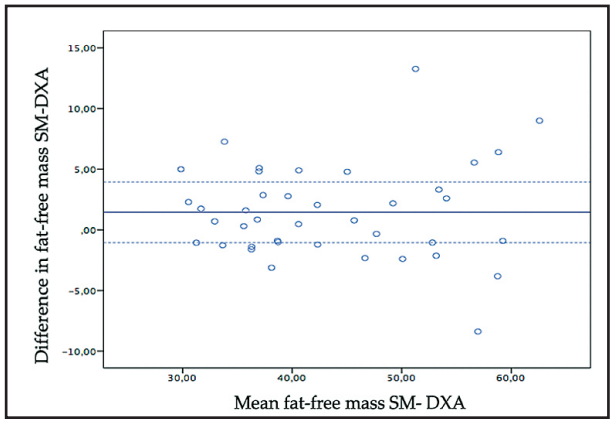

Figure 2.

Comparison between FFM by SM and DXA.

in adults with CF should not be the only parameter used to assess nutritional status. Engelen et al. have warned about the increased prevalence of overweight and obesity in this population (even in association with severe mutations), and BMI may therefore be a confounding factor for nutritional status. It has been observed that between 25-38 % of adult CF patients with a normal or high BMI have low lean mass levels (26). Thus, guidelines on nutrition care for patients with CF recommend evaluating BC as part of the nutritional assessment (3,4).

In CF, one of the most important determinants of morbidity and mortality in relation to malnutrition is the decrease in FFM (10,27). It is therefore useful to measure BC, using different techniques, to estimate FFM; in this sense, the calculation of FFMI is particularly useful (4). In the review by Calella et al. they

conclude that the results showed great variability in the methods used to evaluate BC in patients with CF (10). In the review by Gomes et al. they conclude that further studies are needed to identify and determine which FFM measurements are associated with improved lung function and nutritional status in CF patients (5). The use of DXA-derived FFM measurements in clinical practice among CF patients shows great potential utility and value. Furthermore, together, FFM and BMI may provide a more comprehensive picture of nutritional status during the nutritional evaluation of CF patients (5).

In the present study, we have performed a comparison of simpler techniques as SM with DXA. Some of the potential advantages of DXA for assessing BC are the high accuracy of SM and DXA (28), the good agreement with the results obtained using the 4-compartment model (29), good short-term reproducibility (30), and the possibility of assessing total and segmental BC. On the other hand, the limitations of DXA are the lack of portability of the equipment, the radiation exposure associated with the scan, or the fact that it requires the patient to be in a decubitus position for a few minutes (which may be difficult for patients with severe lung disease) (28). For this reason, several studies have questioned whether DXA could be replaced by other measures of BC (31). A recent study of children with CF found, using DXA, estimated a prevalence of malnutrition of 38.6% based on FFM deficit (defined as FFMI $< 10^{th}$ percentile) (27). In our work, the median and IQR for FFMI determined by DXA were 17.9 (16.7-19.3) kg/m^2 in males and 14.7 (14.2-15.8) kg/m^2 in females, being slightly higher when determined by SM. By DXA, we found a prevalence of FFM malnutrition of 48.6 %, which was much higher in females (68.4 %) compared to males (27.8 %) and using the criteria recommended by ESPEN (17 kg/m^2 in males and 15 kg/m^2 in females) (8). It is possible that the ESPEN criterion for females is too high in this population, overestimating the prevalence of FFM malnutrition. According to the Spanish population data, the FFMI cut-off point for males would remain at 17 kg/m^2; however, in females it would be 14.4 kg/m^2 (32,33). If we consider 14.4 kg/m^2 as the cut-off point for FFMI in females to diagnose FFM malnutrition, the prevalence of malnutrition in females in our study would drop to 47.4 % using DXA.

Assuming that subcutaneous adipose tissue represents a constant proportion of total body fat, and that measurement sites are representative of the average subcutaneous adipose tissue thickness, skinfold thickness measurements are useful to estimate FFM and FM (29). This may vary depending on race, age, gender, and disease (29). Inter- and intra-observer variability are other limitations of this technique (30). The use of SM in CF has been evaluated in several studies (27,30,34-40). The same researcher always performed the anthropometric measurements in our study. We observed that 39.1 % of patients had FFM malnutrition, with 16.7 % of males and 59.1 % of females being affected, estimated by SM. This prevalence is slightly lower, especially in females, which could classify malnourished people as normonourished. In this sense, if we used the cut-off point 14.4 kg/m^2 (32,33) to detect malnutrition according to FFMI, the prevalence of FFM malnutrition would decrease considerably to 13.6 % according to SM.

Chomtho et al. evaluated the use of upper arm anthropometry compared to DXA in healthy children and children with CF, concluding that upper arm anthropometry is less accurate than DXA for determining segmental and total FFM. The results were better for FM determination (35). In the work by Alicandro et al. using DXA as a reference method, they conclude that BC estimation obtained by SM or BIA cannot be part of the standard nutritional assessment of CF patients due to low precision at the individual level, at least until reliable CF-specific equations become available (36). King et al. also compared BIA and SM with DXA in adults with CF (37). SM overestimated lean mass by almost 2.4 kg on average compared to DXA. In a study of our group in people with non-CF BQ, SM also overestimated lean mass with very similar values (2.35 kg on average) and was homogeneously distributed across lean mass values (38). The study by de Meer et al. that assessed changes in lean mass by skinfold measurement in malnourished children with CF after a physical exercise program concluded that regardless of disease severity this technique is applicable to detect changes in lean mass (39). Stettler et al. also assessed prospectively body composition in children with CF using various techniques such as double watermarking, SM and BIA; the study showed high concordance for lean mass but not for FM (40). In our study, there was good statistical agreement between SM and DXA for assessing FM and FFM. However, the concordance was moderate for detecting malnutrition according to FFMI. Using Bland-Altman plot analysis, the mean overestimation with respect to DXA was $+1.44 \pm 0{,}62$ kg, thus, the degree of agreement showed a greater dispersion as FFM increased.

The limitations of our study are mainly due to the fact that it is a single-center study, which prevented us from having a larger sample size. Furthermore, the study design was cross-sectional. These limitations hamper drawing causal conclusions, and therefore, we can only speculate about different associations.

In conclusion, the prevalence of FFM malnutrition is high in CF patients, despite presenting a normal BMI, especially in females. The cut-off point for FFM proposed by the ESPEN may be high in our population. There was good statistical agreement between SM and DXA for assessing FM and FFM. However, the concordance was moderate for detecting malnutrition according to FFMI, and the degree of agreement showed a greater dispersion as FFM increased. Therefore, DXA remains the technique of choice for nutritional assessment in CF, and SM can be used in cases in which it is not available.

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Trabajo Original

Epidemiología y dietética

Does fetuin-A mediate the association between pro-inflammatory diet and type-2 diabetes *mellitus* risk?

¿Fetuína-A media en la asociación entre la dieta proinflamatoria y el riesgo de diabetes mellitus *tipo 2?*

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Abstract

Introduction: recent studies indicate that diet increases T2DM risk via inflammation. Fetuin-A, identified as an acute-phase protein, plays a role in insulin resistance and is an independent predictor of type-2 diabetes.

Objectives: the present study aimed to examine the association between diet and T2DM risk, and whether said association is mediated by fetuin-A, and to determine the effect of fetuin-A on T2DM risk.

Methods: the case group included 40 individuals with T2DM, whereas 40 individuals without T2DM comprised the control group. The Dietary Inflammatory Index (DII), was used to determine the inflammatory potential of diet. A simple mediation analysis was used to investigate whether diet was associated with T2DM risk and whether the association was mediated by fetuin-A.

Results: subjects who consumed a high pro-inflammatory diet had 2.0 times higher risk of developing T2DM (OR = 2.043; 95 % CI: 0.955 to 4.371, p = 0.066). In addition, subjects who had higher levels of fetuin-A had a 1,2 times higher risk of developing T2DM (OR = 1.155; 95 % CI: 1.030 to 1.296, p = 0.014). Both fetuin-A and hs-CRP had a significant full mediator role on the association between DII and HOMA-IR [respectively; $\beta = 0.371$ (95 % CI: -0.029-0.770), $\beta = 0.424$ (95 % CI: -0.007-0.856)].

Conclusion: these findings suggest that a pro-inflammatory diet, by creating an environment of increased inflammatory markers, affects in particular insulin resistance through these markers and ultimately causes T2DM. In addition, fetuin-A also acts as an important novel mediator between diet and T2DM by inducing insulin resistance.

Keywords:

Fetuin A. Dietary inflammatory index (DII). Type 2 diabetes. Inflammation. Mediator.

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Ethical approval: the study was approved by the Clinical Research Ethics Committee of University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital (reference number 70/04 on 26.08.2019). All procedures performed involving human participants were in accordance with the 1964 Helsinki Declaration. All participants provided written informed consent.

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Resumen

Introducción: estudios recientes indican que la dieta aumenta el riesgo de T2DM mediante la inflamación. La fetuína-A,identificada como proteína de fase aguda, desempeña un papel en la resistencia a la insulina y es un predictor independiente de la diabetes de tipo 2.

Objetivos: el presente estudio pretende examinar la asociación entre la dieta y el riesgo de DMT2 y si la asociación está mediada por la fetuína-A y determinar el efecto de la fetuína-A sobre el riesgo de DMT2.

Métodos: en el grupo de casos se incluyeron 40 individuos con DMT2, mientras que 40 individuos sin DMT2 se incluyeron en el grupo de control. El índice de inflamación de la dieta (DII) se usó para determinar el potencial inflamatorio de la dieta. El análisis de mediación simple se usó para investigar si la dieta estaba asociada con el riesgo de DMT2 y si la asociación estaba mediada por la fetuína-A.

Resultados: los sujetos que consumieron una dieta más proinflamatoria tuvieron 2 veces más riesgo de desarrollar DMT2. Además, los sujetos que tenían niveles más altos de fetuína-A tuvieron 1,2 veces más riesgo de desarrollar DMT2. Tanto la fetuína-Acomo la hs-CRP tuvieron un papel significativo como mediadores completos sobre la asociación entre DII y HOMA-IR.

Conclusión: estos hallazgos sugieren que la dieta proinflamatoria, al crear un ambiente con marcadores inflamatorios aumentados, afecta en particular a la resistencia a la insulina a través de estos marcadores y, finalmente, causa DMT2. Además, la fetuína-A también actúa como mediador novedoso importante entre la dieta y la DMT2 al inducir la resistencia a la insulina.

Palabras clave:

Fetuína-A. Índice de inflamación de la dieta (DII). Diabetes de tipo 2. Inflamación. Mediador.

INTRODUCTION

Type-2 diabetes *mellitus* (T2DM) has been defined as a metabolic disease that develops due to a progressive loss of adequate β-cell insulin secretion, frequently in the setting of insulin resistance.

It accounts for 90-95 % of all diabetes cases and includes individuals with insulin deficiency and/or peripheral insulin resistance (1). The prevalence of T2DM is growing in many developing and most developed countries. The International Diabetes Federation (IDF) reported that there were 463 million people with diabetes worldwide in 2019 and that this number will increase to 700 million by 2045 (2). The cause of T2DM is poorly understood, but insulin resistance causing β-cell loss or dysfunction appears to be the main reason for T2DM development (1).

Fetuin-A, also called Alpha 2-Heremans Schmid Glycoprotein (AHSG), is an endogenous glycoprotein predominantly secreted by the liver (3). First discovered in 1944, it has been reported to have a protective effect from ectopic calcium deposition and vascular calcification. Since then, it has been shown to be a multifunctional protein with effects on multiple cellular pathways and associated with the skeletal system, cardiovascular system, metabolism, and nervous system (4). In recent years, emerging evidence suggests that fetuin-A plays a role in insulin resistance, especially in individuals with T2DM, and is an independent predictor of type-2 diabetes (3-5).

One of the effector mechanisms of fetuin-A on insulin resistance and diabetes development is that fetuin-A is a natural endogenous inhibitor of the insulin-stimulated insulin receptor tyrosine kinase (6). In epidemiological studies, it has been shown that there is a relationship between serum fetuin-A level and the risk of developing insulin resistance and diabetes (6,7). Another mechanism that may explain the relationship between high fetuin-A levels and insulin resistance is that fetuin-A causes inflammation by inducing inflammatory cytokines, which in turn causes insulin sensitivity (8). Previous studies have shown that fetuin-A induces the expression of pro-inflammatory cytokines (8,9).

In recent years, diet has been identified as an important modulator of chronic inflammation (10). Besides, it has been suggested that diet may also increase T2DM risk via inflammation (11). In this regard, many nutrients with anti-inflammatory effects have been associated with a lower risk of T2DM whereas nutrients with pro-inflammatory effects have been associated with a higher risk of T2DM in previous studies (12,13).

There is an increasing number of studies investigating the effect of the inflammatory potential of diet on diseases, and the dietary inflammatory index (DII) has been widely used in these studies (14,15). DII is a literature-derived, validated index that was designed to measure the inflammatory potential of diet. Regarding the index, a higher DII score represents a pro-inflammatory diet, whereas a lower score represents an anti-inflammatory diet (16). Besides, only a few studies have investigated the relationship between the inflammatory potential of diet as measured by DII and T2DM (14,17). To the best of our knowledge, no studies have focused on the mediator role of fetuin-A in this relationship. In addition, limited studies are evaluating the effect of fetuin-A on T2DM.

The present study aimed to investigate the effect of an inflammatory diet on the risk of developing T2DM via fetuin-A, an acute phase reactant, and to determine the effect of fetuin-A on T2DM risk.

MATERIALS AND METHODS

STUDY POPULATION

This case-control study included a total of 80 patients aged between 30 and 50 years, with 40 obese women (BMI, 30-35) with T2DM as the case group and 40 obese women (BMI, 30-35) as the control group. The study sample size was calculated using the G*Power, version 3.1.9.2, software package, taking into account the results of previous studies; the error rate was 0.05 and power was 80 %. Individuals who attended the Family Medicine Outpatient Clinic of Health Sciences University Dışkapı Yıldırım Beyazıt Training and Research Hospital, referred to the Nutrition and Dietetics Department, and matching inclusion criteria were included in the study. The individuals excluded from the study were as follows; type-1 diabetes patients, type-2 diabetes patients receiving insulin treatment, those in the menopause period, pregnant or breastfeeding women, those with

acute or chronic inflammatory diseases, liver or kidney failure, severe psychiatric disorder, cancer patients, those who received steroid/antibiotic treatment, anti-inflammatory drugs, medication for obesity for the previous six months, and those who regularly used drugs (except oral antidiabetics).

The study protocol was reviewed by the Clinical Research Ethics Committee of University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital and approved by the report of the decision number 70/04 on 26.08.2019. All participants provided a written informed consent.

ANTHROPOMETRIC MEASUREMENTS

Anthropometric measurements, including height, weight, waist and, hip circumference, were measured with as few and as thin clothes as possible and without shoes. These measurements were done by the researcher in the morning. Body height (m) was measured using a stadiometer attached to the digital weight scale (Seca 769). To measure weight (kg), a digital weight scale with an accuracy of 0.1 kg (Seca 769) was used. Body mass index (BMI) was calculated as weight over height squared (kg/m^2). Individuals between 30 and 35 kg/m^2 were included in the study, considering the World Health Organization (WHO) criteria (18). Waist circumference (cm) was measured at the midpoint between the inferior margin of the last rib and the iliac crest with an inelastic tape in the horizontal plane. Hip circumference (cm) was also measured at the same position, using the same tape at the widest point of the hip. The waist-hip ratio was calculated by dividing the waist circumference of the participants by their hip circumference.

ASSESSMENT OF DIETARY INTAKE AND DIETARY INFLAMMATORY INDEX

The dietary intake of individuals was assessed using a quantitative food frequency questionnaire (QFFQ). The consumed amount of each food was multiplied by the specific coefficient of frequency of consumption, and the average daily amounts of the foods were obtained. The Nutrient Database Programme (BeBiS, Ebispro for Windows, Germany; Turkish Version/BeBiS 8.2) was used to determine average daily energy and nutrient intake for each individual. To measure the dietary inflammatory potential of the diet, the dietary inflammatory index (DII), which is a valid and reliable tool, was used. The calculation steps of the DII have been previously described in detail in its methods paper (16). Briefly, the DII is based on a literature review and analysis of articles published up to 2010 linking dietary components with inflammatory markers, including TNF-α, CRP, IL-1β, IL-4, IL-6, and IL-10. Each dietary parameter associated with inflammation in the articles was scored according to its effects on these six inflammatory markers. Each was assigned a 'food parameter-specific inflammatory effect score'. A global data set including these inflammation-related food parameters' standard global daily intake (mean values and standard deviations of 45 food parameters) and food parameter-specific inflammatory effect score was created. The DII is calculated using this global composite database. When calculating the DII, firstly the inflammatory effect score is calculated separately for each food parameter consumed by the individuals in the dataset, then the sum of these obtained scores represents the inflammatory index score of an individual's diet. In this study, DII was calculated for each individual as follows: Z-scores were obtained by subtracting the standard global mean from the reported amount and dividing that value by the standard deviation. To reduce the effects of right-skewing (a common occurrence with dietary data), Z-scores for each food parameter were converted to percentiles. The percentile score is converted to the center percentile score [(percentile score x 2) – 1]. The central percentile score for each intake parameter was multiplied by the "food parameter-specific inflammatory effect score". The overall DII was calculated by summing the inflammatory effect scores calculated for each nutrient parameter consumed by the individual. In this study, 44 of the original 45 DII food parameters were available from the FFQ and were used for DII calculation. These included mean daily intakes of energy, carbohydrates, fiber, protein, total fat, saturated fat, monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), omega-3 fatty acids, omega-6 fatty acids, cholesterol, alcohol, vitamin A, vitamin D, vitamin E, vitamin B_1 vitamin B_2, niacin, vitamin B_6, vitamin B_{12}, folic acid, vitamin C, beta-carotene, magnesium, iron, zinc, selenium, flavon-3-ols, flavones, flavonols, flavanones, anthocyanidins, isoflavones, caffeine, tea, onion, garlic and pepper, eugenol, ginger, thyme, rosemary, turmeric, and saffron. Higher DII scores (positive or close to positive) represent a pro-inflammatory diet quality and lower DII scores (negative or close to negative) represent an anti-inflammatory diet quality.

SERUM COLLECTION AND LABORATORY MEASUREMENTS

Fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), fasting insulin, white blood cell (WBC), lymphocyte (LYM), neutrophile (NEU), triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and hs-CRP levels were analyzed using standard techniques from blood samples taken after an overnight fast (at least 8 hours). The homeostatic model assessment of insulin resistance (HOMA-IR) value, the indicator of insulin resistance, was calculated with the following formula: fasting blood glucose (mg/dL) x fasting insulin (µU/mL) / 405. Blood samples (10 mL, 2 gel tubes), which were taken to analyze serum fetuin-A, IL-6, and TNF-α levels, were centrifuged and preserved at –80 °C with the serum separated until the analysis. Fetuin-A (Human Fetuin-A ELISA BioVendor Laboratories, Modrice, Czech Republic) (Catalog No.: RD191037100), IL-6 (DIAsource ImmunoAssays S.A., Belgium) (Catalog No.: KAP1261), and TNF-α (DIAsource ImmunoAssays S.A., Belgium) (Catalog No.: KAP1751) were measured using enzyme-linked immunosorbent assay (ELISA) test kits according to the manufacturer's protocol.

STATISTICAL ANALYSIS

Chi-square tests were used for categorical variables, and Student's t-test and Mann-Whitney U-test were used for continuous variables to evaluate differences between different groups. Definitive statistics were presented as mean ($\bar{x}$) ± standard deviation (SD) or median, minimum-maximum (min-max) or frequency, percentage (%), where appropriate. Spearman's correlation analysis was performed to assess the strength of the relationship between continuous variables. Binary logistic regression was used to evaluate the relationship between some predictors and T2DM risk. The simple mediation analysis as described by Preacher and Hayes (19) was used to investigate whether the DII was associated with glucose metabolism markers or whether the association was mediated by fetuin-A and other inflammatory markers (Fig. 1). Total, direct, and indirect effects of DII on glucose metabolism markers were evaluated by using independent, dependent, and mediator variables. Path "c" shows the 'total effect' of DII on glucose metabolism markers without adjusting mediator variables (Fig. 1A); the product of regression coefficients α and β ($\alpha\beta$) shows the 'indirect effect' (mediated effect) of DII on glucose metabolism markers via the mediator variables (Fig. 1B); path "c'" shows the 'direct effect' of DII on glucose metabolism markers after adjusting the effect of the mediator variables (Fig. 1B). When the total and indirect effects are significant, and the direct effect is non-significant (NS), a 'full or complete mediation' occurred; when the total and indirect effects are significant, and the direct effect remains significant, a 'partial or incomplete mediation' occurred. When both the total and indirect effects are NS, the result was designated 'inconsistent mediation'. The mediation effect proportion was calculated using the following equation: [$\alpha\beta$ / $\alpha\beta$ + c']. The statistical analyses were performed using the IBM SPSS (Statistical Package for Social Sciences, SPSS Company, IL, USA) program, version 23. Statistical significance was defined as $p < 0.05$.

RESULTS

The baseline clinical data of the study population for the case and control groups are shown in table I. The average age of the case group was 43.5 ± 4.2 years, and that of the control group was 36.5 ± 5.7 years, with a statistically significant difference between groups ($p < 0.05$). A statistically significant difference was noted between the groups in terms of BMI ($p < 0.05$). However, there was no statistically significant difference between groups in the values of waist circumference, hip circumference, and waist-to-height ratio ($p > 0.05$). The median value of the DII scores of the case group was significantly higher than that of the control group ($p < 0.05$). The case group had significantly higher WBC, LYM, NEU/LYM, triglyceride, total cholesterol, LDL-cholesterol, and all glucose metabolism markers, including fasting blood glucose (FBG), insulin, HbA1c, and HOMA-IR values, in comparison to the control group ($p < 0.05$). Inflammatory markers including fetuin-A, IL-6, and TNF-α were

Table I. Baseline characteristics, biochemical measurements, and DII scores of the case and control groups

Variables	Cases (n = 40)	Controls (n = 40)	p-value*
Age (years)	43.5 ± 4.2	36.5 ± 5.7	*< 0.001*
Family history of DM	27 (67.5)	8 (20.0)	*< 0.001*
BMI (kg/m^2)	33.4 ± 1.6	32.7 ± 1.7	*0.044*
Waist circumference (cm)	101.2 ± 6.8	98.5 ± 6.1	0.074
Hip circumference (cm)	118.1 ± 6.1	115.6 ± 6.2	0.067
Waist-to-hip ratio	0.86 ± 0.04	0.85 ± 0.05	0.783
Waist-to-height ratio	0.64 ± 0.04	0.63 ± 0.04	0.232
DII score	0.23 (-0.88-2.84)	-0.32 (-2.20-1.51)	*0.007*
Fasting blood glucose (mg/dL)	127.0 (83.0-201.0)	88.50 (69.00-109.00)	*< 0.001*
Insulin (uIU/mL)	12.9 (5.5-24.1)	9.9 (4.1-32.7)	*0.049*
HbA1c (%)	7.1 (6.2-11.2)	5.4 (4.8-5.7)	*< 0.001*
HOMA-IR	3.8 (1.3-7.9)	2.3 (0.8-7.2)	*< 0.001*
WBC (10^3/µL)	8.4 ± 2.0	7.6 ± 1.4	*0.049*
LYM (10^3/µL)	2.9 ± 0.7	2.4 ± 0.5	*0.002*
NEU (10^3/µL)	4.6 ± 1.4	4.4 ± 0.9	0.479
NEU/LYM	1.6 (0.9-3.2)	1.8 (1.3-3.5)	*0.039*
Triglycerides (mg/dL)	172.0 (63.0-415.0)	112.5 (44.0-305.0)	*0.015*
Total cholesterol (mg/dL)	210.0 (143.0-276.0)	174.5 (122.0-271.0)	*< 0.001*
LDL-cholesterol (mg/dL)	140.0 (86.0-214.0)	122.4 (89.0-204.0)	*0.024*
HDL-cholesterol (mg/dL)	51.3 ± 9.3	51.1 ± 9.9	0.902
Fetuin-A (mg/dL)	67.3 (20.9-97.2)	53.0 (10.1-97.4)	*0.004*
IL-6 (pg/mL)	36.3 (27.4-306-1)	32.9 (26.9-56.5)	*< 0.001*
TNF-α (pg/mL)	2.9 (1.8-11.1)	2.1 (0.8-4.6)	*< 0.001*
hs-CRP (mg/dL)	5.7 (1.9-16.4)	5.2 (0.3-12.5)	0.055

*Data were presented as mean ± SD, n (%), or median (lower-upper limit), where appropriate. *p-values were obtained using Student's t-test, Mann-Whitney U-test, χ^2 test, and Fisher's exact test, as appropriate. BMI: body mass index; DII: dietary inflammatory index; HbA1c: glycosylated hemoglobin; HOMA-IR: homeostatic model assessment of insulin resistance; WBC: white blood cell; LYM: lymphocyte; NEU: neutrophile; LDL: low-density lipoprotein; HDL: high-density lipoprotein; IL-6: interleukin 6; TNF-α: tumor necrosis factor alpha; hs-CRP: high-sensitivity C-reactive protein.*

also found to be significantly higher in the case group than in the control group ($p < 0.05$). Table II presents the relationship between DII score and energy, nutrients, and food component intake for both the case and control groups and the total study population. As shown in the table, there was a significant negative correlation between the DII score and dietary fiber, iron, vitamin A, β-carotene, vitamin E, vitamin B_6, folic acid, flavones, and flavonols in total ($p < 0.05$). The relationship between the DII score and both glucose metabolism markers and inflammatory markers is displayed in table III. In the total study group,

Table II. Correlation analysis of DII with energy, nutrients, and dietary components between both the case and control groups, and the total study population

Variables	Cases (n = 40)		Controls (n = 40)		Total (n = 80)	
	r value	p value	r value	p value	r value	p value
Energy (kcal/day)	-0.226	0.161	0.058	0.723	-0.074	0.517
Macronutrients						
Protein (% TE)	-0.025	0.879	0.123	0.451	0.059	0.602
Carbohydrates (% TE)	0.069	0.674	-0.144	0.376	0.052	0.646
Fiber (g)	-0.270	0.092	-0.309	0.052	-0.283	*0.011*
Fat (% TE)	-0.154	0.343	0.164	0.313	0.021	0.853
Saturated fat (% TE)	0.104	0.524	0.209	0.195	0.047	0.678
MUFA (% TE)	-0.165	0.308	0.191	0.237	-0.021	0.851
Macronutrients						
PUFA (% TE)	-0.368	*0.020*	0.101	0.537	-0.147	0.193
Omega-3 (g)	-0.312	*0.049*	0.001	0.997	-0.147	0.194
Omega-6 (g)	-0.366	*0.020*	0.060	0.715	-0.152	0.180
Micronutrients						
Magnesium (mg)	-0.227	0.159	-0.170	0.292	-0.190	0.092
Iron (mg)	-0.311	0.051	-0.373	*0.018*	-0.340	*0.002*
Zinc (mg)	-0.307	0.054	-0.027	0.869	-0.150	0.185
Vitamin A (µg)	-0.323	*0.042*	-0.451	*0.003*	-0.413	*< 0.001*
Beta-carotene (µg)	-0.249	0.121	-0.441	*0.004*	-0.440	*< 0.001*
Vitamin E (mg)	-0.339	*0.032*	-0.181	0.264	-0.248	*0.026*
Vitamin B_6 (mg)	-0.390	*0.013*	-0.412	*0.008*	-0.417	*< 0.001*
Vitamin B_{12} (µg)	-0.138	0.395	0.056	0.732	-0.011	0.920
Total folic acid (µg)	-0.369	*0.019*	-0.256	0.110	-0.302	*0.006*
Vitamin C (mg)	-0.186	0.251	-0.640	*0.000*	-0.449	*< 0.001*
Dietary components						
Flavan-3-ols (mg)	-0.029	0.861	-0.168	0.300	-0.200	0.076
Flavones (mg)	-0.279	0.081	-0.504	*0.001*	-0.419	*< 0.001*
Flavonols (mg)	-0.239	0.138	-0.476	*0.002*	-0.392	*< 0.001*
Flavonones (mg)	-0.055	0.737	-0.245	0.127	-0.118	0.299

Spearman's rank correlation coefficient. MUFA: monounsaturated fatty acid; PUFA: polyunsaturated fatty acid.

Table III. Correlation analysis of DII with glucose metabolism markers and inflammatory markers between both the case and control groups and the total study population

Variables	Cases (n = 40)		Controls (n = 40)		Total (n = 80)	
	r value	p value	r value	p value	r value	p value
Fasting blood glucose (mg/dL)	0.225	0.163	-0.009	0.954	0.304	0.006
Insulin (ulU/mL)	0.171	0.291	0.119	0.464	0.185	0.101
HbA1c (%)	0.360	*0.023*	0.192	0.234	*0.391*	*< 0.001*
HOMA-IR	0.295	0.065	0.146	0.370	*0.268*	*0.016*
Fetuin-A (mg/dL)	0.351	*0.026*	0.300	0.060	*0.384*	*< 0.001*
IL-6 (pg/mL)	0.375	*0.017*	0.318	*0.046*	0.406	*< 0.001*
TNF-α (pg/mL)	0.129	0.429	-0.001	0.997	0.166	0.142
hs-CRP (mg/dL)	0.361	*0.022*	0.365	*0.021*	0.444	*< 0.001*

Spearman's rank correlation coefficient. HbA1c: glycosylated hemoglobin; HOMA-IR: homeostatic model assessment of insulin resistance; IL-6: interleukin 6; TNF-α: tumor necrosis factor alpha; hs-CRP: high-sensitivity C-reactive protein.

there was a significant positive correlation between DII and FBG, hbA1c, HOMA-IR, fetuin-A, IL-6, and hs-CRP, whereas a significant positive correlation was found between hbA1c, fetuin-A, and IL-6 in the case group, and IL-6 and hs-CRP in the control group. Table IV shows the ORs and 95 % CIs of the DII score and inflammatory markers for T2DM. After adjusting for potential confounding factors (age, physical activity, standardized energy intake, and BMI), the participants who consumed a high pro-inflammatory diet had a 2.0 times higher risk of developing T2DM (OR = 2.043; 95 % CI: 0.955, 4.371, p = 0.066). Considering the ORs of inflammatory markers, the participants who had higher levels of fetuin-A had a 1,2 times higher risk of developing T2DM (OR = 1.155; 95 % CI: 1.030, 1.296, p = 0.014). Likewise, the participants who had higher levels of IL-6 had 1.1 times (OR = 1.053; 95 % CI: 1.006, 1.102, p = 0.028), and those who had higher levels of TNF-α had a 7.2 times higher risk of developing T2DM (OR = 7.234; 95 % CI: 2.312, 22.631, p = 0.001). Table V presents the β-coefficients (95 % CIs) of the association between DII and glucose metabolism markers. A consistent finding was that IL-6 had a significant partial mediator role on the association between DII and glucose metabolism markers, including FBG [β = 10.574 (95 % CI: 3.705-17.443)], hbA1c [β = 0.469 (95 % CI: 0.174-0.764)] and HOMA-IR [β = 0.544 (95 % CI: 0.143-0.946)]. Both fetuin-A and hs-CRP had a significant full mediator role on the association between DII and HOMA-IR [respectively, β = 0.371 (95 % CI: -0.029-0.770), β = 0.424 (95 % CI: -0.007-0.856)]. The proportion of the effect mediated by fetuin-A was 35.2 %, whereas the proportion of the effect mediated by hs-CRP was 25.9 % (p < 0.05).

Table IV. Odds ratios (ORs) and 95 % confidence intervals (95 % CIs) for T2DM for DII score and inflammatory markers (n: 80)

	Model 1		Model 2		Model 3	
Variables	OR (95 % CI)	p value	OR (95 % CI)	p value	OR (95 % CI)	p value
DII	2.316 (1.276-4.205)	*0.006*	2.312 (1.094-4.890)	*0.028*	2.043 (0.955-4.372)	0.066
Fetuin-A (mg/dL)	1.122 (1.025-1.228)	*0.012*	1.333 (1.171-1.518)	*< 0.001*	1.155 (1.030-1.296)	*0.014*
IL-6 (pg/mL)	1.038 (1.010-1.066)	*0.007*	1.053 (1.014-1.093)	*0.007*	1.053 (1.006-1.102)	*0.028*
TNF-α (pg/mL)	7.301 (2.644-20.162)	*< 0.001*	7.384 (2.399-22.731)	*< 0.001*	7.234 (2.312-22.631)	*0.001*
hs-CRP (mg/dL)	1.152 (0.993-1.337)	0.062	1.186 (0.985-1.427)	0.071	1.129 (1.153-1.450)	0.239

Logistic regression analysis. Model 1: crude model; Model 2: adjusted for age, physical activity, and standardized energy intake; Model 3: adjusted for age, physical activity, standardized energy intake, and BMI. DII: dietary inflammatory index; IL-6: interleukin 6; TNF-α: tumor necrosis factor alpha; hs-CRP: high-sensitivity C-reactive protein.

Table V. Total, direct and indirect effects of DII on glucose metabolism markers with inflammatory markers as mediators (n: 80)

Variables	Total effect (c)		Direct effect (c')		Indirect effect (αβ)	
Mediators and outcomes	**β (95 % CI)**	**p value**	**β (95 % CI)**	**p value**	**β (95 % CI)**	**Proportion of mediation (%)**
Fasting blood glucose (mg/dL)	11.175 (4.321-18.028)	*0.002*				
Via fetuin-A (mg/dL)			8.749 (1.670-15.829)	*0.016*	2.425 (-0.019-5.865)	-
Via IL-6 (pg/mL)			10.574 (3.705-17.443)	*0.003*	0.601 (0.168-5.633)*	5.3
Via TNF-α (pg/mL)			9.301 (2.559-16.043)	*0.008*	1.873 (-0.165-5.172)	-
Via hs-CRP (mg/dL)			9.780 (2.271-17.289)	*0.011*	1.395 (-0.807-4.214)	-
HbA1c (%)	0.498 (0.203-0.793)	*0.001*				
Via fetuin-A (mg/dL)			0.416 (0.108-0.729)	*0.008*	0.082 (-0.006-0.212)	-
Via IL-6 (pg/mL)			0.469 (0.174-0.764)	*0.002*	0.029 (0.124-0.238)*	5.8
Via TNF-α (pg/mL)			0.400 (0.116-0.684)	*0.006*	0.098 (-0.003-0.224)	-
Via hs-CRP (mg/dL)			0.485 (0.160-0.810)	*0.003*	0.013 (-0.090-0.124)	-
Insulin (uIU/mL)	1.016 (-0.371-2.403)	0.148				
via fetuin-A (mg/dL)			0.325 (-1.065-1.715)	0.642	0.690 (0.051-1.580)*	-
Via IL-6 (pg/mL)			0.950 (-0.452-2.352)	0.181	0.065 (-0.452-2.352)	-
Via TNF-α (pg/mL)			0.747 (-0.648-2.143)	0.289	0.268 (-0.064-0.673)	-
Via hs-CRP (mg/dL)			0.499 (-1.001-1.999)	0.509	0.516 (0.018-1.358)*	-
HOMA-IR	0.573 (0.174-0.972)	*0.006*				
Via fetuin-A (mg/dL)			0.371 (-0.029-0.770)	0.068	0.202 (0.025-0.430)*	35.2
Via IL-6 (pg/mL)			0.544 (0.143-0.946)	*0.009*	0.028 (0.000-0.279)*	4.9
Via TNF-α (pg/mL)			0.470 (0.076-0.865)	*0.020*	0.103 (-0.005-0.236)	-
Via hs-CRP (mg/dL)			0.424 (-0.007-0.856)	0.054	0.148 (0.001-0.374)	25.9

*Simple mediation analysis as described by Preacher and Hayes. *p < 0.05. IL-6: interleukin 6; TNF-α: tumor necrosis factor alpha; hs-CRP: high-sensitivity C-reactive protein; HbA1c: glycosylated hemoglobin; HOMA-IR: homeostatic model assessment of insulin resistance.*

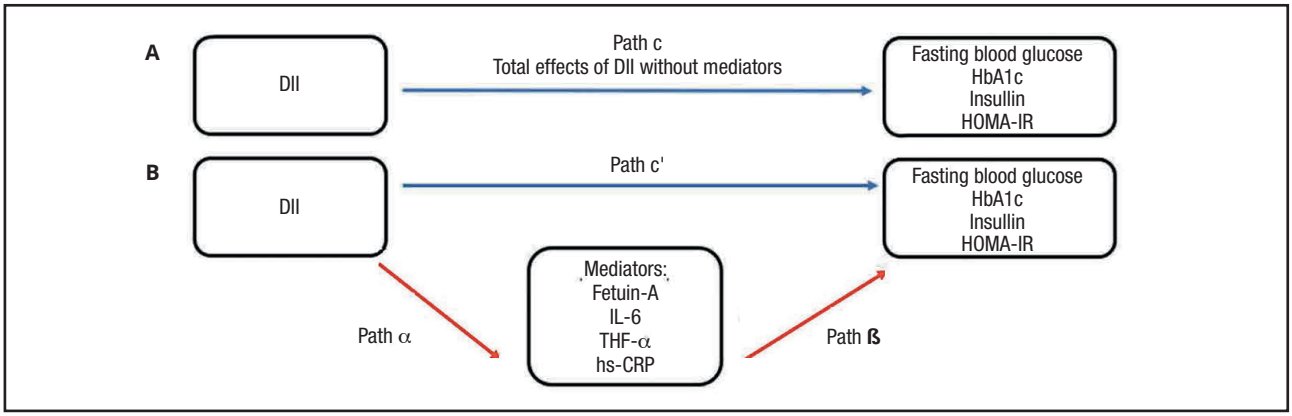

Figure 1.

Model used in the simple mediation analysis of the association between the dietary inflammatory index (DII) and glucose metabolism markers, including fasting glucose, glycated hemoglobin (hbA1c), insulin, and homeostatic model assessment of insulin resistance (HOMA-IR) [adapted from Preacher and Hayes (33)]. Path "c" shows the total effect of DII on glucose metabolism markers without adjusting mediator variables (A); path α shows the regression coefficient between the DII and the mediator variables (b); path β, shows the regression coefficient between the mediator variables and glucose metabolism markers (B); path "c'" shows the 'direct effect' of DII on glucose metabolism markers after adjusting the effect of the mediator variables (B). The product of regression coefficients α and β (αβ) shows the 'indirect effect' (mediated effect) of DII on glucose metabolism markers via the mediator variables (B).

DISCUSSION

In the present study, it was demonstrated that DII scores, which indicate the inflammatory potential of diet, were associated with inflammatory markers and T2DM risk, and that inflammatory markers including fetuin-A, IL-6, and TNF-α were also significantly associated with T2DM risk. In addition, the mediation analysis suggested that these relationships were fully mediated by fetuin-A and were also fully/partly mediated by hs-CRP and IL-6. To the best of our knowledge, this is the first study that investigated the mediator effects of fetuin-A on the association between diet and T2DM.

Studies in the past few decades have shown that inflammation may be one of the important factors in T2DM risk (20,21). It may be said that diet also affects T2DM by causing inflammation. Previous studies have indicated that a western diet, which represents a pro-inflammatory diet, is associated with a high risk of T2DM. In contrast, the Mediterranean diet, which represents an anti-inflammatory diet, has been associated with a low risk of T2DM (12-14). Recently, the DII has been used frequently in studies investigating the effect of the inflammatory load of diet on non-communicable diseases, including diabetes. Denova-Gutiérrez et al. (22) reported having a higher risk of diabetes in participants with high DII scores (who consume a more pro-inflammatory diet) than in those with low DII scores (who consume a more anti-inflammatory diet). In another study that investigated DII and diabetes risk, it was shown that the risk of diabetes increased by 13 % with every 1-point increase in DII score (17). The findings of the present study are in line with these studies, and it was found that the risk of diabetes also became higher as the DII scores of individuals increased.

The utility of the DII for assessing the inflammatory potential of the diet was shown in many studies (23,24). It was shown that individuals with high DII scores had a high consumption of pro-inflammatory nutrients, and individuals with low DII scores had a high consumption of nutrients with anti-inflammatory properties (15,22). Consistent with these findings, in the current study there was also a negative correlation between the DII score and anti-inflammatory nutrients such as MUFA, PUFA, n-3 and n-6 fatty acids, and antioxidant food components, as well as a positive correlation between the DII score and pro-inflammatory nutrients such as carbohydrates, total fat, and saturated fatty acids. Moreover, the DII has been constructed and was validated using inflammatory markers such as hs-CRP and IL-6 in the previous studies (23,24). The results of the present study are also in agreement with other studies in the literature where a significant association was reported between DII and inflammatory biomarkers.

In the current study, a relationship was found between all inflammatory markers and T2DM (hs-CRP was non-significant). Individuals with higher levels of fetuin-A, IL-6, TNF-α, and hs-CRP had a higher risk of developing T2DM. Proinflammatory cytokines that lead to inflammation cause β-cell damage and chronic hyperglycemia by affecting various pathways, and T2DM occurs as a result (25). Stefan et al. (5) demonstrated that fetuin-A was associated with the risk for incident diabetes, and was independently involved in the pathogenesis of T2DM. Their findings support that fetuin-A is a reliable predictor of T2DM. In addition, in many studies a positive correlation of TNF-α and IL-6 with T2DM was shown, and evidence that the pattern and variation of these pro-inflammatory cytokines are important in the pathogenesis of T2DM was provided (26).

The effects of diet on inflammation and inflammation on diabetes suggest that diet may also increase T2DM risk through inflammation (11). One of the possible mechanisms to explain the relationship between diet and T2DM may be that a pro-inflammatory diet causes insulin resistance via inflammatory markers. Diet is a crucial predictor of inflammatory marker levels in the circulation. An anti-inflammatory Mediterranean diet supplemented with virgin olive oil or nuts reduced serum C-reactive protein, IL-6, and endothelial and monocytic adhesion molecules and chemokines in 772 subjects at high risk for CVD (27). In contrast, a pro-inflammatory high-fat diet promotes inflammation (28). Unhealthy diets promote a pro-inflammatory setting marked by higher cytokine levels (IL-1β, IL-6, and TNF-α) and CRP. As a result, a prolonged pro-inflammatory state induced by diet could cause insulin resistance (29). In the present study, inflammatory markers including fetuin-A, IL-6 and hs-CRP had a fully/partly mediator role between DII, indicating dietary inflammatory potential, and HOMA-IR. These results supported the hypothesis that inflammation mediates the relationship between diet and insulin resistance. Van Woudenbergh et al. (11) also showed a significant mediating role of low-grade inflammation in the association between diet and insulin resistance. Conversely, in a study with a black South African population, the mediating effect of inflammation was not found in the association between diet and HOMA-IR and other glucose metabolism markers; however, adiposity had a mediator role (14). It might be that the direct effect of inflammation might be diminished in the presence of obesity, the most detrimental risk factor. Besides, ethnicity may modify the effect of risk factors on insulin resistance (30). In addition, since the inflammation mechanism of action is mediated by paracrine and autocrine effects, the specific effects of inflammation may not be entirely determined (14).

Notably, fetuin-A explained the highest significant proportion of the association between DII and HOMA-IR. The fact that fetuin-A is an endogenous inhibitor of the insulin receptor tyrosine kinase is a major factor in this result (6). It has been shown that fetuin-A inhibits insulin signaling by inhibiting insulin receptor tyrosine kinase in skeletal muscle and hepatocytes, and causes insulin resistance in these target tissues *in vitro* (31,32). In addition, Stefan et al. (33) demonstrated that fetuin-A in rodents inhibited insulin receptor tyrosine kinase phosphorylation. Moreover, human studies showing the relationship between serum fetuin-A and insulin resistance are limited, although increasingly common as of today (7,34,35).

The inability to infer cause-effect relationships due to its design may be considered the main limitation of this study. Besides, the small sample size may have affected the statistical power to

identify some effects. In addition, the study population consists exclusively of women. Therefore, the results should be verified by future prospective longitudinal studies with larger sample sizes including both genders. However, there are several strengths of the present study. First, this is the first study investigating the mediator effects of fetuin-A in the association between diet and T2DM. Because the participants were women, an age limitation was applied due to the unknown effects of the menstrual cycle on fetuin-A and to eliminate the effects of the physiological changes related to menopause. In addition, BMI inclusion criteria were kept within narrow ranges in terms of study homogeneity. Finally, although the FFQ may cause measurement errors even in healthy individuals, it provided access to 44 of the 45 food parameters required to calculate the DII. Many previous studies used fewer parameters (17,22).

In conclusion, these findings suggest that a pro-inflammatory diet, by creating an environment of increased inflammatory markers, may affect glucose metabolism, in particular insulin resistance, through these markers and ultimately cause T2DM. In addition, fetuin-A may also act as an important novel mediator between diet and T2DM by inducing insulin resistance. These results strengthen the fact that diet has an important role in developing T2DM risk in obese women. Considering these findings, adopting an anti-inflammatory diet approach may be a helpful strategy for preventing insulin resistance and reducing risk of diabetes. Further prospective longitudinal studies with a larger sample size are needed to investigate the effects of fetuin-A on insulin resistance, and its mediating role in diet and T2DM. In these studies, the molecular mechanism of fetuin-A may be examined, and whether fetuin-A may be used as a clinical marker in T2DM may also be tested.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Otros

Severe COVID-19 patients have severe vitamin D deficiency in Northeast Mexico

Los pacientes graves con COVID-19 tienen deficiencia grave de vitamina D en el noreste de México

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Abstract

Objective: the association between vitamin D and COVID-19 severity is not consistent. We compared prevalences and analyzed the association between vitamin D deficiency and COVID-19 severity in Northeast Mexico.

Methods: this was a cross-sectional study with individuals consecutively included at a referral diagnostic center during March-September 2020 (n = 181). Concurrently, every patient admitted to intensive care was also consecutively included (n = 116). Serum 25(OH)D < 20 ng/mL was considered vitamin D deficiency. Descriptive, ANOVA, and multivariate ordinal regression analyses were performed.

Results: vitamin D deficiency prevalence was 63.8 % (95 % CI, 54.7, 72.0) in severe COVID-19; 25.6 % (95 % CI, 17.4, 36.0) in mild COVID-19; and 42.4 % (95 % CI, 33.2, 52.3) in non-diseased individuals. Vitamin D deficiency increased 5 times the odds of severe COVID-19 (95 % CI, 1.1, 24.3), independently of sex, age, body mass index, and inflammatory markers.

Conclusions: this study is the first report of vitamin D deficiency in Northeast Mexico. Vitamin D deficiency was associated with COVID-19 severity.

Keywords:

Vitamin D deficiency. SARS-CoV-2. Laboratory parameters. COVID-19. Serum 25(OH)D.

Resumen

Objetivo: la asociación entre la vitamina D y la gravedad de la COVID-19 no es consistente. Se comparó la prevalencia y se analizó la asociación de la deficiencia de vitamina D con la gravedad de los pacientes con COVID-19 en el noreste de México.

Métodos: este fue un estudio transversal. Se incluyó consecutivamente a individuos de un centro de diagnóstico de referencia durante marzo-septiembre de 2020 (n = 181). Paralelamente, se reclutó a todos los pacientes que ingresaron a cuidados intensivos en ese mismo periodo (n = 116). Se consideró que había deficiencia de vitamina D ante cifras de 25(OH)D sérica < 20 ng/ml. Se realizaron un análisis descriptivo, un ANOVA y una regresión ordinal multivariante.

Resultados: la prevalencia de la deficiencia de vitamina D fue del 63,8 % (IC del 95 %: 54,7; 72,0) en la COVID-19 grave, del 25,6 % (IC del 95 %: 17,4; 36,0) en la COVID-19 leve y del 42,4 % (IC del 95 %: 33,2; 52,3) sin COVID-19. La deficiencia aumentó 5 veces las probabilidades de una COVID-19 grave (IC del 95 %: 1,1; 23,9) independientemente del sexo, la edad, el índice de masa corporal y los marcadores inflamatorios.

Conclusiones: este estudio es el primer informe de la deficiencia de vitamina D en el noreste de México. La deficiencia de vitamina D se asoció con la gravedad de la COVID-19.

Palabras clave:

Deficiencia de vitamina D. SARS-CoV-2. Parámetros de laboratorio. COVID-19. 25(OH)D sérica.

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INTRODUCTION

COVID-19 was originated in Wuhan, China, at the beginning of December 2019. Since then a rapid spread has beaten the entire world (1). Mexico has been one of the most affected countries ranking twelfth in number of new cases and fourth in mortality as of January 20th, 2021 (2). High infectivity and considerable variability had defined the clinical presentation of the disease. More than 40 % of patients are symptomless, 30 % to 45 % manifest mild symptoms, and 15 % manifest severe symptoms with hospitalization or intensive care (3). COVID-19 severity has been linked to elevated oxidative stress, exaggerated immune response, uncontrollable liberation of proinflammatory cytokines, and activation of coagulating factors, all of which contribute to severe inflammation (4,5). The effect of vitamin D on maintaining bone health and calcium-phosphorus metabolism is well known. But also, it possesses anti-inflammatory antifibrotic and antioxidant qualities. It modulates the immune system (6,7) and its anti-inflammatory function explains the beneficial effect on immune responses and antimicrobial agent production (8). Also, vitamin D regulates the renin-angiotensin system and expression of angiotensin-converting enzyme 2 linked to a lung protective effect (9,10).

Scientists have centralized their attention on factors that can control or prevent COVID-19 severity. Vitamin D has been suggested for such intentions (11), but its role on SARS-CoV-2 severity is still under investigation (12,13). D'avolio et al. described lower vitamin D levels in patients with COVID-19 symptomatology for the first time (14). There are observational studies that have determined an association between vitamin D levels and COVID-19 severity, but their findings are not consistent (11,15-16); and the literature is limited in Hispanic American populations (17). The objective of the present study was to compare vitamin D concentrations and prevalence of vitamin D deficiency between individuals with no COVID-19 and patients with mild and severe COVID-19. Also, to analyze the association between vitamin D deficiency and COVID-19 severity in Northeast Mexico.

MATERIALS AND METHODS

This was a cross-sectional study. A non-random sampling was carried out in two sites, a referral diagnostic primary care center and an intensive care unit from a secondary care hospital. All individuals with suspected symptoms of COVID-19 who attended the referral center for a real-time polymerase chain reaction (PCR) test between March and September 2020 were consecutively included (n = 181). Concurrently, every patient admitted to intensive care with a diagnosis of COVID-19 was also consecutively included (n = 116). Inclusion criteria consisted of age ≥ 18 years and no pregnancy. The sample size in each group was sufficient for a power greater than 80 % and alpha greater than 95 % given the 10 % observed outcome in the unexposed group and the unadjusted odds ratio obtained. The protocol was approved by the "Dr. Bernardo Sepulveda" Hospital's Committee of Ethics and Health Research (HMBSSSNL-2020/878). An informed consent was provided by all the participants.

COVID-19 SEVERITY STATUS

COVID-19 severity status was classified as negative (individuals with suspected symptoms of COVID-19 with a negative PCR test at the referral diagnostic primary care center), mild (individuals with suspected symptoms of COVID-19 with a positive PCR test at the referral diagnostic primary care center and who were maintained on ambulatory care), and severe (patients admitted to intensive care with a COVID-19 diagnosis).

VITAMIN D STATUS

Serum 25(OH)D was estimated using the 25-OH Vitamin D kit (ARCHITECT i; Abbott Laboratories; reference 5P02-25) and the Vitamin D controls (ARCHITECT; Abbott Laboratories; reference 5P02-10) on Architect i2000 SR analyzer 5P02 (Abbott Diagnostics, Chicago, USA). Values > 40 ng/mL were considered above normal, values between 30 and 39 ng/mL normal, values between 20 and 29 ng/mL mild vitamin D deficiency, values between 10 and 19 ng/mL moderate vitamin D deficiency, and values < 10 ng/mL severe vitamin D deficiency. In addition, a cut-off value of 25(OH)D < 20 ng/mL was used for combining moderate and severe vitamin D deficiency.

OTHER BIOCHEMICAL MEASUREMENTS AND DEMOGRAPHIC DATA

Lactate dehydrogenase (LDH) (U/L), C-reactive protein (mg/L), D-dimer (ng/ml), and fibrinogen (mg/L) were obtained. Also, leukocytes ($\times 10^9$/L), lymphocytes ($\times 10^9$/L), neutrophils ($\times 10^9$/L), platelets ($\times 10^9$/L), and prothrombin time (seconds). Blood samples were taken at admission to intensive care (severe COVID-19 patients) or alongside with the PCR test at the referral diagnostic primary care center (mild and no COVID-19 individuals). All laboratory measurements were prospectively collected from the clinical chart, as well as sex, age, and body mass index (BMI).

STATISTICAL ANALYSIS

Frequencies were obtained for the categorical variables, as were means and standard deviations for the non-categorical variables with normal distribution; otherwise, medians and interquartile ranges (percentile 25th and 75th) were calculated. Vitamin D deficiency point prevalence and 95 % confidence intervals (CI) were estimated for each COVID-19 severity group. The chi-square and non-parametric one-way ANOVA tests with post-hoc analysis were used to make comparisons between groups. Non-parametric coefficient correlations were also estimated between vitamin D concentration and inflammatory biomarkers. The association between vitamin D and COVID-19 severity was analyzed with a multivariate logistic ordinal regression using COVID-19 status as the dependent variable (no, mild and severe),

vitamin D as the independent variable (normal/above normal, mild, moderate, and severe deficiency), and sex, age, BMI, LDH, C-reactive protein, D-dimer, and fibrinogen as control variables.

RESULTS

The study population's mean age was 46.0 ± 17.4 years and 51.1 % were male. Male sex, mean age, mean BMI, and median blood measurements were higher in severe COVID-19 patients than in individuals with no COVID-19 ($p \leq 0.05$). All blood test results were less favorable in the severe COVID-19 group when compared to the non-COVID-19 group. As well as most of the blood tests in the mild group when compared to the non-COVID-19 group (Table I).

VITAMIN D AND COVID-19 SEVERITY STATUS

Median vitamin D was lower in the severe COVID-19 group (16.3 ng/mL; IQR, 10.2, 23.2) than in the mild (23.4 ng/mL; IQR, 19.9, 29.0) or no COVID-19 group (21.0 ng/mL; IQR, 17.6, 27.9) ($p < 0.0001$) (Fig. 1). There were no vitamin D differences by sex, but it was negatively correlated with age (rho = - 0.13, $p < 0.02$). Vitamin D was also negatively correlated with LDH (rho -0.20, $p < 0.0001$) and D-dimer (rho -0.27, $p < 0.0001$).

The prevalence of vitamin D < 20 ng/mL was 63.8 % (95 % CI, 54.7, 72.0) in the severe COVID-19 group, 25.6 % (95 % CI, 17.4, 36.0) in the mild COVID-19 group, and 42.4 % (95 % CI, 33.2, 52.3) in the non-COVID-19 group. Severe vitamin D deficiency increased the odds of severe COVID-19 by five times regardless of sociodemographic, BMI, and inflammatory blood markers (Table II).

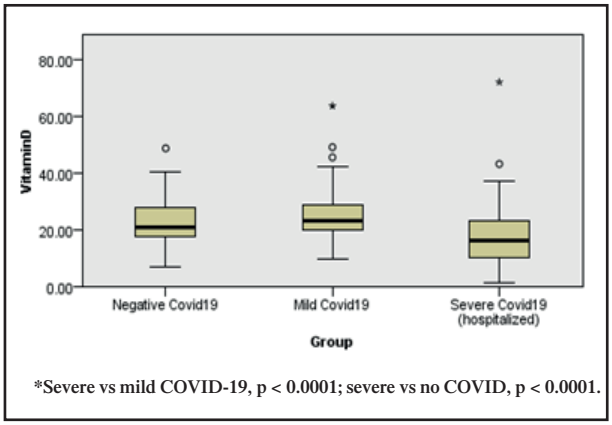

Figure 1.
Vitamin D concentrations by COVID-19 severity status.

Table I. Characteristics of the study population by COVID-19 severity status

	COVID-19 severity status			Non-parametric ANOVA test		
	No disease (n = 99) (1)	Mild disease (n = 82) (2)	Severe disease (n = 116) (3)	3 *vs* 1	3 *vs* 2	2 *vs* 1
Age (mean ± SD)	36.6 ± 13.0	37.7 ± 13.8	58.7 ± 14.6	‡	‡	n.s.
Sex, male	41.4 %	56.1 %	56.9 %	*	n.s.	*
Body mass index	27.4 ± 5.2	27.3 ± 4.2	28.2 ± 5.3	*	n.s.	n.s.
Neutrophil to lymphocyte ratio ≥ 3	20.4 %	28.0 %	93.0 %	‡	n.s.	n.s.
Median (interquartile range)						
Lactate dehydrogenase (U/L)	177 (152.5, 206.5)	205 (174, 244.5)	↑ 457 (381, 654)	‡	‡	†
C-reactive protein (mg/L)	3.1 (1.5, 10.9)	8.5 (2.8, 36.4)	↑ 115.6 (47.3, 209.6)	‡	‡	‡
D-dimer (ng/mL)	249 (157.5, 401.5)	404 (219, 562)	↑ 1,931 (742, 4,741)	‡	‡	*
Fibrinogen (mg/dL)	↑ 478.5 (402.5, 562)	↑ 517.5 (448, 660.5)	↑ 822 (632, 973)	‡	‡	‡
Leukocytes × 10^9/L	7.6 (6.4, 9)	6.1 (4.8, 7.4)	↑ 12.2 (9.2, 15.9)	‡	‡	†
Platelets × 10^9/L	262 (227, 297.5)	229.5 (181, 264)	249 (184.5, 307.5)	*	n.s.	†
Prothrombin time (seconds)	11 (10.5, 11.6)	11.1 (10.5, 11.8)	13 (11.9, 14.3)	‡	‡	n.s.

**p ≤ 0.05, †p < 0.01, ‡p < 0.001; n.s. = non-significance, p > 0.05.*

Table II. Vitamin D multivariate logistic ordinal regression on COVID-19 severity status

	COVID-19 severity status			Odds ratios (95 % confidence interval)		
	No disease (n = 99)	Mild disease (n = 82)	Severe disease (n = 116)	Unadjusted	Adjusted[a]	Adjusted[b]
Vitamin D category						
Normal/Above (≥ 30 ng/mL)	16.2 %	24.4 %	10.3 %	1.0	1.0	1.0
Mild deficiency (20-29 ng/mL)	41.4 %	50.0 %	25.9 %	1.0 (0.5, 1.8)	0.93 (0.48, 1.79)	0.76 (0.35, 1.7)
Moderate deficiency (10-19 ng/mL)	38.4 %	24.4 %	40.5 %	1.5 (0.8, 2.7)	1.51 (0.77, 2.98)	0.85 (0.38, 1.9)
Severe deficiency (< 10 ng/mL)	4.0 %	1.2 %	23.3 %†	10.8 (3.6, 31.9)†	9.83 (3.0, 32.1)†	5.08 (1.07, 24.3)*
Lactate dehydrogenase (> 333 U/L)	2.0 %	11.1 %	82.5 %†	--	--	22.0 (8.3, 58.5)†
D-dimer (≥ 500 ng/mL)	16.7 %	35.8 %	86.0 %†	--	--	3.4 (1.7, 6.8)†

*[a]For sex, age, and body mass index. [b]Other variables in the model were sex, age, body mass index, C-reactive protein, and fibrinogen. *p < 0.05; †p < 0.0001.*

DISCUSSION

The objective of the present study was to compare vitamin D concentrations and prevalence of severe vitamin D deficiency between individuals with no COVID-19 and patients with mild and severe COVID-19. There was a difference in prevalence of vitamin D deficiency between groups (< 20 ng/ml), although it was not in ascending order from non-COVID-19 to moderate and severe COVID-19. De Smet et al. (18) reported vitamin D deficiency rates increasing from 55 % in stage 1 (pulmonary ground-glass opacities) to 67 % in stage 2 and 74 % in stage 3 (diffuse alveolar damage and fibrosis). AlSafar et al. (19) did not find any differences by COVID-19 severity. They identified 76 % of vitamin D deficiency in asymptomatic, 65 % in mild, 67 % in moderate, and 61 % in severe COVID-19 patients ($p > 0.05$). Comparison of vitamin D deficiency in COVID-19 patients in intensive care between countries shows 61 % in the United Arab Emirates (19), 72.1 % in Italy (20), 74 % in Belgium (18), 96.8 % in India (11), and 63.8 % in Northeast Mexico (this study). The prevalence in healthy populations varies. It has been estimated at 37.3 % in European countries (21) and at 40 % (summer time) and 65 % (winter time) in Northeast Mexico (22). Vitamin D deficiency was not associated with sex but with age — the older the age, the lower the vitamin D concentration, contrary to De Smet et al. (18), who identified that male sex doubled the odds of vitamin D < 20 ng/mL but no association could be found with age. Adami et al. (20) found no association with age or sex. Major causes of vitamin D deficiency are inadequate exposure to sunlight, obesity, and kidney disease, among others (23,24). Variations in the causes of deficiency are probably also the origin of differences in prevalence values in addition to severity status.

We identified that the relationship between vitamin D, D-dimer, and LDH was inverse, indicating that the intensity of the inflammatory response was high with low levels of vitamin D. Hernandez et al. (17) also identified an inverse correlation with D-dimer levels. Adami et al. (20) did not find such association but did find one with C-reactive protein. LDH is an important marker of lung damage and D-dimer reflects the progression of disease toward an unfavorable clinical outcome (25). In this study, LDH, D-dimer, C-reactive protein, fibrinogen, and leukocyte values were significantly higher in severe COVID-19. Besides, D-dimer increased 3 times and LDH increased more than twenty times the odds of severe COVID-19. Vitamin D itself is linked to anti-inflammatory antifibrotic qualities, so if vitamin D is low, anti-inflammatory antifibrotic properties fail, and prevention or reduction of COVID-19 severity also fails.

Median vitamin D concentrations were lower in severe COVID-19 than in mild COVID-19 patients with a difference of -7.4 ng/dL (95 % CI, -10.5, -4.3), which was consistent with a review study showing a weighted mean difference of –7.2 ng/mL (95 % CI, -10.9, -4.3) between severe and less severe COVID-19 patients (26). De Smet et al. (18) also reported lower median vitamin D in most severe versus less severe COVID-19 patients. Vitamin D deficiency (< 12 ng/mL) increased 5 times the odds of severe COVID-19 regardless of sex, age, BMI, LDH, D-dimer, C-reactive protein, and fibrinogen. Ye et al. (15) reported an odds ratio of 15.2 (95 % CI, 1.2-187.5) regardless of age, sex, renal failure, diabetes, and hypertension in China. Also, Jain et al. (11) found an association between vitamin D deficiency (< 20 ng/dL) and intensive care admission due to severe COVID disease in India. However, the literature is not consistent. Studies by Cereda et al. (27), Hernández et al. (17), and Szeto et al. (28) have not found an association. AlSafar et al. (19) did not identify that vitamin D < 20 ng/mL increased the odds of severe COVID-19, but they did with vitamin D < 12 ng/mL, independently of sex, age, and comorbidities. The review study by Kazemi et al. (26) estimated an overall effect size of 2.6 (95 % CI: 1.7, 4.0) on a composite measure of COVID-19 severity (at least 1 of the following outcomes: acute respiratory distress syndrome, mechanical ventilation, ICU admission, length of hospitalization, and death). But no significant association was found when intensive care was the only measure of severity (16,17,29).

LIMITATIONS

No data was available on prior vitamin D supplementation. So, prevalence estimation on vitamin D deficiency might not be accurate. However, the association result is not expected to be affected, since such an association occurred between current vitamin level and current disease severity, regardless of how that level was reached. Given the cross-sectional study design, there is no certainty in directionality — if vitamin D deficiency influenced disease severity, or if deficiency was a consequence of disease severity. A cohort design is needed for distinguishing directionality. Better yet, clinical trials on vitamin D supplementation are on their way. Chronic conditions such as hypertension, diabetes, cancer, or cardiovascular diseases may contribute to poor COVID-19 prognosis; we did not have this information available, but we had inflammation biomarkers instead. Finally, only non-pregnant adults were recruited from one referral diagnostic primary care center and one intensive care unit. So, caution is needed when generalizing results to children and pregnant women. Further research is needed with multicenter participation considering populations younger than 18 years and pregnant women.

CONCLUSIONS

This study is the first report of vitamin D deficiency in no-, mild, and severe COVID-19 subjects in Northeast Mexico. Lower vitamin D concentrations and a higher prevalence of vitamin D deficiency were present in patients with severe COVID-19. We found an inverse relationship between vitamin D, LDH, and D-dimer, and an association between vitamin D deficiency and COVID-19 severity. Yet, large-scale observational studies and randomized controlled trials of vitamin D supplementation for controlling COVID-19 severity are necessary in Hispanic American populations.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Otros

Normative data on the subjective gustatory function of Chinese adults

Datos normativos de la función gustativa subjetiva en adultos chinos

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Abstract

Purpose: the study aims to assess the gustatory function of healthy Chinese adults with the whole-mouth test based on five basic tastants, including umami taste.

Methods: the study recruited 464 participants reporting a normal sense of smell/taste (227 females and 237 males with an age range of 19-65 years). A drop (approximately 0.1 mL) of liquid tastant was applied on the anterior third of the extended tongue of each subject. The taste solutions involved 5 tastants (sour, sweet, salty, umami, and bitter) and 7 concentrations. Taste perception scores and recognition scores of the five basic tastants were obtained with this whole-mouth taste method.

Results: total taste score of recognition showed a significant negative correlation with age. The elder group (51-65 years) had the lowest scores. The 10th percentile of total taste score of recognition in the group of 36 to 50 years was used to distinguish normogeusic subjects from hypogeusic subjects. The perception scores and recognition scores of females were higher than those of males. The perception and recognition scores of salty, umami, and bitter for females were high than those for males. Total taste score of recognition for non-smokers was significantly higher than that of smokers. The whole-mouth method showed a high test-retest reliability with an intra-class correlation coefficient (ICC) from 0.774 to 0.833.

Conclusion: this whole-mouth method is simple and time-saving and can be easily adjusted to obtain reliable data. The gustatory function was significantly negatively correlated with age. Females were more sensitive to the sour, salty, umami and bitter tastes than males. The gustatory function of non-smokers was more sensitive.

Keywords:

Gustatory function. Umami. Perception. Recognition. Chinese adult.

Resumen

Propósito: el estudio tiene como objetivo evaluar la función gustativa de adultos chinos sanos con la prueba de boca completa basada en cinco saborizantes básicos, incluido el sabor umami.

Métodos: el estudio reclutó a 464 participantes que informaron tener un sentido del olfato/gusto normal (227 mujeres y 237 hombres con un rango de edad de 19 a 65 años). Se aplicó una gota (aproximadamente 0,1 ml) de saborizante líquido en el tercio anterior de la lengua extendida de cada sujeto. Las soluciones de sabor incluyeron 5 saborizantes (ácido, dulce, salado, umami y amargo) y 7 concentraciones. Los puntajes de percepción del gusto y los puntajes de reconocimiento de los cinco saborizantes básicos se obtuvieron con este método de sabor de boca completa.

Resultados: la puntuación total de reconocimiento del gusto mostró una correlación negativa significativa con la edad. El grupo de ancianos (51-65 años) tuvo las puntuaciones más bajas. Se utilizó el percentil 10 de la puntuación total de reconocimiento del gusto en el grupo de 36 a 50 años para distinguir a los sujetos normogéusicos de los hipogéusicos. Los puntajes de percepción y los puntajes de reconocimiento de las mujeres fueron más altos que los de los hombres. Los umbrales de percepción y reconocimiento de salado, umami y amargo de las mujeres fueron más bajos que los de los hombres. La puntuación total de reconocimiento del gusto de los no fumadores fue significativamente más alta que la de los fumadores. El método de boca completa mostró una alta fiabilidad test-retest con un coeficiente de correlación intraclase (CCI) de 0,774 a 0,833.

Conclusión: este método de boca completa es simple, ahorra tiempo y se puede ajustar fácilmente para obtener datos confiables. La función gustativa se correlacionó significativamente de forma negativa con la edad. Las mujeres fueron más sensibles a los sabores agrio, salado, umami y amargo que los varones. La función gustativa fue más sensible en los no fumadores.

Palabras clave:

Función gustativa. Umami. Percepción. Reconocimiento. Adultos chinos.

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Ethics approval: the study protocol was approved by the Institutional Review Boards of Beijing Anzhen Hospital, affiliated with Capital Medical University (No: 2021074X). Each patient signed an informed consent form prior to enrollment in the study.

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INTRODUCTION

The human taste system can recognize five basic tastes: sweet, sour, bitter, salty and umami. Gustatory function affects nutrition, food choice, pleasure and sensory aspects of food, metabolic efficiency, and even quality of life. According to the National Health and Nutrition Examination Survey, the estimated prevalence of taste impairment was 17.3 % (1). Patients who complain of dysgeusia may actually have olfactory dysfunction. In the previous study 8.7 % of patients reported taste loss, but less than 5 % of patients actually had taste dysfunction according to taste testing. Self-reported gustatory function was not reliably related to psychophysical test results (2). Therefore, it is necessary to carry out a quantitative and qualitative assessment of the gustatory function.

In Asia, Japan was the first country to use the whole-mouth gustatory test to study the gustatory function of Japanese subjects, followed by China, South Korea, and Taiwan (3-6). Hwang CS et al. (4) tested five basic tastes, including sour, sweet, salty, umami, and bitter in 2018, and obtained the normal range for a Korean population. Umami, one of the five basic tastes, was widely present in food. Umami can reduce the use of salt in food processing and increase the flavor of food, which plays a very important role in maintaining health (7,8). In order to fully evaluate the taste function, it is necessary to conduct a functional evaluation of the five basic tastes including umami. In 2010, Yang et al. (6) studied the gustatory function of Chinese subjects with the three-drop method, but the sample size of the study was small and they considered only four basic tastes (bitter, sweet, salty, and sour), without umami. Therefore, the aim of the study was to develop a convenient, fast and reliable tool to assess the taste function with the five basic tastes in healthy Chinese adults.

MATERIALS AND METHODS

STUDY SUBJECTS

Healthy subjects were recruited for physical examination at the health examination center of our hospital from January, 2021 to April, 2021. All subjects had signed a written informed consent. This study had been approved by the Ethics Committee of our hospital (No.: 2021074X). Inclusion criteria were healthy adults aged 18 to 65 years with normal self-rated smell function and gustatory function. Exclusion criteria were subjects with olfactory dysfunction, gustatory dysfunction, acute oral infections, acute otitis media, coma after head trauma, mental illness, neurodegenerative diseases, or previous middle ear surgery, nasal surgery, radiotherapy or chemotherapy. Detailed data about each person's current health status, past history, and chemosensory function were obtained through a questionnaire. Otolaryngological examination excluded subjects with acute otitis media and/or acute pharyngitis.

PROCEDURE

In the assessment of gustatory function with the whole-mouth taste test, five liquid taste solutions were used. Five basic tastant solutions (sour, sweet, salty, umami, and bitter) were respectively prepared with citric acid, sucrose, sodium chloride, monosodium glutamate, and quinine hydrochloride in distilled water. Successive test concentrations were determined based on the study by Hwang CS et al. (4) and preliminary experiments. In order to ensure that the lowest concentration of each taste test was suitable for the Chinese population, we reduced a concentration gradient based on the testing by Hwang CS. Through preliminary

Table I. Concentrations of taste stimuli used in g/mL (solvent: distilled water)

Dilution concentrations	Taste scores	Sour	Sweet	Salty taste	Umami	Bitter
		Citric acid	Sucrose	Sodium chloride	Monosodium glutamate	Quinine hydrochloride
1	7	0.0002425	0.0024	0.0003	0.001	0.0000125
2	6	0.000485	0.0048	0.0006	0.002	0.000025
3	5	0.00097	0.0097	0.0012	0.004	0.00005
4	4	0.00195	0.0195	0.0024	0.008	0.0001
5	3	0.00391	0.039	0.0048	0.016	0.0002
6	2	0.00782	0.0781	0.0096	0.032	0.0004
7	1	0.01564	0.1562	0.0192	0.064	0.0008

No. 1 dilution concentration, the lowest concentration; No. 7 dilution concentration, the highest concentration. If subjects could not perceive/identify the No. 7 dilution concentration, they got a score of 0.

experiments, the concentration was adjusted appropriately and finally 7 concentrations (No. 1 to No. 7) were prepared for each solution. The No. 1 dilution concentration was the lowest concentration and the No. 7 dilution concentration was the highest concentration (Table I). Taste solutions were prepared once a week.

Tastant solutions were administered via a disposable plastic dropper with a standard scale. A drop (0.1 mL) of each tastant solution was dripped in the middle of the anterior third of the extended tongue of each subject. Then subjects swished the drop in their closed mouth. After administration of each solution, subjects were asked to rinse their mouths with tap water. Administration was started with the lowest concentration until the individual tastant was detected. We then re-tested the concentrations that were one level lower and higher in order to confirm the exact threshold concentration. The lowest concentration at which the subject perceived a sensation of taste was defined as the detection threshold. In the course of determining the taste recognition threshold, the subjects were asked to choose one of five tastes to describe the administered taste (salty, sweet, sour, bitter, and umami). The administration concentration gradually increased until the correct recognition of the respective tastant concentration occurred twice. The lowest concentration of the identified tastant solution was defined as the recognition threshold. The administration was carried out in a pseudo-randomized order. Five basic tastes were respectively tested and the bitter was tested at last. The recognition score was obtained based on the recognition threshold. According to the concentration corresponding to the identified taste, the subject got a score between 0 and 7 for each administration. If subjects did not identify the taste at the No. 7 dilution concentration, they received a score of 0. The higher the threshold was, the lower the score was. In order to obtain an overall evaluation of gustatory function, recognition scores of all the five tastants were summed as total scores ranging from 0 to 35. The complete procedure for the five tastes was completed within almost 20 min. The inspection was conducted in the morning (8:30-11:30 am). Subjects were instructed not to eat or drink anything except water, brush their teeth or smoke at least one hour before the test.

TEST RELIABILITY

To verify test-retest reliability, the taste test was repeated in 50 subjects (24 men and 26 women with a mean age of 40 years and an age range of 20 to 63 years) 2 weeks later.

STATISTICAL ANALYSIS

The statistical analysis was performed in SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Student's t-test or analysis of variance for repeated measures (rm-ANOVA) was performed to assess the statistical significance of the differences between subgroup scores. Bonferroni tests were performed for post-hoc comparison. Pearson's correlation coefficient was used to assess the correlation. The intraclass correlation coefficient was used to assess reproducibility and internal consistency. A χ^2 test was used to assess composition ratio. A p-value ≤ 0.05 was considered to be significant.

RESULTS

A total of 464 participants underwent the taste test (227 females and 237 males, age range 19-65 years). Descriptive statistics are provided in table II. Normative values are presented according to different age groups and sex in table III. To assess gustatory function, the perception and recognition thresholds of sour, sweet, salty, umami, and bitter taste were analyzed separately. The total taste scores of recognition showed a significantly negative correlation with age ($r = -0.279$, $p < 0.001$). The perception threshold and recognition threshold of the individual five tastants except the salty taste also demonstrated a significant correlation with age ($-0.356 < r < -0.110$, $p < 0.05$). Total scores decreased with increasing age and showed significant differences ($p < 0.001$) between the three age groups (younger group: 19-35 years, middle aged group: 36-50 years, and older group: 51-65 years). Older subjects (51-65 years) had the lowest scores. Individual tastants' perception threshold and recognition threshold showed no significant differences between the younger-age group and middle-age group ($p > 0.05$). For the sour, sweet, umami, and bitter tastes, the perception scores of the older group were significantly lower than those of the younger group and middle-aged group. For the sour, umami, and bitter tastes, the recognition scores of the elder group were significantly lower than those of the younger group and middle-aged group.

Total score of recognition for women were higher than those for men ($p < 0.001$). In a further exploratory analysis of perception scores, the effect of gender was most significant for sour ($p = 0.024$), salty ($p = 0.044$), umami ($p = 0.046$) and bitter ($p < 0.001$), but it was not significant for the sweet taste ($p = 0.804$). The same results were found in the taste recognition thresholds between men and women (sour, $p = 0.001$; salty, $p < 0.001$; umami, $p < 0.001$; bitter, $p < 0.001$; sweet, $p = 0.154$).

Based on the definition of hypogeusia, the 10th percentile for subjects aged 36-50 was used to differentiate normogeusic subjects from hypogeusic subjects (4,9). Therefore, the subjects with total score of recognition lower than 16 for males and 18 for females were considered hypogeusic subjects in this study.

Subjects were divided into a non-smoking group (giving up smoking or smoking < 100 cigarettes) and a smoking group. The total taste score of recognition for non-smokers was significantly higher than that for smokers (21.23 ± 3.91 vs. 19.90 ± 3.52, $p = 0.014$). In a further exploratory analysis of recognition thresholds, the effect of smoking on salty was the most significant ($p = 0.013$), but the effect of smoking was not significant on sour ($p = 0.082$), sweet ($p = 0.459$), umami ($p = 0.444$), and bitter ($p = 0.056$). Individual tastants' perception threshold showed no statistically significant differences between smokers and non-smokers ($p > 0.05$).

Table II. Descriptive statistics of taste scores for all subjects

	Parameters	Minimum	Maximum	Mean	SD
Perception scores	Sour	1.00	7.00	4.82	0.97
	Sweet	2.00	7.00	4.84	0.86
	Salty	1.00	7.00	4.92	1.05
	Umami	2.00	7.00	5.31	0.96
	Bitter	2.00	7.00	5.00	1.09
	Total	12.00	33.00	24.88	3.33
Recognition scores	Sour	1.00	7.00	3.97	1.23
	Sweet	2.00	7.00	4.66	0.90
	Salty	1.00	7.00	3.60	1.36
	Umami	1.00	7.00	4.18	1.40
	Bitter	1.00	7.00	4.65	1.27
	Total	10.00	31.00	21.06	3.89

n = 464. SD: standard deviation. Taste scores are listed, respectively, according to individual tastes and all tastes.

Table III. Recognition scores from taste testing in the various participant groups of sex and age

Age (years)	Gender	Parameter	Sour	Sweet	Salty taste	Umami	Bitter	Total
18-35	**Men *n* = 83**	Mean	4.07	4.77	3.59	4.31	4.70	21.45
		SD	1.16	0.86	1.42	1.58	1.28	3.83
		10^{th} perc.	3.00	4.00	1.40	1.40	3.00	15.40
		25^{th} perc.	3.00	4.00	3.00	3.00	4.00	19.00
		50^{th} perc.	4.00	5.00	4.00	5.00	5.00	22.00
		75^{th} perc.	5.00	5.00	5.00	5.00	6.00	24.00
		90^{th} perc.	5.60	6.00	5.00	6.00	6.00	26.00
	Women *n* = 85	Mean	4.55	4.85	3.76	4.47	5.16	22.80
		SD	1.04	0.92	1.39	1.35	1.23	3.80
		10^{th} perc.	3.00	4.00	2.00	2.60	3.60	18.00
		25^{th} perc.	4.00	4.00	3.00	4.00	4.00	20.00
		50^{th} perc.	5.00	5.00	4.00	5.00	5.00	23.00
		75^{th} perc.	5.00	5.50	5.00	6.00	6.00	26.00
		90^{th} perc.	6.00	6.00	6.00	6.00	6.40	27.00

(Continues on next page)

Table III (Cont.). Recognition scores from taste testing in the various participant groups of sex and age

Age (years)	Gender	Parameter	Sour	Sweet	Salty taste	Umami	Bitter	Total
36-50	Men *n* = 94	Mean	3.91	4.51	3.21	4.19	4.80	20.63
		SD	1.35	1.09	1.44	1.51	1.15	3.62
		10th perc.	2.00	3.00	1.00	2.00	3.00	16.00
		25th perc.	3.00	4.00	2.00	3.00	4.00	18.00
		50th perc.	4.00	5.00	3.00	4.00	5.00	21.00
		75th perc.	5.00	5.00	4.00	5.25	6.00	24.00
		90th perc.	6.00	6.00	5.00	6.00	6.00	25.00
	Women *n* = 72	Mean	4.36	4.89	3.86	4.64	4.89	22.64
		SD	1.12	0.85	1.19	1.12	1.23	3.27
		10th perc.	3.00	4.00	3.00	3.00	3.00	18.00
		25th perc.	4.00	4.00	3.00	4.00	4.00	21.00
		50th perc.	4.00	5.00	4.00	5.00	5.00	23.00
		75th perc.	5.00	6.00	5.00	5.75	6.00	25.00
		90th perc.	6.00	6.00	5.00	6.00	6.00	27.00
51-65	Men *n* = 60	Mean	3.22	4.50	3.35	3.02	3.68	17.77
		SD	1.11	0.83	1.16	1.08	1.10	3.32
		10th perc.	1.10	4.00	2.00	1.00	2.00	13.00
		25th perc.	3.00	4.00	3.00	2.00	3.00	15.00
		50th perc.	3.00	5.00	3.00	3.00	4.00	18.00
		75th perc.	4.00	5.00	4.00	4.00	4.75	20.00
		90th perc.	4.90	5.00	5.00	4.00	5.00	21.00
	Women *n* = 70	Mean	3.47	4.39	3.86	4.19	4.36	20.26
		SD	1.05	0.57	1.38	1.01	1.14	3.36
		10th perc.	2.00	4.00	2.00	3.00	3.00	16.00
		25th perc.	3.00	4.00	3.00	4.00	4.00	18.00
		50th perc.	4.00	4.00	4.00	4.00	4.00	21.00
		75th perc.	4.00	5.00	5.00	5.00	5.00	23.00
		90th perc.	5.00	5.00	5.00	5.00	6.00	23.00

SD: standard deviation; 10th perc.: 10 percentile of frequency distribution of corresponding scores. Taste scores are listed separately according to individual tastes and all tastes. The 10th percentile of total scores from subjects of the 36-50 year-old group was used to distinguish normogeusic subjects from hypogeusic subjects.

The proportion of smokers showed no signficant difference among the three age groups (45 smokers and 123 non-smokers in the younger group; 34 smokers and 132 non-smokers in the middle-aged group; 32 smokers and 98 non-smokers in the older group; χ^2 test, $p = 0.392$). Smokers were mostly males (smokers included 57 males and 2 females; non-smokers included 180 males and 225 females; χ^2 test, $p < 0.001$).

The intraclass correlation coefficients of taste perception scores and taste recognition scores for the five tastants were 0.774 to 0.833. The study method showed a relatively high reliability.

DISCUSSION

In this study, the gustatory function of Chinese people was tested with the whole-mouth taste method to obtain normative data for the sour, sweet, salty, umami, and bitter tastes.

At present, subjective gustatory function tests mainly include chemical threshold tests and electrical threshold tests. The subjective gustatory function test is a psychophysical test and can quantify the subject's conscious perception of taste stimuli (10). Chemical threshold tests mainly include the whole-mouth taste test and regional taste test (4,10). A cotton swab or filter paper dipped in the tastant solution can be used to evaluate the regional taste function. The regional taste test can be used to determine whether a given taste nerve is dysfunctional (11). The whole-mouth taste test can be performed in cups or small containers, or with droppers of different sizes (9). The whole-mouth test is usually employed to explore the overall gustatory function. Because of its economy, fast speed, and convenience the whole-mouth taste test is the dominant subjective taste test at present. The liquid-drop method and the three-drop method are the most commonly used whole-mouth taste tests. An adequate evaluation of taste function is essential in the diagnosis of chemosensory dysfunction.

Umami has been shown to be the fifth basic taste, and is the reason why human beings can enjoy delicious foods. Japanese scholar Kikunae Ikeda isolated glutamate from kelp for the first time in 1908. It was only in the 1980s that umami was recognized as a basic taste, mainly the taste of sodium glutamate (MSG) (12). Umami can produce a "salty" feeling (7). Adding MSG to foods can reduce the use of salt during food processing, improve the quality of life of the elderly, and partially replace the use of salt in patients with anorexia. The evaluation of the taste sensitivity for umami before adding MSG to foods can also improve the compliance of patients with anorexia (13). In the study, we found that the recognition score of umami gradually decreased with age. According to the study of Satoh-Kuriwada, some patients, especially the elderly, complained that the subjective sensation of umami was continuously impaired, even though the other four basic taste sensations were still normal (8). This unknown impact on umami will be explored in the future.

In the process of clinical testing, many factors affect the subjective taste threshold, including water temperature, saliva volume (14), number of taste buds (15), time interval for each taste stimulation, volume of taste solvent, and duration of stimulation (16). Therefore, in order to control the influencing factors that affect the subjective taste function as much as possible, during the whole test process, the taste solution was placed at room temperature before the actual test. The test was performed by the same examiner in the morning. The taste solution was dripped in the middle of the anterior third of the tongue using a dropper with a standard scale. In order to evaluate the credibility of the whole-mouth test, we analyzed the test-retest reliability of the taste perception scores and recognition scores of sour, sweet, salty, umami, and bitter tastes. In previous studies (4,17,18), the test-retest reliability of the whole-mouth method was analyzed and the ICC value was 0.61 to 0.78. In our study, the taste test showed a high test-retest reliability with an ICC value of 0.774 to 0.833. Therefore, we believed that the taste test was a reliable subjective taste test for Chinese people.

Tastes function are affected by many factors. Aging appears to be the most significant determinant of taste change (19). In epidemiological surveys (20), the incidence of self-reported taste disorders was 19 %, increased gradually with age, and peaked in the elderly aged 80 and older. The incidence of severe gustatory dysfunction was found to be 14.8 % in the adults aged 57 to 85 (21). Clinical studies on taste also confirmed the decline of taste function in the elderly (19,22). In this study, we found that the total taste score of recognition was significantly negatively correlated with age. The taste perception threshold or recognition threshold showed no statistical differences between the younger group and the middle aged group, indicating that the taste function was relatively stable in younger and middle-aged Chinese. However, taste scores declined in those aged above 50, as manifested by a decline in taste perception and recognition ability for sweet, umami, sour, and bitter. According to the result, the 10^{th} percentile of subjects aged 36 to 50 was used to distinguish normogeusic subjects from hypogeusic subjects. Taste disorders in older adults are thought to be related to aging, disease status (especially Alzheimer's disease), medication, surgical interventions, and environmental exposures (23,24). However, the underlying mechanism is not clear. It is speculated that the reduction of gustatory function with aging may be ascribed to a degradation of gustatory peripheral tissues and related to various neural signatures in the central nervous system. The five basic tastes have different receptor cells, so the decline in overall gustatory function might be non-homogeneous (25).

It is generally believed that women's taste sensitivity is better than men's (22,25,26). Our study found that the recognition scores of sour, salty, umami, and bitter, except sweet, in females are higher than those of males. Yamauchi et al. (27) and Yoshinaka et al. (26) reported the same results. According to the study by Heft (28), women were less sensitive to the sour taste than men, but there was no gender difference for the salty taste. A large number of studies suggested that sex differences in taste recognition might be related to differences in sex hormones (29,30). Our study found that smoking led to a decline in taste recognition and mainly affected the recognition of salty. Male smokers were much more numerous than female smokers. It was speculated that the gustatory difference between men and women might be related to living habits, such as smoking (31). In addition, females had more fungiform papillae and taste buds than males, and their gustatory function was superior to that of males (32).

However, in the study we only studied the gustatory function of adults aged 19 to 65, and only considered the influences of age, gender and smoking on taste. In the future, we will add elderly people over 65 years of age and analyze other possible influencing factors on gustatory function.

CONCLUSION

This whole-mouth method is simple and time-saving, and can be easily adjusted to obtain reliable data. The taste function was negatively related to age. In the elderly above 50 years old, taste function was significantly reduced. Taste function was more sensitive in female and non-smokers. Most importantly, this study provided the normative data for the gustatory function of the Chinese.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Otros

Escala de Fenotipos de Comportamiento Alimentario (EFCA), análisis factorial confirmatorio y propiedades psicométricas

Scale of Eating Behavior Phenotypes (EFCA), confirmatory factor analysis and psychometric properties

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Resumen

Introducción: el aumento de peso depende de múltiples factores mediadores modificables, incluido el fenotipo del comportamiento ingestivo. La Escala de Fenotipos de Comportamiento Alimentario (EFCA) es un cuestionario autoadministrado, diseñado como herramienta de uso clínico para caracterizar diferentes subfenotipos de comportamiento ingestivo: hedónico, compulsivo, emocional, desorganizado e hiperfágico.

Objetivos: el objetivo de este estudio es validar las propiedades psicométricas de la Escala de Fenotipos de Comportamiento Alimentario (EFCA) y analizar la estabilidad del constructo y su validez externa.

Materiales y métodos: trescientos participantes adultos completaron una encuesta autoadministrada, desarrollada para identificar fenotipos de conducta alimentaria (EFCA). Se realizó un análisis factorial confirmatorio, se evaluó la consistencia interna mediante el coeficiente alfa de Cronbach y se determinó la validez concurrente mediante el método de correlación de Pearson entre EFCA e IMC.

Resultados: la escala EFCA y las subescalas mostraron una aceptable consistencia interna ($\alpha > 0,70$). El análisis factorial confirmatorio mostró un buen ajuste de los datos a la estructura propuesta ($SB\chi_{92}2 = 155$, $p < 0,05$; CFI = 0,97, TLI = 0,96, RMSEA = 0,05, SRMR = 0,04). Se encontró una correlación positiva y estadísticamente significativa entre el IMC y cada subescala y la puntuación total de la escala.

Conclusiones: la EFCA y sus subescalas son un instrumento válido para evaluar fenotipos alimentarios en adultos. La estructura de cinco componentes muestra una alta estabilidad y resultados consistentes en relación a un estudio previo realizado con una muestra de pacientes con exceso de peso.

Palabras clave:

Comportamiento alimentario. Obesidad. Fenotipos. Estilos de ingesta. Medicina de precisión.

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Abstract

Introduction: weight gain depends on multiple modifiable mediating factors, including ingestive behavior phenotype. The Eating Behavior Phenotypes Scale (EFCA) is a self-administered questionnaire designed as a tool for clinical use to characterize different sub-phenotypes of ingestive behavior: hedonic, compulsive, emotional grazing, disorganized and hyperphagic.

Objectives: the aim of this study is to validate the psychometric properties of the Eating Behavior Phenotypes Scale (EFCA), to analyze the stability of the construct and its external validity.

Materials and methods: three hundred adult participants completed a self-administered survey developed to identify eating behavior phenotypes (EFCA). A confirmatory factor analysis was performed, internal consistency was evaluated using Cronbach's alpha coefficient, and concurrent validity was assessed using Pearson's correlation method between EFCA and BMI.

Results: the EFCA scale and the subscales showed an acceptable internal consistency ($\alpha > 0.70$). The confirmatory factor analysis showed a good adjustment of the data to the proposed structure ($SB\chi^2_{92} = 155$, $p < 0.05$; CFI = 0.97; TLI = 0.96; RMSEA = 0.05; SRMR = 0.04). A positive and statistically significant correlation was found between BMI and both each subscale and total scale scores.

Conclusions: EFCA and its subscales are a valid instrument to assess eating phenotypes in adults. The five-component structure shows high stability and consistent results in relation to a previous study carried out with a sample of obese patients.

Keywords:

Eating behavior. Obesity. Phenotypes. Eating styles. Precision medicine.

INTRODUCCIÓN

La escasa eficacia en el largo plazo de los tratamientos para la obesidad requiere, entre otras estrategias, identificar los fenotipos y subfenotipos de comportamiento alimentario que funcionan como mediadores entre el genotipo de un individuo y el proceso de ganancia de peso a lo largo del ciclo de vida (1-3).

Múltiples dimensiones del comportamiento ingestivo conforman patrones específicos. Estos diferentes patrones de alimentación individuales incluyen, entre otros, el uso de la comida como estrategia de afrontamiento emocional (ingesta emocional o relacionada con el estrés), una mayor sensibilidad a los alimentos agradables o indulgentes (ingesta hedónica), una pérdida de control sobre la ingesta calórica (compulsividad o desinhibición) o falta de moderación en la ingesta (hiperfagia) (4-7). Cuando los estilos ingestivos se consolidan, forman agrupaciones de fenotipos alimentarios que determinan en gran medida la variación individual en la autorregulación de la ingesta calórica y, por tanto, la posibilidad de la ganancia de peso.

Los fenotipos de la conducta alimentaria en personas con sobrepeso y obesidad se han constituido en un área de investigación de creciente interés que permitirá enfoques no farmacológicos y farmacológicos basados en la medicina de precisión (8,9).

OBJETIVO

El presente estudio tuvo como objetivo evaluar las propiedades psicométricas de la Escala de Fenotipos de Comportamiento Alimentario (EFCA) previamente diseñada (10) como herramienta para caracterizar fenotipos de conducta alimentaria. Específicamente, su validación en una muestra no clínica respecto de la consistencia interna, la validez de criterio y la validación del constructo, identificada en el estudio previo.

MÉTODOS

PARTICIPANTES

Un total de 300 sujetos hispanohablantes mayores de 18 años fueron seleccionados aleatoriamente de una muestra de 1096 participantes reclutados a través de redes sociales (Instagram, Twitter, Facebook y Whatsapp) en la República Argentina del 7 al 25 de mayo de 2020. El tamaño de la muestra se estimó en base a las recomendaciones de diferentes autores, que sugieren una proporción de 10 participantes por ítem y un mínimo de alrededor de 200 participantes (11-13). Después de dar su consentimiento informado, los participantes completaron un formulario electrónico autoadministrado que incluía datos demográficos (edad, sexo, nivel educativo), altura, peso y la Escala de Fenotipos de Comportamiento Alimentario (EFCA). Los participantes no recibieron ningún pago ni compensación económica. El presente estudio se realizó de acuerdo con los estándares éticos de la Asociación Médica Mundial y la Declaración de Helsinki.

EFCA

La EFCA (Escala de Fenotipos de Comportamiento Alimentario) es una encuesta autoadministrada, diseñada para identificar los fenotipos conductuales de la alimentación en adultos (10). Consta de 16 ítems estructurados en una escala de tipo Likert de cinco opciones (de nunca a siempre), cada una de las cuales describe una actitud específica hacia la comida. Los participantes deben indicar con qué frecuencia expresan esa actitud específica.

Los diferentes rasgos de conducta alimentaria conforman cinco subescalas o subfenotipos alimentarios, definidos como: *desorganizado:* saltearse al menos una de las comidas principales o un período interprandial mayor de 5 horas; *hedónico*: deseo de comer desencadenado por el aparato sensorial (visual, olfativo) y/o por estímulos cognitivos; *compulsivo:* ingesta rápida y ex-

cesiva de alimentos en cortos períodos de tiempo; *emocional/picoteador*: uso de la alimentación como estilo de afrontamiento desencadenado por emociones negativas (ansiedad, aburrimiento, soledad, miedo, enfado, tristeza y/o cansancio) o refrigerios repetidos, frecuentes y pequeños entre las comidas principales; *hiperfágico:* consumo de porciones excesivas o más de una porción en una sola comida. La estructura factorial de la EFCA mostró un buen ajuste a los datos, con cargas factoriales superiores a 0,40 en todos los casos. El coeficiente alfa de Cronbach indicó una fiabilidad aceptable de 0,86 para la escala total y de entre 0,73 y 0,88 para las subescalas obtenidas (subfenotipos: *picoteador/emocional:* $\alpha = 0,88$; *hiperfágico:* $\alpha = 0,84$; *hedónico:* $\alpha = 0,73$; *desorganizado:* $\alpha = 0,73$; compulsivo: $\alpha = 0,83$). La versión completa de la EFCA se puede encontrar en la tabla I. La puntuación total resulta de la suma de cada ítem (1 = nunca a 5 = siempre, excepto en la pregunta 9, cuya puntuación debe invertirse). En la tabla II se encuentra el descriptivo de los puntajes.

Tabla I. La Escala de Fenotipos de Comportamiento Alimentario (EFCA)

1. Como hasta sentirme muy lleno.
2. Calmo mis emociones con comida.
3. Pido más comida cuando termino mi plato.
4. Tengo la costumbre de picotear (picotear = realizar pequeñas ingestas entre las comidas principales —desayuno, almuerzo, merienda y cena— sin medir la cantidad de lo que se come).
5. Cuando empiezo a comer algo que me gusta mucho, me cuesta detenerme.
6. Suelo comer más de un plato en las comidas principales.
7. Picoteo entre comidas por ansiedad, aburrimiento, soledad, miedo, enojo, tristeza y/o cansancio.
8. Me siento tentado/a de comer cuando veo/huelo comida que me gusta y/o cuando paso frente a un kiosko, una panadería, una pizzería o un local de *fast food*.
9. Desayuno todos los días.*
10. Como en los momentos en que estoy: aburrido/a, ansioso/a, nervioso/a, triste, cansado/a, enojado/a y/o solo/a.
11. Salteo algunas —o al menos una— de las comidas principales (desayuno, almuerzo, merienda o cena).
12. Cuando estoy frente a comida que me gusta mucho, aunque no tenga hambre, termino comiéndola.
13. Como mucha comida en poco tiempo.
14. Cuando como algo que me gusta, finalizo toda la porción.
15. Cuando como algo que me gusta mucho, lo como muy rápido.
16. Paso más de 5 h al día sin comer.

**La puntuación debe invertirse.*

Tabla II. Puntuación EFCA total y de las subescalas

Escala	Bajo	Medio	Alto
Total	16 a 37	38 a 48	49 en adelante
Desorganización	Hasta 4	5 y 6	7 en adelante
Hedónica	Hasta 11	12 a 14	15 en adelante
Compulsiva	Hasta 3	4 a 6	7 en adelante
Emocional	Hasta 8	9 a 12	13 en adelante
Hiperfágica	Hasta 5	6 a 8	9 en adelante

Antropometría

El peso (expresado en kg) y la altura (en cm) antes del inicio de la cuarentena, informados por los encuestados, se utilizaron para calcular el índice de masa corporal (peso/altura^2). Los sujetos se clasificaron en peso bajo, peso normal, sobrepeso y obesidad de acuerdo con los puntos de corte de la IOTF.

ANÁLISIS ESTADÍSTICOS

Para evaluar la validez de criterios se obtuvieron los coeficientes de correlación de Pearson entre la escala —tanto los valores totales como los de las subescalas— y el IMC de los participantes. Debido a que la EFCA es una escala destinada a evaluar estilos de ingesta poco saludables, se seleccionó el IMC como criterio externo. Para evaluar la fiabilidad por consistencia interna se calculó el coeficiente alfa de Cronbach para la escala total y cada una de las subescalas. Finalmente, se evaluó la estabilidad de la estructura descrita por Anger-Katz y cols. (10), realizando un análisis factorial confirmatorio con el método de estimación de máxima verosimilitud.

RESULTADOS

DESCRIPCIÓN DE LA MUESTRA

La muestra estuvo conformada por 300 individuos, de ellos 262 mujeres (87,67 %), de entre 18 y 76 años (M = 40,86), con IMC entre 17,3 y 48,01 (M = 26,42; DT = 5,67). La tabla III muestra las estadísticas descriptivas de las puntuaciones de la la muestra total y las subescalas.

VALIDEZ DE CRITERIOS

El coeficiente de correlación de Pearson, medido con IMC como factor externo, para la escala total fue de 0,77, con IMC de 0,44 ($p < 0,001$); para los subfenotipos fue: desor-

Tabla III. Caracterización de la muestra

	n (%)	M	DE	1er tercil	Md	2do tercil	Mín	Máx
Sexo								
Femenino	262 (87,67)							
Masculino	38 (12,33)							
Edad		40,86	13,62	33	41	48	18	76
IMC		26,42	5,67	23,5	25,5	28,6	17,3	48
Escala EFCA								
Total		44,23	10,69	38	44	49	21	74
Desorganización		6,17	2,5	5	6	7	3	15
Ingesta hedónica		13,44	3,15	12	13	15	5	20
Ingesta compulsiva		5,79	2,16	4	6	7	2	10
Ingesta emocional		11,15	4	9	11	13	4	20
Hiperfagia		7,68	2,75	6	7	9	3	15

M: media; DE: desvío estándar; Md: mediana; Mín: valor mínimo; Máx: valor máximo.

ganizado: 0,40, IMC de 0,21 ($p < 0,01$); hedónico: 0,83, IMC de 0,38 ($p < 0,001$); compulsivo: 0,73, IMC de 0,38 ($p < 0,001$); emocional: 0,84, IMC de 0,26 ($p < 0,001$); hiperfágico: 0,77, IMC de 0,34 ($p < 0,001$) (Tabla IV).

CONSISTENCIA INTERNA

Se obtuvieron los coeficientes alfa de Cronbach para cada subescala y para la escala total, siendo en todos los casos mayores de 0,70 (Tabla V).

VALIDEZ DE CONSTRUCTOS

Se realizó un análisis factorial confirmatorio para evaluar el modelo de EFCA de cinco componentes propuesto por Anger y Katz (10). Debido a que el test de Henze-Zirkler muestra que no se cumple el supuesto de normalidad multivariada, se utilizó el método robusto de estimación de máxima verosimilitud y se reportaron como índices de ajuste aquellos sugeridos por la bibliografía: CFI (*Comparative Fit Index*), TLI (*Tucker-Lewis Index*), RMSEA (*Root Mean Square Error of Aproximation*) y SMRS (*Standardized Root Mean Square residual*). Se eligió reportar adicionalmente la prueba del χ^2 con corrección de Satorra-Bentler por ser una práctica común. Sin embargo, la bibliografía sugiere que es una medida extremadamente sensible al tamaño muestral y, por lo tanto, cuando se exceden los 200 casos, tiende a ser significativa independientemente del ajuste del modelo. Se trata, también, de un estadístico sensible a variables con altas correlaciones, como es el caso de muchas de aquellas incluidas en este modelo (14,15).

Los resultados obtenidos muestran que la estructura propuesta se ajusta adecuadamente a los datos (SB $\chi^2_{92} = 155$, $p < 0,05$; CFI = 0,97, TLI = 0,96, RMSEA = 0,05, SRMR = 0,04). Si bien el SB χ^2 resulta significativo, como se mencionó previa-

Tabla IV. Coeficientes de correlación de Pearson (validez de criterio)

	EFCA total	IMC
1. EFCA total	-	0,44‡
2. Desorganización	0,40‡	0,21†
3. Ingesta hedónica	0,83‡	0,38‡
4. Ingesta compulsiva	0,73‡	0,38‡
5. Ingesta emocional	0,84‡	0,26‡
6. Hiperfagia	0,77‡	0,34‡

**p < 0,05; †p < 0,01; ‡p < 0,001.*

Tabla V. Coeficientes alfa de Cronbach por subescala

	α	$IC_{95\ \%}$ inf	$IC_{95\ \%}$ sup
1. EFCA total	0,81	0,77	0,84
2. Desorganización	0,74	0,71	0,76
3. Ingesta hedónica	0,77	0,72	0,82
4. Ingesta compulsiva	0,80	0,76	0,84
5. Hiperfagia	0,83	0,78	0,87
6. Ingesta emocional	0,89	0,87	0,92

α*: coeficiente alfa de Cronbach; IC: intervalo de confianza.*

mente, no se trata de una medida representativa en este caso. Las cargas factoriales estandarizadas, al igual que la covarianza entre los factores, resultaron significativas ($p < 0,05$) en todos los casos (Fig. 1).

Para facilitar su visualización, la covarianza estimada entre cada factor puede encontrarse en la tabla VI.

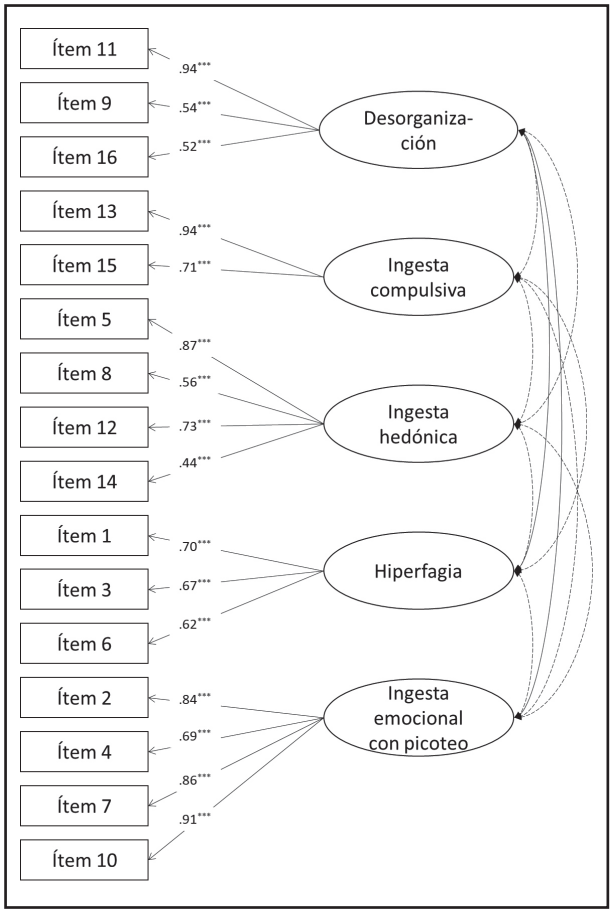

Figura 1.

Cargas factoriales del análisis factorial confirmatorio (**$p < 0,001$).

Tabla VI. AFC. Covarianza entre los factores

	1.	2.	3.	4.	5.
1. Desorganización	-	0,19*	0,18*	0,20*	0,24†
2. Ingesta hedónica		-	0,70‡	0,81‡	0,81‡
3. Ingesta compulsiva			-	0,63‡	0,72‡
4. Ingesta emocional/ picoteo				-	0,73‡
5. Hiperfagia					-

**p < 0,05; †p < 0,01; ‡p < 0,001.*

DISCUSIÓN

Los programas de tratamiento de la obesidad se basan frecuentemente en la prescripción de una dieta con una determinada composición de macronutrientes, un valor calórico específico y un plan de actividad física. Sin embargo, una gran parte de los enfoques de tratamiento ignoran la capacidad particular del individuo para autorregular la ingesta calórica. Este podría ser uno de los principales factores que expliquen la alta tasa de abandono y fracaso de estos tratamientos.

Existe evidencia respecto a la eficacia de las intervenciones basadas en cambios intensivos del estilo de vida para la pérdida y el mantenimiento del peso corporal, que incluyen asesoramiento nutricional, ejercicio y un componente comportamental (16,17).

Los fenotipos conductuales alimentarios son dinámicos y modificables mediante intervenciones farmacológicas y no farmacológicas. Algunos patrones de alimentación están asociados positivamente al IMC (18,19).

Ya se han publicado varios instrumentos que miden diferentes dimensiones del estilo de alimentación que pueden facilitar el aumento de peso debido a una mayor ingesta calórica. Los más utilizados evalúan la desinhibición, la restricción asociada al aumento del hambre (20), los episodios de frecuencia de los atracones (21), la ingesta emocional (22) y la adicción a la comida (23,24), que evalúan aspectos de los alimentos indulgentes (25) o se orientan hacia patologías alimentarias específicas o la alimentación en respuesta a señales de saciedad (26).

Se ha encontrado una fuerte asociación entre los fenotipos conductuales de ingesta y los polimorfismos genéticos del transportador de serotonina (27), el gen del receptor de dopamina D2 (28) el receptor opioide Mu (29) y el gen Clock, que impacta en el ritmo circadiano (28). Sin embargo, la nutrigenómica es hasta la actualidad de difícil acceso, ya sea por su costo o por su compleja implementación en la práctica, pues aún faltan estudios concluyentes para personalizar la prescripción dietética. Así, poder definir los fenotipos del comportamiento ingestivo mediante una herramienta sencilla permitiría diseñar tratamientos de mayor precisión y eficacia.

En este sentido, la EFCA permite la caracterización de los perfiles de conducta alimentaria. Los *clusters* identificados por la EFCA están en línea con los reportados por otros investigadores (30). Debido a la correlación positiva con el IMC obtenida en nuestro estudio, consideramos que la EFCA puede ser útil como herramienta diagnóstica. De hecho, la evaluación periódica del fenotipo de la conducta alimentaria mediante la EFCA podría permitir orientar las estrategias terapéuticas hacia el rasgo conductual predominante que suele funcionar como barrera para la autorregulación de la ingesta calórica (31). Entre sus ventajas podemos mencionar su bajo costo y su facilidad de uso.

LIMITACIONES

Al tratarse de un estudio transversal, queda por investigar la relación temporal entre los diferentes subfenotipos de la conducta alimentaria y el proceso de ganancia de peso mediante estudios de cohortes o a largo plazo.

CONCLUSIONES

La EFCA muestra buenos indicadores de validez por criterios externos, validez de constructo y confiabilidad. Es una herramienta válida y confiable para evaluar los fenotipos de la conducta alimentaria de los adultos.

Son necesarios estudios futuros para validar la EFCA en poblaciones pediátricas o de adultos mayores, así como para correlacionar los fenotipos de la conducta alimentaria con patologías alimentarias específicas como el trastorno por atracón o el síndrome de alimentación nocturna.

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Revisión

The potential mechanisms of white adipose tissue browning: a novel target for the treatment of obesity

Los posibles mecanismos de pardeamiento del tejido adiposo blanco: una diana novedosa para el tratamiento de la obesidad

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Abstract

The increase of the obesity pandemic worldwide over the last several decades has generated a constant need for the scientific world to develop new possibilities to combat obesity. Since the discovery that brown adipose tissue (BAT) exists in adult humans, and BAT activation contributes to a negative energy balance, much more attention has been focused on the understanding of the molecular switches and their different regulatory mechanisms turning on energy expenditure. Recent insights have revealed that a range of stimuli including cold exposure, physical activity and diet, and critical transcription molecules such as PPARγ, PRDM16, PGC-1α and UCP1, aiming at the induction of BAT activation, could cause the browning of white adipose tissue, thereby dissipating energy and increasing heat production. An increasing number of studies that point to the white adipose tissue (WAT) browning strategies aiming at diet-induced and/or genetically determined obesity have been tested in mouse models as well as in human studies. Findings suggested that browning stimulating drugs have been currently or previously assayed as a therapy against obesity. As PPARα agonists, fibrate drugs effectively reduced plasma triglyceride, increased high-density lipoproteins, and improved glycemic control and heat production in brown adipose tissue, which has been used in the treatment of metabolic disorders. Many kinds of natural products promote white adipose tissue browning, such as alkaloids, flavonoids, terpenoids, and long-chain fatty acids, which can also ameliorate metabolic disorders including obesity, insulin resistance and diabetes. The aim of this review is to summarize the transcriptional regulators as well as the various mediators that have been regarded as potential therapeutic targets in the process of WAT browning.

Keywords:

White adipose tissue. Brown adipose tissue. Browning. Obesity. Energy balance.

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Resumen

La creciente prevalencia mundial de la obesidad en las últimas décadas ha hecho que la comunidad científica siga necesitando desarrollar nuevas posibilidades para luchar contra la obesidad. Desde que se descubrió que el tejido adiposo pardo (TAP) existe en los adultos y que la activación del TAP contribuye al equilibrio energético negativo, se ha prestado más atención a la comprensión de los interruptores moleculares y sus diferentes mecanismos de regulación del consumo de energía. Estudios recientes han demostrado que una serie de estímulos, incluyendo la exposición al frío, la actividad física y la dieta, y moléculas clave de transcripción como PPARγ, PRDM16, PGC-1α y UCP1, dirigidos a inducir la activación del TAP, podrían causar un pardeamiento del tejido adiposo blanco (TAB), disipando energía y aumentando la producción de calor. Se han realizado un número cada vez mayor de estudios sobre estrategias de pardeamiento del TAB para la obesidad inducida por la dieta y/o genéticamente determinada, tanto en modelos de ratón como en modelos de líneas celulares humanas *in vitro.* Desafortunadamente, el potencial terapéutico de estas estrategias de pérdida de peso mediante la inducción de la activación del TAP y el pardeamiento del TAB no se ha confirmado en seres humanos. El objetivo de esta revisión es resumir los reguladores de la transcripción y los mediadores que se consideran objetivos terapéuticos potenciales en el proceso de pardeamiento del TAB.

Palabras clave:

Tejido adiposo blanco. Tejido adiposo pardo. Pardeamiento. Obesidad. Balance energético.

INTRODUCTION

Worldwide, obesity is rapidly becoming a global health hazard, which causes healthcare systems a substantial financial burden. According to the World Health Organization, the prevalence of obesity has tripled since the mid-1970s. Globally, more than 1 billion adults are overweight, and 650 million adults and 124 million children and adolescents have obesity. Moreover, the societal ramifications of this grim development are wide ranging — approximately, 90 million U.S. adults (42.4 %) now live with obesity, which is disproportionately present in socioeconomically disadvantaged persons and affects 57 % of black women (1). Obesity is also a major risk factor for, and is tightly associated with, many adverse health conditions, including cardiovascular diseases, type-2 diabetes, metabolic disorders, and multiple types of cancers. Under this disease burden, the available methods of obesity treatment have greatly lagged behind that of any other chronic metabolic diseases in primary care settings.

It is well known that insufficient energy consumption or excessive energy intake by the human body can result in adipose tissue accumulation, which is a major pathological feature of obesity. The increase in fat will generate an accumulation of fatty acids and triglycerides, which mainly exist in white adipose tissue (WAT). In obesity, an increase of WAT can also cause a chronic low-grade pro-inflammatory scenario, due to a dysregulation of secreted molecules. Meanwhile, there is another adipose tissue depot, which serves as a key site for heat production in mammals and has been previously targeted to promote weight loss: the brown adipose tissue (BAT). Recently, increasing lines of evidence have suggested that BAT uses fatty acids to generate heat instead of ATP to protect against obesity through the process of non-shivering thermogenesis (NST) (2). Increasing the metabolic activity of this tissue plays a crucial role in improving glucose and lipid homeostasis, increasing energy expenditure, and reducing weight.

A phenomenon called white adipose tissue browning is seen in various animal models, in which, in response to cold exposure, β-adrenergic and exercise stimuli, WAT cells are transformed into brown adipocyte-like cells. In recent years, a number of studies using animal models have acknowledged that BAT transplantation has beneficial effects on obesity and associated disorders including elevation of lipid profiles, reduction of tissue inflammation, improvement of energy expenditure, and reversal of even weight gain. Meanwhile, emerging experimental studies have demonstrated that changes in the fundamental morphologic, physiologic, or other metabolic activities of adipose tissue, such as the browning of adipose tissue, can affect outcomes in obesity, which unequivocally confirmed that WAT browning could be a feasible therapeutic target of obesity in rodents (3,4). Even so, the underlying mechanisms have not been extensively reviewed to date. In the present study, as a systematic review, the relationship between WAT browning and obesity has been studied, and regarding the evidence achieved from studies, new therapeutic approaches in this field have been proposed.

TYPES OF ADIPOSE TISSUE AND THEIR FUNCTION

As one of the largest endocrine organs in the body, adipose tissue is involved in a large number of physiological processes. Generally, adipose tissue serves as the central player to store excess energy in the form of fat, yet it differs in its ability for energy expenditure and storage based on its anatomical location, mitochondrial density, and thermogenic potential. Traditionally, there are two main types of adipose tissue that differ in their origin, morphology, and function in the body: WAT and BAT. WAT is responsible for energy storage in the form of triglycerides, while the known function of BAT is specialized to maintain body temperature via heat production. The characteristics of the different kinds of adipose tissue are shown in table I.

WHITE ADIPOSE TISSUE

WAT is the predominant deposit of adipose tissue in human adults, representing 10-20 percent of body weight in healthy subjects. It is composed of white adipocytes, which is a complex endocrine organ exhibiting a large nucleus and unilocular lipid droplets located in the periphery. In humans, white adipocytes are derived from mesenchymal stem cells (MESCs), common precursors for chondrocytes, osteoblasts, and adipocytes. MESCs initially differentiate into pre-adipocytes, cells that are morphologically indistinct from MESC precursors but committed to WAT or BAT lineages. Sequentially, a signalling cascade of events

Table I. Characteristics of the different kinds of adipose tissue

	White adipocytes	Beige adipocytes	Brown adipocytes
Anatomic location	Subcutaneous, intra-abdominal, and other visceral sites (pericardial)	Scattered among white adipose tissue in cervical, subcutaneous, intramuscular, and other fat locations	Interscapular, cervical, paravertebral, perirenal
Morphology	Unilocular, rounded shape, large nucleus and lipid droplets	Multilocular, polygonal, round or oval nucleus, lipid droplet size is intermediary between white and classical brown adipocytes	Multilocular, polygonal, round or oval nucleus with many lipid droplets
Developmental origin	Pdgfra	Pdgfra	Myof5+ cells
Mitochondria content	Low	High	Very high
Genetics	No UCP-1 expression	UCP-1 expression	UCP-1 expression
Function	Store energy as lipids	Dissipate energy in the form of heat	Dissipate energy in the form of heat

occurs to develop these cells into mature adipocytes terminally. The process of adipocyte terminal differentiation and the molecular regulation mechanisms which maintain the adipocyte in this differentiated state are well characterized, and several known transcription factors, including peroxisome proliferator-activated factor gamma (PPARγ) and CCAAT/enhancer binding-proteins C/EBPβ, predominantly regulate this differentiation.

The main function of WAT is to store energy in the form of triacylglycerols (TAG), which can be mobilized via lipolysis from fat stores to meet energy demands such as fasting and physical exercise. The process of lipolysis is tightly regulated by complicated regulatory mechanisms involving lipolytic hormones such as catecholamines, which activate cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA) and result in phosphorylation of hormone-sensitive lipase (HSL) and perilipin 1 (Plin1). WAT also has important endocrine functions, being able to secrete adipokines and cytokines such as adiponectin, interleukin-6 (IL-6), leptin, and tumor-necrosis factor alpha (TNFα), which are involved in the regulation of diverse metabolic processes. However, WAT may fail to regulate energy homeostasis when it is dysfunctional during sustained excess energy intake. Excessive fat accumulation has also become the major risk factor for the development of a range of metabolic disorders including atherosclerosis, hypertension, type-2 diabetes, and cancer, thus adipokines are potential targets for these chronic diseases.

BROWN ADIPOSE TISSUE

BAT is a thermogenic organ containing high mitochondrial density and multilocular lipid droplets, thus enables homoiothermic mammals to defend themselves from the cold environment and to maintain body temperature through non-shivering thermogenesis. BAT is metabolically active in individuals with high energy requirement such as newborns, small animals with high-rate metabolism, people under cold exposure, or hibernating animals. It has been estimated that BAT is primarily distributed throughout the interscapular region, accounting for 1-5 % of body weight. Recent studies have provided compelling evidence that BAT cells are not only different from WAT cells histologically, but that they also stem from different precursor cells and display different molecular signatures (5). Several genes that act as transcription co-regulators in the development of BAT adipocytes have been identified, such as the PR domain containing 16 (PRDM16), cytochrome C, type-II iodothyronine deiodinase (DIO2), β3 adrenergic receptor (β3-AR), and the peroxisome proliferation-activation receptor and coactivator 1α (PGC-1α).

Nowadays, it is well established that BAT is strongly governed by the sympathetic nervous system (SNS), which influences BAT activity and metabolism through a variety of stimuli, including cold exposure and exercise. Cold exposure is the most well-studied means to activate BAT, as non-shivering thermogenesis is highly associated with BAT in mammals. Upon stimulation, norepinephrine binding to β3 adrenergic receptors will be released to activate a cascade of metabolic events in the membrane of brown adipocytes, leading to increases in fatty acid β-oxidation and ultimately heat production (6). Data have illustrated that BAT thermogenesis is inhibited in the absence of all three β-adrenergic receptors leading to a rapid drop in core body temperature, which supports the critical role of β3-AR in thermogenesis (7). Mechanistically, the release of β1-adrenergic receptors enhances proliferation of brown preadipocytes, whereas β3-AR mainly acts to regulate the differentiation of mature brown adipocytes through cAMP-dependent signaling pathways (8). Deficits in either of them alter BAT functions. Apart from the well-known cold-activated pathways, the control of BAT thermogenesis has been closely linked to a number of hypothalamic nuclei to allow diet-induced thermogenesis, such as the energy homeostasis regulatory pathway.

In summary, the enormous effect on energy utilization makes this special type of adipose tissue an appealing target for new therapeutic approaches in order to tackle obesity and other metabolic disorders.

WHITE ADIPOSE TISSUE BROWNING

ADIPOCYTE PRECURSORS IN ADULT ANIMALS

Previously, it was thought that brown and white adipocytes were two separate differentiating lineages that diverged developmentally from the same adipocyte progenitor cells (APCs, also known as adipose stem cells, ASCs). However, recent evidence confirms that classical brown adipocytes develop along the myogenic lineage and arise from precursors expressing myogenic factor 5 (Myof5+), whereas white adipocytes derive from precursors positive for platelet-derived growth factor receptor alpha (Pdgfra+). Myof5 initiates the program of myogenic differentiation by encoding a basic-helix-loop-helix transcription factor, whereas Pdgfra determines progenitor commitment to beige adipogenesis via the encoding of a tyrosine kinase (9). Therefore, brown adipocytes may differentiate into skeletal muscle cells, and both types are functionally interrelated with each other subsequently as well. Beige adipocytes derive from the same precursors as white adipocytes, providing evidence that beige adipocytes arise from a completely de novo development as compared to BAT.

Beige adipocytes are found interspersed within WAT with a multilocular morphology similar to that of brown adipocytes. Upon stimulation, beige adipocytes have an increased capacity for thermogenesis and fuel oxidation. Unlike brown adipocytes, inducible beige adipocytes are dependent on external stimuli to induce the expression of UCP1, which is a distinctive feature of beige adipocytes. In the basal state, only a very low level of thermogenic gene expression, similar to that of white adipocytes, will be released by beige adipocytes; however, high levels of UCP1 that resemble brown adipocytes will be expressed by beige adipocytes if fully stimulated. Therefore, the beige adipocyte's capacity to switch between energy dissipation and energy storage usually depends on the type of stimuli it receives, an ability that classic brown adipocytes lack.

In rodents, induction of beige adipose tissue activity is associated with factors produced by several types of tissues and cells through autocrine, paracrine, and systemic mechanisms. M2 (alternatively activated) macrophages produce catecholamines to induce a gene expression profile enriched for proliferation, adhesion, migration, lipolysis, foam cell differentiation, extracellular proteolysis and matrix remodeling, and foam cell differentiation, thereby increasing energy expenditure in mice. Moreover, factors such as fibroblast growth factor-21 (FGF21), BMP7, BMP8b, natriuretic peptides, β-aminoisobutyric acid (BAIBA), and prostaglandins can influence the differentiation of beige adipocytes. All of these factors, which are capable of increasing energy expenditure via various mechanisms, play a positive role on weight loss by improving insulin sensitivity and glucose homeostasis in animals fed a high-caloric diet.

Recently, studies have demonstrated that beige adipose tissue is a distinct type of adipose tissue that defends the body against obesity through thermogenesis, with some beige-selective marker detectable in the WAT of adult animals after exposure to adrenergic agonists or cold environment, such as transmembrane protein 26 (TMEM26), CD137, and other thermogenic markers, including transcriptional co-regulatory PRDM16 and PGC-1β, and mitochondrial genes Cox7a1 and Cox8b. In a previous study, TMEM26 expression was widely detected in all seven depots and was mainly expressed in the visceral adipose tissue (VAT) and the inguinal depots, which was similar to the expression pattern of UCP1. Early studies have shown that the expression level of TMEM26 was significantly increased after treatment with emodin, and more multilocular lipid droplets were found in WAT (10). Moreover, the study by Auffret et al. demonstrated that after the knockout of the prolactin receptor gene, white adipocytes of mice transformed into beige adipocytes. Body weight and adipose tissue mass were significantly reduced in obese mice, and mRNA expressions of PGC-1α, UCP1, and TMEM26 were also significantly up-regulated, suggesting that the activation of TMEM26 can promote white browning (11).

However, there has still been much debate about whether cold-induced beige adipocytes are derived from the de novo differentiation of adipogenic precursor cells or derive from mature white adipocytes directly. Several lines of evidence in recent years now suggest that direct conversion of white to beige adipocytes can be a dominant mechanism of the WAT browning process. Firstly, little changes in adipocyte number or DNA content have been found during the induction of beige adipocytes. Secondly, most beige adipocytes arise from non-dividing cells, which make mature adipocytes the most likely source of such cells. On the other hand, the process of transdifferentiation from white adipocytes to beige adipocytes can be reversible. This process has been supported by an elegant *in vivo* lineage-tracing study using permanent and transient fluorescent cell labelling in transgenic mice. To sum up, further studies are needed to know the stimuli that maintain and enhance WAT browning over time.

BROWNING AS A SYMPATHETIC EVENT

Adipose tissue has allowed mammals to adapt to changes caused by nutrient availability, environmental conditions, and energy demand. White adipose tissue browning is a multistage process, which mainly occurs by interacting with sympathetic stimulation and norepinephrine (NE), with the β3-AR involved triggering a cascade of signal transduction. The primary sympathetic activator of brown adipocytes is a reduction in temperature, which can induce a massive thermogenic response. This effect is mainly mediated by the activation of the sympathetic nervous system.

In general terms, a central regulator of adaptive thermogenesis mediated by the nervous system is hypothalamic AMP-activated protein kinase (AMPK). Activated by low intracellular energy stores, AMPK reduces ATP consumption and switches intracellular processes to ATP production. Inactivation of AMPK in the ventromedial hypothalamus (VMH) results in enhancement of sympathetic output to WAT and BAT, which conveys WAT browning and BAT thermogenesis. Deletion of AMPKα1 (the AMPK subunit)

in the VMH inspires a thermogenic program in BAT, which represents a potential target for the treatment of obesity and other metabolic diseases (12). Even though it seems to bring some metabolic benefits by decreasing hypothalamic AMPK activity, a loss of AMPK expression in adipocytes could exacerbate hepatic steatosis and insulin resistance through impairing BAT function. In order to maximize metabolic benefits, potential therapies targeting AMPK activity must be tissue-specific.

Other modulators of thermogenic activity may also determine WAT browning. For example, the interaction of NE with β3-AR activates the glutamine synthetase (Gs) protein and, in turn, stimulates adenylyl cyclase (AC), which finally induces the production of PKA activator-cAMP. This PKA-dependent transduction signal will end with the overexpression of UCP1 and other thermogenic proteins. The activation of the mitogenic pathway by the p38 Map-kinase that is directly involved in PGC-1α and UCP1 overexpression also plays an essential role in the regulation of thermogenesis. Subsequently, this pathway stimulates the phosphorylation of some transcription factors such as the cAMP response element-binding (CREB), which controls the expression of DIO2 (13). This stimulation activates the type-2 5'-iodothyronine deiodinase (DIO2), catalyzing the conversion of thyroxin (T4) to T3 in the BAT. T3 acts by increasing the capacity of cells depending on its α and β nuclear receptors, respectively, increases, leading to the activation of UCP1 and thyroid receptors.

UCP1, previously referred to as thermogenin, is responsible for the conductance of protons in brown adipocytes. Based on previous studies, the regulation mechanisms of UCP1 are mainly focused on these three pathways: the AMPK-SIRT1-PGC-1α axis, PRDM16, and the PGC-1α-PPAR complex. The master regulator of adipocyte differentiation PPARγ is necessary for the regulation of brown adipocyte-specific characteristics of adipocytes. Upon binding to its receptor, PPARγ promotes the expression of genes such as C/EBP, which stimulates the differentiation of brown adipocytes and links to PRDM16 (14). Subsequently, the coactivator 1α (PGC-1α) of PPARγ can be activated along with the enhancement of UCP1 expression (14). The main role of PGC-1α is to regulate energy balance by enhancing respiratory chain proteins and the expression of UCP1. On the other hand, PGC-1α-PPARγ activity seems to be run by PRDM16, which directly interferes with the transcription of thermogenic proteins (UCP1, DIO2, and PGC-1α), being essential in the promotion of the switch from white pre-adipocytes to brown adipocytes (15). Finally, regarding the AMPK-SIRT1-PGC-1α axis, the mechanism by which some ligands of PPARγ induce the transcription of genes involved in the process of WAT browning includes the activation of sirtuin 1 (SIRT1).

The SIRT family is one of the notably increased thermogenic and mitochondrial 363 factors. In the regulation of energy metabolism, SIRT1 is involved with several transcription factors for the control and function of mitochondrial biogenesis in brown adipocytes. In the muscle, SIRT1 controls the expression of AMPK whereas in hepatocytes it deacetylates PGC-1α (16). AMPK, as a well-recognized energy sensor, plays an important role in the regulation of cellular energy homeostasis. AMPK activation promotes both BAT thermogenesis and the WAT browning process, whereas AMPK ablation results in cold intolerance and a reduction in non-shivering thermogenesis in mouse adipocytes. In relation to AMPK stimulation, SIRT1 is required for muscle mitochondrial function, described as decreased mitochondrial size and oxidation capacity. It is also known that thermogenic genes, such as those encoding for PGC-1α and UCP1, are known to be related to SIRT1 activation. Previous studies documented that overexpression of SIRT1 in the muscle downregulated PGC-1α levels, and while the AMPK activator AICAR increased the expression of PGC-1α, it also decreased the expression of SIRT1. It is therefore clear that elevated AMPK levels may influence PGC-1α activity in a manner that is largely dependent on SIRT1, which exerts a multiple effector-mediated influence on mitochondrial functions and WAT browning.

Besides transcriptional regulation, many other endocrine and locally secreted factors originating in different organs and involved in the regulation of thermogenesis and the development of brown adipose tissue have been discovered. Irisin is a PGC-1α-dependent myokine cleaved from fibronectin type-III domain-containing protein 5 (FNDC5) in direct relation to metabolism regulation. The stimulation of irisin expression in primary subcutaneous white adipocytes increases oxygen consumption together with an induction of UCP1 mRNA and other brown fat-related genes, which sheds new light on irisin's role in the development of brown adipocytes (17). In this regard, a positive correlation between the levels of UCP1 expression and the basal levels of brown gene expression in subcutaneous WAT in response to irisin has been described. Additionally, two important adipokines, leptin and FGF21, involved in regulating the browning process, act in an autocrine/paracrine manner to promote energy expenditure induced by irisin. Leptin crosses the blood-brain barrier affecting the feeding behavior and energy balance in the hypothalamus, including the dorsomedial hypothalamus (DMN), ventromedial hypothalamus (VMN), and ARC (18). Accordingly, mice deficient in FGF21 exhibited an impaired ability to adapt to chronic cold exposure, and decreased adaptive thermogenesis in BAT (19). All these processes are mediated by local (via induction of the PGC-1α protein) and central (via sympathetic activation) mechanisms.

WAT BROWNING AND OBESITY

Based on the great plasticity of adipose tissue, inducing WAT browning and activating BAT has become a potential therapeutic target for counteracting obesity by dissipating chemical energy as heat. The phenotype of WAT browning, which represents a particularly intriguing concept, involves several mechanisms in humans, and exerts a significant influence on thermogenesis, responsible for whole-body energy balance via activation of the sympathetic nervous system and/or via secretion of humoral factors (20). Accordingly, the identification of molecular pathways to manipulate the WAT browning process has gained great interest,

as they may serve as a novel therapy in the treatment of obesity and associated metabolic disorders.

It is unsurprising that participants with abundant BAT had an increased energy expenditure and a lower body mass index (BMI) in a clinical trial. A human experimental research using single-timepoint infrared thermography also evaluated the relationship between BAT and BMI, which additionally confirmed the key role of WAT browning in obesity (21). A large retrospective cohort study demonstrated that BAT activity was negatively associated with visceral adipose tissue and, particularly, with BMI among 4,852 participants who underwent computed tomography scans and diagnostic positron-emission tomography (PET/CT) (22). Those participants with higher levels of BAT had less content of WAT in their subcutaneous adipose tissue and visceral adipose tissue. In subsequent studies, individuals with morbid obesity showed a positive correlation between active BAT and non-shivering thermogenesis after 1-year post bariatric surgery (23). Additionally, we observed that the non-obese mice had a significantly smaller size of adipocytes, mitochondria appearance around lipid droplets, increased mitochondrial density, high levels of UCP1, and WAT browning in an experimental study, all of which obese mice had not (23). This is also supported by the findings observed in obese subjects after interventional studies, in whom the thermogenic function of BAT contributed to body weight reduction (24).

Obesity is also a chronic low-grade inflammation of adipose tissue associated with increased circulating and local levels of pro-inflammatory cytokines, which may negatively affect the development of brown adipose tissue. Interestingly, recent reports have identified the adipocyte-expressed apoptosis signal-regulating kinase 1 (ASK1) as a regulator of WAT browning (25). Importantly, ASK1 signaling can be specifically activated by TNFα and the endotoxin lipopolysaccharide (LPS), resulting in elevated ASK1 activity. In obese human subjects, ASK1 levels were elevated in subcutaneous adipose tissue and found to be a negative modulator of WAT browning, thereby affecting body mass, glucose metabolism, and energy expenditure (26). Moreover, ASK1 depletion in mice fed a high-fat diet reduced body weight, improved glucose metabolism, increased energy expenditure, and induced browning of inguinal WAT, underscoring the potential importance of this inflammatory factor to combat obesity and other associated metabolic disorders (25). Conversely, chow-fed mice with overexpression of adipocyte specific ASK1 blunted browning of inguinal adipose tissue under cold exposure (25).

Numerous potential molecular mechanisms underlying this browning phenomenon have been identified in mice and human assays assessing the ability of candidate molecules to promote energy metabolism and thereby combat obesity, such as the chronic activation of nuclear factor κB (NF-κB) cascade, and increase mitochondrial thermogenesis activity in skeletal muscle. In summary, understanding the regulation pathways involved in BAT activation and WAT browning allowed the identification of some critical transcriptional regulatory factors and steps during both processes, and therefore many important therapeutic strategies for the future.

INTERVENTIONAL APPROACHES TARGETING WAT BROWNING

COLD EXPOSURE

Cold exposure is one of the oldest and most effective ways of inducing WAT browning without eliciting negative cardiovascular effects. Early studies in rodents have demonstrated that both chronic and acute cold exposure stimulated BAT insulin signaling, increased oxygen consumption, and also resulted in the emergence of UCP1-positive cells in mouse parametrial fat pad (26). Accordingly, prolonged exposure to cold at +4 °C leads to an increase in UCP1 expression in experimental animals. The sensation of cold is acquired by skin receptors that convey signals via transient receptor potential (TRP) channels, which finally leads to stimulation of the peripheral sympathetic nervous system and BAT activation. The density of sympathetic innervation in WAT relies on its anatomical location, and chronic exposure to lower temperatures increases the number of sympathetic noradrenergic nerve fibers, which are strongly linked to the development of brown adipocytes.

There is also evidence from human assays that the levels of several hormones (including norepinephrine, ghrelin, and leptin) through a neural circuitry induced by cold exposure leads to a sympathetic outflow to BAT that turns on a thermogenic gene program defining a BAT-like molecular phenotype. Classically, NE, which is released from the sympathetic nerve terminal, can induce the production of FFA for UCP1 activation and lipolysis, and activate the BAT thermogenic program through PKA and p38 MAPK signaling. Recent studies have elucidated that cold exposure promoted a high production of eosinophil interleukin (IL)-4/13, resulting in the activation of M2 macrophages, which stimulated catecholamine production and tyrosine hydroxylase expression leading to browning of subcutaneous WAT (27). On the other hand, meteorin-like (Metrnl), which is a PGC1-α4-regulated hormone, also has an important role in the regulation of WAT browning by activating IL-4/13 and M2 macrophages upon cold exposure.

Moreover, cold exposure resulted in an increase of fatty acid uptake by BAT and oxidative metabolism even by 182 %, and of BAT volume by 45 % in humans. In a functional analysis of WAT and BAT, the results showed that BAT has a greater thermogenic capacity than WAT, while the molecular analysis of adipose tissue demonstrated the upregulation of genes only involved in the lipid metabolism of BAT as induced by cold exposure (28). It was estimated that more than two hours of very mild cold exposure could lead to a reduction of TG in BAT by about ~72 kcal (8 g of TG) with a mean total body BAT mass of 168 g (29). This phenomenon is associated with BAT thermogenesis, which drew attention to cold exposure targeting BAT activation. Together, these data indicate that cold exposure is a powerful stimulus targeting insulin sensitivity and lipid metabolism to promote WAT browning. The effects of cold exposure on WAT browning are shown in figure 1.

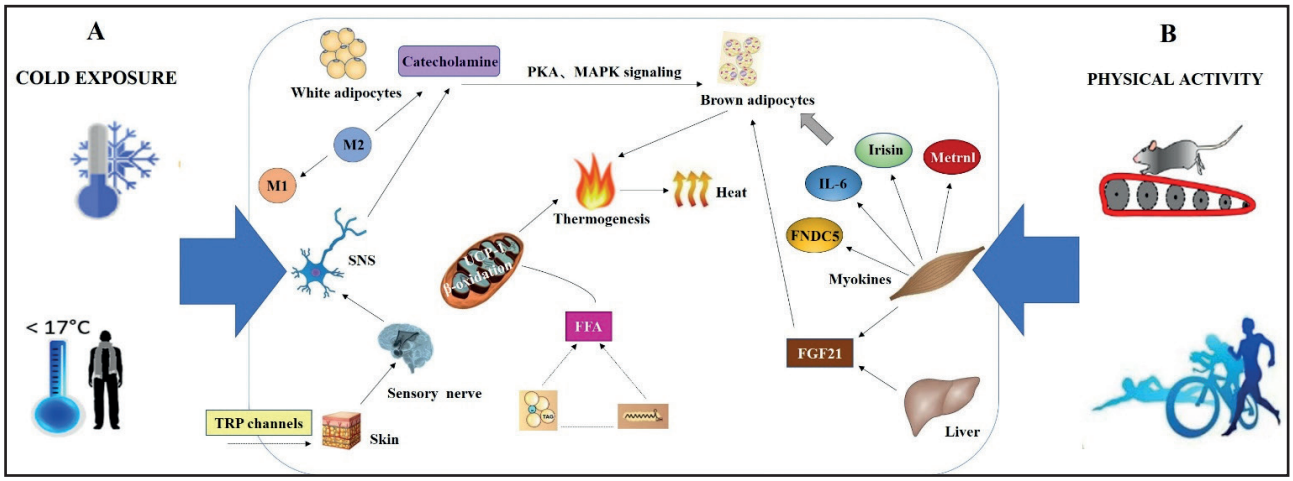

Figure 1.

Effects of cold exposure and physical activity on WAT browning. Cold exposure and physical activity effects can cause the release of hormones and myokines, which act to induce WAT browning and increase energy expenditure in an endocrine and/or paracrine manner. A. Exposure to cold temperatures stimulates the peripheral sympathetic nervous system, resulting in the activation of M2 macrophages, which promotes catecholamine production and activates the BAT thermogenic program through PKA and MAPK signaling. Concurrently, NE, which is released from the sympathetic nerve terminal, induces the production of FFA for UCP1 activation and increases mitochondrial activity. B. Physical activity reduces adipocyte size, increases the number of beige adipocytes and elicits improvements in BAT activities via inducing the production of myokines secreted by skeletal muscle such as Metrnl, IL-6, irisin, and FNDC5, which could affect the thermogenic capacity of BAT. Additionally, physical activity also increases the synthesis of FGF21, which can result in a reduction of whole-body fat mass and an increase in brown adipocyte gene expression, accompanied by a marked enhancement of energy expenditure through the UCP1-mediated mitochondrial thermogenic pathway (M1: macrophages type 1; M2: macrophages type 2; SNS: sympathetic nervous system; PKA: protein kinase A; MAPK: AMP-activated protein kinase; IL-6: interleukin 6; FNDC5: fibronectin type III domain-containing protein 5; FGF21: fibroblast growth factor 21; FFA: free fatty acid).

PHYSICAL ACTIVITY

Exercise and physical activity play a significant role in the prevention of cardiometabolic diseases, eliciting several benefits on adipose tissues. More recently, it has emerged that factors induced during physical activity and secreted by peripheral organs such as the liver, adipose tissue, and potentially skeletal muscle act to induce WAT browning and increase energy expenditure in an endocrine and/or paracrine manner. The regulation mechanism that intervenes in this process is complex and influenced by many factors. Of these, Metrnl has also generated the most interest as an agent for WAT browning induced by PGC-1α4 after resistance exercise. Metrnl promotes the production of catecholamine and the activation of M2 macrophages from these cells, ultimately leading to BAT development and energy expenditure. During *in vitro* experiments, irisin has been shown to have browning capability in the subcutaneous WAT of mice, and upregulated levels of plasma irisin have been found in humans in response to exercise (30). On the contrary, serum analyses in obese individuals have shown a significantly elevated level of serum irisin (31). Numerous other molecular factors that are significantly involved in the browning process are also altered after chronic or acute endurance physical activities, including FGF21, β-aminoisobutyric acid, interleukin-6, and natriuretic peptides (NP's). However, most of these aforementioned factors have only been verified in rodents, and their functional effects still remain to be proven in humans.

FGF21 is an exercise-induced hormone shown to play a key role in the regulation of WAT browning. Administering FGF21 *in vivo* and *in vitro* stimulates the expression of brown fat-related genes such as UCP1 in inguinal and perirenal WAT. Moreover, the effects of FGF21 were found to be dependent on PGC-1α. In fat-specific PGC-1α knockout mice, the administration of FGF21 results in a reduction of whole-body fat mass and an increase in brown adipocyte gene expression, accompanied by a marked enhancement of energy expenditure and improvement of several metabolic indexes after physical activities (32). IL-6 represents another example of an exercise-induced myokine released by the muscles that has an influence on the differentiation of brown adipocytes. Lack of IL-6 diminishes the beneficial effects of thermogenic gene expression during prolonged exercise, suggesting that this myokine serves as an indispensable mediator of thermogenic functions in BAT (33).

Additionally, FNDC5, encoded by Fndc5, happens to act as an endocrine factor of WAT browning through yet unknown pathways. FNDC5 was identified as a myokine specifically regulated by PGC-1α and exercise, and its proteolytic cleavage can lead to the release of irisin. Consistent with these observations, researchers found a concomitant and FNDC5-dependent increase associated with WAT browning in myostatin-deficient mice, which have increased muscle mass (34). Translational studies published in recent years also showed a significant positive correlation between plasma levels of irisin and the expression of PGC-1α in exercise-induced muscle (35). Therefore, the role of FNDC5 and irisin in humans in terms of BAT activation and browning might

be a great strategy for preventing and treating metabolic disorders. Additionally, the influence of exercise on WAT browning can be also attributed to increased mitochondrial activity in multiple tissues. Several animal studies have assessed the effects of exercise on mitochondrial activity and BAT thermogenesis, but resulting in mixed conclusions. Some studies demonstrated that exercise training increased mitochondrial respiration, UCP1 content, and mitochondrial activity, and induced gene expression for mitochondrial biogenesis in brown adipocytes (36). However, the results obtained by other studies showed that there is no direct correlation between exercise and both the mitochondrial and thermogenic activity of BAT (37). Together, these studies suggest that further research is needed to fully establish the role of physical activity on the thermogenic function of BAT. The effects of physical activity on WAT browning are shown in figure 1.

DIET

Data from experimental studies suggest that some dietary components can increase the metabolic rate via thermogenic effects by augmentation of BAT activity. The molecular mechanisms triggered by dietary components to promote thermogenic responses in brown adipocytes include, but are not limited to, activation of AMPK/SIRT1 and PPARγ-PRDM16 signaling pathway, modulation of thermogenic and anti-obesity adipokine secretion, and morphological and epigenetic changes. Several plant-based compounds and dietary factors such as capsaicin, curcumin, caffeine, catechins and resveratrols have been demonstrated to have significant effects on WAT browning based on both *in vitro* and *in vivo* studies. The summary of dietary components that induce WAT browning are shown in figure 2.

Capsaicin (and related capsinoids), as alkaloids present in plants belonging to the *Capsicum* genus, has been shown to induce WAT browning in mice via multiple different mechanisms, including the activation of gastrointestinal transient receptor potential vanilloid 1 (TRPV1) receptors, the modulation of the AMPK/SIRT1 pathway, and the modulation of PPARγ-PRDM16 interaction. In animal studies, the oral administration of capsaicin and/or capsinoids results in an increase in sympathetic nerve activity innervating WAT browning, and whole-body energy expenditure, and a decrease in body fat mass by stimulating TRPV1 expression in sensory nerves within the gastrointestinal tract (38). It was also reported that a lack of TRPV1 in mice

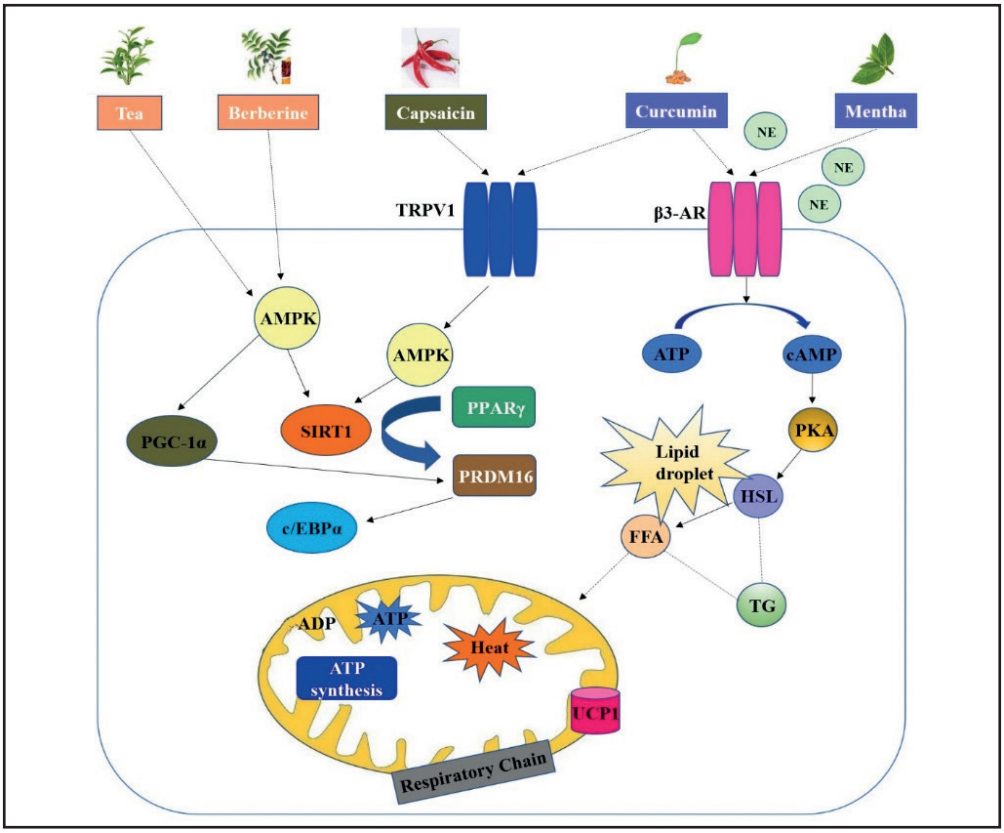

Figure 2.

Summary of dietary components that induce WAT browning (TRPV1: transient receptor potential vanilloid 1; β3-AR: β3 adrenergic receptor; NE: norepinephrine; AMPK: AMP-activated protein kinase; PGC-1α: peroxisome proliferator-activated receptor-gamma coactivator alpha 1; SIRT1: sirtuin 1; PPARγ: peroxisome proliferator-activated factor gamma; PRDM16: PR domain containing 16; C/EBPβ: CCAAT/enhancer binding-proteins; UCP1: uncoupling protein 1; cAMP: cyclic adenosine monophosphate; HSL: hormone-sensitive lipase).

can diminish the weight loss and thermogenic effects caused by capsinoids (39). It is possible that the thermogenic effects of capsinoids are directly subjected to the regulation of TRPV1 as expressed in BAT, thereby increasing energy expenditure. During *in vitro* studies capsaicin stimulated the phosphorylation of SIRT1 by activating AMPK and the expression of transcription factors PPARγ and PRDM16, finally leading to UCP1 synthesis accompanied by a subsequent activation of BAT thermogenesis and browning.

Recently, other representative dietary compounds that have an ability to induce BAT activation is polyunsaturated fatty acids (PUFAs), a polyphenol with protective effects against metabolic alterations such as obesity and dyslipidemias. In animal models, the influence of PUFAs on the expression of UCP1 mRNA in brown adipocytes or WAT browning can be affected by high-fat diets. The results from two other studies demonstrated that supplementation with diets rich in omega n-3, long-chain polyunsaturated fatty acids significantly promoted thermogenic effects by activating the brown adipose tissue (40,41). Furthermore, a maternal diet rich in polyunsaturated fatty acids also contributed to larger interscapular brown adipose tissue depots in animals (42). The underlying molecular mechanisms responsible for the thermogenic function of PUFA are controversial, including the activation of TRPV1, immediately stimulating ADRB3 but also free fatty acid receptor 4 (FFAR4), which ultimately resulted in the up-regulation of several miRNAs involved in adipocyte browning. However, it has to be further proved whether dietary n-3 PUFAs exert thermogenic effects in humans.

Curcumin is a polyphenol compound extracted from the rhizomes of the plant *Curcuma longa*, commonly known as turmeric, with anti-obesity and anti-hyperglycemic properties. A large number of studies have confirmed the hypothesis that the administration of curcumin, by suppressing inflammatory reactions in adipocytes and lipogenesis in the liver, may promote thermogenesis in BAT and/or the browning process in rodents. For instance, Wang et al. (43) reported that mice displayed a reduction of fat mass, body weight gain, and a better tolerance to cold exposure, without any effect of food intake, after the administration of 50 or 100 mg/kg/day of curcumin for 50 days. Particularly, the role of curcumin in the induction of WAT browning has also been described in these animals. *In vitro* studies have shown that curcumin induced mitochondrial biogenesis and WAT browning through an AMPK dependent pathway in 3T3-L1 cells and a primary culture of inguinal white adipocytes, and markedly drove the BAT thermogenic program by increasing several brown fat markers in both types of adipocyte in a dose-dependent manner (doses ranged from 1 to 20 μM) (44). Besides, a proteome analysis aiming at primary inguinal white adipocytes indicated that curcumin increased the expression of critical mitochondrial proteins responsible for lipolysis, browning-specific markers, and the oxidation of fatty acids (2). However, if curcumin induces WAT browning in humans has yet to be determined.

Other intriguing dietary compounds such as caffeine and catechins can also promote energy expenditure and BAT thermogenesis. Green tea is abundant in catechins, and has a high content of polyphenols, which have apparent thermogenic and anti-obesity properties. In humans, an oral administration of catechin-rich tea produced an acute increase in energy expenditure and activation of thermogenesis with higher BAT activities in a similar way in different doses (45). It has been reported that green tea extracts exert their thermogenic response through the direct activation of the AMPK cascade in BAT, including the overexpression of brown-specific and anti-adipogenic genes (46). In addition to the dietary compounds discussed above, various dietary components such as resveratrols, thyme, mentha, and berberine have revealed their thermogenic potential via multiple mechanisms of action during *in vitro* and animal studies. In the future, more clinical trials are necessary to evaluate their involvement in the browning process in humans.

THE CORE REGULATORS OF WHITE ADIPOSE TISSUE BROWNING INVOLVED IN OBESITY

The functional importance of brown adipose tissue for heat generation and energy consumption to protect animals from obesity and other metabolic disorders has been emphasized for decades and has become the new focus in the field of endocrinology in recent years. Understanding the molecular mechanisms responsible for WAT browning allowed the development and administration of new targeted approaches to intensify this process for the induction of energy consumption, the purpose of which is to tackle obesity and/or ameliorate the metabolic profile. Several representative transcription factors and co-regulators that affect WAT browning have sparked an interest in the possibility of further identifying molecular switches in the browning process. The selected molecules involved in white adipose tissue browning and brown adipose tissue activation that could exert potential therapeutic effects on obesity are shown in table II.

ROLE OF PPARγ

Although different routes are followed by white and brown adipocytes during the differentiation process from mesenchymal stem cell to adipocyte, both of them share a similar transcriptional program. PPARγ is highly expressed in both adipocyte types, where it is a key regulator indispensable for adipocyte differentiation and survival. PPARγ belongs to a sub-family of the peroxisome proliferator-activated receptor family, of which the firstly identified PPARγ was able to regulate gene expression by binding to PPARγ Responsive Elements (PPREs) after dimerization with RXRs. Due to alternative promoter usage, PPARγ exists as two protein isoforms, PPARγ1 and PPARγ2 which differ in their N-terminal. Previous studies (47) have demonstrated that the PPARγ2 expression stimulated adipogenesis in cultured fibroblasts including the conversion of cell morphology, lipid accumulation, and expression of target genes closely associated with the adipocyte phenotype.

Table II. Selected molecules involved in white adipose tissue browning and brown adipose tissue activation that could exert potential therapeutic effects on obesity

Browning agents	Type	Experimental model	Role	Reference
AMPK	-, co-regulator	SF1 neuron-specific AMPKa1 knockout mice	Repressing WAT browning and BAT thermogenesis, reducing ATP consumption and promoting ATP production	22-23
C/EBPα	+, TF	Mouse model	Stimulating differentiation of brown adipocytes	26
SIRT1	+, co-regulator	Mouse model	Regulating BAT thermogenesis and the WAT browning process	31
Irisin	+, myokine	Primary subcutaneous white adipocytes	Increasing oxygen consumption, inducing UCP1 mRNA and other brown fat-related genes	32
ASKI	-, co-regulator	Clinical study, ASK1-deficient mice, Mice with adipocyte-specific ASK1 overexpression	Increacing body mass, inhibiting glucose metabolism and energy expenditure, repressing UCP1 gene expression	40-42
FGF21	+, secreted hormone	Clinical study	Reducting whole-body fat mass and brown adipocyte genes, enhancing energy expenditure and upregulating several metabolic indexes	54
FNDC5	+, secreted myokine	Myostatin-deficient mice	Improving capacity and function of BAT	56
PPARγ	+, core TF	Primary adipocytes, PPARγ-deficient mice	Promoting beige adipogenesis, required for the recruitment of PRDM16, inhibiting white-fat genes, increasing thermogenic capacity to generate ATP and brown-specific characteristics that translate into a higher metabolic rate, upregulating UCP1 gene expression.	70, 73, 74
PRDM16	+, core TF	Cultured white preadipocytes, PRDM16-global knockout mice	Leads to upregulation of mitochondrial genes, brings about the induction of BAT-specific genes, upregulating expression of BAT thermogenesis, increasing energy expenditure and O_2 consumption.	74, 76, 77, 78
PGC-1α	+, co-regulator	Subcutaneous white adipose tissue, PGC-1α-deficient mice	Enhancing thermogenic effect in subcutaneous WAT, inducing BAT-specific genes in WAT.	79
β3-AR	+, co-regulator	Cultured brown adipocytes	Regulating the differentiation of mature brown adipocytes, stimulating PKA and lipolysis, and thereby acutely enhancing UCP1 expression.	15, 84
UCP1	+, co-regulator	UCP1-knockout mice	Responsible for BAT thermogenesis and whole body energy homeostasis, resistance to the development of obesity and inability to maintain body temperature.	85

Type indicates whether the regulator has a positive (+) or negative (–) effect on WAT browning; TF: transcription factor.

PPARγ is subjected to several post-translational modifications and interacts with various other transcriptional regulators. It was found that the expression of UCP1, which is a BAT hallmark gene responsible for thermogenesis, would be induced by PPARγ activator rosiglitazone in WAT of both mice and humans. Petrovic et al. (48) treated primary cultures of mouse epididymally-derived white adipocytes differentiated to mature adipocytes with a potent PPARγ agonist *in vitro,* and observed marked UCP1 gene expression in approximately 10 % of these pure white adipocyte cultures, as revealed by immunocytochemical staining. These cells not only increased the expression of UCP1, but also of Elovl3 (elongation of very long-chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 3), PGC-1α (peroxisome proliferator-activated receptor γ coactivator 1α), and other genes related to mitochondrial biogenesis. PPARγ activation can promote beige adipogenesis via PGC-1α, which plays a crucial role in oxidative metabolism, adaptive thermogenesis, and mitochondrial biogenesis. It has also been demonstrated that SIRT1-mediated deacetylation of PPARγ is required for the recruitment of PRDM16, which is the determinant factor of brown fat development and sufficient for

the process of brown adipogenesis in WAT (49). In a chromatin immunoprecipitiation analysis combined with massive parallel sequencing (ChIP-seq) to identify genome-wide PPARγ binding sites in epididymal WAT and primary interscapular BAT, early B-cell factor-2 (Ebf2) has been shown to regulate PPARγ binding activity, which could determine adipocyte identity (50). When Ebf2 is expressed in white pre-adipocytes or myoblasts, PPARγ binding to its brown-selective sites and reprogrammed cells increase. Consistently, brown adipocytes and tissues in PPARγ-deficient mice have displayed a loss of thermogenic capacity to generate ATP and brown-specific characteristics that translates to a lower metabolic rate (51). Several other genes specialized in WAT browning are involved in the process of adipogenic differentiation, many of which contain functional PPARγ response elements such as aP2.

Furthermore, PPARγ was shown to be not only involved in the induction of brown fat genes but also the inhibition of white fat genes during the browning process. For example, the troglitazone-associated inhibition of white fat genes will be prevented in 3T3-L1 adipocytes when mutation has occurred at the PPARγ ligand binding site (51). The interplay of the regulators described above highlights the key role of PPARγ in the browning process, which involves a series of transcription activators and repressors.

ROLE OF PRDM16

PRDM16 is a zinc finger protein that was identified as a brown fat-selective cofactor able to activate the brown adipose differentiation programs. Quantitative analyses evaluating the expression of PRDM16 at the mRNA level demonstrated a 15-fold enrichment in brown adipose tissue relative to white adipose tissue (52). Importantly, PRDM16 mRNA expression increased 20-fold during the differentiation of brown adipocytes in a culture (52). Overexpression of PRDM16 in cultured white preadipocytes will lead to an up-regulation of mitochondrial genes, accompanied by an increase in uncoupled respiration and mitochondrial biogenesis, hallmarks of BAT. These data highly suggest that PRDM16 serves as a determining factor to promote WAT browning in subcutaneous WAT. In a follow-up study, PRDM16 has been demonstrated to be a cell fate switch, which determines myf5 positive precursor cells to become brown adipocytes or skeletal myoblasts, both of which are derived from the same cell type (53). PRDM16 has also been shown to be required for the enhancement of the transcriptional activity of PPARγ by binding to PPARγ in a ligand-independent manner, indicating that PPARγ activation plays an important role in the adipogenic function of PRDM16.

Mechanistically, it has also been confirmed that PRDM16 could bring about the induction of BAT-specific genes such as UCP1 by directly interacting with PGC-1α and PGC-1β. The late-stage embryos (E17) of PRDM16 global knockout mice show that BAT was severely affected accompanied simultaneously by increased expression of skeletal myogenic genes, and reduced expression of BAT thermogenic and selective genes, supporting a role of PRDM16 as a negative regulator of skeletal muscle development and an early determinant of the brown fat lineage (53). An analysis of transgenic mice with *in vivo* overexpression of PRDM16 in white fat, induced by a high-fat diet, demonstrated that the molecular changes present were associated with reduced energy accumulation and increased energy expenditure, protecting the whole body from the weight gain, all of which indicated selective effects of PRDM16 in adaptive thermogenic responses (54). In addition, mice with specific ablation of PRDM16 in adipose tissues showed significant reductions in O_2 consumption and thermogenic gene expression of white adipose tissue both in the basal state and following stimulation under cold exposure, indicating that PRDM16 is required for the browning of white adipose tissue and the healthy effects of subcutaneous adipose tissue (55). However, the effects of PRDM16 ablation appeared to be inguinal fat-specific, altering the function of beige adipose tissue but not causing depletion in brown adipose tissue. In general, these loss- and gain-of-function researches, performed both *in vitro* and *in vivo,* have confirmed the crucial role of PRDM16 in the development of brown adipose tissue and related regulatory programs.

Besides, several other genes that were not previously known to be expressed selectively in white versus brown adipocytes, such as neurotrophic tyrosine kinase receptor type 3 (ntrk3), otopetrin-1 (otop1) and epithelial like antigen-1 (eva1), were significantly induced by PRDM16 expression. Moreover, the expression of several important thermogenic genes was increased in PRDM16-transduced cells via a cAMP-dependent manner, and the mRNA levels of PGC-1α, UCP1, and deiodinase-d2 were elevated to very high levels by PRDM16 in response to cAMP. On the other hand, PRDM16 expression also has a great influence on the mRNA levels of those genes related to mitochondrial oxidative phosphorylation, such as cox4i1, cox5b, and cytochrome c (cyc), that are abundant in brown adipocytes. Altogether, these results strongly suggest a role for PRDM16 as a positive regulator of the WAT browning program.

ROLE OF PGC-1α

PGC-1α was first characterized in the late 1990s after the identification of novel interactors of the master regulator of adipocyte differentiation, PPARγ, in brown adipose tissue, which was performed in a yeast two-hybrid screen. It has now been recognized that PGC-1α can alter the transcriptional activities of a number of key mitochondrial genes encoding for proteins involved in metabolic functions, which ultimately led to an increase in mitochondrial DNA. The expression of PGC-1α is induced upon cold exposure in brown adipose tissue. Once activated, PGC-1α stimulates the transcriptional networks that control the oxidative phosphorylation and mitochondrial biogenesis of energy substrates, leading to the initiation of tissue-specific gene programs that adjust hepatic gluconeogenesis, lipid metabolism, and thermogenesis in the brown adipose tissue. Remarkably, mice with adipose PGC-1α deficiency are cold-sensitive owing to thermogenic dysfunction, mainly caused by diminished UCP1 expression, impaired fatty-acid β-oxidation, and also electron transportation.

In primary human subcutaneous white adipose tissue, adenovirus-mediated expression of PGC-1α stimulates the phenotype of brown adipocytes, accompanied by increased expression of UCP1, fatty acid oxidation enzymes, and respiratory chain proteins. Mice deficient in PGC-1α underwent a blunted expression of mitochondrial genes and diminished thermogenic effects in subcutaneous WAT. However, the physiological role of PGC-1α in a different adipose tissue-specific PGC-1α-deficiency mouse model has been demonstrated to be dispensable for the management of mitochondrial biogenesis and respiration through the regulation of nuclear respiratory factors and the induction of uncoupling proteins, even though it plays an important role for the induction of BAT-specific genes such as UCP1 in subcutaneous WAT (56). The analysis by immunohistochemistry of WAT reveals the presence of UCP1-positive multilocular cells, which are seen as a sign of browning. This suggests that there is cross-talk between PGC-1α and the WAT browning process. This is in line with the definition of PGC-1α as a cold-induced co-activator of thermogenesis under the control of mitochondrial gene expression.

In addition to the classic factors involved in brown adipocyte functions, other inducers such as CREB signaling and β-adrenergic stimuli are known to regulate PGC-1α mRNAs. FGF21 has emerged as an important regulator in this thermogenic recruitment of WAT by regulating PGC-1α protein levels in an autocrine/paracrine fashion, finally prompting PGC-1α-dependent WAT browning. Moreover, it has been demonstrated that the expression of PGC-1α protein can be regulated by factors such as pRb (retinoblastoma protein) and the Rb family member p107, prompting PGC-1α-dependent WAT browning (57). Interestingly, BAT-like features in WAT of p107-knockout mice were displayed with elevated PGC-1α and UCP1 expression, while pRb is significantly reduced in p107-knockout mice. As repressive effects of pRb on PGC-1α expression by binding to its promoter, both pRb and p107 are likely to exert a negative effect on the browning process because of their interaction with PGC-1α. To conclude, PGC-1α is known as a critical transcriptional co-regulator for mitochondrial oxidative metabolism and hence for WAT browning. A great emphasis has been placed on the identification of the signaling pathways activating PGC-1α and its related downstream targets that can ultimately enhance a negative energy balance.

ROLE OF UCP1

UCP1, which resides within the inner mitochondrial membrane, was first isolated from the BAT of cold-exposed rats 40 years ago and originally termed thermogenin for its heat-producing function in non-shivering thermogenesis. UCP1 is known as a brown adipocyte-specific natural, regulated uncoupler of mitochondrial respiration: its activity translates the high oxidation rates of brown adipocytes into heat production to defend core body temperature under cold exposure by dissipating the energy proton gradient from the respiratory chain after the facilitation of proton reentry into the mitochondrial matrix. During cellular respiration, the uncoupling of oxidative phosphorylation represents about 50 % of energy expenditure from the mitochondria of a cell with normal function. Taking the laws of thermodynamics into consideration, most of the energy that is generated by the electrochemical potential of the oxidation process in brown adipocytes is not used for the phosphorylation of ADP, but is dissipated as heat. It is estimated that 60 g of BAT could contribute to more than 20 % of heat generation under controlled cold conditions in the human body.

There is considerable evidence that UCP1 is mainly responsible for BAT thermogenesis and whole-body energy homeostasis. The expression of the UCP1 gene can be activated by thyroid hormones, b3-agonists, cold exposure, cAMP, and adrenergic stimulation, and inhibited by purine nucleotides (ADP and ATP). In previous studies, the sympathetic nervous system was recognized and confirmed as the main trigger of UCP1 induction and activation based on the use of drugs that activate β3-ARs. In addition, the uncoupling of the mitochondrial respiratory chain induced by UCP1 action takes place only after a proper stimulation of cells by norepinephrine. In the basal status, the proton-translocating activity of UCP1 is blocked by the binding of purine nucleotide di-and tri-phosphates at its outer facing cavity. In response to a cold environment or nutrients, norepinephrine is released from the sympathetic circuits onto β3-ARs to activate thermogenesis in thermogenic adipocytes. Subsequently, β3-AR signaling will stimulate PKA and lipolysis by elevating cAMP levels, thereby acutely enhancing UCP1 expression through multiple transcriptional and post-transcriptional mechanisms directly induced by free fatty acids. This finding indicates the existence of thermogenesis effects is physiologically relevant to UCP1 in adipocytes. Accordingly, the potential sites for the induction of brown adipocytes and the regulation of UCP1 are multifarious, and many of the transcription factors and molecules of the signaling pathway are involved in various aspects of adipocyte biology, as well as in muscle structure and function. More recently a proof-of-principle study showed that UCP1-knockout mice at thermoneutrality were slightly prone to diet-induced obesity and resistant to obesity when housed at room temperature, suggesting a central role of a UCP1-independent thermogenic pathway in counteracting the development of obesity in mice (58). Thus, reduced lipid deposition, greater thermogenesis, and higher UCP1 expression in BAT could be helpful for adequate body weight control.

CONCLUSIONS AND FUTURE PERSPECTIVES

Over the last decade, white adipose tissue browning has garnered great interest as a new therapeutic strategy to combat obesity, as numerous studies have established an association between BAT activities and energy balance. In recent years, various research studies both at home and abroad have significantly increased our understanding of the regulation mechanisms related to the process of WAT browning. Currently, the best-explored activators of WAT browning include cold exposure, physical ac-

tivity, and diet, which have been known for years. Many critical transcription molecules, secreted factors, and critical steps have been implicated in the browning process. It is interesting that a majority of these molecules exert their effects through a series of cascade molecular reactions including binding, interacting, inhibiting, or activating the primary transcriptional regulators during the development of traditional brown adipose tissue: PPARγ, PRDM16, PGC-1α, and UCP1. The metabolic activation of brown adipose tissue does not only promote energy expenditure by regulating BAT thermogenesis, but also serves as an effective adjunct therapeutic target for metabolic complications such as obesity, insulin resistance, and disturbances in glycolipid homeostasis. In terms of the metabolic advantages resulting from the initiation of WAT browning, the most important future perspective will focus on exploring new molecular factors and related signaling mechanisms, thus elucidating WAT browning as well as BAT activation.

Since the recruitment and activation of BAT in obese individuals plays an especially important role for promoting a negative energy balance, the critical issue with regard to the relationship between inactive BAT and energy metabolism under the obesity condition needs to be further addressed. An increasing number of studies in mouse models as well as *in vitro* models of cell lines point to WAT browning strategies aiming at diet-induced and/or genetically determined obesity. Unfortunately, this hypothesis has not been confirmed in an *in vivo* model by inducing BAT activation and WAT browning in humans. It remains challenging to identify BAT activators that will still work properly under other conditions other than cold exposure, physical exercise, and diet. Moreover, there is still controversy over the issue of how to activate and maintain a significant number of brown adipocytes for anti-obesity effects. Another major goal for future research is a clarification of brown adipokines or batokines, which probably could be candidates for drug development to combat obesity and related metabolic disorders.

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Revisión

Will intestinal flora therapy become a new target in type-2 diabetes *mellitus?* A review based on 13 clinical trials

¿Puede la terapia de flora intestinal convertirse en un nuevo objetivo para la diabetes mellitus *de tipo 2? Revisión basada en 13 ensayos clínicos*

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Abstract

Background: diabetes *mellitus* (DM) is a chronic disease and its pathogenesis is still inconclusive. Current evidence suggests an association between intestinal flora and type-2 diabetes *mellitus* (T2DM). In this paper, we summarized the current research, determining whether intestinal flora may become a new method to treat T2DM, and providing a theoretical basis and literature references for the prevention of T2DM based on the regulation of intestinal flora.

Method: we carried out a review based on 13 published clinical trials to determine the correlation between T2DM and intestinal flora, and between changes in clinical outcomes and in intestinal flora in the development of T2DM; to assess the pathological mechanisms; and to discuss the treatment of diabetes based on intestinal flora.

Results: we found that intestinal flora is involved in the occurrence and development of T2DM. Several pathological mechanisms may be involved in the process, including improving the gut barrier, alleviating inflammation, increasing glucagon-like peptide (GLP) 1 and GLP 2, increasing the production of short-chain fatty acids (SCFAs), and so on. Several measures based on intestinal flora, including exercise, food, specific diets, drugs and probiotics, would be used to treat and even prevent T2DM.

Conclusions: high-quality studies are required to better understand the clinical effects of intestinal flora in T2DM.

Keywords:

Intestinal flora. T2DM. Therapy.

Resumen

Antecedentes: la diabetes *mellitus* (DM) es una enfermedad crónica cuya patogénesis no está clara. La evidencia actual sugiere una asociación entre la flora intestinal y la diabetes *mellitus* de tipo 2 (DMT2). Este artículo revisa la investigación actual para determinar si la flora intestinal puede ser un nuevo método de tratamiento de la diabetes *mellitus* de tipo 2 y proporciona la base teórica y las referencias de la literatura para la prevención de la diabetes *mellitus* de tipo 2 basada en la regulación de la flora intestinal.

Métodos: se revisaron 13 ensayos clínicos publicados para determinar la correlación entre la DMT2 y la flora intestinal, los cambios en los resultados clínicos y los cambios en la flora intestinal durante el desarrollo de la DMT2; para resumir su mecanismo patogénico; y, desde el punto de vista de la flora intestinal, para explorar el tratamiento de la diabetes.

Resultados: se encontró que la flora intestinal estaba involucrada en el desarrollo de la diabetes *mellitus* de tipo 2. Este proceso puede implicar una variedad de mecanismos patológicos, incluyendo la mejora de la barrera intestinal, la reducción de la inflamación, el aumento del péptido similar al glucagón (GLP) 1 y GLP 2, y el aumento del rendimiento de los ácidos grasos de cadena corta (SCFA). Algunas medidas basadas en la flora intestinal, como el ejercicio, los alimentos, las dietas especiales, los medicamentos y los probióticos, se utilizarán para tratar e incluso prevenir la DMT2.

Conclusión: se necesitan estudios de alta calidad para comprender mejor los efectos clínicos de la flora intestinal en los pacientes con diabetes *mellitus* de tipo 2.

Palabras clave:

Flora intestinal. Diabetes *mellitus* de tipo 2. Tratamiento.

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INTRODUCTION

Nowadays, diabetes *mellitus* has gradually become an increasingly striking social health problem around the world. In 2017, the eighth edition of the International Diabetes Federation (IDF) Diabetes Atlas showed that there were about 425 million diabetics worldwide and the number may increase to 700 million by 2045 (1). The incidence of diabetes *mellitus* (DM) in China is about 10 % (2), and the number has reached 114 million, amounting to 1/3 of the total of global diabetics. T2DM accounts for more than 90 % of total diabetes patients (3,4).

The intestinal flora is to date considered a complex organ composed of 500-1000 species and 10^{14} bacteria, which is more than 10 times the number of human cells, including bacteria, viruses, fungi, and protozoa, that are commensal with the human intestinal tract (5). Among these, bacteria represent the best studied group and will be the main focus of this review. Overall the predominant bacterial groups in the microbiome are Gram-positive *Firmicutes* and Gram-negative *Bacteroidetes* (6,7). Studies have shown that lots of chronic diseases may be related to intestinal microecological disorders (8), that intestinal flora is an important factor among environmental factors, and that its changes are related to a series of metabolic diseases such as obesity and DM (9,10).

At the same time, a lot of factors can contribute to changes in intestinal flora. Firstly, it is now understood that diet plays a significant role in shaping the microbiome, with experiments showing that dietary alterations can induce large, temporary microbial shifts within 24 h. The gut microbiota of patients with type-2 diabetes has been functionally characterized with diabetes-associated markers, showing enriched membrane transport of sugars and branched-chain amino acids, xenobiotic metabolism, and sulfate reduction along with decreased bacterial chemotaxis, butyrate synthesis, and metabolism of cofactors and vitamins (11). Revealed by metagenome analysis, gut microbiota composition transforms through early stages of human development, and is influenced by the diet (12). Secondly, regular exercise has an anti-inflammatory effect, which improves the immunological profile in type-2 diabetes *mellitus* (13). Thirdly, the intestinal flora changes with aging. Besides these, some other factors, such as drugs (16-17), lifestyle (30), etc., also play a role in the development of intestinal flora.

It is of huge importance to fully understand the changes of intestinal flora in T2DM, and the pathological mechanism of involvement of intestinal flora in the development of T2DM. Similarly, an in-depth study of risk factors associated with bacterial reduction in patients with T2DM is needed, including the impact of exercise, food, specific diets, drugs and probiotics. In this article, we carried out a review based on several published clinical trials to determine the correlation between T2DM and intestinal flora. We hope that this article may provide a theoretical basis and literature references for the regulation of intestinal flora in the treatment of T2DM and its complications.

MATERIALS AND METHODS

IDENTIFICATION OF ELIGIBLE STUDIES

One search strategy was run using "Intestinal flora" and "Type 2 diabetes *mellitus"* with no limitations. Besides, another search strategy was also run using the terms "Intestinal flora" and "Type 2 diabetes *mellitus"* limited to "humans" and "clinical trial". A broad search of the English-language literature for randomized controlled trials (RCTs) in patients with T2DM was performed by using Cochrane, Medline, PubMed, Central Register of Controlled Trials, Web of Science, and trial registry databases. All the relevant publications were reviewed, and duplications of articles from the two search strategies were avoided. The articles in reference lists were also hand-searched for potentially relevant publications. The search was conducted by two investigators. Any disagreements were resolved by consensus with involvement of the third author.

INCLUSION AND EXCLUSION CRITERIA

Human-associated studies, regardless of year of publication, would be included if they met the following criteria: 1) RCT; 2) patients had been diagnosed with T2DM; 3) were older than 18 years; 4) sufficient data were available of clinical outcomes. Studies would be excluded if they met the following criteria: animal experiment, review, mechanism research, case report, collection of papers, literature with incomplete data and/or duplicates, and no full manuscript availability. Participants would be excluded if they 1) had severe conditions, including digestive dysfunction, heart failure, renal failure, malignant tumors, severe cerebrovascular diseases, ketosis, hyperthyroidism, liver dysfunction, or severe gallbladder and pancreatic diseases; 2) were pregnant or lactating; 3) suffered from mental illness; 4) used anti-depressants, sedatives, neurological or psychiatric medications; 5) required insulin therapy or had arterial hypertension and dyslipidemia controlled by statins and either ace-inhibitors or angiotensin receptor blockers; 6) had diabetes-specific complications and ischemic heart disease; 7) lacked the ability to perform physical activities.

DATA EXTRACTION

Two investigators extracted the data independently and reached a consensus on all items. For each study, the following information was collected: first author, year of publication, sample size, mean age, gender, anthropometric measurements (weight, height, body mass index (BMI), waist circumference, and body composition by bioelectrical impedance analysis), dietary record, trial duration, and clinical outcomes. Clinical outcomes included: glycated hemoglobin (HbA1c), low-density lipoprotein-cholesterol (LDL), high-density lipoprotein-cholesterol (HDL), cholesterol (CHOL), triglycerides (TG), aspartate aminotransferase (AST) and

alanine transaminase (ALT), free fatty acids, CRP, homeostasis model assessment of insulin resistance (HOMA-IR), biochemical analyses, fasting GLP-1 concentration, and gut microbiota. Data could be extracted separately as long as there was enough information available in the trials.

RESULTS

LITERATURE SEARCH

We used the terms "Intestinal flora" and "Type 2 diabetes *mellitus"* with a broad search for randomized controlled trials (RCTs) in patients with T2DM. The results: Cochrane (700), Medline (733), PubMed (711), Central Register of Controlled Trials (688), Web of Science (699). In the end, a total of 744 articles (all published) were retrieved from the databases. A total of 360 articles about animal experiments, 262 articles with reviews, 9 articles on meta-analyses, 3 articles in letter format, 1 case report, 15 articles without full text, and 69 articles about non-randomized controlled trials were excluded, and 12 articles with incomplete data were also excluded. Thus, a total of 13 publications met the inclusion and exclusion criteria, and details from these trials were extracted separately. Figure 1 shows a flowchart of article selection and inclusion. Because of the heterogeneity found among patients and trial methods, and the large variety of outcome measurements used in these trials, the pooling of data for a meta-analysis was inappropriate. Results were, therefore, summarized qualitatively.

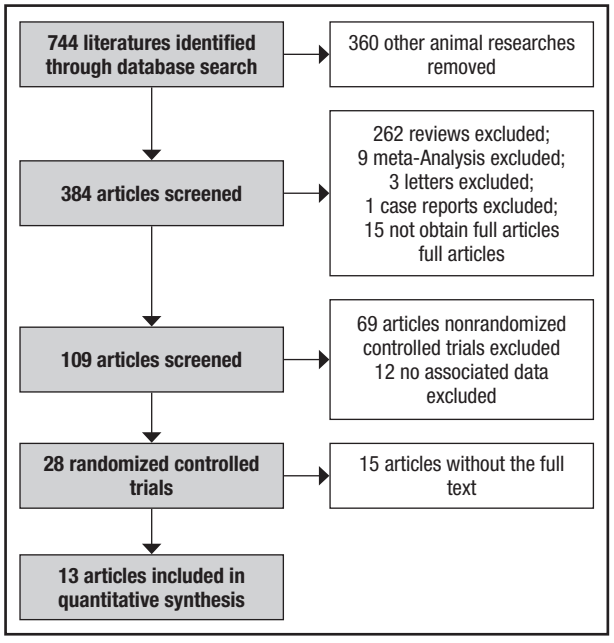

Figure 1.

Flow diagram illustrating the literature search and evaluation.

STUDY CHARACTERISTICS

Details from 13 eligible published trials are discussed in table I. Table I summarizes the characteristics of the 13 trials. The number of participants in these trials ranged from 12 to 504, with median age ranging from 41 to 72 years. Trial duration ranged from 1 to 6 months, and intervention included exercise, food, specific diets, drugs, and probiotics. The intestinal flora of all patients in our study were classified in categories.

CLINICAL OUTCOMES

Effect of exercise on intestinal flora in diabetes

A total of 2 trials in table II demonstrated that the exercise group had shown significant improvements of lean mass from baseline amomg diabetes patients. Otherwise, fat mass and fasting glucose had decreased obviously. According to Evasio Pasini et al. (15), those who received exercise training had improved blood sugar, as well as functional and anthropometric variables. Moreover, chronic exercise reduced intestinal fungus overgrowth, leaky gut, and systemic inflammation. As well, in the research by Yan Liu et al. (22), the microbiome of responders exhibited an enhanced capacity for biosynthesis of short-chain fatty acids and catabolism of branched-chain amino acids.

Effect of food and specific diets on intestinal flora in diabetes

A total of 3 trials involved food and specific diets with effects measured on intestinal flora (Table III). They improved HbA1c ($p < 0.01$) and helped with weight loss. In the study of Mengxiao Ren et al. (14), A-LCD significantly increased the short-chain fatty acid (SCFAs)-producing bacteria *Roseburia, Ruminococcus* and *Eubacterium*. Liping Zhao et al. (19) showed that a select group of SCFA-producing strains was promoted by dietary fibers and that most other potential producers were either diminished or unchanged in patients with T2DM. However, in the trial by Yanislava Karusheva et al. (26), the oral glucose sensitivity index was 24 % ($p < 0.01$) and circulating growth factor 21 was 21 % higher ($p < 0.05$), whereas meal-derived insulin secretion was 28 % lower ($p < 0.05$). Then it could be seen that the effect of food and specific diets was obvious in improving glucose in diabetics, and may impact some pathological mechanisms.

Effect of drugs on intestinal flora in diabetes

In the work by Hao Wu et al. (16), their findings provide support for the notion that an altered gut microbiota mediates some of metformin's antidiabetic effects. In the study of Xiaolin Tong et al. (17), they also found that both metformin and AMC significantly alleviated hyperglycemia and shifted gut microbiota structure in diabetic patients.

Table I. Baseline characteristics of the references included

Author, year	Sample size	Gender (%)	Mean age (years)	Trial duration	Diet	Intervention	Intestinal flora
Mengxiao Ren et al., 2020 (14)	45	Male (56)	72	3 months	LCD	Almond	*Roseburia, Ruminococcus* and *Eubacterium*
Evasio Pasini et al., 2019 (15)	30	Male (100)	70	6 months	Mediterranean diets	Exercise	*Mycetes* and *Candida albicans*
Hao Wu et al., 2017 (16)	40	Male (43)	54	4 months	Calorie-restricted diets	Metformin	*Escherichia* and *Intestinibacter*
Xiaolin Tong et al., 2017 (17)	450	NR	NR	12 weeks	Normal diets	Metformin and a traditional Chinese herbal formula	*Blautia* and *Faecalibacterium* spp.
Ming-Chia Hsieh et al., 2018 (18)	68	NR	NR	6 months	65 % cornstarch diets; 65 % fructose diets; 65 % fructose diets	ADR-1 ADR-3	*Bidobacterium* spp and *Lactobacillus* spp.
Liping Zhao et al., 2018 (19)	43	NR	NR	12 weeks	WTP	Fiber	A group of the acetate- and butyrate-producing bacterial strains
Yifei Zhang et al., 2020 (20)	409	Male (60)	54	12 weeks	Normal diets	Berberine and probiotics	*Ruminococcus bromii*
Talia Palacios et al., 2017 (21)	60	NR	NR	12 weeks	Healthy diets	Probiotic microorganisms	NR
Yan Liu et al., 2020 (22)	20	NR	41	12 weeks	Routine diets	Exercise	*Firmicutes, Bacteroidetes*, and *Proteobacteria*
Yoriko Heianza et al., 2018 (23)	504	NR	NR	6 months	Weight-loss diets	The POUNDS Lost	TMaO, choline and L-carnitine
Somayyeh Firouzi et al., 2015 (24)	136	Male (52)	54	12 weeks	Balanced diets	Multi-strain microbial cell preparation	*Lactobacillus* and *Bifidobacterium*
Talia Palacios et al., 2020 (25)	60	Male (47)	59	12 weeks	Normal diets	Multi-strain probiotic	A group of butyrate-producing bacterial strains
Yanislava Karusheva et al., 2019 (26)	12	Male (67)	54	4 weeks	Isocaloric diets	Reduction of branched-chain amino acids	*Bacteroidetes*

NR: not reported; LCD: low carbohydrate diets; WTP: wholegrain, 80 traditional Chinese medicinal foods and prebiotics.

Table II. Raw outcomes for change of clinical indicators and intestinal flora through exercise by individual trials

Author year	Intestinal flora	Intervention	Rates (week)	Fasting glucose (mmol/l)		Lean mass, %		Fat mass, %	
				Before	After	Before	After	Before	After
Evasio Pasini et al., 2019 (15)	*Mycetes* and *Candida albicans*	Endurance, resistance and training	3-times; 90 minutes each session	5.65 ± 0.09	4.95 ± 0.11	72.47 ± 5.19	75.83 ± 4.04	27.67 ± 5.15	24.17 ± 4.04
Yan Liu et al., 2020 (22)	*Firmicutes, Bacteroidetes,* and *Proteobacteria*	Aerobic and strength training	3 times; 70 minutes each session	8.05 ± 0.65	7.14 ± 0.67	60.98 ± 1.24	63.26 ± 1.11	36.13 ± 1.33	33.82 ± 1.22

Data is expressed as mean ± SD.

Table III. Raw outcomes for change of clinical indicators and intestinal flora through food and specific diets by individual trials

Author, Year	Intestinal flora	Intervention food and diets	Rates	HbA1c %		Weight (kg)	
				Before	After	Before	After
Mengxiao Ren et al., 2020 (14)	*Roseburia, Ruminococcus* and *Eubacterium*	Almonds, LCD	56 g/day almonds	7.67 ± 1.60	6.85 ± 1.02	66.60 ± 8.81	59.34 ± 8.90
Liping Zhao et al., 2018 (19)	A group of the acetate- and butyrate-producing bacterial strains	Fiber, WTP	Three ready-to-consume pre81 prepared foods	8.27 ± 0.27	6.36 ± 0.11	68.82 ± 2.12	65.83 ± 1.96
Yanislava Karusheva et al., 2019 (26)	*Bacteroidetes*	Reduction of branched-chain amino acids, isocaloric diets	AA-powder: 40 ~60 % of the protein	NR	NR	NR	NR

Data is expressed as mean ± SD.

They significantly increased a co-abundant group represented by Blautiaspp, which significantly correlated with the improvements in glucose. Yifei Zhang et al. (20) measured alterations in gut microbiota using oral intake of probiotics or berberine (BBR), a bacteriostatic agent. All 3 trials demonstrated drugs had an impact on intestinal flora (Table IV). The three studies suggested that after the intervention with drugs, body weight loss and HOMA improve along with changes in intestinal flora.

Effect of probiotics on intestinal flora in diabetes

The intestinal flora was significantly changed in diabetic patients after an intervention with *Lactobacillus* ADR-1 or ADR-3. According to Ming-Chia Hsieh et al. (18), the consumption of different strains of *L. reuteri* may influence changes in intestinal flora, which may lead to different outcomes after probiotic intake (Table V). In the study by Talia Palacios et al. (21), intentional manipulation of gastrointestinal microbial profiles may be useful for preventing and controlling type-2 diabetes *mellitus* and its associated metabolic complications. Somayyeh Firouzi et al. (24) proved that probiotics can also modestly improve HbA1c and fasting insulin in people with type-2 diabetes. Besides, Talia Palacios et al. (25) suggested that probiotics may act as an adjunctive to metformin by increasing the production of butyrate, which may consequently enhance glucose management.

Table IV. Raw outcomes for change of clinical indicators and intestinal flora through drugs by individual trials

Author, year	Intestinal flora	Intervention	Doses (day)	Body weight (kg)		HOMA	
				Before	After	Before	After
Hao Wu et al., 2017 (16)	*Escherichia* and *Intestinibacter*	Metformin	1,700 mg/d (in three doses)	96.5 ± 4.1	91.4 ± 3.9	8.3 ± 1.2	6.0 ± 0.8
Xiaolin Tong et al., 2017 (17)	*Blautia* and *Faecalibacterium* spp.	Metformin	750 mg/d (in three doses)	77.0 ± 10.8	74.8 ± 11.0	5.59 ± 5.82	4.70 ± 3.92
		AMC	57.6 g/d (in two doses)	79.9 ± 13.9	77.5 ± 13.7	6.78 ± 5.12	5.15 ± 4.16
Yifei Zhang et al., 2020 (20)	*Ruminococcus bromii*	BBR	0.6 g per 6 pills, twice daily	72.1 ± 12.5	71.1 ± 13.6	4.45 ± 1.40	3.74 ± 0.93
		Probiotics	4 g per 2 strips of powder, once daily	72.1 ± 12.5	71.9 ± 11.8	4.45 ± 1.40	4.14 ± 1.56

Data is expressed as mean ± SD. BBR: berberine.

Table V. Raw outcomes for change of clinical indicators and intestinal flora through probiotics by individual trials

Author, year	Intestinal flora	Intervention	Rates (Day)	Fasting glucose (mmol/l)		HbA1c (%)		HOMA-IR	
				Before	After	Before	After	Before	After
Ming-Chia Hsieh et al., 2018 (18)	Bidobacterium spp. and Lactobacillus spp.	Lactobacillus ADR-1	ADR-1: 4 × 109 CFUs	--	Δ –0.32 ± 31.92	--	Δ –0.39 ± 0.80	--	Δ –0.91 ± 5.82
		Lactobacillus ADR-3	ADR-3: 2 × 1010 cells	--	Δ –9.38 ± 58.45	--	Δ 0.24 ± 0.93	--	Δ 6.57 ± 19.17
Talia Palacios et al., 2017 (21)	NR	Multi-species probiotic	Take two capsules twice per day	NR	NR	NR	NR	NR	NR
Somayyeh Firouzi et al., 2015 (24)	Lactobacillus and Bi dobacterium	Probiotics	1010 CFUs	8.00 ± 2.00	8.10 ± 2.20	7.65 ± 1.31	7.58 ± 1.30	4.20 ± 2.40	3.20 ± 1.80
Talia Palacios et al., 2020 (25)	A group of butyrate-producing bacterial strains	Multi-strain probiotic	Two capsules twice a day	5.90 ± 0.80	5.70 ± 0.60	6.10 ± 0.60	5.90 ± 0.50	3.40 ± 1.90	2.70 ± 1.50
		Multi-strain probiotic. Metformin	Probiotic: two capsules twice a day. Metformin: 500 to 3000 mg per day	8.60 ± 4.50	7.80 ± 4.30	7.30 ± 1.70	6.80 ± 1.70	5.00 ± 4.70	3.50 ± 3.50

Data is expressed as mean ± SD. Δ: after - before; NR: not reported

Effect of other methods on intestinal flora in diabetes

In the study by Yoriko Heianza et al. (23), they found the importance of changes in TMaO, choline and l-carnitine in improving insulin sensitivity during a weight-loss intervention for obese patients. Dietary fat intake may modify the associations of TMaO with insulin sensitivity and glucose metabolism.

SIDE EFFECTS

In these studies, more participants experienced gastrointestinal AEs in the treated groups, although the AEs did not affect the antidiabetic effect or gut microbiome features related to interventions in these studies. Again, this concern needs to be addressed in trials with longer intervention durations. Although the consumption of live probiotics products is generally considered safe for most human beings, some side effects have been reported under certain conditions. For example, live probiotics may become pathogenic when used in subjects with severe immune deficiency (27). In infants with short bowel or cardiac stenosis, bacteremia has been reported in some cases (28).

DISCUSSION

Research evidence from human intestinal microbial profiles demonstrates that each individual has a unique intestinal bacterial composition (in diversity and abundance). Modern pharmacological studies have shown that intestinal flora plays an important role in the occurrence and development of T2DM, ditto that for genetic, environmental, and dietary factors (29,30). However, the differences in intestinal flora may be due to different ethnicity, age, and gender. In addition, the mechanisms responsible for ecological imbalance, as well as the mechanistic link between altered gut flora and diabetes, is not yet clear.

EXERCISE AND INTESTINAL FLORA IN DIABETES

Exercise increased lean mass, reduced fat mass and inflammation with better glycemic control and physical performance. Some experimental research shows that physical activity may modify fecal short-chain fatty acids, which increases the presence of fecal butyrate and in turn butyrate-producer intestinal bacteria (31). Short-chain fatty acids activate muscular AMPK, an enzyme that regulates muscle metabolism of glucose and li-

pids. These metabolic effects may be important in diabetes and confirm cross-communication between microbiota, exercise, and global metabolism (32). And they suggest a link between microbiota, muscle, the brain, and human metabolism. The cure of intestinal microbiota with physical exercise and/or specific therapies could be an important step for tailored therapy allowing traditional therapy and global patient metabolism to function properly.

FOOD, SPECIFIC DIETS AND INTESTINAL FLORA IN DIABETES

An acute change in diet—for instance, one that is strictly animal-based or plant-based—alters microbial composition within just 24 h of initiation, with reversion to baseline within 48 h of diet discontinuation (33). Furthermore, the gut microbiome of animals fed a high-fat or high-sugar diet is more prone to circadian rhythm disruption (34). Studies also suggest that overwhelming systemic stress and inflammation—such as that induced via severe burn injury—can also produce characteristic acute changes in the gut microbiota within just one day of the sustained insult (35).

Several popular diets, including western, gluten-free, omnivore, vegetarian, vegan, and Mediterranean, have been studied for their ability to modulate the intestinal microbiota. In several studies, a western diet (high in animal protein and fat, low in fiber) led to a marked decrease in numbers of total bacteria and beneficial *Bidobacterium* and *Eubacterium* species (36-38).

Across the spectrum, the Mediterranean diet is highly regarded as a healthy balanced diet. It is distinguished by a beneficial fatty acid profile that is rich in both monounsaturated and polyunsaturated fatty acids, high levels of polyphenols and other antioxidants, high intake of fiber and other low glycemic carbohydrates, and relatively greater vegetable versus animal protein intake. Specifically, olive oil, assorted fruits, vegetables, cereals, legumes, and nuts, moderate consumption of fish, poultry, and red wine; and a lower intake of dairy products, red meat, processed meat and sweets characterize the traditional Mediterranean diet (39).

DRUGS AND INTESTINAL FLORA IN DIABETES

Wu et al. (16) showed that metformin interacts with different gut bacteria, possibly through the regulation of metal homeostasis. Furthermore, microbiota-based interventions may reduce gastrointestinal symptoms associated with metformin administration, with a consequent improvement in medication compliance (40).

Probiotics exhibit metabolic benefits by improving the gut barrier and alleviating inflammation (41), which are also key to the development of ageing-related diseases (42). Health-associated *Bifidobacterium* spp. have been shown to be depleted with ageing but enriched in extremely aged healthy subjects (43). It has been proposed that the intake of probiotics might improve the integrity of intestinal epithelium and diminish the toll-like receptor-4 pathways to reduce pro-inflammatory signaling and to enhance insulin sensitivity (44,45).

PROBIOTICS AND INTESTINAL FLORA IN DIABETES

Fermented foods containing lactic acid bacteria, such as cultured milk products and yogurt, represent a source of ingestible microorganisms that may beneficially regulate intestinal health (46). They are thought to accomplish this through their effects on the existing gut microbiome, in addition to a possible induction of anti-inflammatory cytokines such as IL-10 (47). Based on these properties, foods enriched for these modulatory microorganisms are referred to as probiotics. Several groups have reported increased total bacterial loads after regular consumption of fermented milk or yogurt (48-51). Notable increases in beneficial gut bifidobacteria and/or lactobacilli have also consistently been observed with several different types of probiotics (52).

Individuals with metabolic disorders such as obesity and diabetes have been shown to have an intestinal imbalance when compared to healthy individuals (53,54).

THE MECHANISMS OF PROBIOTICS IN DIABETES

Some possible mechanisms behind the effect of probiotics on glycemic control are presented. Researchers have hypothesized several mechanisms of action according to the previous literature. The effect of probiotics in improving glycemic control can be firstly explained through the action of primary bile acids on the farnesoid-X-receptor (FXR). Certain strains of *Lactobacillus* and *Bifidobacterium* are known to possess the bile salt hydrolase enzyme (BSH). This enzyme can directly increase the levels of primary bile acid, which in turn binds and activates the FXR, leading to increased storage of glucose, decreased production of glucose from non-glucose nutrients, increased synthesis of insulin and increased secretion of insulin (55,56). Secondly, probiotics are also known to increase glucagon-like peptide (GLP) 1 and GLP 2, which are able to decrease low-grade inflammation associated with diabetes, and to decrease insulin resistance, which in turn decreases ß-cell toxicity and improves glycemic control. Furthermore, GLP-1 and GLP-2 also decrease hunger and increase satiety, thus decreasing energy intake, which collectively improve glycemic control (57). Another possible mechanism is the increased production of short-chain fatty acids (SCFAs) by mainly *Bifidobacterium* in the colon via its action on insoluble dietary fibers. These SCFAs, especially butyrate, can decrease insulin resistance by promoting pancreatic ß-cell differentiation, proliferation and development; increase secretion of GLP-1, thus increasing secretion of insulin, and decrease the release of pro-inflammatory cytokines by adipose tissue (58,59).

In conclusion, notwithstanding some limitations, these findings may have important implications for managing T2DM in patients by treating the microecological imbalance. These studies will also provide empirical evidence to address currently unresolved issues with the efficacy and safety of probiotics. Future research should focus on identifying the role of and the complex interaction among probiotics and the proportion of the various phyla in the gut of individuals.

CONCLUSIONS

All in all, probiotics have emerged as a possible therapeutic option, and prospective clinical trials have shown promising results in T2D patients. But up to now, there is still a dearth of such studies, so there was a need for high-quality studies to better understand the clinical effects of the intestinal flora on the occurrence and development of diabetes. This issue remains unanswered at present, primarily because large, long-term prospective trials of probiotic therapy are absent. However, several problems such as the possible side effects of long-term use of probiotics remain to be solved. The effects of probiotics are also slow, and some patients and doctors may be afraid of delaying illness.

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Artículo Especial

Guía Práctica ESPEN: nutrición clínica en las enfermedades del hígado

ESPEN Practical Guideline: clinical nutrition in liver disease

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Resumen

Introducción: la Guía Práctica se basa en la actual guía científica de la ESPEN sobre nutrición clínica en las enfermedades hepáticas.

Métodos: se ha reducido y transformado en diagramas de flujo para facilitar su uso en la práctica clínica. La guía está dedicada a todos los profesionales, incluidos médicos, dietistas, nutricionistas y enfermeras, que trabajan con pacientes con enfermedad hepática crónica.

Resultados: la guía presenta un total de 103 pronunciamientos y recomendaciones con breves comentarios para el manejo nutricional y metabólico de pacientes con (i) insuficiencia hepática aguda grave, (ii) esteatohepatitis alcohólica, (iii) enfermedad hepática grasa no alcohólica, (iv) cirrosis hepática, y (v) cirugía o trasplante de hígado.

Conclusión: las recomendaciones relacionadas con enfermedades están precedidas por recomendaciones generales sobre el diagnóstico del estado nutricional en los pacientes hepáticos y sobre las complicaciones hepáticas asociadas a la nutrición médica.

Palabras clave:

Desnutrición. Sarcopenia. Insuficiencia hepática aguda grave. Enfermedad del hígado graso. Esteatohepatitis alcohólica. Cirrosis. Trasplante. Cirugía.

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Conflictos de interés: los miembros expertos del grupo de trabajo fueron acreditados por el Grupo de Guidelines de ESPEN, el Comité Educacional y de Práctica Clínica de ESPEN y el Comité ejecutivo de ESPEN. Todos los expertos han declarado sus conflictos de intereses individuales de acuerdo con las reglas del Comité Internacional de Editores de Revistas Médicas (ICMJE). Si se han indicado posibles conflictos, estos han sido revisados por los responsables de las Guidelines de ESPEN y, en caso de duda, por el Comité Ejecutivo de ESPEN. Ninguno de los miembros del panel de expertos tuvo que ser excluido del grupo de trabajo o de la coautoría debido a conflictos graves. Los formularios de conflicto de intereses están almacenados en la oficina de Guidelines de ESPEN y pueden ser revisados por los miembros de ESPEN con interés legítimo, previa solicitud al Comité Ejecutivo de ESPEN.

Reconocimiento: los autores quieren expresar su gratitud a Anna Schweinlin por la experta asistencia proporcionada en este proyecto de guía. También quieren agradecer a Cees Smit su participación como representante del paciente en la conferencia de consenso final en abril de 2017 y por sus valiosos consejos sobre el manuscrito.

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Abstract

Background: the Practical Guideline is based on the current scientific ESPEN guide on Clinical Nutrition in Liver Disease.

Methods: it has been shortened and transformed into flow charts for easier use in clinical practice. The guideline is dedicated to all professionals including physicians, dieticians, nutritionists and nurses working with patients with chronic liver disease.

Results: a total of 103 statements and recommendations are presented with short commentaries for the nutritional and metabolic management of patients with (i) acute liver failure, (ii) alcoholic steatohepatitis, (iii) non-alcoholic fatty liver disease, (iv) liver cirrhosis, and (v) liver surgery/transplantation. Disease-related recommendations are preceded by general recommendations on the diagnosis of nutritional status in liver patients and on liver complications associated with medical nutrition.

Conclusion: this Practical Guideline gives guidance to health care providers involved in the management of liver disease on how to offer optimal nutritional care.

Keywords:

Acute liver failure. Cirrhosis. Fatty liver disease. Malnutrition. Sarcopenia. Transplantation.

INTRODUCCIÓN

Es bien conocido que la nutrición tiene un papel pronóstico y terapéutico clave en el manejo de los pacientes con enfermedad hepática. Por lo tanto, la ESPEN ha producido guías científicas sobre este tema desde 1997. Para mejorar la implementación y difusión de estas guías en la práctica clínica, se ha creado una versión abreviada basada en la guía ESPEN más reciente sobre nutrición clínica en las enfermedades hepáticas (1). Además de acortar los comentarios, hemos agrupado las recomendaciones de manera diferente según las cinco principales enfermedades hepáticas con fuerte relación con la nutrición, incluidas la insuficiencia hepática aguda grave (IHAG), la esteatohepatitis alcohólica y no alcohólica (EHA y EHNA), la cirrosis hepática, el trasplante hepático (TxH) y otras cirugías. Además, el texto está complementado con diagramas de flujo que apoyan las decisiones sobre la terapia nutricional y permite versiones en línea de la guía, como una aplicación y una versión web (Fig. 1). Esta guía

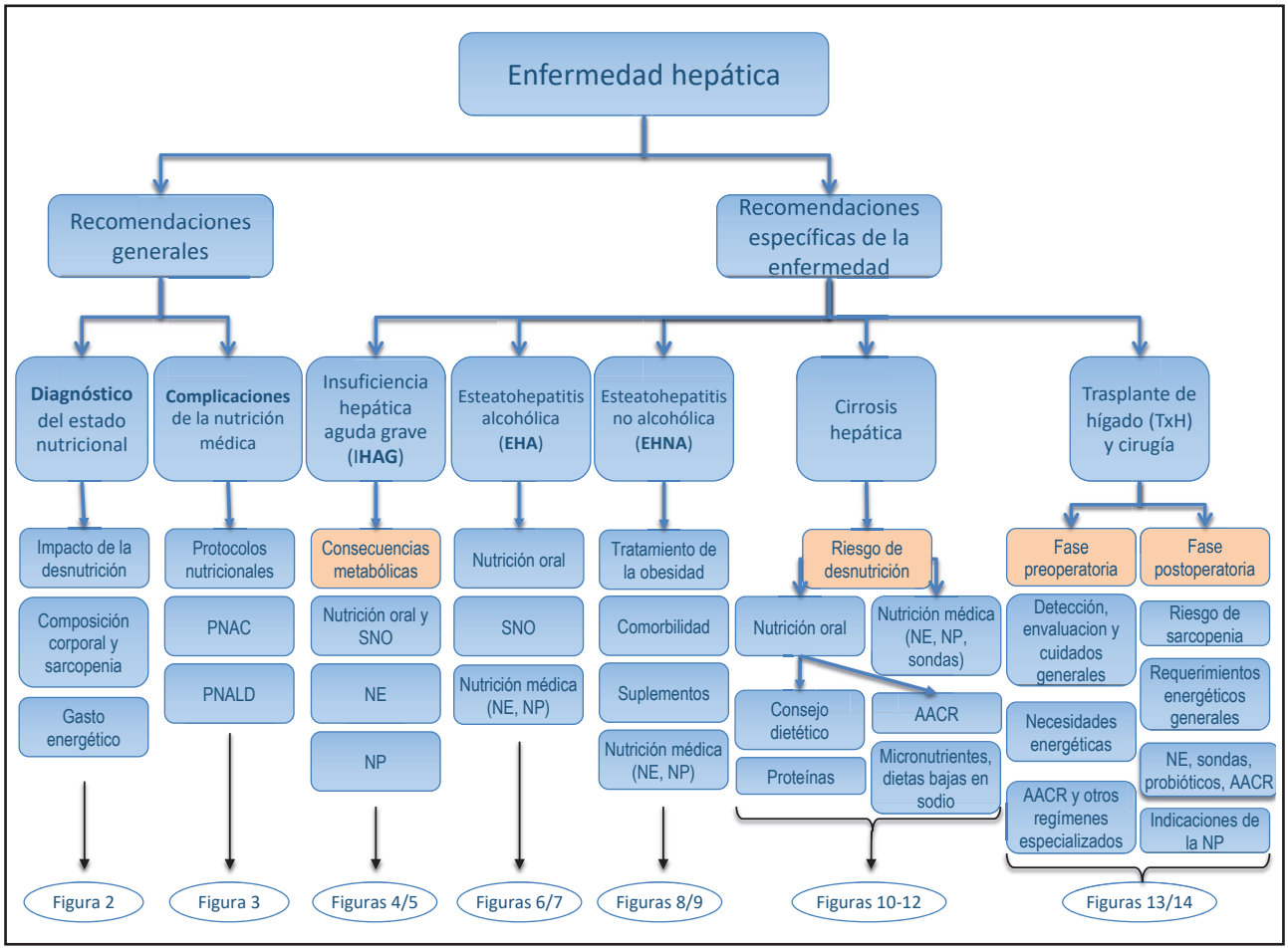

Figura 1.

Diagrama de flujo para la toma de decisiones en cuanto a la terapia nutricional.

tiene como objetivo abordar cuestiones clínicamente relevantes para el manejo nutricional y metabólico de los pacientes adultos con enfermedad hepática. Los usuarios de la guía son todos aquellos proveedores de atención médica involucrados en el cuidado de pacientes con enfermedad hepática, como médicos especialistas involucrados en el manejo de enfermedades hepáticas, médicos de familia, farmacéuticos, enfermeras, dietistas y nutricionistas, así como líderes médicos y administradores de unidades hepáticas.

METODOLOGÍA

La presente guía práctica consta de 85 recomendaciones y 17 declaraciones, todas basadas en la actual Guía ESPEN sobre nutrición clínica en las enfermedades hepáticas, la versión práctica (2) y la versión científica (1). La guía original se ha acortado al restringir los comentarios a la evidencia recopilada y la literatura en que se basan las recomendaciones. Las recomendaciones no se han modificado pero tanto las recomendaciones como las declaraciones se han reordenado y agrupado por entidades patológicas. Lo más importante es que la presentación del contenido se ha transformado en una presentación gráfica basada en diagramas de flujo para la toma de decisiones siempre que ha sido posible. La guía original se ha desarrollado de acuerdo con el procedimiento operativo estándar (SOP, por sus siglas en inglés) para las guías ESPEN (3). Este SOP está basado en la metodología de la Scottish Intercollegiate Guidelines Network (SIGN). Se han realizado búsquedas en la literatura y se han clasificado del 1 al 4 de acuerdo con la evidencia; asimismo, las recomendaciones se han creado y clasificado en cuatro clases (A / B / 0 / GPP). Todas las recomendaciones no solo se basan en la evidencia sino que también se han sometido a un proceso de consenso, representado en un porcentaje de acuerdo (%). Siempre que ha sido posible, han participado representantes de diferentes profesiones (médicos, dietistas, enfermeras u otros profesionales) así como representantes de los pacientes. El proceso de la guía ha sido financiado exclusivamente por la ESPEN. La abreviación y difusión de la guía ha sido financiada en parte por la UEG (United European Gastroenterology) y también por la ESPEN. Para obtener más detalles sobre la metodología, consulte la versión completa de la guía ESPEN (1) y el SOP de la ESPEN (3).

1. RECOMENDACIONES GENERALES

1.1. DIAGNÓSTICO DEL ESTADO NUTRICIONAL (Fig. 2)

1.1.1. Impacto de la nutrición

1) La desnutrición puede alterar todo el espectro de las funciones metabólicas hepáticas. La desnutrición puede por sí sola causar un hígado graso grave, pero no se conoce que cause enfermedad hepática crónica. (Declaración 14, consenso fuerte, 100 % de acuerdo.)

Comentario

La desnutrición severa en los niños puede causar un hígado graso que, en general, es completamente reversible con la realimentación. En los niños con kwashiorkor parece haber una mala adaptación asociada a una degradación menos eficiente de las grasas y la oxidación de los ácidos grasos en comparación con los niños con marasmo. No se ha podido observar ningún deterioro de la eliminación de ácidos grasos en el hígado.

2) Los pacientes con enfermedad hepática deben someterse a pruebas de cribado de desnutrición mediante una herramienta validada. (Recomendación 3, Grado B, consenso fuerte, 93 % de acuerdo.)

Comentario

NRS-2002 y MUST son herramientas validadas para detectar el riesgo de desnutrición en pacientes hospitalizados (4,5) y están recomendadas por la ESPEN. La herramienta de Priorización Nutricional del Royal Free Hospital se ha desarrollado como instrumento de cribado de la desnutrición en pacientes con enfermedades hepáticas. En una comparación directa, la herramienta de Priorización Nutricional del Royal Free Hospital fue más sensible que la NRS-2002 para identificar a los pacientes hepáticos en riesgo de desnutrición (6). La NRS-2002 se consideró útil para identificar a los pacientes cirróticos desnutridos con carcinoma hepatocelular (7). Según una revisión reciente, ninguna de las herramientas de detección disponibles se ha validado rigurosamente en pacientes con cirrosis, lo que deja la herramienta de Priorización Nutricional del Royal Free Hospital como la mejor opción disponible actualmente (8).

1.1.2. Composición corporal y sarcopenia

3) El ángulo de fase (medido por análisis de impedancia bioeléctrica) o la fuerza de prensión permiten evaluar el riesgo de mortalidad. (Declaración 10, consenso fuerte, 93 % de acuerdo.)

Comentario

La fuerza de prensión es un buen predictor de la tasa de complicaciones durante el año siguiente a la realización de la prueba (9). La fuerza de prensión parece ser una herramienta valiosa para medir la eficacia de la intervención nutricional (10). Las lecturas de reactancia y resistencia de BIA se pueden usar para calcular el ángulo de fase o la masa celular corporal como una medida de la masa y la función celulares para la evaluación nutricional. En los casos de cirrosis hepática, un ángulo de fase bajo se asocia a una mayor mortalidad, así como en muchas otras enfermedades (11).

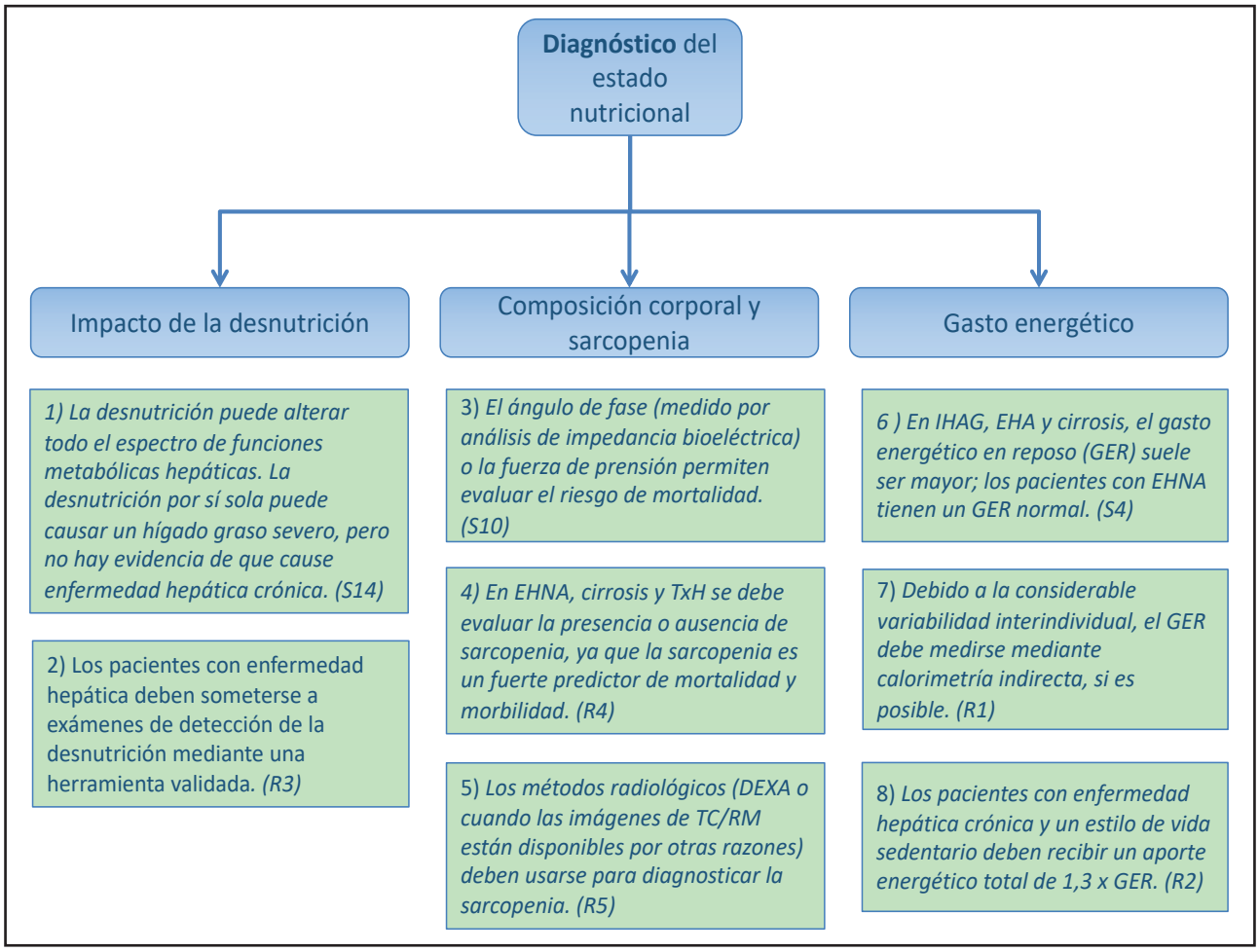

Figura 2.

Diagnóstico del estado nutricional.

4) En la esteatohepatitis no alcohólica (EHNA), la cirrosis y el TxH se debe evaluar la presencia o ausencia de sarcopenia, ya que la sarcopenia es un predictor fuerte de mortalidad y morbilidad. (Recomendación 4, Grado B, consenso fuerte, 100 % de acuerdo.)

Comentario

En los pacientes con cirrosis en lista de espera para trasplante, una función muscular deteriorada —evaluada con el test de la marcha de 6 minutos, la fuerza de prensión y la batería corta de rendimiento físico— pero sin pérdida de masa muscular —evaluada con el índice muscular esquelético medido con tomografía computarizada (TC)—, se ha asociado a un aumento de la mortalidad (12). En los pacientes con cirrosis se ha demostrado que la fragilidad expresada como una disminución funcional de la fuerza de prensión, la velocidad de la marcha, la prueba de levantarse y sentarse en la silla o la batería corta de rendimiento físico se asocian a un mayor riesgo de complicaciones que requieren hospitalización (13), de muerte en la lista de espera o de exclusión de la lista (14,15).

5) Los métodos radiológicos (absorciometría de rayos X de energía dual (DXA, por sus siglas en inglés) o las imágenes de TC o tomografía por resonancia magnética (RM) disponibles por otras razones) deben usarse para diagnosticar la sarcopenia. (Recomendación 5, Grado B, consenso fuerte, 100 % de acuerdo.)

Comentario

La sarcopenia es la característica clave de la desnutrición en los pacientes con cirrosis y puede evaluarse mediante métodos radiológicos (DXA, TC) para detectar la pérdida de masa muscular, o mediante pruebas de función muscular como la prueba de esfuerzo o la distancia caminada en 6 minutos. La sarcopenia se puede diagnosticar cuando hay pérdida de masa o de función musculares. En las imágenes de TC a nivel de la vértebra lumbar 3 (16) o la vértebra lumbar 4 (17) se puede medir y normalizar el área de músculo esquelético en función de la estatura. Se ha demostrado que el área del músculo esquelético en L3 se correlaciona linealmente con la masa muscular del cuerpo entero (18). La pérdida de masa de músculo esquelético

en la TC se ha asociado a un aumento de la mortalidad en los pacientes con cirrosis (16,17,19), los pacientes cirróticos con obesidad (20), los pacientes con cirrosis en lista de espera para trasplante (21) y los receptores de trasplante hepático ortotópico (22-24).

1.1.3. Gasto energético

6) En la insuficiencia hepática aguda grave (IHAG), la esteatohepatitis alcohólica (EHA) y la cirrosis, el gasto energético en reposo (GER) suele aumentar; los pacientes con enfermedad hepática grasa no alcohólica (EHGNA) presentan un GER normal. (Declaración 4, consenso, 90 % de acuerdo.)

Comentario

Los estudios en pacientes con IHAG que usaron la calorimetría indirecta muestran un aumento del GER de un 18 % o 30 %, respectivamente, en comparación con los controles sanos (25,26). Por tanto, en términos del GER, los pacientes con IHAG no son diferentes de los pacientes críticamente enfermos con otras etiologías. En los pacientes con EHA, la relación entre el GER medido y el estimado no ha sido diferente de la de los individuos sanos o los pacientes con cirrosis hepática. Sin embargo, cuando se relaciona con su masa muscular reducida, el GER de los pacientes con EHA es claramente más alto que el de los controles sanos. En los alcohólicos sin evidencia bioquímica de enfermedad hepática, pero no en los pacientes con cirrosis alcohólica, se observa un aumento del GER (25,8 *vs.* 20,8 kcal·kg^{-1}·d^{-1}) (27). Asimismo, en los alcohólicos con hígado graso, EHA o cirrosis, el consumo excesivo de alcohol se asocia a un aumento del GER (26 %). En la EHGNA o la EHNA es difícil trazar una imagen clara porque las poblaciones de pacientes estudiadas varían según la presencia o ausencia de sobrepeso u obesidad, inflamación crónica o síndrome metabólico.

7) Debido a la gran variabilidad interindividual, el GER debe medirse mediante calorimetría indirecta, si está disponible. (Recomendación 1, Grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

Siempre que esté disponible, se debe utilizar la calorimetría indirecta para medir el GER ya que, en un paciente individual, el GER medido puede diferir considerablemente de los valores estimados (28). El GER medido es más alto que el estimado en hasta el 35 % de los pacientes cirróticos (hipermetabolismo) y se sitúa por debajo del valor estimado en el 18 % de los pacientes (29,30). En la cirrosis hepática, el hipermetabolismo se asocia con una reducción de la supervivencia libre de eventos y con un resultado desfavorable después del trasplante (29,31), y parece corregirse con la mejora de la composición corporal (32). Como alternativa menos costosa, válida y rápida, se ha propuesto la calorimetría portátil (33). Los calorímetros portátiles, que solo miden el consumo de oxígeno y calculan el gasto energético suponiendo un cociente respiratorio de 0,85, son más precisos que las ecuaciones predictivas para determinar el GER.

8) Los pacientes con enfermedad hepática crónica y estilo de vida sedentario deben recibir un aporte energético total de 1,3 · GER. (Recomendación 2, Grado B, consenso, 81 % de acuerdo.)

Comentario

Las estimaciones del gasto energético total (32 kcal·kg^{-1}·d^{-1}) indican que el requerimiento energético a lo largo de 24 horas de los pacientes con cirrosis asciende a, aproximadamente, 1,3 · GER medido (24 kcal·kg^{-1}·d^{-1}) (34,35). La termogénesis inducida por la dieta y el gasto energético de la actividad física definida en los pacientes con cirrosis estable no muestran diferencias con los valores obtenidos en individuos sanos. Sin embargo, el nivel de actividad física espontánea es considerablemente más bajo en los pacientes con cirrosis. Es probable que el aumento de las necesidades energéticas en una enfermedad avanzada se equilibre con la disminución de la actividad física, que refleja la mala condición física. En los cirróticos sin ascitis se debe utilizar el peso corporal real para calcular la tasa metabólica basal. En los pacientes con ascitis se debe utilizar el peso ideal según la altura corporal, a pesar del informe de un conjunto de diez pacientes con cirrosis —de los que solo cuatro se evaluaron por completo (36)— en el que se sugirió que no se debe omitir la masa de ascitis al calcular el gasto energético. Los pacientes con trasplante de hígado tienen, en promedio, necesidades energéticas similares a las de la mayoría de los pacientes sometidos a cirugía abdominal mayor (37).

1.2. COMPLICACIONES ASOCIADAS A LA NUTRICIÓN MÉDICA (Fig. 3)

1.2.1. Protocolos nutricionales

9) En bebés, niños y adultos se deben implementar protocolos de nutrición especializados que hagan un uso óptimo de la NE. (Recomendación 83, Grado B, consenso fuerte, 92 % de acuerdo.)

Comentario

En lactantes y recién nacidos, varios trabajos sugieren que la institución de protocolos de nutrición especializados es beneficiosa para lograr la rehabilitación intestinal. Dichos protocolos tienen como objetivo limitar la infusión de lípidos a base de soja y maximizar la estimulación oral y enteral, así como la administración de la nutrición parenteral (NP) cíclica. Un estudio retrospectivo mostró que la implementación de las pautas de alimentación dio como resultado una disminución de los tiempos sin nutrición, una duración más corta del soporte con NP y una cantidad significativamente menor de lactantes que desarrollaron enfermedad hepática asociada a la NP (PNALD) después de la implementación de las guías (38). En un análisis multivariante, los episodios

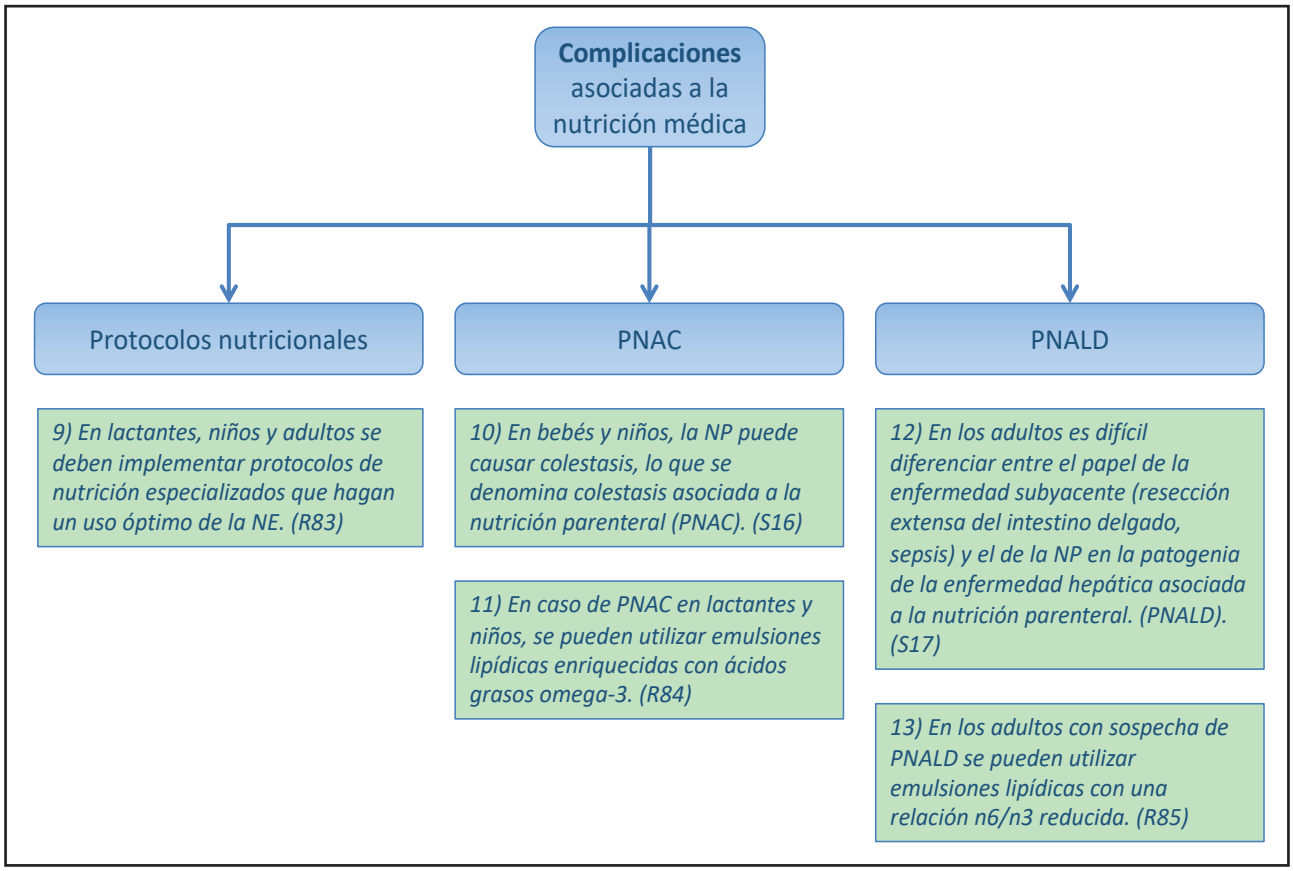

Figura 3.
Complicaciones asociadas a la nutrición médica.

sépticos (*odds ratio*: 3,23), los días de lípidos > 2,5 g·kg^{-1}·d^{-1} (*odds ratio*: 1,04) y los 60 días con lípidos máximos (*odds ratio*: 10) fueron elementos clave para el desarrollo de la colestasis asociada a la NP (PNAC) (39).

1.2.2. Colestasis asociada a la NP (PNAC)

10) En bebés y niños, la nutrición parenteral (NP) puede causar colestasis, por lo que se denomina colestasis asociada a la NP (PNAC). (Declaración 16, consenso fuerte, 92 % de acuerdo.)

Comentario

Debido a las diferentes características de la PNAC en recién nacidos y lactantes y la enfermedad hepática asociada a NP (PNALD) en adultos, la PNAC se aborda como una excepción en estas guías sobre nutrición de pacientes hepáticos adultos. El efecto beneficioso de los protocolos de nutrición especializados, los cuales limitan la cantidad de lípidos infundidos en los recién nacidos y lactantes, así como en los adultos, apunta al papel patogénico de la NP en el desarrollo de la colestasis (véanse también los puntos 11-13). Un segundo factor independiente que causa daño hepático es la extensión de la pérdida de masa intestinal, tal y como se muestra en el artículo original de Stanko y colaboradores, que muestra una asociación entre la lesión hepática y la extensión de la resección intestinal, pero no con la NP (40). Por lo tanto, la enfermedad hepática asociada a insuficiencia intestinal (IFALD, por sus siglas en inglés) y la PNALD son difíciles de separar en el paciente individual y ocurren en hasta el 60 % de los lactantes y el 85 % de los recién nacidos que requieren NP a largo plazo por insuficiencia intestinal (41,42). Mientras que los adultos tienen más probabilidades de desarrollar esteatosis únicamente, los lactantes y los recién nacidos son más susceptibles a la lesión hepatocelular o la colestasis, probablemente debido a la inmadurez del metabolismo y transporte de la bilis. Esto se refleja en el término PNAC, que se utiliza con frecuencia en la literatura pediátrica (43), mientras que el término PNALD se utiliza para pacientes tanto adultos como pediátricos. En los lactantes y recién nacidos, la mortalidad es alta, de hasta el 40 %, y la PNAC se ha convertido en una indicación importante de TxH pediátrico (43). En los adultos, la incidencia de la IFALD/PNALD avanzada varía del 0% al 50 % y la mortalidad varía del 0 % al 22 % (42). La IFALD/PNALD progresiva es una indicación aceptada para el trasplante de intestino delgado en el momento oportuno para salvar la vida (44).

11) En el caso de la PNAC en lactantes y niños, se pueden utilizar emulsiones lipídicas enriquecidas con ácidos grasos omega-3. (Recomendación 84, Grado 0, consenso fuerte, 100 % de acuerdo.)

Comentario

Se ha propuesto que las emulsiones lipídicas que contienen aceite de pescado como fuente de triglicéridos pueden ser protectoras en la PNAC/PNALD. Esto se ha evaluado en una serie de publicaciones en las que se infundió una emulsión de aceite de pescado al 100 %, a una velocidad limitada y a dosis 1,0 $g \cdot kg^{-1} \cdot d^{-1}$, mientras que la emulsión de soja se administró a dosis de hasta 4,0 $g \cdot kg^{-1} \cdot d^{-1}$ y, por lo tanto, no se puede excluir que la cantidad de lípidos infundidos, en lugar de su composición, determinara el mejor resultado observado (45,46). En un análisis retrospectivo de 51 pacientes pediátricos con PNALD y cirrosis, el uso de una emulsión lipídica basada en aceite de pescado se acompañó de una resolución de la colestasis en el 76 % (47). En un ensayo controlado aleatorio que comparó una emulsión de aceite de pescado al 100 % con una emulsión de lípidos de soja, ambas a una dosis de 1,0 $g \cdot kg^{-1} \cdot d^{-1}$, se finalizó tempranamente el ensayo debido a una incidencia inesperadamente baja de PNAC (48). Ningún paciente desarrolló deficiencia de ácidos grasos y ambos regímenes se toleraron bien y fueron seguros.

En un enfoque diferente, la reducción de lípidos a base de soja se ha logrado mediante la adición de una emulsión de aceite de pescado (49), o el uso de emulsiones de lípidos que consisten en una mezcla de lípidos a base de soja y triglicéridos de cadena media (TCM) (50), o una mezcla de una emulsión de aceite de pescado y una emulsión de aceite de oliva y soja (51), o lípidos a base de soja y aceite de oliva, y TCM y aceite de pescado (50). En ensayos controlados aleatorizados que compararon una emulsión SMOF (lípidos derivados de la soja, aceite de oliva, TCM y aceite de pescado) con una emulsión a base de soja, la emulsión SMOF que contiene aceite de pescado resultó ser segura y más eficaz para reducir los niveles de bilirrubina y el estrés oxidativo (52).

1.2.3. Enfermedad hepática asociada a la NP (PNALD)

12) En adultos, es difícil diferenciar entre el papel de la afección subyacente (resección extensa del intestino delgado, sepsis) y el de NP en la patogenia de la PNALD. (Declaración 17, consenso fuerte, 100 % de acuerdo.)

Comentario

La lesión hepática colestásica ocurre en aproximadamente el 50 % de los pacientes con NP domiciliaria a largo plazo. En 1985, Bowyer y cols. (53) describieron la esteatohepatitis en 9 de 60 pacientes con NP a largo plazo. La lesión hepática persistió durante una mediana de 15 meses y progresó a cirrosis en tres pacientes. Stanko y sus colaboradores (40) estudiaron a adultos que habían estado con NP durante un año. Encontraron enzimas hepáticas normales en aquellos que no tenían o solo tenían una pérdida escasa de intestino, mientras que 4/6 pacientes con pérdida masiva de intestino desarrollaron colestasis progresiva y esteatohepatitis entre cuatro y diez meses después del inicio de la NP. Su observación demostró que la lesión hepática puede ocurrir no solo como secuela de la NP —la denominada PNALD— sino también por insuficiencia intestinal, denominándose IFALD. En la práctica clínica, a menudo es difícil una distinción clara entre IFALD y PNALD. Se cree que la patogenia de la IFALD/PNALD es multifactorial, incluyendo factores como la alteración del ciclo enterohepático de reabsorción de los ácidos biliares, la infección sistémica, el sobrecrecimiento bacteriano, la ausencia de nutrientes enterales y la composición de la NP. Tanto la falta como el exceso de componentes específicos de NP se están discutiendo como causales en la PNALD. La composición de ácidos grasos de las emulsiones lipídicas, así como la deficiencia de colina y la toxicidad del manganeso, se han relacionado con la aparición de esteatosis hepática y colestasis en adultos y niños.

13) En adultos con sospecha de PNALD se pueden usar emulsiones lipídicas con una relación n6/n3 reducida. (Recomendación 85, Grado 0, consenso fuerte, 92 % de acuerdo.)

Comentario

En adultos, se dispone de datos limitados sobre el efecto de modificar la cantidad y/o composición de los lípidos parenterales en el curso de la PNALD. También se ha sugerido limitar en los adultos los lípidos a base de soja a $\leq$ 1,0 $g \cdot kg^{-1} \cdot d^{-1}$ (54). Se ha reportado que el cambio de lípidos a base de soja por una emulsión de aceite de pescado al 100 % es eficaz en la PNALD (55,56). En una serie de 15 pacientes, la adición de una emulsión de aceite de pescado a una emulsión de lípidos a base de soja se asoció con la reversión de una PNALD comprobada por biopsia (57). En un caso, el uso de una emulsión de aceite de pescado junto con un régimen de NP a base de aceite de oliva se asoció a una reducción de la esteatosis y la inflamación hepáticas (58). En conjunto, se necesitan más datos antes de que se pueda recomendar el uso rutinario de las emulsiones grasas que contienen aceite de pescado para el tratamiento de la PNALD.

2. RECOMENDACIONES ESPECÍFICAS DE CADA ENFERMEDAD

2.1. INSUFICIENCIA HEPÁTICA AGUDA GRAVE (IHAG) (Figs. 4 y 5)

2.1.1. Consecuencias metabólicas y riesgo de obesidad

14) En la IHAG, debido a la pérdida subtotal de la función hepatocelular y la consiguiente insuficiencia multiorgánica, se debe

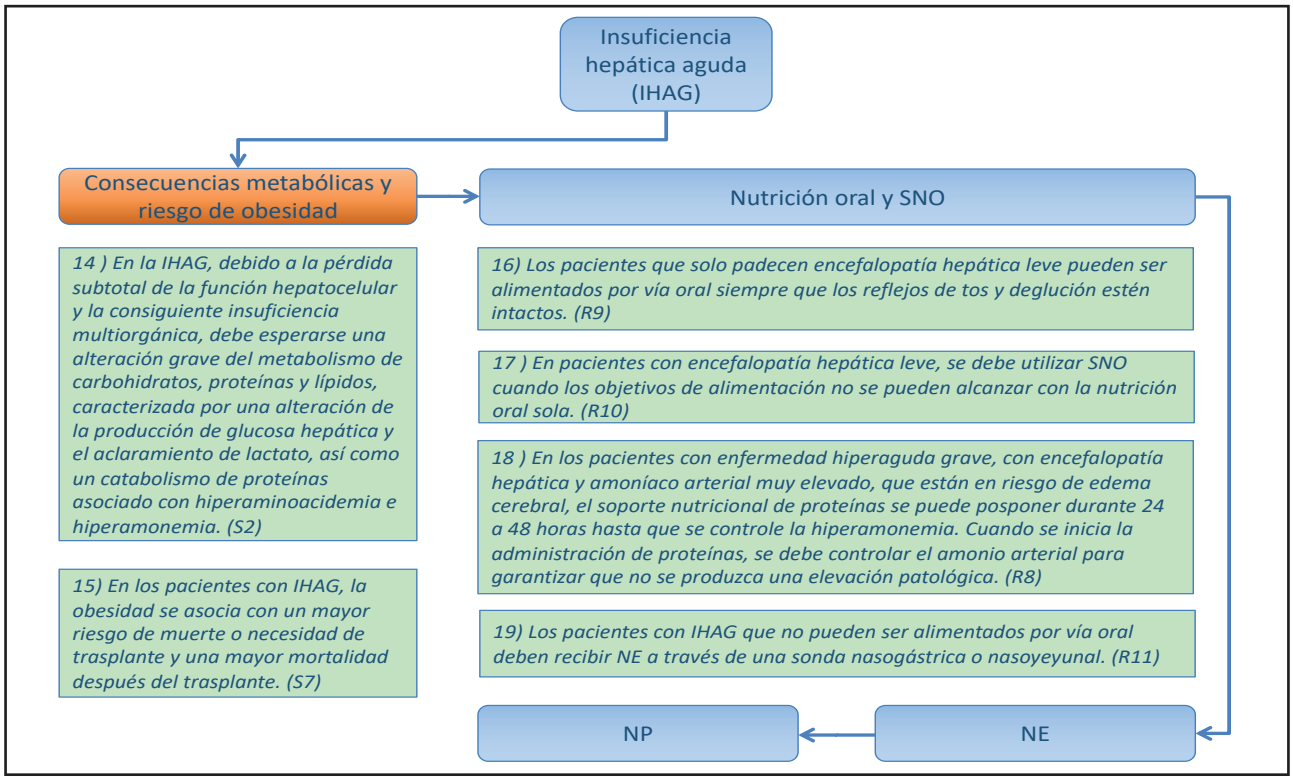

Figura 4.

Insuficiencia hepática aguda (IHAG).

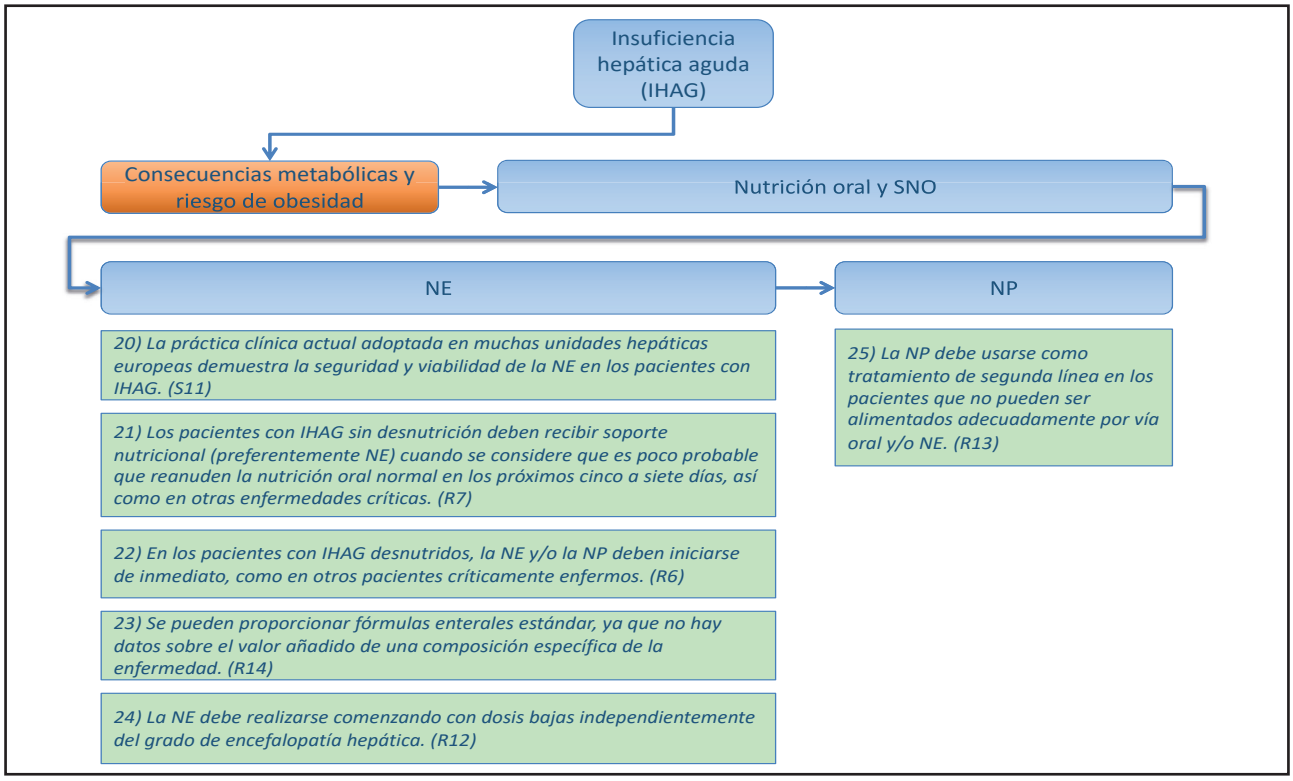

Figura 5.

Insuficiencia hepática aguda (IHAG) (cont.).

esperar una alteración grave del metabolismo de carbohidratos, proteínas y lípidos, caracterizada por una alteración de la producción de glucosa hepática y el aclaramiento de lactato, así como un catabolismo de proteínas asociado con hiperaminoacidemia e hiperamonemia. (Declaración 2, consenso fuerte, 100 % de acuerdo.)

Comentario

Los niveles plasmáticos de aminoácidos aumentan de 3 a 4 veces en la IHAG. El patrón de aminoácidos se caracteriza por una disminución de los aminoácidos de cadena ramificada (AACR) y un aumento del triptófano y de los aminoácidos aromáticos, así como los aminoácidos sulfurados. La hipoglucemia es una característica ominosa de la IHAG y se cree que es el resultado de: a) una depleción del glucógeno hepático, b) una alteración de la gluconeogénesis debido a la pérdida de hepatocitos y c) hiperinsulinemia debida al aumento de la secreción y reducción de la degradación. En la IHAG, los tejidos esplácnicos muestran una alteración desde la liberación neta de glucosa hasta la absorción neta de glucosa (59). Estos cambios se acompañan de una intolerancia a la glucosa caracterizada por una disminución del 50 % en la tasa de eliminación de la glucosa corporal, una disminución grave (hasta el 15 % en los controles) de la sensibilidad a la insulina y un aumento de los niveles de glucagón en la sangre (60). En contraste con las observaciones en pacientes con sepsis, en la IHAG, los tejidos esplácnicos no extraen sino que liberan ácidos grasos libres y la cetogénesis se reduce (61).

15) En los pacientes con IHAG, la obesidad se asocia a un mayor riesgo de muerte o necesidad de trasplante y a una mayor mortalidad después del trasplante. (Declaración 7, consenso fuerte, 96 % de acuerdo.)

Comentario

En la IHAG solo hay datos muy limitados disponibles con respecto al efecto del estado nutricional sobre su curso y pronóstico. La obesidad y la obesidad severa tienen un riesgo entre 1,6 y 1,9 veces mayor de trasplante o muerte por IHAG. Los pacientes obesos tienen un riesgo 3,4 veces mayor de morir después del trasplante. En una pequeña serie retrospectiva se encontró que los pacientes con sobrepeso son más susceptibles a la IHAG (62).

2.1.2. Nutrición oral y suplementos nutricionales orales

16) Los pacientes que solo padecen encefalopatía hepática (EH) leve pueden ser alimentados por vía oral siempre que los reflejos de tos y deglución estén intactos. (Recomendación 9, Grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

No hay datos de ensayos clínicos controlados sobre la IHAG para informar esta recomendación.

17) En los pacientes con encefalopatía hepática leve se deben utilizar suplementos nutricionales orales (SNO) cuando los objetivos nutricionales no se pueden alcanzar con la nutrición oral sola. (Recomendación 10, Grado GPP, consenso, 85 % de acuerdo.)

Comentario

No hay datos de ensayos clínicos controlados sobre la IHAG para informar esta recomendación.

18) En los pacientes con enfermedad hiperaguda grave, encefalopatía hepática y amonio arterial muy elevado que tienen riesgo de edema cerebral, el aporte nutricional de proteínas se puede aplazar durante 24 a 48 horas hasta que se controle la hiperamonemia. Cuando se inicia la administración de proteínas, se debe monitorizar el amonio arterial para garantizar que no se produzca una elevación patológica. (Recomendación 8, Grado GPP, consenso, 90 % de acuerdo.)

Comentario

Los pacientes con IHAG hiperaguda y niveles de amonio arterial elevados y sostenidos (> 150 µmol/L) pueden tener un mayor riesgo de edema cerebral y desarrollo de hipertensión intracraneal (63,64). En esta situación específica, en donde puede haber un deterioro breve pero profundo de la función hepática, la administración de proteínas puede elevar aun más los niveles de amonio y aumentar el riesgo de edema cerebral. Su administración puede posponerse solo por un período corto (24-48 horas) a medida que mejora la función hepática y, cuando se inicia, se debe monitorizar el amonio arterial.

19) Los pacientes con IHAG que no pueden ser alimentados por vía oral deben recibir NE por sonda nasogástrica o nasoyeyunal. (Recomendación 11, Grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

De acuerdo con las Guías ESICM (65), la NE debe iniciarse en dosis bajas cuando los trastornos metabólicos agudos que ponen inminentemente en peligro la vida se controlan con o sin estrategias de soporte hepático, independientemente del grado de encefalopatía. Se deben monitorizar los niveles de amonio arterial.

2.1.3. Nutrición enteral (NE)

20) La práctica clínica actual adoptada en muchas unidades hepáticas europeas demuestra la seguridad y viabilidad de la NE en los pacientes con IHAG. (Declaración 11, consenso fuerte, 100 % de acuerdo.)

Comentario

Véase el comentario del punto 19.

21) Los pacientes con IHAG sin desnutrición deben recibir soporte nutricional (preferentemente NE) cuando se considere que es poco probable que reinicien la nutrición oral normal en los próximos cinco a siete días, como en otras enfermedades críticas. (Recomendación 7, Grado GPP, consenso fuerte, 96 % de acuerdo.)

Comentario
Véase el comentario del punto 19.

22) En los pacientes desnutridos con IHAG, la nutrición enteral (NE) y/o la NP deben iniciarse de inmediato, como en otros pacientes críticamente enfermos. (Recomendación 8, Grado GPP, consenso fuerte, 96 % de acuerdo.)

Comentario
En general, las decisiones sobre cuándo iniciar el soporte nutricional y qué vía utilizar se toman de acuerdo con las recomendaciones de soporte nutricional para otros pacientes críticos. Se pueden clasificar tres subtipos de IHAG según su curso clínico. En la insuficiencia hepática hiperaguda, la encefalopatía hepática se produce dentro de los siete días posteriores a la aparición de la ictericia y los pacientes suelen recuperarse rápidamente con tratamiento médico únicamente o después del trasplante, o mueren poco después del inicio de la enfermedad. Debido a la corta duración de la enfermedad en la mayoría de los pacientes, se cree que el soporte nutricional juega un papel relativamente menor: el pronóstico es más favorable en este subtipo. En la insuficiencia hepática aguda, el intervalo entre el inicio de la encefalopatía hepática después de que el paciente presenta ictericia es de 8 a 28 días, y en la insuficiencia hepática subaguda este intervalo es de 29 a 72 días. En estos dos últimos subtipos de IHAG, el soporte nutricional precoz es más a menudo necesario.

23) Se pueden administrar fórmulas enterales estándar, ya que no hay datos sobre el valor de una fórmula específica de la enfermedad. (Recomendación 14, Grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario
No hay estudios publicados que comparen fórmulas enterales en pacientes con IHAG. Con respecto a otros pacientes críticamente enfermos, se recomienda evitar el uso de todas las fórmulas especiales en aquellos que están en un entorno de UCI médica y las fórmulas específicas de la enfermedad si están en la UCI quirúrgica. No hay evidencia de que el uso de la NE enriquecida con AACR mejore los resultados de los pacientes en comparación con las formulaciones estándar con proteína completa en otros pacientes críticamente enfermos con enfermedad hepática. Rara vez se usan en el tratamiento de pacientes con IHAG (66,67).

24) La NE debe realizarse comenzando con dosis bajas independientemente del grado de EH. (Recomendación 12, Grado GPP, consenso, 80 % de acuerdo.)

Comentario
Véase el comentario del punto 19.

2.1.4. Nutrición parenteral (NP)

25) La NP debe utilizarse como tratamiento de segunda línea en los pacientes que no pueden ser alimentados adecuadamente por vía oral y/o con NE. (Recomendación 13, Grado GPP, consenso, 90 % de acuerdo.)

Comentario
No hay evidencia procedente de ensayos en pacientes con IHAG para informar estas recomendaciones, y la práctica adoptada refleja la de otras formas de enfermedad hepática y enfermedad crítica. En la mayoría de los pacientes con IHAG es práctico y seguro usar la NE, y las fórmulas pueden administrarse en cantidades comparables a las utilizadas en otras enfermedades críticas. Como se ha documentado anteriormente (véase el punto 22), un pequeño subgrupo de pacientes hiperagudos pueden tener un riesgo transitorio de empeoramiento de la hiperamonemia con las cargas proteicas elevadas y, por tanto, podrían no tolerar la dosis completa de NE en la fase inicial de su enfermedad. En otros pacientes críticamente enfermos que requieren terapia de soporte nutricional, la NP no tiene ninguna ventaja clara sobre la NE y puede aumentar las complicaciones infecciosas: lo mismo puede ser el caso de la IHAG.

2.2. ESTEATOHEPATITIS ALCOHÓLICA (EHA) (Figs. 6 y 7)

2.2.1. Nutrición oral

2.2.1.1. Todos los pacientes

26) En el tratamiento de pacientes con EHA gravemente desnutridos se prevé una peor supervivencia en comparación con los pacientes no desnutridos. (Declaración 8, consenso fuerte, 100 % de acuerdo.)

Comentario
Los pacientes con EHA desnutridos tienen una mayor tasa de morbilidad y mortalidad en los trabajos con los datos agregados del estudio *American Veteran Affairs* (68-70). Los datos del estudio del *Veteran Affairs* muestran una clara asociación entre una baja ingesta de alimentos normales y una alta mortalidad (68), y este hallazgo se ha confirmado recientemente (71).

27) Se debe utilizar el consejo nutricional individualizado para mejorar la ingesta de alimentos. (Recomendación 23, Grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario
No hay estudios para evaluar el beneficio de la terapia nutricional individualizada en comparación con la alimentación libre o la suplementación nutricional con 30-35 kcal·kg^{-1}·d^{-1} y 1,2-1,5 g·kg^{-1}·d^{-1} de proteína. Sin embargo, dadas las sugerencias sobre la restricción de sodio, líquidos y otros sustratos dependiendo de condiciones comórbidas tales como la insuficiencia renal o la diabetes *mellitus,* es probable que un programa nutricional estructurado e individualizado sea más beneficioso que la alimentación libre.

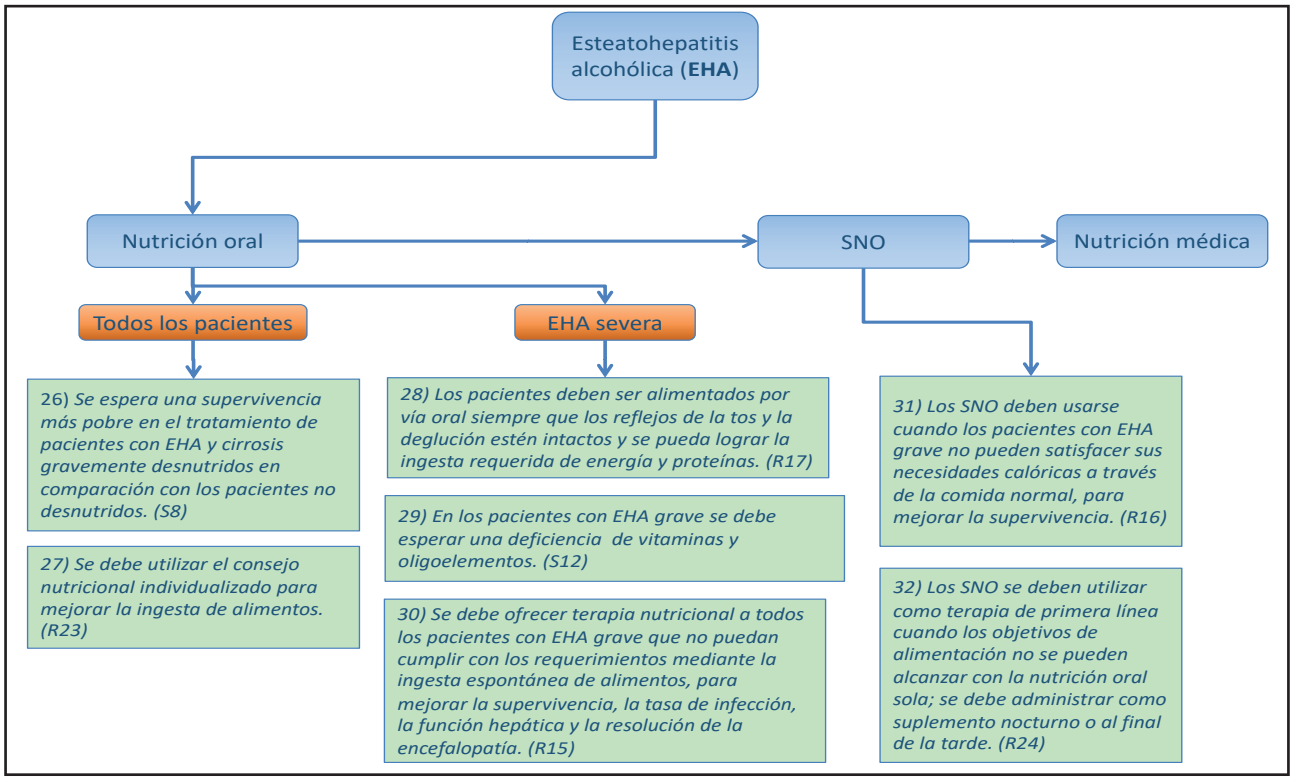

Figura 6.

Esteatohepatitis alcohólica (EHA).

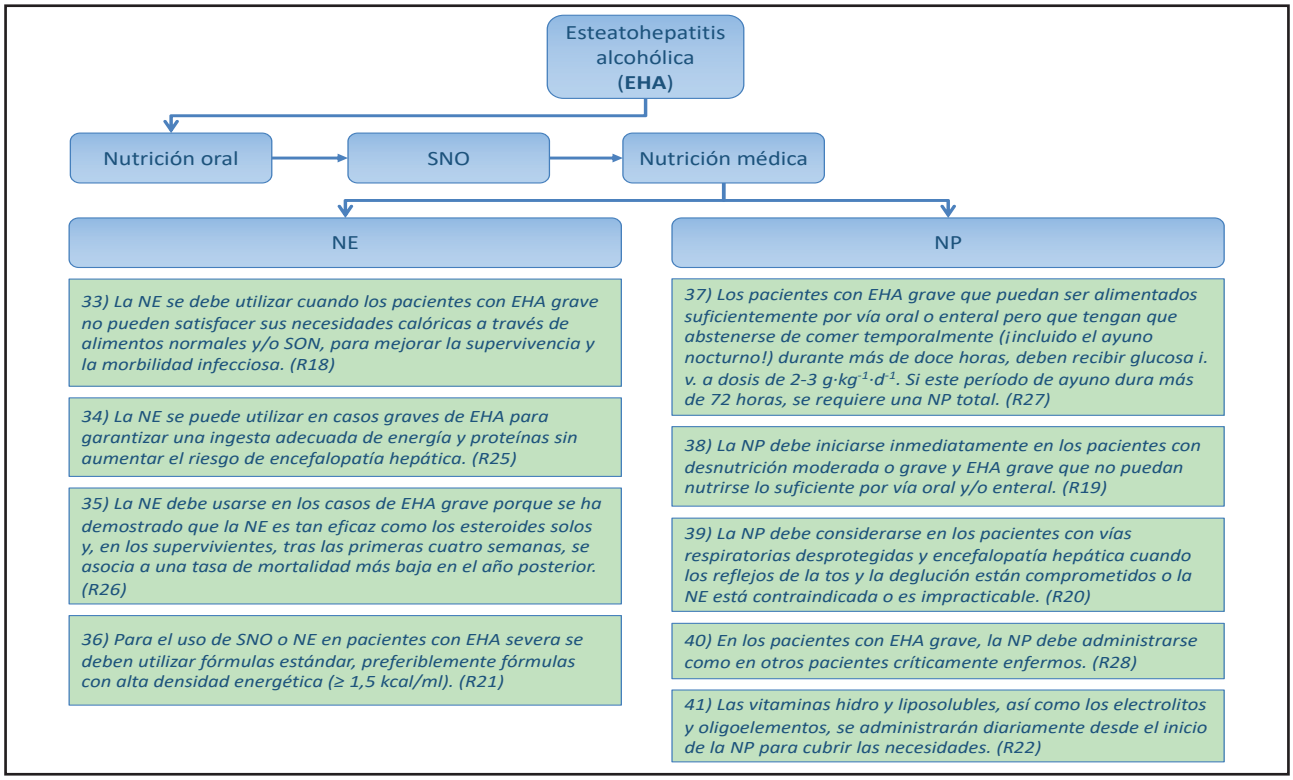

Figura 7.

Esteatohepatitis alcohólica (EHA) (cont.).

2.2.1.2. EHA grave

28) Los pacientes deben ser alimentados por vía oral siempre que los reflejos de tos y deglución estén intactos y se puedan alcanzar los objetivos de ingesta de energía y proteínas. (Recomendación 17, Grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

La alimentación suplementaria en pacientes con EHA grave se basa en datos casi universales de que estos pacientes tienen una ingesta oral deficiente, así como una ingesta menor de calorías y proteínas, que contribuyen a la mortalidad y la morbilidad (68,69). Por lo tanto, existe una justificación convincente para proporcionar una nutrición suficiente. Sin embargo, cuando se logra una ingesta oral adecuada, no parece haber una ventaja específica en la vía de administración. De hecho, la NP se asocia a un mayor riesgo de complicaciones, incluida la infección (72). También existen ventajas de la alimentación oral con una dieta regular sobre la NE o la NP en cuanto a la integridad de la mucosa intestinal y, según datos más recientes, con respecto al mantenimiento del microbioma intestinal protector, brindando beneficios en términos de tasas de infección que podrían afectar la mortalidad.

29) En los pacientes con EHA grave se debe esperar una deficiencia de oligoelementos y vitaminas. (Declaración 12, consenso fuerte, 100 % de acuerdo.)

Comentario

Hay diversos estudios observacionales que muestran deficiencias de micronutrientes en los pacientes con trastornos por consumo de alcohol y enfermedad hepática alcohólica, y estudios muy limitados en el caso de la EHA (73-75). Debido a la mala ingesta oral que precede a la enfermedad aguda, se debe esperar y reponer la deficiencia de micronutrientes en los pacientes con EHA grave. No se puede responder con base a la evidencia si todos los pacientes deben someterse a un cribado del riesgo de desnutrición o si debe haber un reemplazo universal de micronutrientes. Basándonos en la frecuencia del déficit de vitamina B, zinc y vitamina D, la reposición de estas puede ser beneficiosa. La administración oral de preparados multivitamínicos y de zinc es razonable en la EHA grave porque la deficiencia es frecuente y la suplementación oral empírica es menos costosa que las mediciones de laboratorio para establecer el déficit antes de reponer los micronutrientes individuales. La suplementación con tiamina se utiliza de forma rutinaria en la práctica clínica para prevenir la encefalopatía de Wernicke y la psicosis de Korsakoff.

30) Se debe ofrecer la terapia nutricional a todos los pacientes con EHA grave que no puedan cumplir con los requerimientos mediante la ingesta espontánea de alimentos, para mejorar la supervivencia, la tasa de infección, la función hepática y la resolución de la encefalopatía. (Recomendación 15, Grado B, consenso fuerte, 100 % de acuerdo.)

Comentario

Datos consistentes han demostrado que la desnutrición, definida por una serie de herramientas de medición, es prevalente en la mayoría (50-100 %) de los pacientes con EHA grave (68,69,76). La presencia de desnutrición es un predictor independiente de mortalidad y afecta negativamente a la respuesta a los corticosteroides y la oxandrolona solo en la EHA moderada pero no en la grave (68,77,78). En la EHA grave, la ingesta calórica reducida se asocia a una mayor mortalidad y mayores tasas de complicaciones. La ingesta oral está disminuida en estos pacientes y, por lo tanto, es necesaria la suplementación para mantener una ingesta adecuada de calorías y proteínas. La suplementación nutricional, en múltiples estudios aleatorizados, para mantener la ingesta calórica requerida reduce la incidencia de infecciones y facilita una resolución más rápida de la encefalopatía hepática, así como la mejora de la función hepática. En el estudio multicéntrico más reciente, independientemente del tratamiento, una menor ingesta de calorías (21,5 $kcal \cdot kg^{-1} \cdot d^{-1}$) se asoció con peores resultados clínicos (71,79). La ingesta calórica se reduce significativamente incluso en los pacientes con EHA abstinentes y el aumento de la ingesta calórica mejora los resultados (68,80), pero no hay ensayos controlados y aleatorizados que comparen directamente la nutrición suplementaria sola con la ingesta oral libre sola y que apoyen una mejor supervivencia con la nutrición adicional.

2.2.2. SNO

31) Se debe utilizar el SNO cuando los pacientes con EHA grave no puedan alcanzar sus necesidades calóricas a través de la alimentación convencional, para mejorar la supervivencia. (Recomendación 16, Grado B, consenso fuerte, 100 % de acuerdo.)

Comentario

En los pacientes con hepatitis alcohólica grave, la ingesta oral se reduce constantemente (68,69,76). Cuando los tratamientos son comparables entre los grupos, la nutrición suplementaria sí mejora la infección y la mortalidad aguda, específicamente las muertes hospitalarias, frente a la ingesta dietética oral libre (81-83). Se han evaluado la alimentación enteral o la suplementaria en la hepatitis alcohólica grave, pero no se ha hallado ningún beneficio sobre la mortalidad de forma consistente. Sin embargo, estos datos deben ser atenuados por la existencia de trabajos que indican reiteradamente que la ingesta calórica $< 21,5$ $kcal \cdot kg^{-1} \cdot d^{-1}$ se asocia a una mayor mortalidad (71), y existe un fuerte consenso entre los expertos de que la suplementación nutricional debe ofrecerse a los pacientes con ingesta oral deficiente ya que puede proporcionar una ventaja en cuanto a supervivencia (83).

32) El SNO se debe usar como terapia de primera línea cuando los objetivos nutricionales no se puedan alcanzar con la nutrición oral sola, debiéndose administrar como suplemento nocturno o al final de la tarde. (Recomendación 24, Grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

La ingesta oral reducida se asocia a una mayor mortalidad y es probable que la suplementación nutricional resulte en una resolución más rápida de la encefalopatía hepática y la bilirrubina sérica elevada, y en un menor riesgo de infección; la EHA grave también es un estado hipermetabólico. Estos datos apoyan el uso de una ingesta adecuada de calorías y proteínas mediante la suplementación. Dado que se han informado datos convincentes sobre un refrigerio nocturno en la cirrosis hepática, incluida la cirrosis alcohólica (84), es razonable ampliar estos datos para respaldar el uso de suplementos antes de la noche o nocturnos para reducir la duración del ayuno.

2.2.3. Nutrición médica

2.2.3.1. Nutrición enteral (NE)

33) La NE debe utilizarse cuando los pacientes con EHA grave no pueden alcanzar sus necesidades calóricas mediante la alimentación normal y/o el SNO, para mejorar la supervivencia y la morbilidad infecciosa. (Recomendación 18, Grado B, consenso fuerte, 100 % de acuerdo.)

Comentario

Cuando se reduce la ingesta calórica, la mortalidad es mayor en la EHA grave (71). Si bien la suplementación con calorías adicionales no mejora la supervivencia en la mayoría de los estudios aleatorizados, en los pacientes con desnutrición se han documentado tasas de infección más bajas (83). A pesar de una serie de estudios negativos, el consenso entre los expertos es que, en los pacientes con EHA grave que no pueden ingerir las calorías adecuadas por vía oral, la nutrición suplementaria puede proporcionar una ventaja de supervivencia, especialmente en el grupo con desnutrición moderada (68). La resolución de la infección es mejor con la nutrición suplementaria, pero no se sabe si es menor la tasa de aparición de nuevas infecciones. Dado que, en los pacientes no alcohólicos con enfermedad hepática, la mala ingesta oral y la desnutrición se asocian con un mayor riesgo de infección, se puede considerar que una mejor ingesta oral podría reducir el riesgo de infección en la EHA grave, aunque no se han obtenido datos publicados que apoyen esta afirmación.

34) La NE se puede utilizar en la EHA grave para garantizar una ingesta adecuada de energía y proteínas sin aumentar el riesgo de EH. (Recomendación 25, Grado 0, consenso fuerte, 92 % de acuerdo.)

Comentario

La NE ha demostrado su eficacia para proporcionar una nutrición adecuada a los pacientes con cirrosis alcohólica (85) o cirrosis con encefalopatía hepática de grado I-III (86). En un estudio, diez pacientes recibieron una solución enriquecida con AACR que equivalía a 70 g de proteína por día y su estado mental mejoró (86). En otro estudio, 16 pacientes recibieron 1,5 $g \cdot kg^{-1} \cdot d^{-1}$ de proteína utilizando una fórmula enteral basada en la caseína (85). Asimismo, en 136 pacientes, la baja ingesta de proteínas se asoció con un empeoramiento de la encefalopatía hepática, mientras que los pacientes con una mayor ingesta de proteínas mostraron una mejoría del estado mental (87).

35) La NE debe usarse en la EHA grave porque se ha demostrado que es tan eficaz como los esteroides solos y, en los supervivientes de las primeras cuatro semanas, se asocia a una tasa de mortalidad más baja al año siguiente. (Recomendación 26, Grado B, consenso, 85 % de acuerdo.)

Comentario

Un estudio aleatorizado que comparó los esteroides solos con la NE total no mostró diferencias en cuanto a mortalidad pero sí una mortalidad más temprana en los sujetos tratados con esteroides (79). Aunque la mortalidad en los pacientes con encefalopatía hepática fue similar en los brazos tratados con NE y con esteroides, no se informó de si la resolución de la encefalopatía hepática fue diferente (79). Otros estudios sobre la NE tampoco informaron de beneficios de supervivencia, pero la NE dio como resultado una mayor mejora de la encefalopatía hepática y una reducción de la bilirrubina (85). Aunque se ha cuestionado el beneficio de los esteroides en la EHA grave (88), un ensayo controlado y aleatorizado mostró que la mortalidad en la EHA grave con NE total fue similar a la de la EHA grave tratada con esteroides durante 28 días. Sin embargo, los pacientes con NE murieron antes y los que recibieron esteroides murieron más tarde durante el tratamiento a lo largo de 28 días. El seguimiento a más largo plazo mostró una mayor mortalidad en el grupo tratado con esteroides, relacionada con la infección (79). Los autores concluyeron que es necesario evaluar el efecto sinérgico de los esteroides y la NE en la EHA grave. En un estudio reciente, la comparación específica de la NE con esteroides y la nutrición convencional con esteroides no mostró ningún beneficio de supervivencia de la NE sobre los esteroides (71). Sin embargo, una ingesta calórica más baja aumentó la mortalidad en ambos grupos, lo que sugiere que la NE podría proporcionar una ventaja de supervivencia precoz en la EHA (71,79).

36) En pacientes con EHA grave se deben utilizar formulas estándar tanto para el SNO como para la NE, preferiblemente fórmulas de alta densidad energética (≥ 1,5 $kcal \cdot ml^{-1}$). (Recomendación 21, Grado GPP, consenso fuerte, 92 % de acuerdo.)

Comentario

No existen estudios directos que evalúen en ensayos aleatorizados los protocolos de nutrición específicos para la EHA grave. Dichos protocolos incluyen el uso de mezclas de AACR, dietas con proteínas vegetales e inmunonutrición con suplementos de arginina. Los datos publicados solo evalúan los aminoácidos intravenosos, lassoluciones parenterales comerciales o la glucosa intravenosa, que no muestran ningún beneficio de mortalidad en los pacientes críticamente enfermos (89). Se ha informado que la inmunonutrición no proporciona ninguna ventaja terapéutica específica en un ensayo controlado y aleatorizado en pacientes sometidos a TxH (90). En la EHA grave no hay ensayos contro-

lados que muestren beneficios de la fórmula específica sobre la fórmula estándar. El uso de suplementos de alta densidad calórica puede reducir la administración de líquidos en los pacientes con restricción de líquidos. Estos suplementos también reducen el tiempo durante el cual se administran.

2.2.3.2. Nutrición parenteral (NP)

37) Los pacientes con EHA grave que puedan ser alimentados suficientemente por vía oral o enteral pero que tengan que abstenerse de comer temporalmente (¡incluido el ayuno nocturno!) durante más de doce horas, deben recibir glucosa endovenosa a dosis de 2-3 g·kg^{-1}·d^{-1}. Cuando este período de ayuno dura más de 72 horas, se requiere la NP total. (Recomendación 27, Grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

En los pacientes cirróticos, después del ayuno nocturno, las reservas de glucógeno se agotan y las condiciones metabólicas son similares a la inanición prolongada en los individuos sanos. Se ha demostrado que un refrigerio de carbohidratos a última hora de la tarde o una toma nocturna de SNO se asocian a un mejor metabolismo de las proteínas en los pacientes cirróticos (91,92). No hay datos correspondientes de pacientes con EHA grave, pero parece seguro asumir que existe también una depleción similar de glucógeno, con todas sus consecuencias sobre el metabolismo de las proteínas, en los pacientes con EHA grave. Por lo tanto, recomendamos a los pacientes con EHA grave que eviten ayunar durante más de doce horas e instituir oportunamente la infusión de glucosa o una NP periférica hipocalórica. Se recomienda la NP estándar en los pacientes que necesiten tal intervención pero es probable que la mortalidad no mejore, según la mayoría de los datos publicados.

38) La NP debe iniciarse inmediatamente en los pacientes EHA grave y desnutrición moderada o grave que no puedan nutrirse lo suficiente por vía oral y/o enteral. (Recomendación 19, Grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

La suplementación nutricional con mezclas de aminoácidos o con calorías reduce las tasas de infección y facilita la resolución de la encefalopatía hepática, pero los efectos beneficiosos sobre la supervivencia solo se documentaron en pacientes con EHA moderada, no en aquellos con EHA grave (77,78,80,82,83,85). La NP puede incluir aminoácidos y/o la infusión de glucosa, por vía periférica o central, para apoyar la ingesta dietética en los pacientes cuya ingesta oral es insuficiente. Varios estudios han evaluado diferentes suplementos parenterales, en su mayoría infusiones de aminoácidos o glucosa; siete de estos suplementos se aleatorizaron en un estudio de pacientes con EHA. Un estudio mostró una ventaja de supervivencia con los aminoácidos intravenosos, pero esto nunca se ha reproducido en ningún otro estudio (80). Hay datos limitados sobre el impacto de la intervención nutricional sola sobre la histología hepática en la EHA grave. Ningún estudio ha evaluado la progresión a cirrosis, pero los aminoácidos intravenosos solos, o junto con glucosa, se asociaron a una mayor resolución de la infiltración grasa (82) o de los cuerpos de Mallory (93). La mejoría o reversión de los cuerpos de Mallory puede predecir una menor tasa de progresión. Las revisiones sistemáticas y los metaanálisis también sugieren que la suplementación nutricional mejora las tasas de resolución de la encefalopatía hepática (82,83).

39) La NP debe considerarse en los pacientes con vías respiratorias desprotegidas y encefalopatía hepática cuando los reflejos de tos y deglución estén comprometidos o la NE esté contraindicada o sea impracticable. (Recomendación 20, Grado GPP, acuerdo mayoritario, 72 % de acuerdo.)

Comentario

No hay evidencia directa que evalúe el papel de la NP en el subgrupo de pacientes con encefalopatía hepática y/o vías respiratorias desprotegidas con reflejos protectores deteriorados. Aunque algunos (94) recomiendan el uso de la NP en los pacientes encefalopáticos o críticamente enfermos con tos o reflejo nauseoso (94), hay otros que no creen en el uso de la NP para la EHA (95).

40) En los pacientes con EHA grave, la NP debe administrarse como en los demás pacientes críticamente enfermos. (Recomendación 28, Grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

Aunque no existen ensayos aleatorizados que comparen diferentes fórmulas, tasas o componentes de la NP, se pueden sacar algunas conclusiones del uso de la NP en los pacientes críticos. Es probable que un enfoque multidisciplinario pueda proporcionar beneficios y no hay evidencia que respalde el papel beneficioso de las fórmulas con nutrientes específicos en la EHA grave. No hay ventajas asociadas al tipo de soluciones parenterales utilizadas y, por lo tanto, se recomienda la práctica de la NP estándar en los pacientes con EHA grave.

41) Las vitaminas hidro y liposolubles, así como los electrolitos y los oligoelementos, se deben administrar diariamente desde el inicio de la NP para cubrir los requerimientos. (Recomendación 22, Grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

En los pacientes con EHA grave, dada la reducción casi universal de la ingesta alimentaria, existe una alta prevalencia de la deficiencia de micronutrientes, que tiene efectos adversos sobre las respuestas fisiológicas al estrés y la infección. Por lo tanto, se deben administrar vitaminas y oligoelementos para proporcionar, al menos, las cantidades diarias recomendadas. En este grupo de pacientes de alto riesgo parece prudente administrar una primera dosis de tiamina antes de comenzar la NP, para prevenir la encefalopatía de Wernicke o el síndrome de realimentación. Se debe considerar la reposición en todos los pacientes con NP, aunque no se haya documentado ninguna deficiencia. Dado que

es probable que la NP se administre a corto plazo, el riesgo de eventos adversos debido a la reposición de vitaminas y micronutrientes a largo plazo es bajo, incluso sin cuantificar las concentraciones séricas. Se deben administrar vitaminas específicas, incluidas las vitaminas A, D y K junto con tiamina, ácido fólico y piridoxina, para corregir los déficits.

2.3. ESTEATOHEPATITIS NO ALCOHÓLICA (EHNA) (Figs. 8 y 9)

2.3.1. Tratamiento de la obesidad

42) La sobrenutrición puede causar EHGNA o EHNA, que es una afección precursora de la cirrosis hepática. (Declaración 15, consenso fuerte, 100 % de acuerdo.)

Comentario

La evidencia disponible se revisa en los puntos 43-61 del capítulo 2.3 sobre la EHNA.

43) En pacientes con EHNA con sobrepeso u obesidad, se utilizará como tratamiento de primera línea una intervención intensiva en el estilo de vida que lleve a la pérdida de peso junto con un aumento de la actividad física. (Recomendación 30, Grado A, consenso fuerte, 100 % de acuerdo.)

Comentario

Se ha demostrado que todo cambio de estilo de vida que conlleve una pérdida de peso moderada (< 5 %) mejora la acumulación de grasa hepática solo cuando se utilizan una dieta hipocalórica y ejercicio, pero no cuando se aplica una dieta hipocalórica sola (96,97). Se ha demostrado que todo cambio de estilo de vida que produzca una pérdida de peso del 5-10 % mejora la histología cuando se emplean la dieta hipocalórica y el ejercicio (98-102). Los análisis de subgrupos indican que el grado de pérdida de peso parece estar correlacionado con el grado de mejoría histológica. Se ha observado una mejora profunda de la esteatosis, la inflamación y la balonización cuando se logra una pérdida de peso > 7-9 % (98,100,101), mientras que únicamente la pérdi-

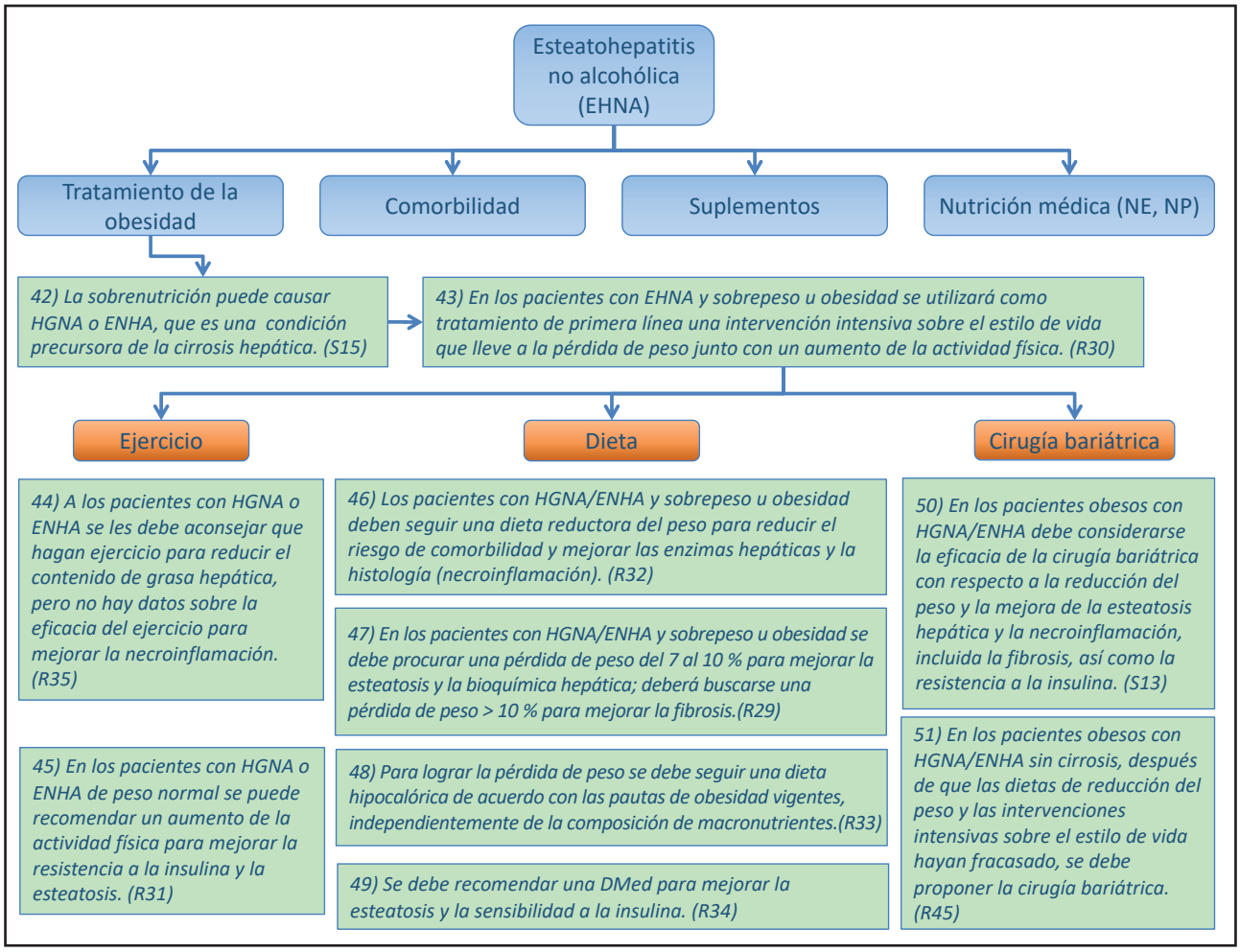

Figura 8.

Esteatohepatitis no alcohólica (EHNA).

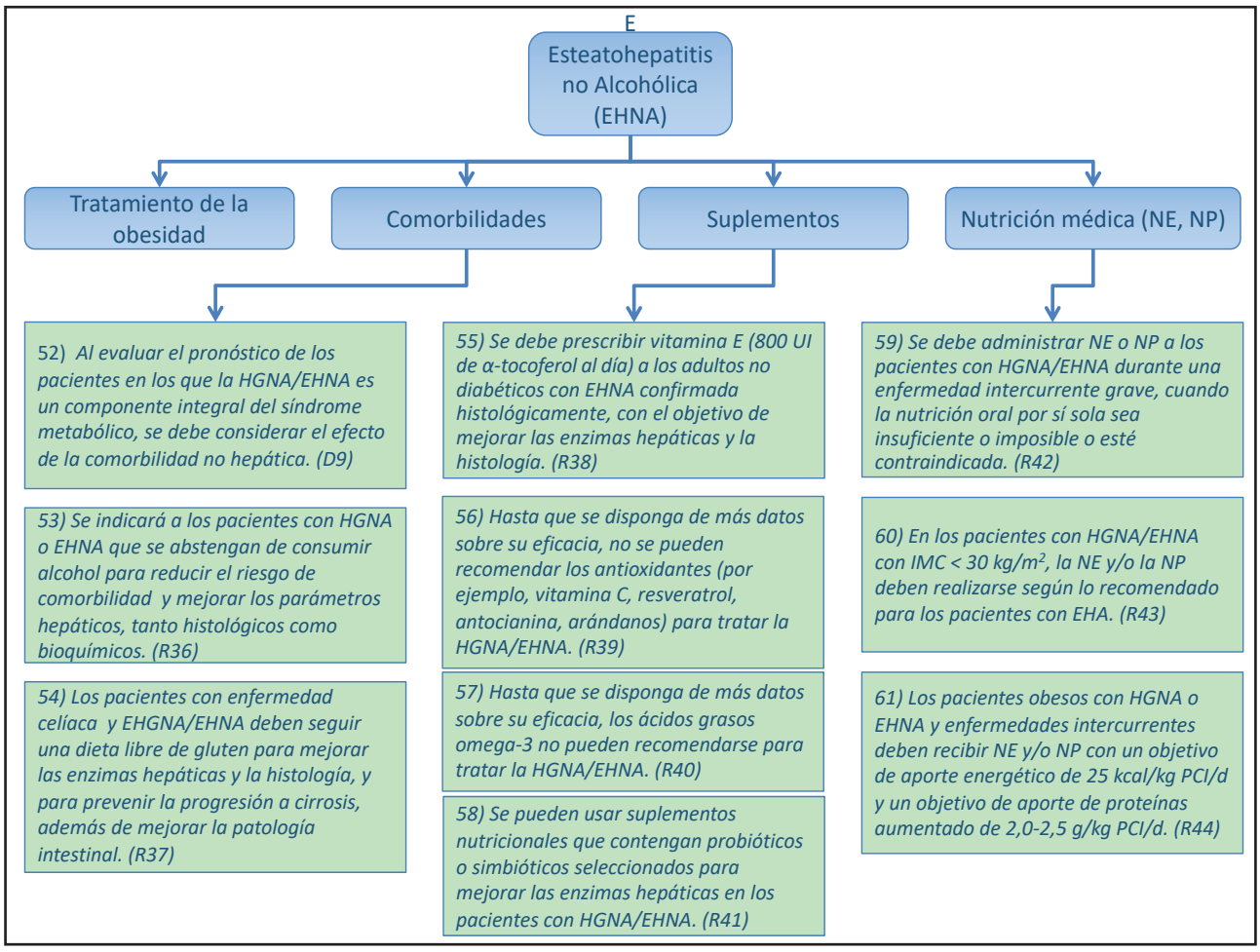

Figura 9.

Esteatohepatitis no alcohólica (EHNA) (cont.).

da de peso > 10 % se asocia a una mejoría de la fibrosis (102). En un ensayo sistemático, la misma modificación del equilibrio energético bien mediante una ingesta reducida sola o bien mediante una restricción calórica menor combinada con un mayor gasto energético (ejercicio) produjo la misma pérdida de peso (-10 %) y la misma mejora de la grasa hepática, la ALT y la sensibilidad a la insulina (103). Sin embargo, la predisposición a cambiar de estilo de vida es baja en los pacientes con sobrepeso/obesidad y EHGNA, y solo el 10 % trabajan activamente o se preparan para cambiar Ejercicio

2.3.1.1. Ejercicio

44) Se debe recomendar a los pacientes con hígado graso no alcohólico HGNA/EHNA que hagan ejercicio para reducir el contenido de grasa hepático, pero no hay datos sobre la eficacia del ejercicio para mejorar la actividad necroinflamatoria. (Recomendación 35, Grado A, consenso fuerte, 100 % de acuerdo.)

Comentario

Las mediciones no invasivas demuestran de manera convincente una reducción de los triglicéridos intrahepáticos y viscerales en los sujetos que simplemente hacen ejercicio sin perder peso (104-106). Tres meses de entrenamiento de resistencia mejoraron el índice ultrasónico hepatorrenal como una lectura de esteatosis hepática, pero no afectaron a las enzimas hepáticas, los triglicéridos séricos, ni el HOMA-IR (107). Recomendar hacer ejercicio parece valioso y efectivo en los pacientes motivados, ofreciendo una verdadera opción para el manejo de los pacientes delgados con EHGNA, en quienes no se puede recomendar una gran pérdida de peso. Hasta la fecha, no hay datos sobre el efecto del ejercicio solo sobre las características histológicas de la EHNA, la balonización, la inflamación y, sobre todo, la fibrosis.

45) En los pacientes con HGNA/EHNA con normopeso se puede recomendar un aumento de la actividad física para mejorar la resistencia a la insulina y la esteatosis. (Recomendación 31, Grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

Para la pequeña proporción de pacientes con HGNA/EHNA que tienen normopeso, no se pueden hacer recomendaciones basadas en ensayos de intervención. Dado que se ha demostrado que el ejercicio solo mejora el contenido de grasa hepática y la resistencia a la insulina en los pacientes con HGNA/EHNA con sobrepeso u obesidad (104-107), parece plausible recomendar el ejercicio a las personas con peso normal para mejorar la esteatosis y la resistencia a la insulina. Asimismo, se debe considerar una reducción del consumo de refrescos edulcorados con fructosa.

2.3.1.2. Dieta

46) Los pacientes con HGNA/EHNA y sobrepeso u obesidad deben seguir una dieta para bajar de peso con el fin de reducir el riesgo de comorbilidad y de mejorar las enzimas hepáticas y la histología (actividad necroinflamatoria). (Recomendación 32, Grado A, consenso fuerte, 100 % de acuerdo.)

Comentario

En un estudio aleatorizado multicéntrico, las dietas bajas en calorías fueron eficaces y seguras para reducir el peso corporal y mejorar la EHGNA en doce semanas (108). Asimismo, una dieta baja en calorías fue eficaz para lograr una pérdida de peso de al menos un 5 % y una mejoría de la EHGNA (103,109,110). Los datos de dos ensayos sugieren que la restricción de carbohidratos en la dieta es más efectiva que la restricción calórica general sobre la pérdida de peso a corto plazo (dos semanas) y la reducción de los triglicéridos hepáticos (111,112), mientras que Kirk y cols. reportaron la misma disminución de lípidos intrahepáticos después de 11 semanas con una dieta baja o alta en carbohidratos (113). Otro ensayo mostró los mismos efectos beneficiosos independientemente de si la dieta era baja en grasas o baja en carbohidratos (114). Dos ensayos han reportado también los efectos beneficiosos de una dieta baja en grasas saturadas (115,116). En un estudio prospectivo de diabéticos obesos que comparó dietas isocalóricas ricas en proteínas animales o vegetales, se observó una disminución de la grasa intrahepática y la resistencia a la insulina después de 6 semanas (117). Véase también el punto 48.

47) En los pacientes con HGNA/EHNA con sobrepeso u obesidad se debe buscar una pérdida de peso del 7-10 % para mejorar la esteatosis y la bioquímica hepática; deberá buscarse una pérdida de peso > 10 % para mejorar la fibrosis. (Recomendación 29, Grado A, consenso fuerte, 96 % de acuerdo.)

Comentario

La pérdida de peso generalmente reduce la esteatosis hepática independientemente de cómo se logre. Los resultados de la evaluación de biopsias pareadas de pacientes con EHNA que lograron perder peso indican que solo una pérdida de peso sustancial (> 9-10 %) se acompaña de una mejoría de la fibrosis e incluso una resolución completa de la EHNA (98,102,121-127). La pérdida de peso se asocia a una mejora de la esteatosis, la inflamación y las enzimas hepáticas, pero no de la fibrosis (101,102,114,128,129). El potencial de la cirugía bariátrica para mejorar la fibrosis de la EHNA se subraya en dos metaanálisis (130,131). Véanse también los puntos 50 y 51.

48) Para lograr la pérdida de peso se debe seguir una dieta hipocalórica de acuerdo con las pautas de obesidad vigentes, independientemente de la composición de macronutrientes. (Recomendación 33, Grado A, consenso fuerte, 93 % de acuerdo.)

Comentario

El asesoramiento nutricional de los pacientes con EHGNA y sobrepeso u obesidad debe realizarse de acuerdo con las pautas actuales para el tratamiento dietético de la obesidad. No existe evidencia sólida que respalde alguna composición particular de la dieta hipocalórica única para su uso en pacientes con HGNA/EHNA. Sin embargo, parece más probable que el consumo de café beneficie a la salud, no que la perjudique, y las estimaciones resumidas indican que la mayor reducción del riesgo para varios resultados de salud se produce con tres o cuatro tazas al día. Los pacientes con enfermedad hepática crónica parecen ser los más beneficiados. Se ha planteado la hipótesis de que la creciente prevalencia de la obesidad en las últimas cuatro décadas se relaciona con un mayor consumo de fructosa en la dieta y de jarabe de maíz con alto contenido de fructosa como edulcorante en refrescos y otros alimentos (132). Se ha observado un mayor consumo de fructosa y una mayor concentración de fructoquinasa hepática y de ARNm de sintasa de ácidos grasos en los pacientes con EHGNA en comparación con los controles (133). El consumo elevado de fructosa puede aumentar el riesgo de EHNA y fibrosis avanzada, aunque la asociación puede confundirse con la ingesta excesiva de calorías o con los estilos de vida poco saludables y el comportamiento sedentario, que son más comunes en la EHGNA (118,134). Sin embargo, la evidencia disponible no es lo suficientemente sólida para sacar conclusiones sobre los efectos promotores de la EHGNA específicos de la fructosa cuando esta se consume como ingrediente de una dieta normocalórica (135,136). Véase también el punto 46.

49) Se debe recomendar una dieta mediterránea (DMed) para mejorar la esteatosis y la sensibilidad a la insulina. (Recomendación 34, Grado B, consenso fuerte, 100 % de acuerdo.)

Comentario

Existen numerosos estudios intervencionistas (137-139) y observacionales (140,141) que sugieren que la DMed tiene efectos beneficiosos sobre el peso corporal, la sensibilidad a la insulina y la esteatosis y fibrosis hepáticas, pero sin evidencia clara con respecto a la prevención de la aparición de la EHGNA. Sin embargo, existe una sólida evidencia clínica que respalda el efecto beneficioso de la DMed en términos de reducir el riesgo de enfermedades cardiovasculares y el desarrollo de la diabetes, afecciones que comparten factores etiológicos comunes con la EHGNA como son la resistencia a la insulina y la obesidad (142).

Una mayor adherencia a la DMed no se asocia a una menor probabilidad de tener EHGNA, pero sí se asocia a un menor grado de resistencia a la insulina y a una menor gravedad de la enfermedad hepática entre los pacientes con EHGNA (140). Incluso sin pérdida de peso, la DMed redujo la esteatosis hepática y mejoró la sensibilidad a la insulina en una población resistente a la insulina con EHGNA, en comparación con los consejos dietéticos actuales (143).

2.3.1.3. Cirugía bariátrica

50) En los pacientes obesos con HGNA/EHNA se debe considerar la eficacia de la cirugía bariátrica en términos de reducción del peso, de mejora de la esteatosis hepática y la actividad necroinflamatoria, incluida la fibrosis, y de resistencia a la insulina. (Declaración 13, consenso fuerte, 100 % de acuerdo.)

Comentario

El efecto de la cirugía bariátrica sobre la histología hepática en biopsias pareadas se ha reportado en varios estudios (121-123,125,126,144). Claramente, la profunda pérdida de peso lograda con este enfoque tiene el potencial de resolver la EHNA hasta en un 80-100 % de los casos, y de mejorar sustancialmente la fibrosis, siendo este último el resultado más relevante con respecto a la supervivencia del paciente (145). Además, mejora la sensibilidad a la insulina y una proporción considerable de pacientes diabéticos no necesitarán más tratamiento antidiabético.

51) En los pacientes obesos con HGNA/EHNA sin cirrosis, una vez que las dietas de reducción del peso y las intervenciones intensivas sobre el estilo de vida hayan fracasado, se debe proponer la cirugía bariátrica. (Recomendación 45, grado B, consenso fuerte, 100 % de acuerdo.)

Comentario

La intervención sobre el estilo de vida, aunque es eficaz en algunos pacientes, a menudo no es suficiente para lograr la pérdida de peso a largo plazo y la resolución de la EHNA. Actualmente, ningún tratamiento farmacológico ha demostrado ser eficaz, aunque muchos compuestos están bajo investigación. La cirugía bariátrica es una posible opción de tratamiento para la EHGNA, en particular para su forma progresiva, la EHNA. No hay ensayos sistemáticos, controlados y aleatorizados que evalúen ningún procedimiento quirúrgico bariátrico para tratar específicamente la EHGNA o la EHNA. Una revisión sistemática y un metaanálisis de 15 estudios, que informaron sobre 766 biopsias hepáticas pareadas, mostraron que la proporción combinada de pacientes con mejoría o resolución de la esteatosis era del 92 %. La mejoría de la esteatohepatitis fue del 81 %, la de la fibrosis fue del 66 % y la resolución completa de la EHNA fue del 70 % (130). La mortalidad perioperatoria de la cirugía bariátrica es menor en los pacientes sin cirrosis en comparación con los pacientes con cirrosis compensada o descompensada (0,3 % frente a 0,9 % y 16,3 %) (146). Las guías europeas conjuntas de EASL, EASD y EASO establecen que, en los pacientes que no responden a los cambios de estilo de vida y la farmacoterapia, la cirugía bariátrica es una opción para reducir el peso y las complicaciones metabólicas, con resultados estables en cuanto a los efectos a largo plazo (118).

2.3.2. Comorbilidades

52) Al evaluar el pronóstico de los pacientes en los que la EHGNA/EHNA es un componente integral del síndrome metabólico, se debe considerar el efecto de la comorbilidad no hepática. (Declaración 9, consenso fuerte, 100 % de acuerdo.)

Comentario

En la EHGNA, la mortalidad general y cardiovascular aumenta en comparación con la población general. La EHGNA se asocia con una mayor tasa de mortalidad estandarizada en comparación con la población general, y la enfermedad hepática se sitúa ahora después de la enfermedad cardiovascular y el cáncer como principal causa de muerte. La obesidad grave antes del TxH se asocia con una mayor prevalencia de comorbilidades (diabetes, hipertensión), cirrosis criptogénica y mayor mortalidad por complicaciones infecciosas, enfermedades cardiovasculares y cáncer (147,148). El riesgo de diabetes y de diabetes de tipo 2 manifiesta se asocia con la EHGNA más grave, la progresión a EHNA, la fibrosis avanzada y el desarrollo del carcinoma hepatocelular (149,150), independientemente de las transaminasas séricas. Los pacientes con EHGNA también tienen un mayor riesgo (hasta 5 veces mayor) de desarrollar diabetes de tipo 2 después de ajustar los diversos factores de confusión metabólicos y de estilo de vida (151). Por lo tanto, las directrices europeas recomiendan que las personas con EHGNA se sometan a pruebas de detección de la diabetes y que los pacientes con diabetes de tipo 2 se evalúen para detectar la presencia de EHGNA, independientemente de las transaminasas séricas (118).

53) Se indicará a los pacientes con HGNA/EHNA que se abstengan de consumir alcohol para reducir el riesgo de comorbilidad y mejorar los parámetros hepáticos tanto histológicos como bioquímicos. (Recomendación 36, grado A, consenso fuerte, 100 % de acuerdo.)

Comentario

Al abordar la pregunta de si existen un patrón continuo de dosis-respuesta, un valor umbral, un efecto de género o desenlaces finales (morbilidad frente a mortalidad) del consumo de alcohol, Rehm y sus colaboradores analizaron 17 estudios en su revisión sistemática y metaanálisis (152). Concluyeron que existe un umbral para la morbilidad por cirrosis, pero no para la mortalidad, independientemente del sexo. Una vez que existen signos de enfermedad hepática de cualquier etiología, proponen abstenerse debido al mayor riesgo relativo de cualquier consumo asociado con la mortalidad (152). Además, en la HGNA/EHNA, los riesgos pueden verse agravados por la interacción con los fármacos tomados en asociación con entidades del síndrome

metabólico. A diferencia de la población general, es posible que el consumo de alcohol no reduzca el riesgo de enfermedad cardiovascular en los pacientes con EHGNA (153).

54) Los pacientes con enfermedad celíaca y EHGNA/EHNA deben seguir una dieta libre de gluten para mejorar las enzimas hepáticas y la histología, y para prevenir la progresión a cirrosis, además de mejorar la patología intestinal. (Recomendación 37, grado B, consenso fuerte, 96 % de acuerdo.)

Comentario

Los pacientes con enfermedad celíaca tienen un mayor riesgo de enfermedad hepática antes o después del diagnóstico de la enfermedad. Según un análisis sistemático (154), la razón de riesgos (HR) de la HGNA/EHNA es de 2,8 (IC del 95 %: 2,0-3,8) en los pacientes con enfermedad celíaca e incluso mayor en el subgrupo de los niños (HR: 4,6; IC del 95 %: 2,3-9,1). Hay varios informes de la mejoría o incluso la normalización de las transaminasas, con tasas de respuesta de hasta el 75 % a 100 %, al instaurar una dieta libre de gluten (155-159). Un estudio de casos de Finlandia informó sobre cuatro pacientes con enfermedad hepática grave remitidos al centro de trasplantes, en los que se les diagnosticó una enfermedad celíaca durante la evaluación. Todos los pacientes respondieron a la dieta sin gluten y, en dos pacientes, la enfermedad hepática se resolvió por completo (160). De cinco pacientes estadounidenses con cirrosis hepática y enfermedad celíaca, la ALT, la AST y la bilirrubina mejoraron en los cuatro pacientes que cumplieron con la dieta; la puntuación MELD empeoró en un paciente con cirrosis por EHGNA pero mejoró en los tres restantes (161). Existe una asociación entre la enfermedad celíaca y la enfermedad hepática autoinmune (hepatitis autoinmune, colangitis biliar primaria). Asimismo, la restricción del gluten parece tener un papel en la reducción del riesgo de complicaciones (malabsorción, osteoporosis, malignidad) en este grupo de pacientes.

2.3.3. Suplementos

55) Se debe prescribir vitamina E (800 UI de α-tocoferol al día) a los adultos no diabéticos con EHNA confirmada histológicamente, con el objetivo de mejorar las enzimas hepáticas y la histología. (Recomendación 38, grado B, consenso fuerte, 100 % de acuerdo.)

Comentario

La eficacia de la vitamina E como antioxidante para mejorar las anomalías bioquímicas y/o histológicas de la EHNA se ha investigado en varios ensayos (100,162,163). Sin embargo, existe una gran heterogeneidad entre estos ensayos en cuanto a potencia estadística, criterios de inclusión, dosis de vitamina E, formulaciones de vitamina E utilizadas, uso adicional de otros antioxidantes u otros fármacos y datos histológicos para evaluar los resultados. A pesar de estas limitaciones, se pueden sacar las siguientes conclusiones con respecto a los adultos con EHNA: 1) el uso de la vitamina E se asocia a una mejora de las enzimas hepáticas (disminución de ALT y AST); 2) los ensayos que evalúan las características de la EHNA en biopsias hepáticas pareadas muestran una mejora de la esteatosis y la inflamación, y la resolución de la esteatohepatitis en los pacientes tratados con vitamina E en comparación con los controles; 3) la vitamina E tiene un efecto limitado o nulo sobre la fibrosis hepática. En el ensayo clínico aleatorizado (ECA) más grande (ensayo PIVENS), el criterio de valoración principal predefinido se logró en un número significativamente mayor entre los participantes que recibieron vitamina E oral (800 UI/d durante dos años) en comparación con el placebo (42 % frente a 19 %, $p < 0,001$, número necesario a tratar (NNT) = 4,4) (163). El reanálisis del ensayo PIVENS mostró que las respuestas de la ALT fueron más frecuentes en los receptores de vitamina E y se asociaron a una mejoría de la puntuación del índice de actividad de la EHGNA (NAS), pero no de las puntuaciones de fibrosis (164). Curiosamente, la vitamina E tuvo un efecto adicional en la mejora de las puntuaciones de ALT, índice de actividad de la EHGNA (NAS) y fibrosis obtenidas por una pérdida de peso > 2,0 kg (164).

56) Hasta que se disponga de más datos sobre su eficacia, no se pueden recomendar los antioxidantes (por ejemplo, vitamina C, resveratrol, antocianina, arándanos) para tratar la HGNA/EHNA. (Recomendación 39, grado 0, consenso fuerte, 100 % de acuerdo.)

Comentario

El resveratrol oral (3000 mg) durante ocho semanas no tuvo ningún efecto sobre la resistencia a la insulina, la esteatosis, la distribución de la grasa abdominal y los lípidos plasmáticos o la actividad antioxidante. Los niveles de ALT y AST, sin embargo, aumentaron significativamente en el grupo del resveratrol (165). En otro ensayo, se observó que 2 · 150 mg de resveratrol v.o. durante tres meses mejoraban los niveles de AST, ALT, LDL, colesterol total, HOMA-IR y mediadores de la inflamación (166). Una cápsula de 500 mg de resveratrol junto a una intervención sobre el estilo de vida fueron más eficaces que la intervención sobre el estilo de vida en solitario en pacientes con sobrepeso en términos de mejora de la ALT, las citocinas inflamatorias y la esteatosis hepática (167,168). El zumo de arándano, que contiene altos niveles de polifenoles, no tuvo ningún efecto sobre las medidas antropométricas y el HOMA-IR en pacientes chinos con normopeso y EHGNA en la ecografía (169). En un ensayo piloto controlado y aleatorizado, el flavonoide antocianina (320 mg v.o. durante doce semanas) disminuyó la ALT y el nivel de glucosa a las 2 horas de la carga (170). Se ha reportado que la suplementación con coenzima Q10 oral reduce la circunferencia de la cintura, los niveles séricos de AST y la capacidad antioxidante total de la sangre (171). En estudios epidemiológicos de pacientes con EHGNA se ha descrito una ingesta de vitamina C por debajo de la cantidad diaria recomendada, lo que sugiere una asociación entre los hábitos alimentarios, la enfermedad y la deficiencia de vitamina C. Los ECA actualmente disponibles no han encontrado ningún efecto de la vitamina C superior al del

placebo. Por lo tanto, el papel de la vitamina C en la EHGNA debe investigarse en futuros ECA adecuadamente controlados. Se han implicado niveles anormalmente bajos de colina en la patogenia de la enfermedad hepática asociada a la nutrición parenteral, algunas de cuyas características morfológicas se asemejan a la EHGNA/EHNA (172). Un análisis secundario de los cuestionarios de alimentos de 664 participantes de tres ensayos de la Red de Investigación Clínica de EHNA mostró que, en las mujeres posmenopáusicas, una menor ingesta de colina se asoció con un aumento de la fibrosis (173). En esta línea, los datos sugieren que una mayor ingesta de colina en la dieta puede estar asociada con un menor riesgo de EHGNA. Por otro lado, en la EHNA se ha observado una estrecha relación entre los niveles plasmáticos de colina libre y el grado de esteatosis y fibrosis hepática (174). No hay datos de los ensayos de intervención con colina. En comparación con el placebo, la suplementación oral de L-carnitina (1 g dos veces al día durante 24 semanas) fue eficaz para reducir el TNF-α y la PCR, y para mejorar la función hepática, el nivel de glucosa en plasma, el perfil de lípidos, el HOMA-IR y las manifestaciones histológicas de la EHNA (175). En pacientes diabéticos con EHNA, el orotato de carnitina oral (3 · 824 mg durante doce semanas) se asoció a una mejoría significativa de la ALT, la esteatosis hepática y la HbA1c en un ensayo doble ciego controlado con placebo (176). Estos son resultados preliminares y, por lo tanto, todavía no se puede recomendar la L-carnitina.

57) Hasta que se disponga de más datos sobre su eficacia, los ácidos grasos omega-3 no pueden recomendarse para tratar la HGNA/EHNA. (Recomendación 40, grado 0, consenso fuerte, 100 % de acuerdo.)

Comentario

En pacientes con solo EHGNA, hubo una tendencia hacia la mejora de la esteatosis hepática en los casos tratados con 4 g de ácidos grasos omega-3 (177). Sin embargo, un ensayo multicéntrico que comparó dos regímenes de dosis de ácido etil-eicosapentanoico (1800 mg/d o 2700 mg/d) con placebo no encontró efecto alguno sobre las enzimas hepáticas, la resistencia a la insulina, la adiponectina, la queratina 18, la proteína C-reactiva, el ácido hialurónico o la histología hepática en 243 pacientes con EHNA comprobada por biopsia (178). En un ensayo controlado más pequeño, 3 g de ácidos grasos omega-3 mejoraron el contenido de grasa hepático, pero fallaron en mejorar la histología de la EHNA (mejoría ≥ 2 puntos del NAS) (179). En un ensayo que comparó el efecto de 4 g de ácidos grasos omega-3 y de la dapagliflozina, sola o en combinación, solo la combinación fue más efectiva que el placebo para reducir los lípidos intrahepáticos (180). Los autores de una revisión sistemática y un metaanálisis concluyeron que, en los pacientes con EHGNA, los ácidos grasos omega-3 reducen la grasa hepática, pero no se determinó la dosis óptima, por lo que se necesitan estudios controlados de mejor calidad (181). Sin embargo, en una revisión sistemática reciente, los autores concluyen que es probable que los AGPI n-3 marinos sean una herramienta importante para el tratamiento de la EHGNA, aunque se necesitan más estudios para confirmarlo (182). Los autores de otro metaanálisis concluyeron que los AGPI de cadena larga omega-3 son útiles en el tratamiento dietético de los pacientes con EHGNA, pero son ineficaces sobre los hallazgos histológicos de los pacientes con EHNA (183).

58) Se pueden usar suplementos nutricionales que contengan probióticos o simbióticos seleccionados para mejorar las enzimas hepáticas en los pacientes con HGNA/EHNA. (Recomendación 41, grado 0, consenso, 89 % de acuerdo.)

Comentario

Una revisión sistemática identificó nueve artículos de texto completo sobre ensayos clínicos aleatorizados que habían evaluado probióticos, prebióticos o simbióticos en el tratamiento de la EHGNA en adultos; de ellos, seis fueron excluidos debido a deficiencias metodológicas (184). Un ensayo controlado, aleatorizado y doble ciego de 30 pacientes con EHGNA comprobada por biopsia mostró una disminución significativa pero muy modesta de ALT, AST y GGT después de tres meses de tratamiento con el probiótico, pero no con placebo (185). Una comparación de los probióticos frente a la atención estándar mostró una disminución de los triglicéridos intrahepáticos (espectroscopía de RM) y de la AST sérica en los diez pacientes del grupo con probióticos (186). En pacientes con EHNA comprobada por biopsia, el tratamiento con *Bifidobacterium longum*, con fructooligosacáridos y con modificación del estilo de vida durante 24 semanas, en comparación con la modificación del estilo de vida sola, redujeron los niveles de AST, los marcadores de inflamación, el HOMA-IR, la endotoxina sérica y la histología de la EHNA en ambos grupos, pero más en el grupo tratado con simbiótico (187). En un ensayo clínico aleatorizado, doble ciego y controlado con placebo, 52 pacientes con EHGNA fueron aleatorizados para tomar dos veces al día, durante 28 semanas, una cápsula de simbiótico o placebo, además de la modificación del estilo de vida. En el grupo del simbiótico, los niveles de ALT, AST, GGT, PCR y citocinas inflamatorias disminuyeron en mayor grado que en el grupo del placebo (188). Se ha informado de que el consumo diario de 300 g (8 semanas) de yogur con probióticos mejora las enzimas hepáticas en los pacientes con EHGNA en comparación con el yogur convencional (189).

2.3.4. Nutrición médica (NE, NP)

59) Se debe administrar NE o NP a los pacientes con HGNA/EHNA durante una enfermedad intercurrente grave, cuando la nutrición oral por sí sola sea inadecuada o imposible o esté contraindicada. (Recomendación 42, grado GPP, consenso fuerte, 96 % de acuerdo.)

Comentario

No hay datos de ensayos formales de terapia nutricional que aborden estas preguntas. Un análisis que utilizó la base de datos de la Encuesta Nacional de Examen de Salud y Nutrición de Corea encontró que el 12 % de los sujetos con EHGNA eran sarcopénicos y, curiosamente, su IMC era significativamente más

alto que el de los individuos no sarcopénicos (190). Además, la sarcopenia se asoció sistemáticamente con una fibrosis hepática significativa. Basándose en los numerosos informes sobre el papel pronóstico del mal consumo de alimentos entre los pacientes hospitalizados en general y entre pacientes con EHA o cirrosis hepática en particular, los expertos recomiendan el soporte nutricional también en los pacientes con EHGNA/EHNA que no pueden lograr una ingesta adecuada de alimentos mientras padecen enfermedades intercurrentes graves. Además, en este grupo de pacientes se recomienda la detección del riesgo de desnutrición y una evaluación nutricional adecuada.

60) En los pacientes con HGNA/EHNA y un IMC < 30 kg/m^{2,} la NE y/o la NP deben realizarse según lo recomendado para los pacientes con EHA (Recomendación 43, grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

Véanse el comentario del punto 59 y los comentarios de los puntos 33, 34, 38 y 40 sobre la NE/NP en pacientes con EHA.

61) Los pacientes obesos con HGNA/EHNA y enfermedades intercurrentes deben recibir NE y/o NP con un objetivo de aporte energético de 25 kcal·kg^{-1} de peso corporal ideal (PCI)·d^{-1} y un objetivo de aporte de proteínas aumentado de 2,0-2,5 g·kg^{-1} PCI·d^{-1}. (Recomendación 44, grado GPP, acuerdo mayoritario, 71 % de acuerdo.)

Comentario

Un número creciente (30-35 %) de pacientes adultos en las UCI son obesos, y al menos el 5 % son obesos mórbidos. El soporte nutricional de estos pacientes es un desafío y uno de los aspectos más difíciles de la nutrición clínica. La obesidad repercute sobre la incidencia y la gravedad de las comorbilidades y el resultado final del paciente. De acuerdo con las pautas de la ASPEN, estos pacientes deben ser atendidos de acuerdo con los principios básicos de la nutrición de cuidados intensivos, con el objetivo de un aporte alto de proteínas (2,0-2,5 g·kg^{-1} PCI·d^{-1}) para la preservación de la masa corporal magra pero un régimen hipocalórico (25 kcal·kg^{-1} PCI·d^{-1}) destinado a reducir la masa grasa y la resistencia a la insulina (191). Entre el grupo de consenso, el acuerdo sobre esta recomendación fue limitado debido a la débil evidencia disponible. Sin embargo, ante el creciente número de pacientes obesos con HGNA/EHNA, se consideró apropiada la referencia a la guía de cuidados críticos de la ASPEN.

2.4. CIRROSIS HEPÁTICA (Figs. 10-12)

2.4.1. Riesgo de desnutrición

62) En los pacientes con cirrosis hepática debe esperarse una alta prevalencia de la desnutrición, la depleción de proteínas y la deficiencia de oligoelementos. (Declaración 1, consenso fuerte, 100 % de acuerdo.)

Comentario

En la cirrosis hepática, la prevalencia y la gravedad de la desnutrición proteico-energética de tipo mixto están relacionadas con la etapa clínica de la enfermedad hepática crónica, aumentando del 20 % en los pacientes con enfermedad compensada a más del 60 % en aquellos otros con cirrosis avanzada. La etiología de la enfermedad hepática *per se* no parece influir en la prevalencia y el grado de desnutrición y depleción de proteínas, y la prevalencia más alta y el grado más profundo de desnutrición en los alcohólicos probablemente sean el resultado de factores adicionales que incluyan un estilo de vida poco saludable y carencias socioeconómicas. La composición corporal de los cirróticos se altera profundamente y se caracteriza por la depleción de proteínas y la acumulación de agua corporal total, que puede manifestarse incluso en los pacientes con enfermedad en fases tempranas, Child-Pugh clase A (192-194). Esto es paralelo a la retención de sodio y, por lo tanto, rara vez se asocia con hipernatremia. Con frecuencia se produce una depleción de potasio, magnesio, fosfato y otros minerales intracelulares. La deficiencia de vitaminas hidrosolubles, principalmente del grupo B, es común en la cirrosis, especialmente en la de origen alcohólico. Se ha observado deficiencia de vitaminas liposolubles en la esteatorrea relacionada con la colestasis, en la deficiencia de sales biliares y en los alcohólicos. En la cirrosis, la desnutrición se asocia con una mayor prevalencia de la ascitis y el síndrome hepatorrenal, una mayor duración de la estancia y los costes hospitalarios (195), y una mayor mortalidad (194). En varios estudios descriptivos se reportan tasas más altas de morbilidad (23,196,197) y mortalidad (24,31,197-199) en los pacientes con desnutrición preoperatoria y/o sarcopenia que se someten a trasplante por enfermedad hepática crónica en etapa terminal.

63) En la cirrosis hepática debe esperarse un deterioro progresivo, dependiente del estadio, del metabolismo de carbohidratos, proteínas y lípidos, caracterizado por depleción del glucógeno hepático, alteración del metabolismo no oxidativo de la glucosa y reducción de la tasa de síntesis de albúmina (Declaración 3, consenso fuerte, 100 % de acuerdo.)

Comentario

En la cirrosis, en el estado postabsortivo, la tasa de oxidación de la glucosa se reduce y la tasa de producción de glucosa hepática es baja, a pesar del aumento de la gluconeogénesis, debido a la depleción del glucógeno hepático (200). Por lo tanto, después de una noche de ayuno, las condiciones metabólicas son similares a las del ayuno prolongado en los individuos sanos (201). La resistencia a la insulina afecta al metabolismo del músculo esquelético: la captación de glucosa, la eliminación no oxidativa de la glucosa y la síntesis de glucógeno se reducen, mientras que la oxidación de la glucosa y la producción de lactato son normales después del suministro de glucosa. Entre el 15 % y el 37 % de los pacientes desarrollan diabetes, lo cual se asocia con un pronóstico desfavorable (202,203). La utilización de combustibles oxidativos se caracteriza por una mayor tasa de oxidación de lípidos en ayunas y la aparición frecuente de resistencia a la insulina (incluso en pacientes Child-Pugh A) (201,204).

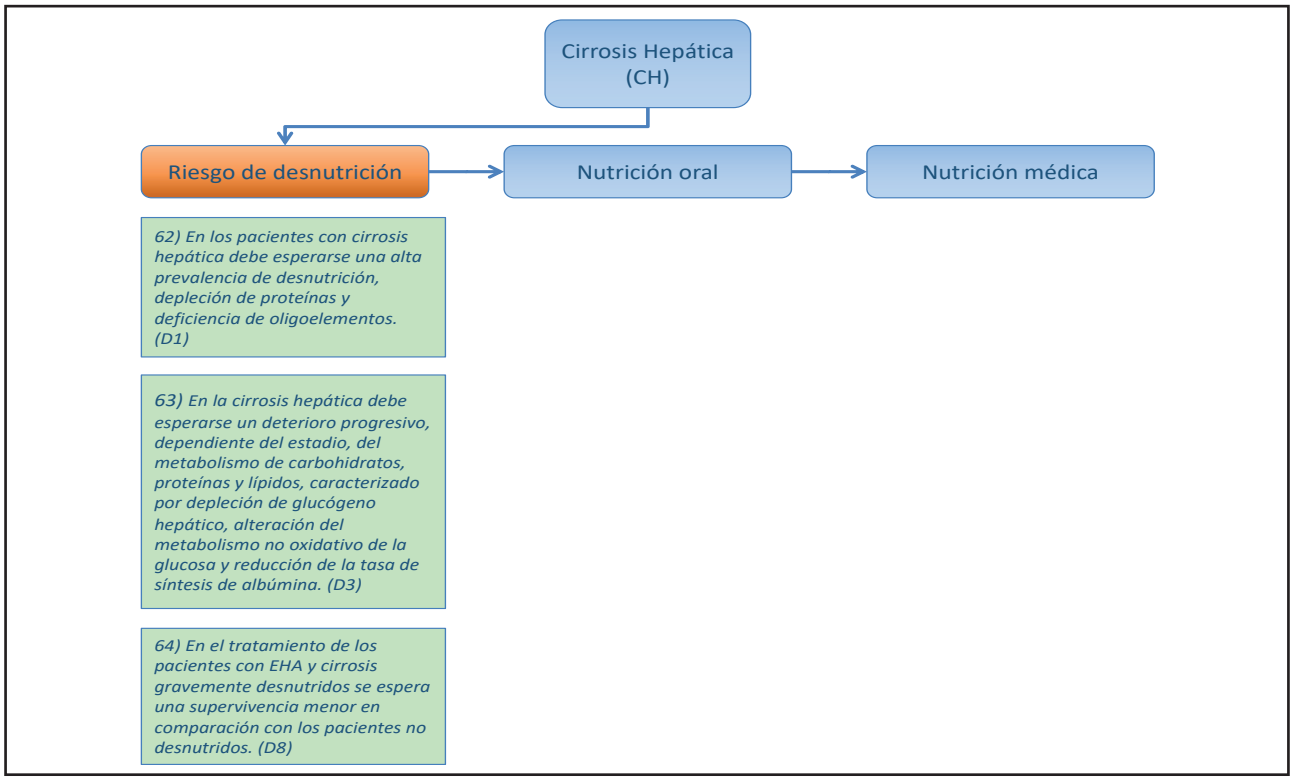

Figura 10.

Cirrosis hepática (CH).

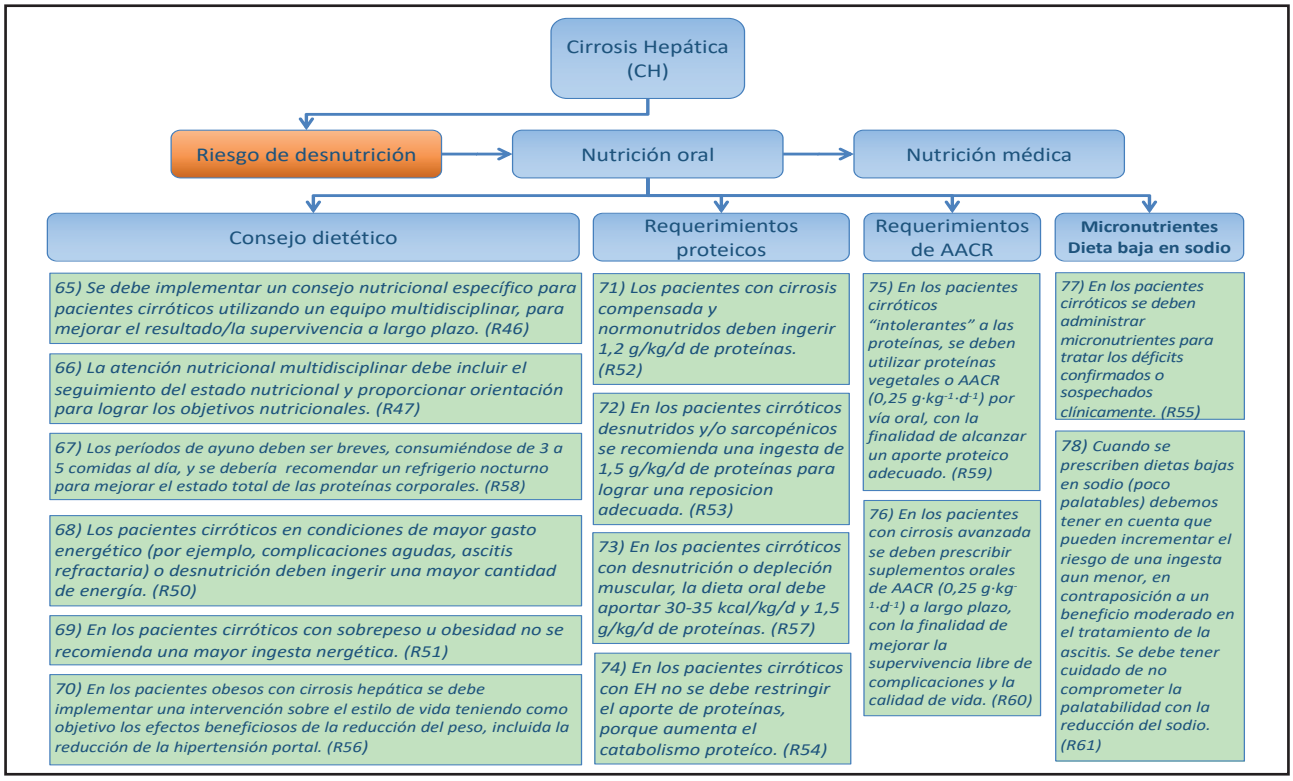

Figura 11.

Cirrosis hepática (CH) (cont.).

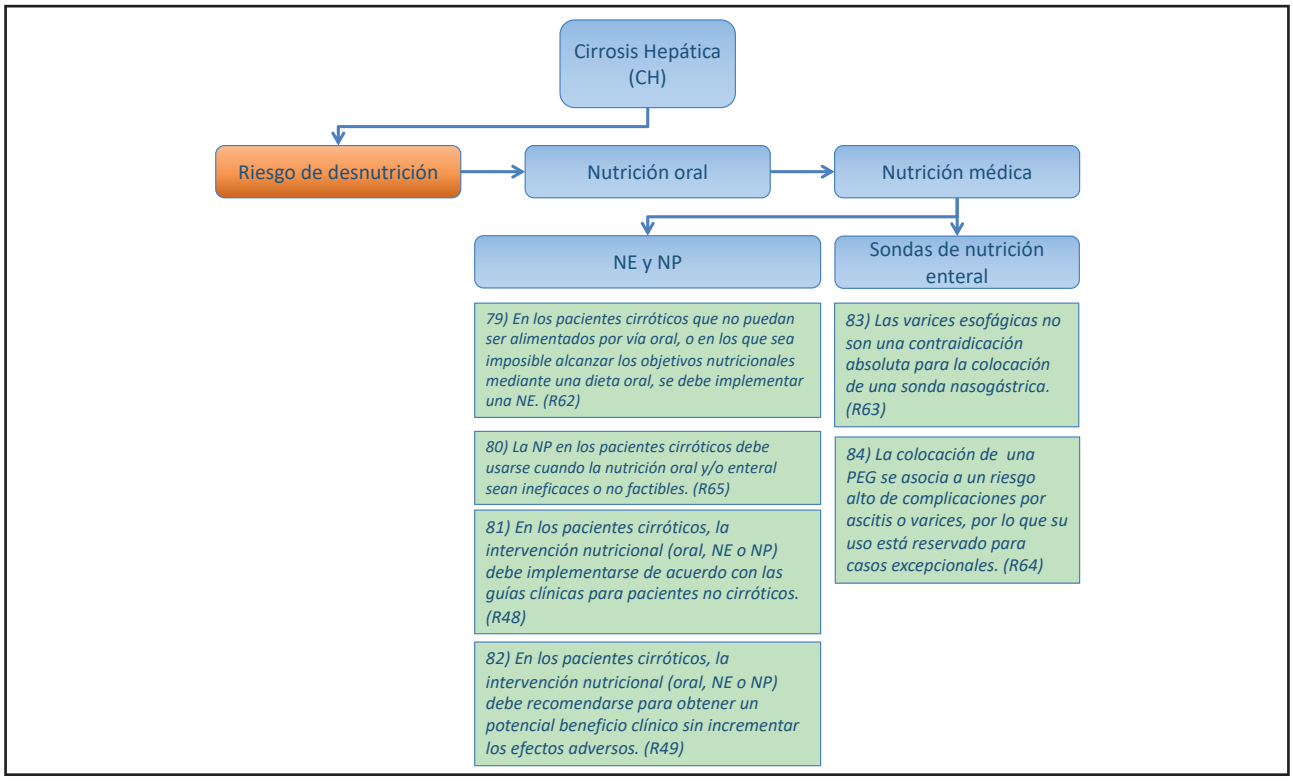

Figura 12.
Cirrosis hepática (CH) (cont.).

Los niveles plasmáticos de ácidos grasos esenciales y poliinsaturados disminuyen en la cirrosis, y esta reducción se correlaciona con el estado nutricional y la gravedad de la enfermedad hepática (205,206). En la cirrosis se ha observado un recambio de proteínas normal o aumentado debido a una mayor degradación de las proteínas y/o una menor síntesis de proteínas. Las tasas de síntesis de albúmina, pero no de fibrinógeno, se correlacionan con las pruebas cuantitativas de la función hepática y las etapas clínicas de la cirrosis. Sin embargo, los cirróticos estables aparentemente son capaces de una retención eficiente de nitrógeno y una formación significativa de masa corporal magra a partir del aumento de la ingesta de proteínas durante la realimentación oral (34).

64) En el tratamiento de los pacientes con cirrosis gravemente desnutridos se espera una supervivencia menor, en comparación con los pacientes no desnutridos. (Declaración 8, consenso fuerte, 100 % de acuerdo.)

Comentario

En los pacientes con cirrosis gravemente desnutridos, varios estudios reportaron una mayor morbilidad y mortalidad (194,207), así como una mayor mortalidad después del TxH (31,196,199,207-210). Los datos son controvertidos con respecto a la mayor prevalencia de la encefalopatía hepática en los pacientes desnutridos con cirrosis (204,211).

2.4.2. Nutrición oral

2.4.2.1. Consejo dietético

65) Se debe implementar un consejo nutricional específico para los pacientes cirróticos, utilizando un equipo multidisciplinar para mejorar el resultado/la supervivencia de los pacientes a largo plazo. (Recomendación 46, grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

La terapia nutricional debe incluirse en el tratamiento de los pacientes con cirrosis ya que tiene el potencial de alterar el comportamiento de los pacientes. Debe incluir la educación de los pacientes acerca de los beneficios de una dieta saludable adaptada a la condición clínica, así como orientada a abordar necesidades específicas. Cuando es necesario cambiar las prescripciones nutricionales en respuesta a la gravedad de la enfermedad, el consejo nutricional puede facilitar la forma de afrontar estos cambios. Un pequeño estudio retrospectivo unicéntrico mostró un beneficio sobre la supervivencia cuando los pacientes con cirrosis recibieron consejo nutricional especializado en comparación con ningún consejo (212). Los autores también informaron de que el asesoramiento en el que participa un equipo multidisciplinar, con médicos, enfermeras, farmacéuticos y dietistas, se asoció con una mejor supervivencia, frente al asesoramiento por una sola profesión (212).

66) La atención nutricional multidisciplinar debe incluir el seguimiento del estado nutricional y proporcionar orientación para lograr los objetivos nutricionales. (Recomendación 47, grado GPP, consenso fuerte, 95 % de acuerdo.)

Comentario
Véase el comentario del punto 65.

67) Los períodos de ayuno deben ser breves, consumiéndose de tres a cinco comidas al día, y se debería recomendar un refrigerio por la noche para mejorar el estado total de las proteínas corporales. (Recomendación 58, grado B, consenso fuerte, 100 % de acuerdo.)

Comentario
Según los datos publicados disponibles, los pacientes deben tener una ingesta energética de 30-35 $kcal \cdot kg^{-1} \cdot d^{-1}$ y una ingesta de proteínas de 1,2-1,5 $g \times kg^{-1} \cdot d^{-1}$. En un ensayo prospectivo bien realizado, que mide el nitrógeno corporal total, se ha demostrado que la administración nocturna de suplementos nutricionales orales (SNO) es más eficaz para mejorar el estado de las proteínas corporales totales que la administración diurna (91). Anteriormente, se había demostrado que un refrigerio con carbohidratos al final de la noche mejoraba el metabolismo de las proteínas en la cirrosis (92,213). En su revisión sistemática, Tsien y colaboradores (84) demostraron que un refrigerio al final de la noche mejora el balance de nitrógeno, independientemente de la composición o el tipo de formulación utilizada. Llegan a la conclusión de que acortar los períodos de ayuno mediante un refrigerio nocturno es un concepto prometedor para revertir la resistencia anabólica y la sarcopenia de la cirrosis.

68) Los pacientes cirróticos en condiciones de mayor gasto energético (es decir, complicaciones agudas, ascitis refractaria) o desnutrición deben ingerir una mayor cantidad de energía. (Recomendación 50, grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario
En general, los requerimientos energéticos de los pacientes con cirrosis compensada no son mayores que los de los individuos sanos (ver puntos 8 y 10). Además, los pacientes con cirrosis tienen un nivel de actividad física reducido (33) y, por tanto, un gasto energético reducido debido a la actividad física. Los pacientes cirróticos, durante el curso natural de la enfermedad, tienden a disminuir espontáneamente su ingesta dietética (85,214). Esto es de especial relevancia en el subgrupo de pacientes con cirrosis hipermetabólica (hasta el 35 % de los pacientes con cirrosis) (29,30) o en aquellos con cirrosis avanzada con complicaciones, cuando el gasto energético puede aumentar. Por lo tanto, se recomienda medir el gasto energético siempre que sea posible (ver la recomendación 1). La nutrición oral, la NE y la NP se han utilizado en estudios a corto y largo plazo en pacientes cirróticos descompensados y/o desnutridos con algunas ventajas en términos tanto de morbilidad como de mortalidad.

69) En pacientes cirróticos con sobrepeso u obesidad no se recomienda una mayor ingesta energética (Recomendación 51, grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario
La proporción de pacientes con cirrosis y sobrepeso u obesidad ha aumentado incluso en las cohortes en lista de espera para trasplante (12,215,216). En la enfermedad hepática crónica, la obesidad se ha identificado como un factor de riesgo independiente de peor resultado clínico (217,218). Se ha propuesto que la obesidad podría promover la hipertensión portal. La hipertensión portal podría mejorarse mediante una intervención sobre el estilo de vida durante 16 semanas, mediante una dieta hipocalórica y un aumento del ejercicio en los pacientes con cirrosis (219). Por tanto, no se recomienda una mayor ingesta energética en los pacientes cirróticos obesos.

70) En los pacientes obesos con cirrosis hepática se debe implementar una intervención sobre el estilo de vida, teniendo como objetivo los efectos beneficiosos de la reducción del peso, incluida la reducción de la hipertensión portal. (Recomendación 56, grado B, consenso fuerte, 100 % de acuerdo.)

Comentario
En un reciente estudio multicéntrico no controlado (219) se valoró la respuesta a una dieta hipocalórica normoproteica más actividad física supervisada de 60 min/semana, durante 16 semanas, en pacientes con cirrosis compensada y con sobrepeso/obesidad (IMC $\geq$ 26 kg/m^2), demostrándose que la intervención sobre el estilo de vida redujo significativamente el peso corporal (media: -5,0 $\pm$ 4,0 kg). Estos pacientes también presentaron una disminución significativa de la hipertensión portal, determinada mediante la medición del gradiente de presión portal. Aunque no se reportaron otros resultados, de confirmarse, estos hallazgos apoyan fuertemente la intervención sobre el estilo de vida de los pacientes cirróticos con obesidad u sobrepeso.

2.4.2.2. Requerimientos proteicos

71) Los pacientes con cirrosis compensada y normonutridos deben ingerir 1,2 $g \cdot kg^{-1} \cdot 2d^{-1}$ de proteínas. (Recomendación 52, grado B, consenso fuerte, 100 % de acuerdo.)

Comentario
Los pacientes cirróticos sarcopénicos y desnutridos presentan depleción proteica tanto por una elevada degradación de las proteínas corporales como por la disminución de su síntesis en los músculos (192,220). El incremento de la ingesta de proteínas se tolera generalmente bien y es seguro, habiéndose demostrado en estudios previos que mejora el anabolismo proteico (34,221). En un pequeño grupo de pacientes desnutridos, seguidos cuidadosamente, se demostró que una realimentación adecuada es capaz de inducir un incremento significativo de la síntesis proteica (222). Véase también el punto 72.

72) En los pacientes cirróticos desnutridos y/o sarcopénicos se recomienda una ingesta de 1,5 g·kg^{-1}·d^{-1} de proteínas para una reposición adecuada. (Recomendación 53, grado B, consenso fuerte, 100 % de acuerdo.)

Comentario

Los pacientes cirróticos sarcopénicos, incluidos aquellos con obesidad sarcopénica, pueden necesitar una ingesta mayor de proteínas junto con ejercicio para lograr la recuperación muscular. En los estudios de intervención que implementaron un protocolo con un aporte elevado de proteínas se observó una mejora de la circunferencia braquial, de la fuerza prensil de la mano y de los niveles de albúmina (10,223-226). Así mismo, se observó una mejoría del estado proteico cuando los SNO se administraron en horario nocturno (91), lo que refuerza las observaciones previas que apuntaban a un efecto beneficioso de la administración de un refrigerio nocturno de carbohidratos o proteínas en los pacientes cirróticos (92,213,221).

73) En los pacientes cirróticos con desnutrición o depleción muscular, la dieta oral debe aportar 30-35 kcal·kg^{-1}·d^{-1} y 1,5 g·kg^{-1}·d^{-1} de proteínas. (Recomendación 57, grado B, consenso fuerte, 100 % de acuerdo.)

Comentario

Véase el comentario del punto 67.

74) En los pacientes cirróticos con encefalopatía hepática no se debe restringir el aporte de proteínas porque aumenta el catabolismo proteico. (Recomendación 54, grado B, consenso fuerte, 100 % de acuerdo.)

Comentario

Hay un subgrupo seleccionado de pacientes cirróticos, los denominados "intolerantes a las proteínas", que desarrollan encefalopatía hepática con la dieta normoproteica, pero esto parece ser un fenómeno histórico puesto que, en la actualidad, rara vez vemos estos pacientes. En base a una serie de ensayos, se sugirió que la restricción de proteínas podría no ser necesaria para la prevención de la encefalopatía hepática (85,87,222). Finalmente, Córdoba y colaboradores, en un ECA (227), demostraron que la restricción de proteínas no tiene ningún beneficio sobre el curso de la encefalopatía hepática y puede empeorar el catabolismo proteico. Tras este estudio se abandonó definitivamente el dogma de prescribir la restricción proteica a los pacientes cirróticos con encefalopatía hepática, centrándose todos los esfuerzos en conseguir una ingesta adecuada de proteínas en este grupo de pacientes.

2.4.2.3. Requerimientos en AACR

75) En los pacientes cirróticos "intolerantes" a las proteínas se deben utilizar proteínas vegetales o AACR (0,25 g·kg^{-1}·d^{-1}) por vía oral con la finalidad de alcanzar un aporte adecuado de proteínas. (Recomendación 59, grado B, consenso, 89 % de acuerdo.)

Comentario

En un metaanálisis que excluyó los ensayos con SNO enriquecidos con AACR, en el análisis de un subgrupo de estudios se demostró una reducción de la mortalidad de los pacientes suplementados con SNO (228). Después del tratamiento exitoso de la hipertensión portal mediante derivación percutánea portosistémica intrahepática (DPPI), los pacientes cirróticos con alimentación normal (según las recomendaciones de la ESPEN) mejoraron su composición corporal (32,229).

En el caso muy raro de un paciente cirrótico "intolerante a las proteínas" que desarrolle encefalopatía hepática con una ingesta normal de proteínas mixtas, una dieta con proteínas vegetales puede ser beneficiosa. Aunque se ha abordado este problema en algunas revisiones (230), no hay datos de ensayos controlados y aleatorizados que comparen regímenes normocalóricos y normoproteicos. Un estudio no era controlado y en uno más reciente se comparó el soporte nutricional con una dieta con proteínas vegetales frente a ningún soporte (232).

76) En los pacientes con cirrosis avanzada se deben prescribir suplementos orales de AACR (0,25 g·kg^{-1}·d^{-1}) a largo plazo, con la finalidad de mejorar la supervivencia libre de complicaciones y la calidad de vida. (Recomendación 60, grado B, consenso, 89 % de acuerdo.)

Comentario

No hay datos disponibles de ensayos que comparen una fórmula enteral estándar con fórmulas enriquecidas con AACR en pacientes cirróticos. Sin embargo, existen ensayos en los que se demuestra una mejoría de la supervivencia en pacientes severamente desnutridos con EHA o cirrosis (68,69,233,234) o del estado mental en un grupo muy seleccionado de pacientes cirróticos con encefalopatía hepática e intolerancia a las proteínas (235). En los dos ensayos más grandes (174 y 646 pacientes), la suplementación oral con AACR (12 y 24 meses) fue útil para prevenir la insuficiencia hepática progresiva y mejorar los marcadores indirectos, así como la calidad de vida relacionada con la salud (236,237). En pacientes cirróticos, después de un episodio de EH, la suplementación con AACR durante doce meses mejoró la encefalopatía hepática mínima y la masa muscular, pero no disminuyó la recurrencia de la encefalopatía hepática clínica o manifiesta en comparación con el grupo de control (238). En los ensayos en los que se informó de efectos beneficiosos sobre el estado mental y/o el metabolismo proteico, los AACR se administraron en una dosis de 0,20-0,25 g·kg PCl^{-1}·d^{-1} (236,237,239,240) o 30 g·d^{-1} (235,238). En un metaanálisis de la Cochrane se encontró un efecto beneficioso de los AACR sobre la encefalopatía hepática (241), aunque la calidad metodológica de los estudios incluidos es baja (242,243). Además, hay que tener en cuenta que los suplementos orales de AACR en muchos países no están financiados, lo que, unido a la palatabilidad, puede afectar al cumplimiento de los tratamientos.

2.4.2.4. Micronutrientes/dieta baja en sal

77) En los pacientes cirróticos se deben administrar micronutrientes para tratar los déficits confirmados o sospechados clínicamente. (Recomendación 55, grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

Los pacientes cirróticos pueden presentar déficit de vitaminas hidrosolubles, en particular de tiamina, y de vitaminas liposolubles como la vitamina D (244,245). Aunque no existen estudios que evalúen sistemáticamente la necesidad de micronutrientes de los pacientes cirróticos, igual que en otras patologías, no se ha probado el efecto beneficioso de su administración aparte de la prevención o corrección de estados carenciales ya probados. Algunos estudios señalan que los suplementos de zinc y vitamina A, al mejorar la disgeusia, pueden mejorar indirectamente la ingesta y el estado nutricional (246,247). En los pacientes con hepatopatía alcohólica y no alcohólica se han observado déficits de zinc y selenio, y en series de casos se ha descrito una asociación importante entre la encefalopatía hepática y el déficit de zinc. Sin embargo, los ensayos clínicos controlados y aleatorizados no mostraron ningún efecto beneficioso de la administración de suplementos de zinc sobre la encefalopatía hepática (250-252). La suplementación con zinc puede aumentar la producción de urea cuando se normalizan los niveles previamente bajos (253). En un enfoque pragmático, se recomienda una suplementación libre en las dos primeras semanas de soporte nutricional, porque el diagnóstico de déficit de un oligoelemento específico o vitamínico puede ser costoso y puede retrasar el inicio de la suplementación. Debido a la alta prevalencia de la desnutrición, los pacientes cirróticos tienen riesgo de desarrollar síndrome de realimentación y déficit de tiamina.

78) Cuando se prescriben dietas bajas en sodio (poco palatables), debemos tener en cuenta que pueden incrementar el riesgo de una ingesta aun menor de alimentos, en contraposición a un beneficio moderado en el tratamiento de la ascitis. Se debe tener cuidado de no comprometer la palatabilidad de la dieta tras la reducción del sodio. (Recomendación 61, grado GPP, consenso, 78 % de acuerdo.)

Comentario

Basándonos en la fisiopatología de la ascitis, generalmente se recomienda una ingesta moderada de sodio (60 mmol/día). El efecto beneficioso de la restricción de sodio puede verse contrarrestado por una ingesta calórica y proteica disminuida debido a la palatabilidad de dicha dieta (254,255). Por lo tanto, se debe tener mucho cuidado y procurar garantizar una nutrición adecuada al prescribir dietas con restricción de sodio. En un estudio de pacientes cirróticos con ascitis refractaria se demostró que las tasas de morbilidad y mortalidad fueron menores en quienes recibieron una dieta equilibrada con AACR, con o sin aporte de NP complementaria, en comparación con un grupo de pacientes que solo recibieron una dieta baja en sodio (256).

2.4.3. Nutrición médica

2.4.3.1. NE y NP

79) En los pacientes cirróticos que no puedan ser alimentados por vía oral o en los que sea imposible alcanzar los objetivos nutricionales mediante una dieta oral, se debe utilizar la NE. (Recomendación 62, grado B, consenso fuerte, 100 % de acuerdo.)

Comentario

Existe una amplia evidencia que indica que asegurar una ingesta de nutrientes cuantitativamente adecuada debería ser el objetivo principal (85,233). Si los requerimientos nutricionales no se pueden alcanzar mediante una nutrición oral sola o en combinación con SNO, debemos recurrir a la NE. Se ha demostrado que la NE mejora la función hepática y la supervivencia (85,233). Un reciente ensayo controlado, aleatorizado y multicéntrico no mostró ningún beneficio ni sobre la función hepática ni sobre la supervivencia tras un año de seguimiento, utilizando una fórmula estándar de NE durante un promedio de 2,8 semanas seguido de SNO durante 2 meses (257). Los autores no proporcionan datos sobre la adherencia al tratamiento con SNO. La ingesta total de energía durante la NE solo se evaluó en un subgrupo de pacientes y superó la ingesta recomendada en un 28 % (3292 +/- 781 kcal/d), por lo que se plantea un interrogante sobre los efectos perjudiciales de la sobrealimentación. En un metaanálisis, Ney y colaboradores (228), al analizar un subgrupo de 3 de los 4 estudios con SNO incluidos, encontraron una reducción de la mortalidad, pero no para el grupo completo de 6 estudios incluidos en dicho metaanálisis. Además, los resultados se ven ensombrecidos por incluirse un estudio en el que el tratamiento con NE era solo durante 3 días (258) y por no incluir 2 ensayos controlados relevantes sin motivos justificables (85,233).

80) La NP, en los pacientes cirróticos, debe usarse cuando la nutrición oral y/o enteral son ineficaces o no factibles. (Recomendación 65, grado B, consenso fuerte, 100 % de acuerdo.)

Comentario

La indicación de la NP en los pacientes cirróticos que no pueden ser alimentados por vía oral o mediante NE mantiene las mismas recomendaciones que la de los pacientes no cirróticos (94). Hay que tener cuidado para evitar infecciones de las vías de acceso parenteral, ya que estos pacientes son más propensos a las infecciones y la sepsis. Hay que mencionar dos aspectos específicos de la cirrosis: en la cirrosis, los lípidos infundidos se eliminan del plasma y se oxidan a velocidades similares a las observadas en los individuos sanos. En lactantes y niños, las emulsiones que contienen aceite de pescado parecen estar asociadas con un menor riesgo de colestasis y daño hepático (véanse los puntos 10 y 11). Sin embargo, hasta el momento no hay resultados de ensayos clínicos que muestren un beneficio de tales emulsiones en pacientes cirróticos adultos. En cuanto a la composición de las soluciones de aminoácidos, se puede usar una solución estándar en los pacientes con cirrosis compensada. Las soluciones específicas hepáticas ("fórmula hepática") de aminoácidos,

destinadas a la corrección del desequilibrio de aminoácidos plasmáticos, son soluciones completas con alto contenido de AACR (35-45 %) pero bajo de triptófano, aminoácidos aromáticos y aminoácidos azufrados, y se han desarrollado para pacientes cirróticos con encefalopatía hepática clínica. La eficacia de los AACR o las soluciones enriquecidas con AACR se ha investigado en ensayos controlados, aunque estos son muy heterogéneos (259,260) y sus resultados, contradictorios. Los metaanálisis de estos estudios mostraron una mejora de la encefalopatía hepática en el grupo con soluciones enriquecidas con AACR, pero no demostraron beneficio alguno sobre la supervivencia (242,261).

81) En los pacientes cirróticos, la intervención nutricional (oral, NE o NP) debe implementarse de acuerdo con las guías de práctica clínica vigentes para pacientes no cirróticos. (Recomendación 48, grado A, consenso, 89 % de acuerdo.)

Comentario

En principio, las indicaciones diferenciales de la nutrición oral, la NE y la NP en los pacientes cirróticos no son distintas de las recogidas en las guías de práctica clínica para los pacientes no cirróticos. Sin embargo, cabe señalar que los pacientes cirróticos suelen presentar depleción de glucógeno hepático y recurren al catabolismo proteico para la gluconeogénesis mucho antes que los pacientes no cirróticos; por ejemplo, tan pronto como después de un ayuno nocturno (véase el Capítulo 1, Recomendaciones generales). Por lo tanto, la instauración oportuna del soporte nutricional es de primordial importancia para proporcionar combustible metabólico y sustrato al anabolismo proteico.

82) En los pacientes cirróticos, la intervención nutricional (oral, NE o NP) debe recomendarse para obtener un posible beneficio clínico sin que se incrementen los efectos adversos. (Recomendación 49, grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

Como se ha comentado previamente, varios estudios de terapia nutricional en pacientes cirróticos han mostrado beneficio en los resultados clínicos, incluso en la supervivencia. Sin embargo, los recientes metaanálisis no confirman el beneficio sobre la supervivencia (81-83,228). Metodológicamente, estos metaanálisis adolecen de varios defectos, como incluir pacientes cirróticos y con esteatohepatitis alcohólica (EHA), incluir estudios con solo 3 días de tratamiento nutricional o excluir ensayos adecuados sin una razón obvia.

2.4.3.2. Sondas de nutrición enteral

83) Las varices esofágicas no son una contraindicación absoluta para la colocación de una sonda nasogástrica. (Recomendación 63, grado 0, consenso fuerte, 100 % de acuerdo.)

Comentario

En 10 pacientes con encefalopatía hepática aguda de grado I-II, la alimentación por sonda nasogástrica usando una fórmula enriquecida con AACR fue beneficiosa con respecto a la recuperación de la encefalopatía hepática, sin complicaciones por hemorragia varicosa (86). No hay evidencia en la literatura actual (85,233,258,262) que indique que las varices esofágicas representan un riesgo inaceptable para el uso de sondas de alimentación de pequeño calibre para la NE.

84) La colocación de una PEG (gastrostomía endoscópica percutánea [por sus siglas en inglés]) se asocia a un riesgo alto de complicaciones por ascitis o varices, por lo que su uso está reservado para casos excepcionales. (Recomendación 64, grado 0, consenso fuerte, 100 % de acuerdo).

Comentario

En cuanto a la colocación de una sonda de gastrostomía, la guía europea (263) establece como contraindicaciones las alteraciones graves de la coagulación (INR > 1,5, TTP > 50 s, plaquetas < 50.000/mm^3) y la ascitis severa. De acuerdo con esas guías, no se observó ningún incremento de la morbilidad cuando se colocó una PEG en presencia de ascitis leve a moderada. Sin embargo, en una serie de 26 pacientes se produjeron 2 fallecimientos como consecuencia directa de la colocación de la PEG (264). Debe tenerse en cuenta que, en la cirrosis, la hipertensión portal puede conducir a un aumento del número y el calibre de los vasos en la pared gástrica, que en caso de ser lesionados durante la colocación de la PEG pueden convertirse en causa de hemorragia significativa.

2.5. TRASPLANTE HEPÁTICO (TxH) Y CIRUGÍA (Figs. 13 y 14)

2.5.1. Fase preoperatoria

2.5.1.1. Cribado, valoración y cuidados generales

85) Los pacientes con cirrosis hepática programados para cirugía electiva o en lista de trasplante deben ser cribados y valorados oportunamente para detectar si existe desnutrictición, con el fin de tratarla antes de la cirugía y así mejorar su estado proteico. (Recomendación 66, grado B, consenso fuerte, 100 % de acuerdo.)

Comentario

En los pacientes cirróticos desnutridos, el riesgo de morbilidad y mortalidad está incrementado tras la cirugía abdominal (265,266). Numerosos estudios descriptivos han demostrado una mayor morbilidad y mortalidad en los pacientes cirróticos con desnutrición proteica cuando se someten a TxH (31,199,208-210,267-269). Recientemente, se ha demostrado que la sarcopenia y la fragilidad conllevan un mayor riesgo de morbilidad y mortalidad tanto en la lista de espera de trasplante como después del trasplante (12,13,15,16,21-24,197,216,234). Los pacientes en lista de espera están en riesgo debido a una ingesta alimentaria inadecuadamente baja, y los que consumen una dieta baja en proteínas (< 0,8 g·kg^{-1}·d^{-1}) tienen un riesgo incrementado de mortalidad en lista de espera (270).

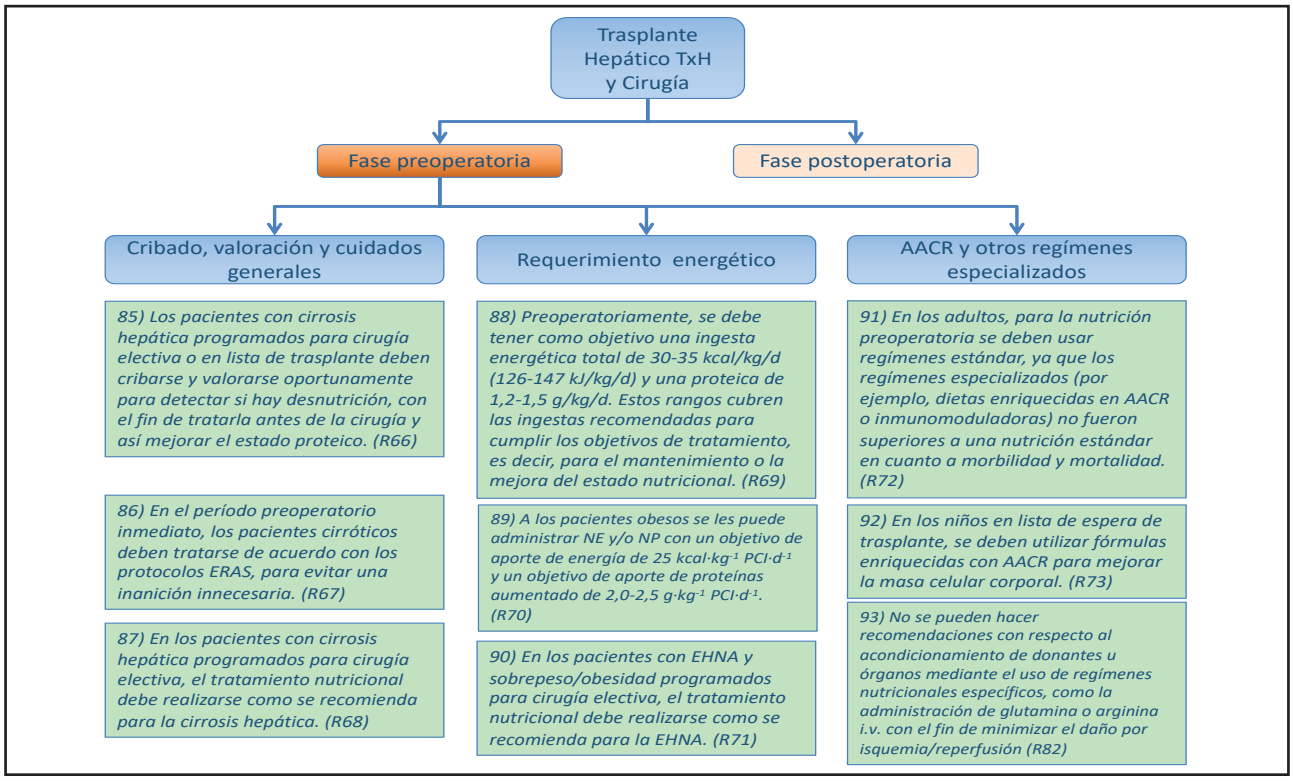

Figura 13.

Trasplante hepático (TxH) y cirugía.

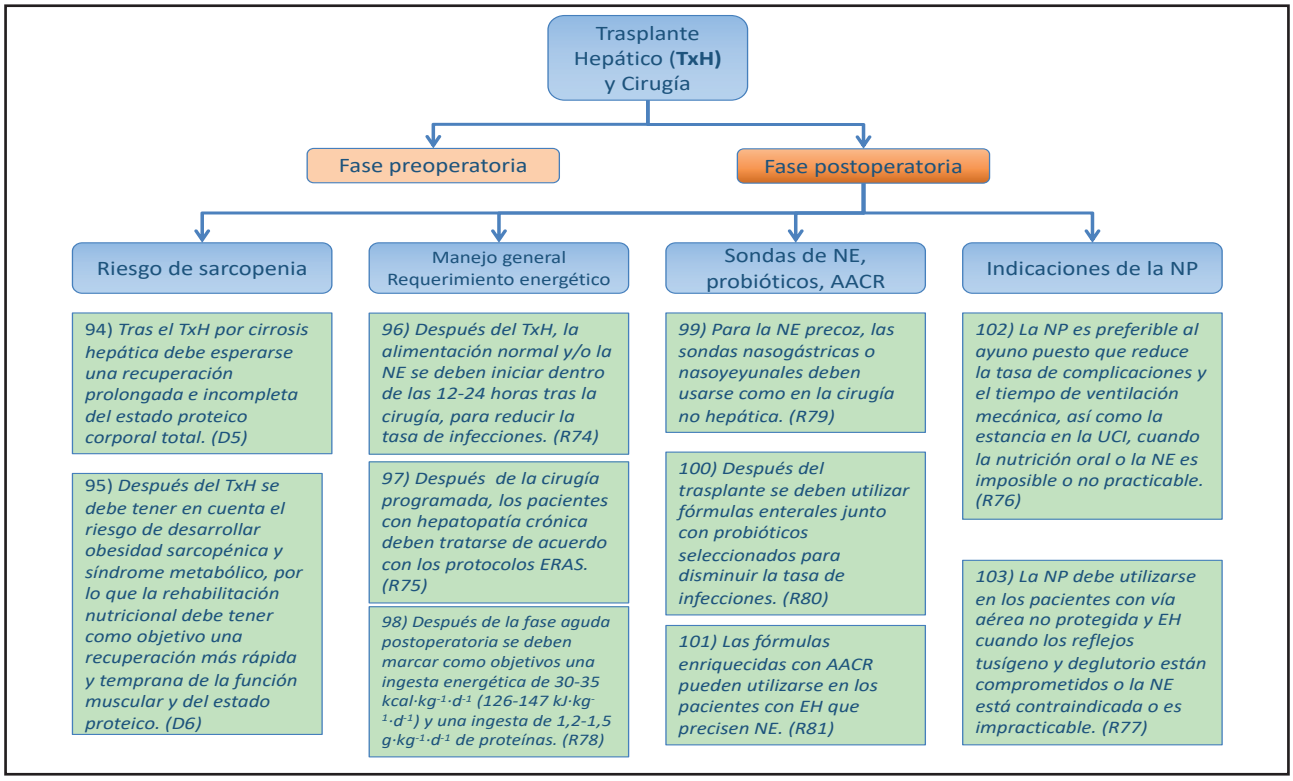

Figura 14.

Trasplante hepático (TxH) y cirugía (cont.).

Los resultados de un estudio piloto sugieren que el soporte nutricional preoperatorio mejora el estado proteico y disminuye las tasas de infección postoperatoria (271), pero no hay ensayos controlados que demuestren que la intervención nutricional mejore los resultados clínicos.

86) En el periodo preoperatorio inmediato, los pacientes con cirrosis hepática deben ser tratados de acuerdo con los protocolos ERAS, para evitar una inanición innecesaria. (Recomendación 67, grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

El glucógeno hepático está deplecionado en los pacientes con cirrosis. Por ello se recomienda acortar lo máximo posible los periodos sin ingesta de nutrientes, para evitar la neoglucogénesis a partir de proteínas musculares en individuos que basalmente ya presentan depleción proteica. En la cirugía hepática, la adopción de protocolos ERAS mejora la morbilidad y la estancia media hospitalaria cuando, entre otras medidas, los pacientes reciben carbohidratos en forma de líquidos claros hasta dos horas antes de la cirugía, así como alimentación y movilización precoz (37,272,273).

87) En los pacientes con cirrosis hepática programados para cirugía electiva, el tratamiento nutricional debe realizarse como se recomienda para la cirrosis hepática. (Recomendación 68, grado GGP, consenso fuerte, 100 % de acuerdo.)

Comentario

Los pacientes con cirrosis hepática programados para cirugía electiva deben ser tratados como pacientes cirróticos no obesos, utilizando los mismos objetivos de ingesta de energía y proteínas. Tanto la desnutrición (IMC $< 18,5$ kg·m^{-2}) como la obesidad de grado III (BMI > 40 kg·m^{-2}) antes del TxH se asocian a un incremento de las tasas de mortalidad y morbilidad (147,148).

2.5.1.2. Requerimiento energético

88) Preoperatoriamente, se debe tener como objetivo una ingesta energética total de 30-35 kcal·kg^{-1}·d^{-1} (126-147 kJ·kg-1·d^{-1}) y proteica de 1,2-1,5 g·kg-1·d^{-1}. Estos rangos cubren las ingestas recomendadas para cumplir los objetivos de tratamiento, es decir, para el mantenimiento o mejora del estado nutricional. (Recomendación 69, grado GGP, consenso fuerte, 100 % de acuerdo.)

Comentario

Véanse los comentarios de los puntos 71-73.

89) A los pacientes obesos se les puede administrar NE y/o NP con un objetivo de aporte de energía de 25 kcal·kg^{-1} PCI·d^{-1} y un objetivo de aporte de proteínas aumentado de 2,0-2,5 g·kg^{-1} PCI·d^{-1}. (Recomendación 70, grado GPP, consenso fuerte, 93 % de acuerdo.)

Comentario

La obesidad severa antes del TxH se asocia a una alta prevalencia de comorbilidades (diabetes *mellitus,* hipertensión arterial), a la cirrosis criptogénica y a un aumento de la mortalidad por complicaciones infecciosas, enfermedades cardiovasculares y cáncer (147,148). En este grupo de pacientes, la presencia y el grado de ascitis parecen aumentar con el grado de obesidad, por lo que la sustracción de la cantidad de líquido ascítico extraído puede usarse para calcular el "IMC seco". Algunos autores encontraron que la obesidad grave se asocia a mayor morbilidad y mortalidad incluso cuando los pacientes se clasifican según el "IMC seco" (147,274), mientras que otros estudios señalan que es la cantidad de ascitis la que aumenta el riesgo de mortalidad y no el IMC (147) y otros más no abordaron directamente este problema (274,148). También hay que señalar que, en la hepatopatía crónica, la obesidad es un factor de riesgo de peores resultados clínicos (217,218).

90) En los pacientes con EHNA y sobrepeso/obesidad programados para cirugía electiva, el tratamiento nutricional debe realizarse como se recomienda para la EHNA. (Recomendación 71, grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

Véase el comentario del punto 89.

2.5.1.3. AACR y otros regímenes especializados

91) En los pacientes adultos, para la nutrición preoperatoria se deben usar regímenes nutricionales estándar, ya que los regímenes especializados (como, por ejemplo, las dietas enriquecidas con AACR o inmunomoduladoras) no fueron superiores a la nutrición estándar en cuanto a morbilidad y mortalidad. (Recomendación 72, grado A, consenso fuerte, 100 % de acuerdo.)

Comentario

El consejo nutricional más el SNO y el consejo nutricional solo fueron igual de efectivos en los pacientes cirróticos en lista de espera de trasplante (225). En un ensayo clínico controlado y aleatorizado de pacientes cirróticos sometidos a trasplante, el uso de suplementos orales inmunomoduladores no aportó ninguna ventaja con respecto a los suplementos estándar dentro del soporte nutricional preoperatorio (90). Sin embargo, en un ensayo clínico controlado y aleatorizado, el uso de probióticos desde la inclusión en lista hasta el trasplante se asoció con menos infecciones, un descenso más rápido de ALT y AST, y menores niveles de bilirrubina en el postoperatorio, en comparación con los controles (275). Kaido y colaboradores mostraron en sus trabajos, aunque estos no fueron aleatorizados, que los pacientes que recibieron fórmulas de SNO enriquecidas con AACR en la fase preoperatoria presentaron menos infecciones postoperatorias (276,277). Un estudio retrospectivo concluye que los pacientes suplementados con AACR por vía oral en el preoperatorio presentaban menores tasas de bacteriemia en el postrasplante (278).

92) En los pacientes pediátricos en lista de espera de trasplante se deben utilizar fórmulas enriquecidas con AACR para mejorar la masa celular corporal. (Recomendación 73, grado B, consenso fuerte, 93 % de acuerdo.)

Comentario

Los pacientes pediátricos trasplantados, afectados predominantemente de enfermedades hepáticas colestásicas, mejoraron su masa celular corporal al recibir fórmulas enriquecidas con AACR (279).

93) No se pueden hacer recomendaciones con respecto al acondicionamiento de donantes u órganos mediante el uso de regímenes nutricionales específicos, como la administración de glutamina o arginina i.v., con el objetivo de minimizar el daño por isquemia/reperfusión. (Recomendación 82, grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

Los estudios en animales indican que una nutrición equilibrada de los donantes de hígado en muerte cerebral, usando una moderada cantidad de carbohidratos, lípidos (ácidos grasos de cadena larga y posiblemente aceite de pescado) y aminoácidos, se asocia a un mejor funcionamiento del órgano trasplantado (280). No obstante, actualmente se desconoce el impacto que puede tener el acondicionamiento de donantes u órganos con la finalidad de disminuir el daño de isquemia-reperfusión mediante la administración de altas dosis de arginina o glutamina.

2.5.2. Fase postoperatoria

2.5.2.1. Riesgo de sarcopenia

94) Tras el TxH por cirrosis hepática debe esperarse una recuperación prolongada e incompleta del estado proteico corporal total. (Declaración 5, consenso fuerte, 100 % de acuerdo.)

Comentario

Plank y colaboradores informaron de una pérdida de 1,0 kg de proteína corporal total (equivalente a 5 kg de músculo esquelético), principalmente a partir del músculo esquelético, inmediatamente después de la cirugía, y que esta pérdida no se recuperaba hasta doce meses después del TxH (281). En un estudio que empleó la medición del potasio corporal total, con seguimiento de 24 meses tras el trasplante, se observó una pérdida postoperatoria inicial que no se siguió de una recuperación de la masa celular corporal (282). Desde el punto de vista fisiológico, Selberg y colaboradores (283,284) demostraron que la captación de glucosa y la eliminación no oxidativa de glucosa por el músculo esquelético no se habían normalizado hasta doce meses después del TxH. Como era de esperar, la función de los músculos respiratorios no volvió a la normalidad hasta 12 meses después del trasplante (281).

95) Después del TxH, se debe tener en cuenta el riesgo de desarrollar obesidad sarcopénica y síndrome metabólico, por lo que la rehabilitación nutricional debe tener como objetivo una recuperación más rápida y temprana de la función muscular y del estado proteico. (Declaración 6, consenso fuerte, 100 % de acuerdo.)

Comentario

Después del trasplante, muchos pacientes desarrollan obesidad sarcopénica y síndrome metabólico. Algunos estudios mostraron un aumento de la masa grasa y persistencia de la sarcopenia y alteraciones de la eliminación de glucosa por parte del músculo esquelético. Estos hallazgos demuestran que el trasplante por sí solo no es capaz de revertir la disfunción metabólica en este grupo de pacientes (285). Los pacientes cirróticos en lista de espera de TxH presentan fatiga crónica y, dependiendo del estadio de la enfermedad, pérdida de capacidad física, empeoramiento de su calidad de vida, niveles muy bajos de actividad física (215) y pérdida progresiva de la masa muscular. En un estudio se demostró que el ejercicio estructurado durante 12 semanas mejoró los resultados del test de la caminata de 6 minutos y la calidad de vida (286). Después del trasplante, el nivel de actividad, la calidad de vida y la capacidad de ejercicio en general no se normalizan; sin embargo, los pacientes trasplantados que participaron en un protocolo estructurado de ejercicio y nutrición presentaron niveles significativamente superiores de VO_2 máxima y mejor calidad de vida (287).

2.5.2.2. Manejo general/requerimiento energético

96) Después del TxH, la alimentación normal y/o la NE se deben iniciar dentro de las 12 a 24 horas siguientes a la cirugía para reducir la tasa de infecciones. (Recomendación 74, grado B, consenso fuerte, 100 % de acuerdo.)

Comentario

El inicio precoz de la NE, incluso 12 horas después de la cirugía, se asoció a una menor tasa de infecciones que la obtenida con la ausencia de soporte nutricional (288). En una comparación directa entre la NP y la NE precoz, ambas estrategias se mostraron igualmente efectivas para mantener el estado nutricional de los pacientes (289). En el postoperatorio hay una pérdida considerable de nitrógeno y los pacientes tienen un balance nitrogenado negativo durante períodos prolongados (90,281,290), por lo que requieren un aporte alto de proteínas y aminoácidos. Se han reportado aportes de proteínas o aminoácidos de 1,2-1,5 $g \cdot kg^{-1} \cdot d^{-1}$ (290).

97) Después de la cirugía programada, los pacientes con hepatopatía crónica deben tratarse de acuerdo con los protocolos ERAS. (Recomendación 75, grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

Véanse los comentarios de los puntos 86 y 96.

98) Después de la fase aguda postoperatoria se debe marcar como objetivo una ingesta energética de 30-35 $kcal \cdot kg^{-1} \cdot d^{-1}$

(126-147 kJ·kg^{-1}·d^{-1}) y una ingesta de 1,2-1,5 g·kg^{-1}·d^{-1} de proteínas. (Recomendación 78, grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

Véanse los comentarios de los puntos 71 a 73.

2.5.2.3. Sondas de NE, probióticos, AACR

99) Para la NE precoz, las sondas nasogástricas o nasoyeyunales deben usarse como en la cirugía no hepática. (Recomendación 79, grado B, consenso fuerte, 100 % de acuerdo.)

Comentario

Los pacientes trasplantados que reciben NE precoz, doce horas después de la cirugía, desarrollan menos infecciones virales y tienen un mejor balance nitrogenado que aquellos que no reciben soporte nutricional (288). En comparación con la NP, la NE reduce las tasas de complicaciones y los costos en los pacientes trasplantados (289). Para la NE precoz de los trasplantados hepáticos adultos se han utilizado tanto fórmulas poliméricas (291-294), con y sin prebióticos y probióticos, como fórmulas peptídicas (288,295,296). Las fórmulas se administraron mediante sondas nasogástricas o nasoyeyunales (288,289,293,295) o bien mediante sonda de yeyunostomía colocada durante la cirugía (291).

100) Después del trasplante se deben utilizar fórmulas enterales junto con probióticos seleccionados para disminuir la tasa de infecciones. (Recomendación 80, grado B, consenso, 86 % de acuerdo.)

Comentario

La administración perioperatoria de una mezcla de pre y probióticos (*Lactobacillus* spp. y otras bacterias metabolizadoras de ácido láctico) dio lugar a la reducción de las complicaciones infecciosas, comparada con la administración de prebióticos (293). Un metaanálisis reciente (297) que incluía ese estudio y dos estudios aleatorizados en los que usaron un solo *Lactobacillus* sp. (292) y dos *Lactobacillus* spp. y un *Bifidobacterium* sp. (291) mostró una reducción de la tasa de infecciones en el grupo de pacientes que recibieron prebióticos y probióticos.

101) Las fórmulas enriquecidas con AACR pueden utilizarse en los pacientes con encefalopatía hepática que precisen NE. (Recomendación 81, grado 0, acuerdo mayoritario, 79 % de acuerdo.)

Comentario

Un metaanálisis reciente (241) mostró que el uso de AACR por vía oral o enteral, comparado con los controles, tiene un efecto beneficioso en los pacientes cirróticos con encefalopatía hepática. Hasta la fecha no se ha abordado en estudios bien diseñados si las fórmulas enriquecidas con AACR u otros componentes nutricionales especiales pueden prevenir la obesidad sarcopénica en los supervivientes a largo plazo de un TxH.

2.5.2.4. Indicadores de la NP

102) La NP es preferible al ayuno ya que reduce la tasa de complicaciones y el tiempo de ventilación mecánica, así como la estancia en la UCI, cuando la nutrición oral o la NE es imposible o impracticable. (Recomendación 76, grado B, consenso, 86 % de acuerdo.)

Comentario

Después del trasplante, la NP postoperatoria es superior a la infusión de fluidos y electrolitos en materia de reducción del tiempo de ventilación mecánica y estancia en la UCI (298). Después de la cirugía abdominal (no del trasplante), los pacientes cirróticos tienen una menor tasa de complicaciones y un mejor balance nitrogenado si reciben soporte nutricional en lugar de solo fluidos y electrolitos (299,300). La NE (vía yeyunostomía) se ha asociado con un mejor balance del nitrógeno a los 7 días, comparada con la NP/NE secuencial (300).

103) La NP debe utilizarse en los pacientes con vía aérea no protegida y encefalopatía hepática cuando los reflejos tusígeno y deglutorio están comprometidos o bien la NE está contraindicada o es impracticable. (Recomendación 77, grado GPP, consenso fuerte, 100 % de acuerdo.)

Comentario

Véase el comentario del punto 39.

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Nutritional imbalances in a Mexican vegan group: urgent need for country-specific dietary guidelines

Desequilibrios nutricionales en un grupo mexicano de veganos: necesidad de guías alimentarias para cada país

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Abstract

Introduction: vegan diets exclude the consumption of animal-derived products, and health advantages have been reported when followed. However, heterogeneous eating habits, food availability, and sociocultural characteristics among regions could lead to different physiological results.

Case reports: twelve patients following a strict vegan diet for an uninterrupted period of ≥ 3 years were subjected to clinical assessment. Patients significantly exceeded the suggested intake for sugar, presented six mineral deficiencies, and exhibited three vitamins below the recommended consumption. We further identified hyperglycemia, hypertriglyceridemia, subnormal serum vitamin B_{12} concentrations, as well as macrocytosis and microcytic anemia in several participants.

Discussion: this Mexican vegan diet is strongly influenced by endemic and cultural adaptations that could limit the benefits reported in other populations. Professional guidance is required to avoid specific deficiencies with potential repercussions. We urge country-specific vegan guidelines considering local eating habits, food availability, and sociocultural perspectives around food.

Keywords:

Vitamin B_{12} deficiency. Veganism. Vegan diet. Nutrition status. Health status disparities.

Resumen

Introducción: la dieta vegana excluye el consumo de productos de origen animal y se ha vinculado con una disminución del riesgo de morbimortalidad. Sin embargo, los distintos hábitos alimentarios entre países podrían condicionar los beneficios reportados para las dietas basadas en vegetales.

Casos clínicos: doce pacientes siguiendo una estricta dieta vegana por ≥ 3 años se sometieron a una evaluación clínica. Exhibieron una ingestión de azúcar que supera el consumo sugerido, presentaron tres deficiencias vitamínicas y seis de minerales. Se identificó la presencia de hiperglucemia, hipertrigliceridemia, concentraciones séricas subnormales de vitamina B_{12}, macrocitosis y anemia microcítica en varios participantes.

Discusión: la dieta vegana de este grupo resultó fuertemente influenciada por adaptaciones culturales que podrían limitar los beneficios reportados en otras poblaciones. Se requiere orientación profesional para evitar desequilibrios nutricionales. Enfatizamos la necesidad del desarrollo de guías alimentarias y de práctica clínica que consideren los hábitos alimentarios locales, la disponibilidad de alimentos en la región y las perspectivas socioculturales en torno a la dieta vegana.

Palabras clave:

Deficiencia de vitamina B_{12}. Veganismo. Dieta vegana. Estado nutricio. Disparidades en el estado de salud.

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INTRODUCTION

Vegan diets exclude animal product consumption. An appropriately planned plant-based diet is nutritionally adequate and provides health benefits for preventing several metabolic diseases and cancer — reducing premature mortality (1). Evidence also suggests potential nutrient deficiencies, especially vitamin B_{12}, vitamin D, iron, iodine, calcium, zinc, and omega-3 polyunsaturated fatty acids (2).

Notably, contrasting eating habits, diverse food availability, and inequivalent sociocultural characteristics around vegan diets across countries may lead to different metabolic outcomes. The Mexican diet differs from other regions of the world, and consequently, different physiological results may be expected when following a plant-based diet due to local and cultural adaptations (3).

To our knowledge, the Mexican population following a vegan diet had not been described, and country-specific guidelines do not exist. Therefore, providing a comprehensive clinical and nutritional diagnosis in a group of patients following a vegan diet for an extended period is relevant to health providers making dietary recommendations and can be used for evidence-based dietary guidelines in Mexico.

METHODS

DESCRIPTION OF PARTICIPANTS

Twelve patients from a local vegan-vegetarian community attended the Universidad Marista de Mérida (Mexico) for medical and nutritional assessment. The group was integrated by nine females and three males following a strict vegan diet for an uninterrupted period of ≥ 3 years.

A first interview verified that patients' physical activity did not reach intensities prescribed for therapeutic purposes, discard the presence of pre-existent chronic diseases or alcoholism, and confirmed the absence of pregnancy or lactation among women. We further verified that patients were not active users of medications — particularly absorption-inhibition or modifiers of micronutrients or glucose metabolism drugs.

All patients provided written informed consent allowing clinical information dissemination. The present case report received approval from the Ethics Committee from the Marist University of Merida (CE_UMM002A_2017), according to the Secretary of Health of Mexico (NOM-012-SSA3-2012). Anthropometric, dietary, and biochemical parameters were evaluated as health indicators.

ANTHROPOMETRIC ASSESSMENT

Participants were evaluated after eight hours of fasting, liquid intake and exercise avoidance for twelve hours, and an empty bladder. We also provided standardized clothing (light clothing, consistently weighing 1 kg, without metal pieces). A previously calibrated Tanita BC-418 Segmental Body Composition Analyzer® scale was used following the protocol proposed by Khalil and colleagues (4). For height determination, the International Society for the Advancement of Kinanthropometry methods were followed, using a SECA stadiometer (model 700). Body composition was further assessed through an octopolar multifrequency segmented bioelectric impedance analysis (BIA) (Tanita BC 418).

DIETARY EVALUATION

A Semi-Quantitative Food Frequency Questionnaire previously validated in the Mexican population (5) was used to estimate monthly eating patterns and ensure total exclusion, consciously and unconsciously, of animal-derived products. Daily nutrients intake was calculated through The Food Processor Software® (ESHA research) Version 10.15.41 and compared with the nutritional reference values for the Mexican population (6). Information about healthcare professional aid regarding diet planning or supplementation habits and other health-related behaviors were also registered.

BIOCHEMICAL EXAMINATION

Fifteen milliliters of total blood were collected in three SSP and EDTA tubes (BD Vacutainer®) for their immediate analysis. A complete blood count was obtained after performing fluorescent flow cytometry and hydrodynamic focusing. We used a 5-part Sysmex equipment® (model XS-1000i) previously calibrated (Sysmex calibrator® and Liquicheck hematology-16 trilevel, Cat: 760 Biorad®, as third opinion quality control material). Sulfolyzer, Stromatolyser 4-DL, Cell Pack, and Stromatolyser 4-DS were used as reagents (Sysmex®). Cut-off points to identify abnormalities were those established by the World Health Organization for populations located below 1000 meters' sea level.

A high-performance liquid chromatography (HPLC) was performed to evaluate glycated hemoglobin (Hb_{A1c}). Biorad® equipment (model D10) previously calibrated (internal calibrator Biorad® with Lyphocheck diabetes control bi-level, Cat.740 as quality control material) was used with D-10 Hemoglobin A1C, Ref: 2200101 as reagent (Biorad®). A threshold of 5.7 % was considered to identify normal glycemia for persons without glucose intolerance.

The serum concentration of vitamin B_{12} was further quantified through high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) detector methodology according to the American Chemical Society. A level of < 200 pg/mL (148 pmol/L) was considered as threshold for vitamin deficiency.

Serum creatinine was measured through spectrophotometry. Abbott® equipment (model Architect c4000) previously calibrated (Clin Chem Cal Abbott® calibrator REF: 6K30-10, Cat.740 and Lyphocheck Assayed Chemistry Cat. C-315-5 and C-310-5 Biorad® as third opinion quality control material) was used with

Creatinine REF: 8L24-31 as reagent (Abbott®). Values between 0.50 and 1.40 mg/dL were considered as an optimal criterion.

For analytic purposes, the group's nutrient daily intake was compared in the Dietary Reference Intake (DRI) for the Mexican Population through a two-tailed hypothesis test using an alpha value of 0.05. The association between dietary intake and serum concentrations of vitamin B_{12} was assessed with a Pearson's correlation coefficient. According to distribution, data is presented as means ± SD and medians (IQR). Results were generated using the Statgraphics Centurion® software version XVII and Graph Pad Prism® version 8.

RESULTS

Twelve Mexican adults (three males and nine females), consumers of a vegan diet for over three years, completed all anthropometric, dietetic, and biochemical evaluations as proxy measurements of their current health status.

Patient mean age was 29 ± 9 years and body mass index (BMI) was 22.5 ± 3.6 kg/m^2. The complete and segmental composition analysis derived from the bioelectrical impedance assessment is presented in figure 1. No abnormalities were identified in the body composition examination.

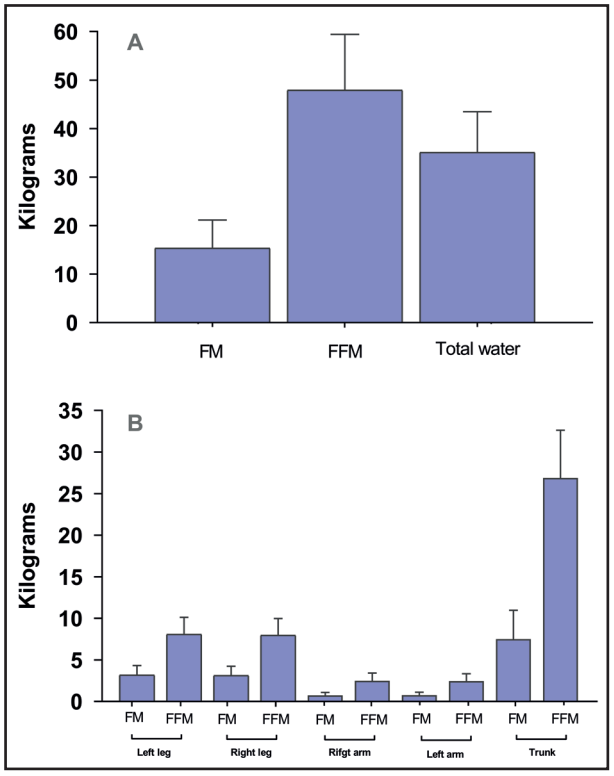

Figure 1.

Bioelectrical impedance analysis among Mexican vegans (A. Complete body composition assessment. B. Segmental body composition assessment. Data are presented as means and standard deviations. FM: fat mass; FFM: fat-free mass).

Energy and nutrients daily intake are presented in table I. Patients significantly exceed the recommended intake for refined sugars, and two patients exhibited Hb_{A1c} levels above the 5.7 % recommended threshold, and other three presented hypertriglyceridemia.

Table I. Daily energy and nutrient intake (diet and supplements) in patients following a vegan diet (≥ 3 years) compared to reference values for the Mexican population[1]

Dietary assessment		Vegans (n = 12)	Ideal criteria	*p*-value[2]
Energy (kcal)[3]		1,717.5 ± 641.4	1,823	0.580
Kilocalories from fat		545.4 ± 169.7	547	0.977
Kilocalories from SF		137.9 ± 59.5	< 128	0.287
Fat (g)[4]		61.2 ± 19.0	61	0.969
Protein (g)[5]		43.3 ± 12.6	48.6	0.172
Carbohydrates (g)[6]		250.8 ± 104.0	251	0.992
Dietary fiber (g)		34.3 ± 9.3	30	0.138
Soluble fiber (g)		5.8 ± 2.0	-	-
Total sugars (g)[7]		93.2 ± 32.3	< 22	*< 0.001*
Monosaccharides (g)		28.1 ± 11.5	-	-
Disaccharides (g)		17.8 ± 5.8	-	-
Other carbohydrates (g)		57.7 (44.2)	-	-
Retinol (IU)	Vit. A	9,190.5 ± 4,014.5	1,893.3	*< 0.001*
Thiamine (mg)	Vit. B_1	1.4 ± 0.7	0.8	*0.013*
Riboflavin (mg)	Vit. B_2	1.2 ± 0.5	0.84	*0.030*
Niacin (mg)	Vit. B_3	12.6 ± 4.1	11	0.204
Pantothenic acid (mg)	Vit. B_5	3.2 ± 0.83	4.0	*0.007*
Pyridoxine (mg)	Vit. B_6	1.3 (0.8)	0.93	0.138
Folic acid (µg)	Vit. B_9	767.4 ± 294.4	380	*< 0.001*

(Continues on next page)

Table I (Cont.). Daily energy and nutrient intake (diet and supplements) in patients following a vegan diet (≥ 3 years) compared to reference values for the Mexican population[1]

Dietary assessment		Vegans (n = 12)	Ideal criteria	*p*-value[2]
Cobalamin (mg)	Vit.B_{12}	0.05 (0.04)	2.1	*< 0.001*
Biotin (µg)		24.7 ± 9.3	30	0.075
Ascorbic acid (mg)	Vit. C	214.9 ± 75.2	60	*< 0.001*
Calciferol (µg)	Vit. D	0.04 (0.09)	10	*< 0.001*
Tocopherol (mg)	Vit. E	12.8 ± 3.9	11	0.138
Menadiol (mg)	Vit. K	258.7 ± 163.0	78	*0.003*
Calcium (mg)		377 (250)	900	*< 0.001*
Chromium (µg)		3.2 ± 1.2	22	*< 0.001*
Copper (mg)		1.4 ± 0.4	0.65	*< 0.001*
Fluoride (mg)		0.02 (0.04)	2.2	*< 0.001*
Iodine (µg)		15.7 ± 6.4	150	*< 0.001*
Iron (mg)		21.8 ± 11.8	17	0.186
Magnesium (mg)		358 (205)	248	0.090
Manganese (mg)		4.3 (1.8)	1.8	*< 0.001*
Molybdenum (µg)		86.9 ± 24.4	45	*< 0.001*
Phosphorus (mg)		755.6 (451)	664	0.499
Potassium (mg)		3,043.8 ± 832.3	3,400	*< 0.001*
Selenium (µg)		44.2 ± 20.8	41	0.607
Sodium (mg)		2,259.3 ± 1,562.4	< 2,500	0.999
Zinc (mg)		7.3 (2.7)	10	*0.005*

[1]Data presented in means ± SD or medians (IQR) according to distribution. [2]Obtained using hypothesis tests. [3]Ideal caloric intakes established according to national recommendations at 30 kcal/kg. [4]Ideal fat consumption established at 30 % of total ideal caloric intake. [5]Ideal protein intakes considered to be 0.8 g/kg. [6]Ideal carbohydrate consumption established at 55 % of total ideal caloric intake. [7]Ideal sugar consumption considered to be < 5 % of total caloric intake. Vit.: vitamin.

Only two patients declared receiving professional dietetic guidance and evidence-based supplementation. According to the DRI, vegan-diet consumers presented six mineral deficiencies (calcium, chromium, fluoride, iodine, potassium, and zinc), and three of vitamins (pantothenic acid, cobalamin, and calciferol).

Hematological examination (Table II) confirmed subnormal serum vitamin B_{12} concentrations (≤ 200 pg/mL, 148 pmol/L) in eight patients. Macrocytosis (mean corpuscular volume > 97 fL) and microcytosis (mean corpuscular volume < 97 fL) were identified in two and four vegan participants, respectively. Additionally, two vegan females were diagnosed with microcytic anemia (< 12 g/dL in women).

NUTRITIONAL DIAGNOSIS

– Disproportionate refined carbohydrates consumption, related to an unbalanced food selection and insufficient nutritional-related knowledge, evidenced by sugar intake as high as 93.2 ± 32.3 g/day, surpassing the recommended dietary intake for this macronutrient.

Table II. Biomarkers in Mexican patients following a vegan diet (≥ 3 years), compared to the ideal criteria[1]

Serum biomarkers	Vegans (n = 12)	Ideal criteria
Hb (g/dL)	13.4 ± 1.7	> 13
Hct (%)	40.0 ± 4.1	35-42
MCV (fL)	89.3 ± 7.3	84.0-96.0
MCH (pg)	31.0 (3.7)	27.0-33.0
MCHC (%)	34.0 (1.0)	32.0-35.0
Erythrocytes (cell/mm^3)	4,496,667 ± 488,826	3,600,000-5,100,000
Total cholesterol (mg/dL)	154.1 ± 36.2	< 200
LDL-cholesterol (mg/dL)	81.4 ± 30.7	< 100
HDL-cholesterol (mg/dL)	51.9 ± 10.9	> 45
Triglycerides (mg/dL)	102.7 ± 46.4	< 150
Hb_{A1c} (%)	5.2 ± 0.4	< 5.7
Vit. B_{12} (pg/dL)	205.5 ± 153.4	> 200
Creatinine (mg/dL)	0.79 ± 0.13	0.5-1.40

[1]Data presented as means ± SD or medians (IQR) according to their distribution. Vit.: vitamin. International System of Units conversions: 1 g/dL of Hb is equivalent to 0.62 mmol/L; 1 pg of MCH is equivalent to 0.062 fmol; 1 pg/mL of vitamin B_{12} is equivalent to 0.74 pmol/L; 1 mg/dL of creatinine is equivalent to 88.4 µmol/L.

– Inadequate oral intake of vitamin B_{12} associated with deficient evidence-based supplementation and insufficient professional guidance, evidenced by subnormal cobalamin levels in plasma and microcytosis.
– Insufficient consumption of highly bioavailable iron food sources, associated with the exclusive incorporation of dietary non-heme iron and the lack of adequate supplementation, evidenced by microcytic anemia.

TREATMENT

We provided individualized dietary guidance according to each patients' age, sex, physiologic status, and clinical situation. First, we designed an appropriately planned vegan diet for each patient and provided comprehensive nutritional information, emphasizing balanced food group selection.

Evidence-based supplementation schemes for vitamin B_{12} were recommended (sublingual, intramuscular, or oral dosage, together with regular consumption of fortified foods). We also prescribed iron supplementation for women of reproductive age undergoing anemia and for those declaring menorrhagia.

For the subsequent semester, monthly medical and nutritional counseling was recommended to evaluate patients' progress. However, as this pilot study was initially designed as a transversal assessment, the collection of prospective data on biochemical parameters was contemplated within our research purposes.

DISCUSSION

This clinical case report provides an overall health depiction of Mexican patients following a vegan diet.

As anticipated, dietary protein does not differ significantly from DRI. Due to regular consumption of legumes typically included in plant-based diets, vegans meet or exceed the recommended protein consumption (2). These results may explain the adequate proportion of fat-free mass identified through BIA, and we hypothesized no negative impact on body composition associated with protein consumption. Supporting our findings, Nadimi and colleagues (7) did not identify variations in fat-free mass among vegan participants. On the contrary, the large body of evidence indicates that plant-based diet consumers display a lower prevalence of overweight and obesity, and present less abdominal and body fat. Furthermore, adequate protein consumption may explain the acceptable creatinine concentrations found among these participants. However, further research is needed to expand on its possible health benefits — such as the improvement in renal function (8).

Two vegans exhibited glycemic concentrations surpassing 5.7 %, possibly attributed to excessive carbohydrate daily consumption. Other studies have also found a disproportionate intake of refined carbohydrates to replace meat, generating metabolic alterations (3).

Nevertheless, vegans also displayed adequate low-digestible carbohydrate and fiber intakes. These results may implicate positive microbiota modulations: a recent review concluded that vegans' gut profile presented a reduced abundance of pathobionts and a greater abundance of protective species (9). Possible health benefits related to fiber intake may be assumed in favor of this plant-based diet group. Further research will benefit from exploring this topic in this specific population.

Only two patients declared professional dietetic guidance and evidence-based supplementation. Our findings on vitamins deficiencies could predispose patients to a higher risk of peripheral neuropathy, glossitis, or seborrheic dermatitis related to pyridoxine deficiency; megaloblastic anemia, hyperuricemia, hyperhomocysteinemia, or subacute combined degeneration of spinal cord associated with cobalamin deficiency. Notably, macrocytosis (mean corpuscular volume > 97 fL) and microcytosis (mean corpuscular volume < 97 fL) were identified in two and four vegan participants, respectively.

Additionally, females were diagnosed with microcytic anemia (< 12 g/dL in women). We could address non-heme iron intake and menstruation's cyclic blood loss as possible etiology. These may also indicate that adult vegan females present a higher risk of developing hematologic repercussions, and closer medical-nutritional counseling in this potentially vulnerable group may be addressed. Other studies have also shown that vegetarians have a high prevalence of iron depletion — addressing the importance of premenopausal vegetarian women's iron status (10).

Participants displayed an estimated vitamin D and calcium daily intake of 0.04 mcg and 377 mg, respectively. Notably, the recommended daily Vitamin D intake is 10 micrograms for people < 70 years old. As for calcium, the recommended intake is 1200 mg for Mexican postmenopausal women and 900 mg for other adults (6).

Chronic and sustained low dietary intake of vitamin D might predispose vegans to osteoporosis and fractures at later stages of life (11). Inadequate calcium intake predisposes to hypertensive disorders.

Given the increased prevalence of veganism among the pediatric population (12), further research may be warranted to expand the role of both calcium and vitamin D in vegan children. Inadequate calcium and vitamin D intake has been associated with stunting growth (13).

Despite these seemingly adverse health outcomes, other studies suggest a lower incidence of chronic diseases in vegans. These results could partially be attributed to a favorable impact of the dietary fatty acid composition. Espinosa-Marrón and colleagues reported decreased pro-inflammatory serum fatty acids suggestive of protective vascular effect on Mexican individuals with a vegan diet (14). Additionally, regular physical activity, stress management through meditation techniques, avoidance of alcohol and tobacco, and other healthy behaviors that characterize the vegan diet in other countries are fundamental to producing positive results. However, we did not entirely identify those health-related behaviors in our participants.

DIRECTIONS FOR FUTURE RESEARCH

We strongly encourage research emphasizing plant-based diets in Mexico. This case report provides a basis on the relationship between a local Mexican vegan diet and its health implications due to insufficient professional guidance and the lack of country-specific dietary recommendations. Our results coincide partially with what has been reported in the international literature and reinforce the hypothesis that an unbalanced vegan diet implies potential nutrients deficiencies, especially vitamin B_{12}. Future research may explore homocysteine, holotranscobalamin, and methyl-malonic acid as additional biochemical screening addressing cobalamin deficiency in this vegan community.

Even in the context of a case report, we recognize that our reduced sample size with unequal male and female participants limits generalizability. Nevertheless, including twelve participants is considered appropriate for pilot studies based on the feasibility and precision around the estimates that can serve future studies (15). Furthermore, our anthropometric, dietetic, and biochemical findings, together with our holistic interpretation in this unexplored population, are relevant to the international literature and provide valuable information for health providers.

We also acknowledge that the dietary tool used to collect data was validated in Mexico but not specifically designed for a self-defined vegan population. To our knowledge, there is no such Food Frequency Questionnaire published in the Mexican literature — which emphasizes the need for developing country-specific research regarding plant-based diets.

URGENT NEED FOR COUNTRY-SPECIFIC DIETARY GUIDELINES

We present an extensive description of the nutritional content of a Mexican vegan diet that is strongly influenced by endemic and cultural adaptations. As noted, these adaptations could limit the benefits reported in other latitudes, and clinical and nutritional guidance is required to avoid specific deficiencies with potential health repercussions.

Given the diversity between countries, the well-developed European and American guidelines for vegans are not entirely suitable for other regions. Developing country-specific guidelines will help provide correct information on appropriate diet planning.

Based on our results, we suggest that Mexican guidelines should contemplate the following key points:

1. Include an extensive description of the role of evidence-based vitamin B_{12} and D supplementation.
2. Promote constant monitoring of blood iron levels and hematological profile, recommend iron food sources, and describe supplementation schemes when needed.
3. Promote adequate food selection and combination:
   – Depict iron absorption enhancers (vitamin C) and absorption-inhibitors (i.e., calcium, phytates, oxalates).
   – Improve carbohydrates' quality and quantity selection and preventive assessments for hypertriglyceridemia and glucose intolerance.
4. Recommend locally available vegetable oils to support plant-based fat sources (i.e., avocado, chia seeds, flaxseeds), as conventional recommendations for vegetable oils that are not widely available in Mexican cuisine (olive oil, nuts, walnuts, hemp seeds, among others).

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Carta al Director

GEN DEL NEUROPÉPTIDO Y (NPY), RESPUESTA A LA DIETA E ÍNDICE DE MASA CORPORAL

Sr. Editor:

Primo y cols. (1) han reportado una asociación estadística entre el alelo A del SNP rs16147, ubicado en la región promotora del gen del neuropéptido Y, y una alta respuesta metabólica a la dieta mediterránea, de acuerdo con los niveles de resistencia a la insulina y la insulina basal. Este estudio se realizó con 363 voluntarios "caucásicos". Por otra parte, existe asociación de ese mismo alelo con al aumento del IMC en niños (2,3).

Considerando que la muestra estudiada –de aquí en adelante, muestra "estudio"– comprende individuos obesos, hemos comparado las frecuencias alélicas y genotípicas reportadas con las disponibles para la población ibérica de España –de aquí en adelante "IBS"– en la base de datos 1000Genomes (1KG; www.internationalgenome.org) (4) (Tabla I).

Tabla I. Frecuencias alélicas y genotípicas de rs16147 en diversas poblaciones

Muestra	Frecuencias genotípicas observadas				fG	fA	Prueba H-W	
	GG	GA	AA	GA + AA			Chi^2	P_{chi}^2
Estudio	85	192	86	278	362	364	1,215	0,270
	(0,23)	(0,53)	(0,24)	(0,77)	(0,50)	(0,50)		
IBS	15	58	34	92	88	126	1,526	0,217
	(0,14)	(0,54)	(0,32)	(0,86)	(0,41)	(0,59)		
Primo + IBS	100	250	120	370	450	490	2,032	0,154
	(0,21)	(0,53)	(0,26)	(0,79)	(0,48)	(0,52)		
AFR	92	296	273	569	480	842	0,668	0,414
	(0,14)	(0,45)	(0,41)	(0,86)	(0,36)	(0,64)		
EAS	203	240	61	301	646	362	0,599	0,438
	(0,40)	(0,48)	(0,12)	(0,6)	(0,64)	(0,36)		
SAS	121	248	120	368	490	488	0,1	0,751
	(0,25)	(0,51)	(0,25)	(0,76)	(0,5)	(0,5)		
EUR	131	248	124	372	510	496	0,095	0,758
	(0,26)	(0,49)	(0,25)	(0,74)	(0,51)	(0,49)		
AMR	164	135	48	183	463	231	5,337	*0,0208*
	(0,47)	(0,39)	(0,14)	(0,53)	(0,67)	(0,33)		
1KG	711	1167	626	1793	2589	2419	11,179	*0,0008*
	(0,28)	(0,47)	(0,25)	(0,72)	(0,52)	(0,48)		

Estudio: muestra de Primo y cols. (1); IBS: población ibérica de España; AFR: población africana; EAS: población del este de Asia; SAS: población del sur de Asia; EUR: población de Europa; AMR: población mestiza de América; 1KG: muestra total del proyecto 1000Genomes; H-W: prueba de equilibrio de Hardy-Weinberg.

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

Mientras en la muestra "estudio" el alelo A tuvo una frecuencia del 50 % (364 de 726 cromosomas), en "IBS" esta fue del 59 % (126 de 214 cromosomas). Al usar las frecuencias alélicas para predecir el número de alelos A, la prueba exacta de Fisher rechaza la hipótesis de nulidad (p = 0,0291), es decir, el número de alelos A en "IBS" es significativamente mayor que en "estudio". Al comparar las frecuencias genotípicas agrupadas (GG y GA + AA), las diferencias son también significativas entre ambos grupos (P_{Fisher} = 0,0433); mientras que la frecuencia de GA + AA es del 86 % en "IBS", alcanza a un 77 % en la muestra "estudio".

En dos recientes artículos, los genotipos GA y AA estarían asociados a un mayor IMC (5,6), contrariamente a los resultados aquí mostrados, lo que refuerza la interrogante acerca de estos genotipos, por una parte asociados a una buena respuesta a la dieta mediterránea y, por otra, con evidencia contradictoria acerca de su efecto sobre el IMC (1,7,8). Se han reportado análisis de asociación de rs16147 con decenas de fenotipos de relevancia clínica (www.ncbi.nlm.nih.gov/snp/rs16147) (9). Parece ser que la asociación entre el neuropéptido Y y la obesidad está mediada por diversos factores, como la edad y el sexo (2,3), y con otras variables confundentes como el nivel de estrés (10). Para lograr identificar el papel de rs16147 en la determinación de la obesidad, sugerimos realizar un análisis multivariado que integre estas y otras variables, y lo mismo para el estudio de su efecto sobre las dietas.

Finalmente, hemos sistematizado la información disponible para los genotipos de rs16147 en diversas poblaciones (Tabla I), incorporando una prueba de Hardy-Weinberg. Nuestros resultados indican que, a nivel mundial, este marcador se encuentra fuera del equilibrio, al igual que en la población americana. Esto se debería al efecto de uno o más factores evolutivos, siendo el más plausible la ausencia de panmixia, es decir, de estructuración genética de las poblaciones a lo largo de su historia. Esta información podría ser de relevancia para posteriores estudios del papel del neuropéptido Y y, más específicamente, sobre la respuesta a las dietas –como las analizadas en el artículo de Primo y cols. (1)– y su efecto en la obesidad.

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Carta al Director

MEDIACIÓN PARENTAL COMO MODULADOR DEL NIVEL DE ACTIVIDAD FÍSICA, EL COMPORTAMIENTO SEDENTARIO Y EL SUEÑO EN LA PRIMERA INFANCIA

Sr. Editor:

Recientemente leímos el trabajo denominado "Nivel de actividad física, comportamiento sedentario y sueño en la población de la primera infancia" (1). El propósito de la investigación fue determinar el cumplimiento de las recomendaciones de actividad física, comportamiento sedentario y sueño según los días de la semana, el sexo y la edad de los niños (as) entre 2 a 5 años. Las investigadores utilizaron un diseño de investigación transversal analítico, donde incluyeron a 361 niños y niñas en edad preescolar. Para llevar a cabo el trabajo de investigación, utilizaron el Cuestionario para la Medición de Actividad Física y Comportamiento Sedentario en niños Preescolar a Cuarto Grado (C-MAFYCS), el cual evalúa los siguientes comportamientos: actividad física, comportamiento sedentario y sueño.

Es fundamental plasmar, que las investigadoras mediante el análisis realizado en su muestra, nos están alertando sobre cambios conductuales que se generaron los días sábados y domingos (fin de semana), convergiendo en un tiempo dedicado a la práctica de actividad física total de 178,6 ± 144 minutos. En relación al comportamiento sedentario, el cual involucra los siguientes aspectos: Tiempo sentado dedicado a la lectura; Tiempo frente a la televisión; Tiempo frente a computadores; Tiempo frente a videojuegos; Tiempo sentado en cursos extracurriculares; Tiempo sentado en transporte motorizado y Comportamiento sedentario total.

No deja de llamar nuestra atención los resultados encontrados en los siguientes ítems:

Comportamiento sedentario frente a un televisor, el cual presenta un promedio de 70,7 ± 69,4 minutos; Tiempo frente a videojuegos 47,5 ± 27,5 minutos y el tiempo que pasan frente a un computador 42,5 ± 30,8 minutos. Si se consideran todos los puntos evaluados en el ítem "Comportamiento sedentario", arroja un total de 74,8 ± 79,6 minutos. En el ítem Tiempo de sueño, la muestra presentó un total de 10,2 ± 0,9 horas. Una vez plasmados los resultados del trabajo citado previamente, y con el propósito de ampliar la información en lo que respecta al nivel de actividad física, el comportamiento sedentario y la calidad del sueño en los preescolares, es que nos gustaría exponer algunos comentarios para contribuir al debate científico en esta área.

Según la conclusión de las autoras, los preescolares que fueron estudiados no lograron los 180 min/sem recomendados por las guías canadienses y la Organización Mundial de la Salud (OMS) (1). En base a esto, la literatura científica indica que la interacción entre padres e hijos es un método eficaz para reducir la conducta de externalización en los niños, presentando una diferencia de medias (DM) -0,87; intervalo de confianza 95 % (IC 95 %) -13,64 a -6,09. Por tanto, se sugiere que un modelo de mediación parental de orientación educativa, psicosocial y de estilos de crianza podría reducir el comportamiento sedentario relacionado con la dependencia digital y la adquisición de estilos de vida saludables como el aumento de los niveles de actividad física y del tiempo dedicado al sueño (2-4). En este sentido, reportes recientes han mostrado que el uso de ciertas plataformas de tipo *streaming* (YouTube, Instagram y Facebook), aplicaciones (app) y videojuegos de realidad aumentada (Xbox, Kinetics, Zwift, FullGaz y Rouvy) pueden ser herramientas útiles para la promoción de estilos de vida saludable en los preescolares (5,6).

Antes de finalizar, queremos felicitar a las autoras del trabajo "Nivel de actividad física, comportamiento sedentario y sueño en la población de la primera infancia" (1) quienes han logrado plasmar de muy buena forma la conducta sedentaria que involucra el tiempo que pasan los preescolares frente a la televisión, computadores, videojuegos y su vez, dejar de manifiesto que los preescolares estudiados no están realizando los 180 min/sem recomendados por las guías canadienses y la OMS, lo que puede converger en retrasos en el desarrollo motor grueso, entre otros problemas que puede conllevar el sedentarismo.

Conflictos de intereses: los autores declaran no tener conflictos de intereses.

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Carta al Director

SUPLEMENTACIÓN CON VITAMINA D: ¿ES SEGURA Y EFICAZ PARA EL TRATAMIENTO DE LA COVID-19?

Sr. Editor:

Leímos con interés el artículo titulado "Vitamina D y su importancia en la infección por SARS-CoV-2" (1), que a partir de un análisis realizado al trabajo denominado "Interaction between age and vitamin D deficiency in severe COVID-19 infection" (2), nos alerta sobre la importancia de la vitamina D como posible factor de riesgo y pronóstico para la COVID-19. No obstante, sobre la base de la revisión bibliográfica realizada por el autor, nos parece interesante intentar responder a la interrogante final plasmada en su escrito, referente a la seguridad y eficacia de los suplementos de vitamina D para el manejo de pacientes con COVID-19.

Para responder a esta interrogante realizamos una búsqueda de información en la base de datos Medline/PubMed a partir del tercer eslabón del sistema 6S de Haynes (3), de modo tal que ingresamos la estrategia de búsqueda "pandemic" AND "Coronavirus" OR "COVID-19" AND "vitamin D" junto a los filtros "Sistematic Review" y "Meta-Analysis", logrando identificar 52 trabajos, de los que 3 revisiones sistemáticas con metaanálisis de estudios clínicos aleatorizados (ECA) y cruzados *(cross-over)* lograron responder a esta interrogante (4-6) (Tabla I).

La tabla I muestra que el uso de la vitamina D parece tener un papel potencial sobre el tratamiento de la COVID-19 dependiendo de la dosis utilizada, los niveles de vitamina D basales y la evolución del cuadro clínico; sin embargo, la seguridad y eficacia de esta vitamina es incierta, producto de inconsistencias sobre la notificación de eventos adversos por lo que las decisiones clínicas deben interpretarse con precaución, producto de las limitaciones metodológicas observadas en los metaanálisis reportados.

Tabla I. Resumen de las revisiones sistemáticas con metaanálisis

Autor principal	Objetivo	Conclusión
da Rocha	Evaluar si la suplementación con vitamina D es segura y eficaz para el tratamiento de la COVID-19	El uso de vitamina D más atención estándar parece proporcionar beneficios a los pacientes con COVID-19. Sin embargo, el uso para el tratamiento de la COVID-19 parece depender de la dosis, los niveles basales de vitamina D y el grado de gravedad de la COVID-19
Shah	Comprender el efecto de la suplementación oral con vitamina D sobre la necesidad de la unidad de cuidados intensivos (UCI) y la mortalidad en pacientes hospitalizados con COVID-19	La vitamina D parece indicar un papel potencial en la mejora del cuadro de COVID-19 en los pacientes hospitalizados; se necesitan datos más sólidos de ECA para corroborar sus efectos sobre la mortalidad
Stroehlein	Evaluar si la suplementación con vitamina D es efectiva y segura para el tratamiento de la COVID-19 en comparación con un comparador activo, un placebo o el estándar de atención solo	La efectividad de la suplementación con vitamina D para pacientes con COVID-19 es incierta, producto de inconsistencias en la notificación de eventos adversos que impidieron una evaluación de la seguridad de la suplementación como tratamiento para la COVID-19

Fuente: elaboración propia.

Conflictos de intereses: los autores declaran no tener conflictos de intereses.

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In Memoriam

Dr. Juan Ramón Urgelès Planella

Nació en Lleida y realizó la especialidad de Endocrinología y Nutrición en el Hospital de la Santa Creu i Sant Pau de Barcelona. Llegó a Mallorca en 1991 y desde el inicio fue un gran impulsor de la Nutrición Hospitalaria. Gracias a su perseverancia y tenacidad consiguió crear una unidad que pudiera dar asistencia a pacientes de gran complejidad, por lo que fue nombrado coordinador de la misma.

Sus pacientes lo describen como un médico dedicado, vocacional, cercano, bondadoso, empático y con una bonhomía extraordinaria. Sus compañeros, como una persona extraordinaria, amable y conciliadora, lo que lo llevó a ser Jefe del Servicio de Endocrinología por unanimidad.

Aunque fuera de "Ses Illes" no era muy conocido, el Dr. Urgelès era un referente de conocimientos nutricionales y bioquímicos que aplicaba traslacionalmente con la habilidad de un ingeniero metabólico. Un gran maestro tímido, sutil, apasionado, con un humor peculiar que te hacía ver la Nutrición como un mundo fascinante por descubrir.

Aunque dejaste un inmenso vacío con tu partida el 17 de noviembre siempre recordaremos tu fortaleza, genialidad y enseñanzas.

Dra. Josefina Olivares Alcolea[1];
en nombre de todos tus compañeros de Baleares

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