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# Nutrición Hospitalaria

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

## Editorial



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SENPE

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# Los estudios de costes, herramienta imprescindible en la nutrición clínica del siglo XXI

## Cost-effectiveness studies, a necessary tool in clinical nutrition in the XXI century

editorial

Seguro que todos compartimos que el gasto sanitario ha crecido progresivamente año tras año en las últimas décadas. Los expertos apuntan, de una forma muy simplista, que el aumento de la demanda sanitaria (aumento de crónicas y degenerativas; envejecimiento de la población) y el incremento de costes de los elementos que comportan la oferta (avances tecnológicos) son las causas que lo provocan. También entendemos que este tipo de presión, lejos de disminuir, en un futuro próximo se prevé que seguirá en crecimiento. Es fácil compartir la idea que, siempre y especialmente en una época de dificultades financieras, toma protagonismo la evaluación económica.

La medida de los costes así como de las consecuencias de las actividades y la elección objetiva son características que definen a la evaluación económica también en el ámbito de la medicina. En el amplio panorama que atiende la economía de la salud se incluyen aspectos interrelacionados que van desde el análisis conceptual de ¿qué es la salud? y ¿cuáles son sus determinantes (producción y demanda de salud)?, hasta la evaluación sistémica (equidad y eficiencia asignativa, planificación, financiación y regulación de los sistemas sanitarios), pasando por el análisis de la oferta y la demanda de la atención sanitaria y de los sectores, así como la evaluación microeconómica (coste-minimización, coste-efectividad, coste-beneficio, coste-utilidad de las intervenciones sanitarias) (1).

Por todo esto la economía de la salud se ha convertido en un instrumento indispensable para la gestión sanitaria y la asignación de recursos. Los estudios de costes, herramientas utilizadas en la evaluación microeconómica, nos permiten plantear alternativas razonables y eficientes que formen parte de la cartera de prestaciones de un servicio. En definitiva, nos ayuda a orientar la toma de decisiones, nos permiten racionalizar la elección de recursos en las políticas sanitarias, erigiéndose como una línea de trabajo imprescindible en progresivo desarrollo.

A finales del siglo XX, paralelamente a la preocupación de la Organización Mundial de la Salud por llamar la atención sobre la preocupación creciente de la situación de los recursos para la salud (mayor complejidad y costes de los servicios más elevados), la atención domiciliaria cobró mayor importancia precisamente como consecuencia del aumento de costes asociados al tratamiento hospitalario. Así se estableció que la infusión intravenosa de tratamientos especializados en el domicilio puede suponer un ahorro significativo con respecto a la administración del mismo tratamiento en el ámbito hospitalario. Fue por tanto la economía la que potenció la puesta en marcha del movimiento extrahospitalario sin olvidar las ventajas psicosociales para el paciente de la atención domiciliaria.

La nutrición parenteral (NP) se desarrolló como iniciativa terapéutica para proveer por vía intravenosa los nutrientes necesarios a pacientes hospitalizados con fallo intestinal y fue en 1969 cuando se considera la opción del tratamiento domiciliario. Así, la nutrición parenteral domiciliaria (NPD) se define como la modalidad de soporte o apoyo nutricional que permite la administración de soluciones de nutrición parenteral (NP) en el propio domicilio del paciente. Es decir, permite realizar una compleja terapia nutricional en un ambiente familiar y confortable exigiendo el compromiso y la responsabilidad de los propios pacientes y sus cuidadores (2). No disponemos de datos fidedignos que nos informen del número de pacientes que reciben NPD en los distintos países. Los que disponemos no están actualizados ya que se obtienen de encuestas parciales y registros voluntarios (3,4). Los datos españoles del último registro NADYA publicado, que también es voluntario, establece que la tasa de pacientes con NPD en España es de 4,73 pacientes/millón de habitantes/año 2014, siendo una de las patologías

editorial

más frecuentes en los adultos las neoplasias en tratamiento paliativo seguida de las que están en tratamiento activo (5). Un buen ejemplo de la utilidad de la evaluación económica en este campo lo tenemos en una reciente revisión que evalúa la calidad de vida, la supervivencia y el coste efectividad de la NPD en pacientes con obstrucción maligna intestinal. Sus resultados arrojan argumentos económicos que deben ser tenidos en cuenta para establecer los criterios de selección de pacientes (6). O en los estudios de simulación que nos permiten conocer el coste-efectividad de programas de rehabilitación y trasplante intestinal en niños y adultos para decidir si dedicamos recursos a la implementación de los mismos (7,8). O cómo establecer la organización de los recursos de un territorio (9). O simplemente el ahorro de coste que supone la incorporación de las nuevas tecnologías de la información y la comunicación en el día a día del control de pacientes con NPD (10).

En este número de *Nutrición Hospitalaria,* Burgos y cols. (11) publican el primer estudio de costes de nutrición parenteral domiciliaria en España. En el artículo, los autores analizan el coste directo medio por pacientes estableciéndolo en 8.265,36 € para patología benigna y en 9.133,66 € para la maligna. Incluyen en el análisis el coste de las bolsas de NP administradas, las diferentes vías de accesos venosos y el coste de las diferentes complicaciones sufridas directamente relacionadas con la NPT. Aunque no se han analizado algunos aspectos de interés como el coste sanitario asociado al manejo de los pacientes, los relativos al ingreso hospitalario, pruebas complementarias, visitas médicas, así como los costes indirectos derivados de gastos de personal o instalaciones, ni los debidos a la enfermedad de base, nos parece que los datos presentados son reveladores en la evaluación económica de esta intervención e inician una línea de trabajo multicéntrico a seguir que cree un cuerpo de doctrina en la evaluación económica de esta forma de soporte nutricional especializado en nuestro país.

En la era de la medicina basada en la evidencia y en la eficiencia, la evaluación económica se erige como una herramienta sustancial a cualquier iniciativa terapéutica. Los estudios de costes, como los anteriormente comentados, añaden valor al desarrollo de la NPD y fortalecen su papel en la oferta asistencial de la Nutrición Clínica, ayudando a establecer criterios organizativos que permitan el desarrollo de una gestión de recursos más eficientes.

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# Estándares de crecimiento infantiles: ¿cuáles son los más adecuados?

## Growth charts: which are the appropriate?

editorial

De todos es conocido que el crecimiento es un indicador indirecto del estado de salud y de la evolución socioeconómica de una determinada población (1). En la infancia el interés es aún mayor puesto que, de una adecuada interpretación del mismo, se deriva una actitud terapéutica correcta. En el momento actual, la determinación de peso, talla, índice de masa corporal y otros datos antropométricos, forman parte esencial de la práctica clínica diaria y de los exámenes periódicos incluidos en los programas de salud infantil. Una vez explorados estos datos, es necesario compararlos con estándares de referencia específicos para edad y sexo; es entonces cuando surge el problema.

Resulta evidente que no tienen el mismo valor los datos obtenidos a nivel local, que aquellos de ámbito nacional o los que, con la misma metodología, aúnan referencias de varios países. Estos últimos, aunque son los más extensos, tienen como limitación que se refieren a lo que sucede en las zonas geográficas estudiadas, resultados que no tienen porqué ser extrapolables a todas las regiones del mundo (2).

Tampoco son iguales los estudios de diseño longitudinal y los de tipo transversal (3). Los primeros son más dificultosos en su realización, suelen tener un tamaño muestral menor y suponen seguimientos de larga duración. Algunos autores sostienen que además de lo anterior tienen como inconveniente que, una vez finalizados, no reflejan la situación actual de la población estudiada (2). Sin embargo, son los más adecuados para evaluar el brote de crecimiento puberal. Los estudios transversales tienen como ventaja que pueden contar con un tamaño muestral mayor. Sin embargo, tienen como inconveniente que los criterios de inclusión y de exclusión de los individuos deben de estar muy bien definidos con el objeto de que los estándares obtenidos reflejen de forma real la situación de la población estudiada.

En España ha existido una amplia tradición de estudios de crecimiento locales (Barcelona, Bilbao, Madrid, Reus y Zaragoza, entre otros) que han demostrado que, al igual que en otros países, se ha producido una aceleración secular del crecimiento asociada a la mejoría en las condiciones de vida, la disminución de infecciones crónicas y a que, posiblemente, la nutrición de la población es mejor (4). Más recientemente, se ha hecho un esfuerzo en fusionar los datos de distintos estudios de crecimiento locales siempre que hubieran sido realizados con la misma metodología y en el mismo periodo de tiempo. Este último aspecto es crucial y no siempre ha sido tenido en cuenta en el diseño de otros estándares internacionales. Es así como surge el Estudio Transversal Español 2010 con una muestra de 38.461 niños nacidos en cuatro regiones de España entre los años 2000 y 2004 (Andalucía, Barcelona, Bilbao y Zaragoza). Este estudio ha demostrado que la población española ha tenido una evolución similar a la de otros países europeos mostrando un incremento de talla de unos 3 cm, pero evidenciando también un aumento en el índice de masa corporal, sobre todo en edades próximas a la pubertad. Lo anterior no solo puede ser atribuido al aumento de prevalencia global del exceso de peso en nuestro medio, sino además a otros aspectos metodológicos. En referencia a estos últimos, algunos autores insisten en que dentro de los criterios de exclusión utilizados se encontraban la malnutrición y las enfermedades crónicas y se preguntan si hubiera sido necesario excluir a los niños con exceso de peso (2). Esto último se ha realizado en otros estándares internacionales, aunque también se ha sometido a debate, pues no reflejaría la situación real de la población. Los autores del estudio indican claramente que la población estudiada es caucásica y que en los últimos años se ha asistido en España a un incremento en la prevalencia de otras etnias procedentes de diversas áreas geográficas,

editorial

por lo que es absolutamente necesario un seguimiento de estas poblaciones que aportan datos al respecto poco concluyentes hasta el momento (5).

Tampoco hay que olvidar el hecho de que en la infancia existen tres etapas de crecimiento: crecimiento rápido (primeros tres años de vida), crecimiento estable (tres años hasta la pubertad) y crecimiento puberal (4). Cada una de estas etapas viene condicionada por factores reguladores que predominan más o menos según el momento de la vida. En los primeros años el factor nutricional es crucial, de ahí la controversia suscitada a la hora de interpretar el crecimiento de un niño alimentado exclusivamente con lactancia materna o sin ella. Los estándares de la OMS aportan estudios longitudinales de 1.737 niños nacidos en Brasil, Gana, India, Noruega y Estados Unidos entre los años 1997 y 2000 alimentados con lactancia materna exclusiva durante al menos 3 meses (6). Los estándares de Euro-Growth aportan datos longitudinales de 2.245 niños nacidos en doce países europeos entre los que se encuentra España (7). Las diferencias mayores entre estos estudios se encuentran en los primeros seis meses de vida y se atribuyen fundamentalmente al peso y longitud al nacer, y al tipo de alimentación recibida durante esos primeros meses de vida. Se hace referencia a que tanto las poblaciones como los criterios de inclusión y exclusión de los estudios han sido diferentes (8,9).

Por tanto, el interesante estudio de Escartín y cols. (10), que se publica en este número de *Nutrición Hospitalaria,* vuelve a traer a la actualidad la eterna discusión de cuáles deben ser los estándares más adecuados a la hora de estudiar el crecimiento y desarrollo de la población pediátrica, sobre todo durante los dos primeros años de vida. Se trata de un estudio longitudinal de 1.430 niños nacidos a término desde el periodo neonatal hasta los dos años de edad y compara la evolución dependiendo de si el recién nacido es hijo de madre inmigrante (n = 331) o no lo es (n = 1.099). El seguimiento longitudinal de esta cohorte hasta su talla final puede aportar datos muy relevantes sobre la situación sociodemográfica actual.

En definitiva, el interés por encontrar el estándar de crecimiento más apropiado y perdurable en el tiempo ha sido y será un motivo de discusión frecuente en los foros pediátricos tanto nacionales como internacionales. Y es que cualquiera que sea el estándar de crecimiento utilizado tiene sus ventajas e inconvenientes. Lo importante es el conocimiento de las fortalezas y limitaciones de cada uno de ellos, lo que traerá consigo una correcta interpretación de nuestros datos.

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Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

# Drugs via enteral feeding tubes in inpatients: dispersion analysis and safe use of dispensers

## *Medicamentos a través de las sondas de nutrición enteral en pacientes: análisis de dispersión y uso seguro de los dispensadores*

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## Abstract

**Objective:** This study aimed to improve knowledge about drug administration through enteral feeding tubes (EFTs) in order to minimize efficacy and safety problems.

**Material and methods:** The study was performed in a public secondary care hospital with level II accreditation by the National Accreditation Organization (Organização Nacional de Acreditação ONA), in Fortaleza, Ceará, north-eastern Brazil.

**Results:** One hundred and eight oral solid medications that could be administered through EFTs and were not available in liquid forms were evaluated via transformation of their solid dosage forms into liquid forms. Dispersion times and conditions were assessed to determine which medications should be crushed. We compared the use of dispensers and syringes and their connections to enteral feeding tubes and intravenous devices. Medications whose dispersion occurred within 20 minutes and could be visually perceived and whose content could be expelled without occluding the oral syringe were considered "satisfactory".

**Conclusions:** The dispersion was "satisfactory" in 82 (75.9%) of the medications; they were classified as capable of being dispersed in water in the oral syringe for further administration via EFTs without the need for crushing. Use the dispenser instead of the syringe for drug administration was safer because the dispenser apparatus did not fit into equipment for intravenous drug administration.

**Key words:**

Tablets. Capsules. Enteral nutrition. Drug administration routes. Patient safety.

## Resumen

**Objetivo:** este estudio tuvo como objetivo aumentar el conocimiento de la administración de medicamentos a través de las sondas de nutrición enteral (SNE), con el fin de reducir al mínimo los problemas de eficacia y seguridad inherentes al uso de esta vía.

**Material y métodos:** el estudio se realizó en un hospital público en la atención secundaria, con el nivel II de acreditación por la Organización Nacional de Acreditación (ONA) en Fortaleza, Ceará, noreste de Brasil.

**Resultados:** se evaluaron 108 preparaciones galénicas en forma sólida que podrían administrarse por SNE, no disponibles en forma líquida, mediante su preparación en una dilución. Se evaluaron los tiempos y las condiciones de dispersión para determinar qué medicamentos deberían triturarse. Se comparó el uso de dispositivos de distribución y de jeringas y sus conexiones con las SNE. Los fármacos cuya dispersión se produjo a los 20 minutos, que pudieran percibirse visualmente y cuyo contenido podría ser administrado sin ocluir la jeringa se consideraron de dispersión "satisfactoria".

**Conclusiones:** la dispersión fue "satisfactoria" en 82 (75,9%) de los fármacos y se calificaron como capaces de dispersarse en agua en una jeringa, para la administración posterior a través de SNE, sin necesidad de ser triturados. El uso del dispensador en lugar de la jeringa para la administración enteral de medicamentos se considera más seguro debido a que el dispensador no se ajusta a los conectores utilizados para la administración de fármacos por vía intravenosa.

**Palabras clave:**

Pastillas. Cápsulas. Nutrición enteral. Rutas de administración de fármacos. Seguridad del paciente.

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## INTRODUCTION

Discussions on the benefits, harms, and limitations of the administration of medication via enteral feeding tubes (EFTs) have been held to ensure its efficacy, safety, and, above all, effectiveness and convenience for patients. Although parenteral administration ensures a high degree of absorption, it poses potentially high risks of complications and discomfort, is costly, and is not commonly used in long-term treatments (1-5). Transdermal, sublingual, rectal, and topical routes are limited to certain drugs; the oral route is a good alternative but it is not always available (6).

In particular, drug administration via EFTs is a challenge in clinical practice due to the scarce information about its use and the lack of commercially-available adequate formulations (4,7). Among other aspects, drug administration via EFTs carries a considerable risk of prescription incompatibility (3,6); in many situations, the administration of a drug via EFTs requires transformation of the drug's original physical properties, which can have implications for its effectiveness and safety (8). Additionally, such formulations must be prepared immediately before administration (1).

The dissolution or suspension of a solid dosage form in a compatible vehicle may require crushing; therefore, the chemical and physicochemical properties of the drug and its starting formulation, which determine its stability and pharmacokinetic profile, must be well known to avoid compromising the treatment's effectiveness and safety (3,5,9,10).

A study by Mota et al. (6) showed that it is difficult for the nursing team to administer drugs via EFTs. Most of the team members reported using metal, wood, or plastic mortars to crush solid dosage forms; the use of mortars may result in the loss of drug fragments in the mortars, potential reactions between the prescribed dosage form and the mortar material, and potential drug-drug interactions if the mortars are not washed thoroughly between each use.

The administration of medication via EFTs is a common practice but often done without adequate technical criteria. Enhancing the knowledge of practitioners involved in the care of patients might prevent problems with the efficacy and safety of pharmacological treatments and avoid inconveniencing the patients or causing problems with their diets. Nurses, nutritionists, and physicians should be encouraged to work with pharmacists to determine the best pharmacological management of patients receiving enteral nutrition (3,6,9-15).

When the oral route is unavailable and it is infeasible and/or inconvenient to use the parenteral route, the medication should be administered via EFTs (10). In fact, although the use, safety, and effectiveness of many drugs administered via EFTs are not well established, drug administration via EFTs has been used routinely in clinical practice due to a lack of options (16).

This study aimed to present a method of drug delivery via EFTs as a safe and convenient proposal that is suitable for use by inpatients.

## MATERIAL AND METHODS

### SETTING

The study took place in a public secondary care hospital accredited with level II accreditation by the National Accreditation Organization (Organização Nacional de Acreditação ONA). The hospital is located in the city of Fortaleza, Ceará, north-eastern Brazil.

### EVALUATION OF STANDARDIZED ORAL SOLID MEDICATIONS

We analysed all the standardized oral solid medications (tablets, capsules, and dragees) used in the hospital where the study took place. There were 108 solid dosage forms that were not commercially available in liquid forms in Brazil but could be prescribed for administration via EFTs.

### DISPERSION OF SOLID DOSAGE FORMS

All 108 oral solid medications were selected for evaluation of the transformation of the solid dosage form into a liquid form, which is the only form that can be administered through a feeding tube in the proposed method. Hard capsules were opened to assess the dispersion of their internal contents (powders) in water.

For the evaluation of the dispersion of the medications selected, the following steps were taken:

1. The medication was drawn into the oral syringe;
2. 10 mL of mineral water were drawn into the syringe;
3. After mixing the medication with the water, the dispersion time of the medication was measured to assess its adequacy for EFT administration;
4. The time (minutes) that the medication took to fully disperse was recorded on a spreadsheet;
5. We also recorded visual assessments after 1, 5, 10, and 20 minutes as the feasibility cut-off value for dispersion in the dispenser; medications that dispersed in 20 minutes or less were considered feasible.

Standardized medications intended for administration via EFTs were selected according to their dispersion times and analysed for any contraindications against EFT administration and the need for crushing prior to dispersion. Medications whose dispersion could be visually perceived and whose content could be expelled without occluding the oral syringe were considered "satisfactory".

### STUDY ON THE SAFETY OF THE USE OF ORAL SYRINGES

The safety of the extemporaneous preparations obtained from the dispersion of the solid dosage forms in the oral syringes was

also studied. Given the high risk of administering these formulations through intravenous devices, oral syringes and parenteral syringes and their connections to EFT and intravenous devices were compared.

Regarding the safety analysis, the following parameters were evaluated: connection to infusion set, stopcock, and extension set; connection to venous access (central and peripheral); connection to the feeding tube; graduation; and risk of occlusion, which was estimated by assessing EFT diameter.

## STATISTICAL ANALYSIS

The results obtained from the evaluation of the dispersion time of tablets were analysed using descriptive statistics and a Microsoft Excel 2010 database.

## ETHICAL APPROVAL

The study was approved by the Research Ethics Committee of the Federal University of Ceará upon submission of the research project to the *Plataforma Brasil* system. The study was approved under Opinion No. 507.830 and CAAE No. 21180413.1.0000.5054. The researchers had no conflicts of interest in performing this research and it did not pose any risks to the patients.

## RESULTS

### DISPERSION OF SOLID DOSAGE FORMS

Of the 108 solid medications dispersed in oral syringes with 10 mL of mineral water, only one needed a volume of water greater than 10 mL to disperse: the tablet provided by the Brazilian government to treat tuberculosis, which contained rifampicin, isoniazid, pyrazinamide, and ethambutol.

Dispersion occurred immediately or took up to one minute in 25% (n = 27) of the items tested; two to five minutes in 21.3% (n = 23); six to ten minutes in 15.7% (n = 17); and eleven to twenty minutes in 13.9% (n = 15). Thus, 75.9% (82 items) of the analysed medications were classified as capable of being dispersed in water in the oral syringe for further administration via EFTs without the need for crushing.

Tablets without satisfactory dispersion, in terms of quality and dispersion time, were indicated for crushing by a mortar and pestle. After crushing, these medications were placed into the oral syringe with mineral water to evaluate the dispersion. A total of 9.2% (n = 10) of the items tested did not disperse, even after crushing; these medications were classified as "inappropriate" for administration via EFTs (Table I), given that these medications could cause tubal occlusion or blockage and/or generate drug ineffectiveness.

**Table I.** Standardized medications classified as contraindicated for administration via EFT

| Medications | Concentration | Dosage form |
|---|---|---|
| Bisacodyl | 5 mg | Tablet |
| Calcitriol | 0.25 µg | Capsule |
| Calcium carbonate | 500 mg | Tablet |
| Diltiazem | 30 mg | Extended-release tablet |
| Doxycycline | 100 mg | Tablet |
| Gliclazide | 30 mg | Extended-release tablet |
| Omeprazole | 20 mg | Capsule |
| Pentoxyfilline | 400 mg | Tablet |
| Racecadotril | 100 mg | Capsule |
| Sulfasalazine | 500 mg | Tablet |

The dosage form and concentration are very important data; therefore, the data presented here cannot be applied to other dosage forms and concentrations since they have not undergone testing for dispersion. A practical example is that, according to our study, both morfin 10 mg and morfin 30 mg tablets must be crushed in a mortar with a pestle for further dispersion, whereas in the case of warfarin sodium 2.5 mg and 5 mg tablets, only the 2.5 mg tablets need to be crushed.

A total of 14.8% (n = 16) of the tested items were successfully dispersed after crushing. Crushing is recommended for the preparation of these medications prior to administration via EFTs and should follow the steps described in table II.

The list of medications that were successfully dispersed after being crushed in a mortar and pestle is presented in table III.

**Table II.** Steps to prepare oral solid medications for administration via enteral feeding tubes

- Always wash hands before preparing medication
- Separate, wash, and dry the needed material
- Only remove a tablet from the packaging when ready to crush
- Crush the tablet well using a mortar and pestle
- If more than one drug is to be administered, crush them separately
- Add 10 mL of water to the mortar, rinse it well, and stir until the crushed tablet is completely dissolved
- Flush the tube with 30 mL of water before administering the medication
- Administer the diluted medication (crushed tablet + 10 mL of water) by slowly plunging a 20-mL oral syringe
- Flush the tube with 30 mL of water after administering the medication

**Table III.** Medications crushed in a mortar and pestle to administration via enteral tube

| Medication | Concentration | Dosage form |
|---|---|---|
| Aminophylline | 100 mg | Tablet |
| Bamifylline | 300 mg | Tablet |
| Carvedilol | 6.25 mg | Tablet |
| Clopidogrel | 75 mg | Tablet |
| Hydroxychloroquine | 400 mg | Tablet |
| Dexamethasone | 4 mg | Tablet |
| Isosorbide dinitrate | 10 mg | Tablet |
| Isoniazid + rifampicin + pyrazinamide + ethambutol | 75 mg +150 mg + 400 mg + 275 mg | Tablet |
| Losartan | 50 mg | Tablet |
| Methadone | 50 mg | Tablet |
| Metformin | 500 mg | Tablet |
| Methyldopa | 250 mg | Tablet |
| Morphine | 10 mg | Tablet |
| Morphine | 30 mg | Tablet |
| Nimodipine | 30 mg | Tablet |
| Promethazine | 25 mg | Tablet |
| Thiamine | 300 mg | Tablet |
| Warfarin sodium | 2.5 mg | Tablet |

## STUDY ON THE SAFETY OF THE USE OF ORAL SYRINGES

Table IV shows the safety analysis of the use of dispensers or syringes for administration of tablets via EFTs and the testing of their connections to intravenous infusion sets and feeding tubes.

Regarding graduation, the 10-mL syringe has a pair-numbered graduation of 0.2 mL and a Luer lock tip that perfectly fits intravenous needles and infusion sets. The 10-mL dispenser has a 0.2 mL graduation and all mL graduation marks are printed on it; it has a Luer slip tip that connects better to feeding tubes.

The diameter of the dispenser and syringe tips are 3 and 2 mm, respectively. The dispenser has a 50% larger tip that does not fit intravenous devices (Figs. 1 and 2); therefore, its use safely avoids accidental intravenous administration.

## DISCUSSION

Solid dosage forms, such as tablets, capsules, and dragees, are administered to hospitalized patients through EFTs. In the study by Heydrich (14), solid dosage forms were used more frequently than liquid forms, indicating that, in clinical practice, patients with EFTs

**Table IV.** Results of the testing of the 10 mL parenteral syringe and 10 mL oral syringe connections to intravenous infusion sets and feeding tubes

| Tested device | 10 mL parenteral syringe connection | 10 mL oral syringe connection | Risk/benefit |
|---|---|---|---|
| Central line | Yes | No | Increases safety |
| Peripheral line | Yes | No | Increases safety |
| 20 cm extension set | Yes | No | Increases safety |
| Macro-drip infusion set | Yes | No | Increases safety |
| Infusion pump set | Yes | No | Increases safety |
| 3-way stopcock | Yes | No | Increases safety |
| Nasoenteric tube | Yes | Yes | Indifferent |
| Nasogastric tube | No | Yes | Indifferent |

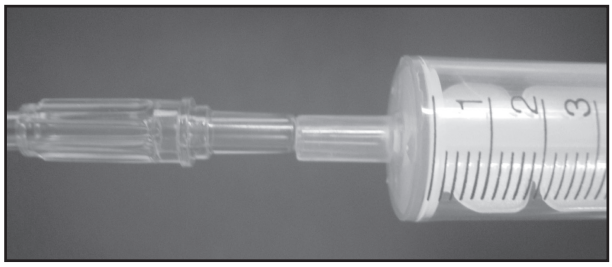

**Figure 1.**

The oral syringe does not fit in the port of the 20-cm extension set.

generally do not receive medications as indicated by the data in the literature regarding drug administration, inconveniencing both the patient and the health professional involved in the treatment.

In our study, circa 90% of the oral solid medications tested for administration via EFT presented a "satisfactory" dispersion time or could be crushed for administration via EFTs; however, it is important to emphasize that it is necessary to standardize the administration technique. To promote a standardized procedure, the volumes of water used to disperse such drugs for administration via EFTs were recorded, allowing nursing staff to work in a standardized way to minimize individual errors. Further, in our study, only the drugs that had no alternative oral liquid forms were tested, i.e., those whose dosage forms could not be changed by pharmaceutical intervention.

According to Heineck, Bueno, and Heydrich (13), 95% of the prescribed drugs were solid preparations: tablets (71.9%), capsules (12.2%), coated tablets (9.5%), soluble tablets (2.2%), powders (0.8%) and granules (0.2%). These authors also showed that 23% of the prescribed drugs were solid preparations whose prescription of liquid dosage forms was possible; however, only 5% of the drugs were administered in their liquid forms. Triki et al. (2) reported that it is possible to reduce the risk of administration errors and facilitate drug administration via EFTs through the prescription of oral liquid dosage forms or dispersible oral solid dosage forms. Other studies mentioned that another way to contribute to safer drug administration via EFT is through cooperation with the pharmacist in order to adapt dosage forms for administration more accurately and retain the administration protocol (2,5,16,17).

Our research so far has not studied the content and effectiveness of the tested drugs; it was verified that the administration of medications via EFT is a common, but unregulated, practice in the hospital. It is worth noting that this practice should be suggested when there are no other suitable alternative treatments because solid dosage forms need to be transformed into liquid forms prior to administration via EFTs. Therefore, standardization and practical procedures are required for the implementation of extemporaneous formulations in order to minimize errors in the administration of solid medications via EFTs.

Dashti-Khavidaki et al. (16) showed that clinical pharmacists' education programs significantly improved nurses' knowledge about medication administration via EFTs. Renovato, Carvalho, and Rocha (18) observed, however, that among the nursing professionals interviewed, 86.96% did not undergo a refresher course on pharmacology and medication administration. In view of this alarming number, continuing education concerning this subject is important to reduce errors in the preparation and administration of medications, which can compromise both nutritional support and the effectiveness of drug therapy (18).

Assessing medication dispersion time is crucial to avoid significant reductions in drug efficacy, reduce the risk of contamination from exposure, and avoid taking more of the nursing staff's time than necessary. Complete dispersion of the medication should not take much time, which is why our study established a period of 20 minutes or less for satisfactory dispersion.

When multiple medications are to be administered at the same time, each should be given separately and the feeding tube should be flushed between each medication. Non-compliance with these recommendations may result in future EFT complications, since the mixture of drugs, both in a disposable cup and in the EFT itself, enables interactions (10,17).

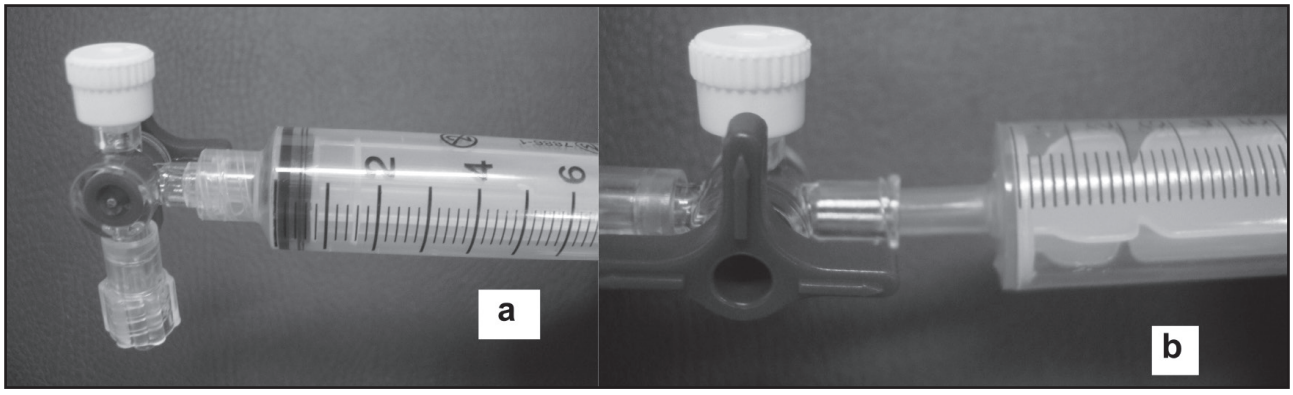


**Figure 2.**

The difference between the perfect fit of the 10-mL Luer lock tip parenteral syringe into the stopcock (A) and the impossibility of fitting the Luer slip tip oral syringe into the stopcock (B).

The study by Lohmann et al. (15) presents the development and validation of an algorithm to facilitate drug prescription for inpatients with EFTs. The authors found that 83.5% of the tested drugs could be switched to suitable drugs for administration via EFTs; in our study, we found that 90% of the tested oral solid drugs could be adapted for administration via EFTs.

In the study by Heineck, Bueno, and Heydrich (13), omeprazole was one of the most common drugs given to patients. This drug is available in capsules or as soluble tablets; capsules were used in 69.5% of the patients and soluble tablets in 30.5%, even though soluble tablets are more appropriate for EFT cases and were available in the hospital where the research took place. Similarly, paracetamol tablets and codeine and ranitidine-coated tablets also had alternative oral dosage forms and yet the tablet preparations were used in 96.4% and 97.1% of the patients, respectively, while the liquid preparations were only used in 2.9% of the cases where patients had EFTs.

It is important to emphasize that clinical evaluation is sovereign, and it is up to the multidisciplinary team to assess the risk-benefit ratio of the administration of the items contraindicated for administration via EFTs and all the other medications. Thus, as with all interventions in patients that use EFTs, these interventions could not be performed without accounting for the unique medical history of each patient. Taking this into consideration, in the study by Do Nascimento et al. (10), the interventions were made only after an evaluation of their clinical relevance (30.2% of the total potential interventions).

Another aspect that should be considered is the possible changes in dispersion times due to different drug manufacturers. At the hospital where our study took place, the same brands of drugs are not always available for a particular specification since it is a public hospital that buys its medicines through bidding. Differences in formulations are also expected, although they have been minimized by the requirement of bioequivalence for generic or similar pharmaceutical products established by the Collegiate Board of Directors of the Brazilian Health Surveillance Agency, Resolution No. 134, on May 29, 2003 (19).

The existing literature has shown that the inadequate administration of medications via the intravenous route can expose patients to increased risks of morbidity and mortality worldwide (9,20,21). The use of the dispenser for administering oral medication via EFTs reduces the risk of giving medications intravenously because its tip does not fit the intravenous devices, as shown by the results of our study concerning the characteristics of the instrument. The dispenser tip has a larger diameter and reduces the need for crushing solid dosage forms for administration via EFTs since small fragments will not occlude the tip. It is important to highlight that medication errors concerning the administration of incomplete doses are the responsibility of everyone involved in the process, from the dispensing to the infusion; therefore, using adequate equipment to avoid incomplete doses can help to minimize the problem (6,9).

## CONCLUSIONS

It is possible to standardize the technique for administration of solid dosage forms by dispersing them in 10 mL of water in the dispenser since most studied dosage forms dispersed in a "satisfactory" way. Promoting the use of the dispenser at the expense of the syringe is of utmost importance, as this simple change in behavior can prevent serious incidents with the administration of the dispersion of solid dosage forms via intravenous devices.

Thus, the administration of medications via EFTs in hospitalized patients requires a substantiated and standardized practice that should involve the analysis of the dispersion of these medications and the safe use of dispensers in order to enable the benefits of the proposed pharmacotherapy and the patient's improvement.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

# Quality control of enteral nutrition therapy in cancer patients at nutritional risk

## *Control de calidad en terapia nutricional enteral en el paciente oncológico con riesgo nutricional*

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## Abstract

**Introduction:** Quality indicators in nutritional therapy (QINTs) allow for the practical assessment of quality in the management of enteral nutrition therapy (ENT) among hospitalized patients.

**Objective:** To control ENT quality in cancer patients at nutritional risk.

**Methods:** A prospective, observational study was performed with cancer patients over 19 years of age who had undergone exclusive ENT for at least 72 h. Nutritional Risk Screening was used to assess nutritional risk; in the presence of nutritional risk, the Subjective Global Assessment (SGA) was used. Six QINTs were applied.

**Results:** Our study included 211 patients (mean age: 59 ± 10 years, 67.3% men). Most common cancer diagnoses were head and neck (68.2%) and gastrointestinal (18%). Nutritional risk was identified in 93.3% (n = 197) of patients; SGA identified malnutrition in 84.2% of patients (n = 166). ENT was used for 9.7 ± 7 days, presenting a daily deficit of -243.1 ± 141 ml of dietary volume, -363.3 ± 214.1 kcal, and -14.2 ± 8.41 g of protein. Three of the six QINTs were in accordance with the proposed goal: frequency of SGA application, calculations of nutritional needs, and frequency of diarrhea. Three of the six QINTs were in disagreement with the proposed goal: ENT infused volume exceeding 70% of prescribed volume, frequency of digestive fasting exceeding 24 h, and frequency of constipation. Prescriptions for anticholinergic drugs (p = 0.023) and diuretics (p = 0.007) were associated with diarrhea.

**Conclusion:** Nutritional risk and malnutrition are frequent among ENT cancer patients. Quality control in ENT was moderately impaired by episodes of fasting and intestinal motility disorders.

**Key words:**

Cancer. Quality indicators. Enteral nutrition. Malnutrition. Diarrhea. Constipation.

## Resumen

**Introducción:** los indicadores de calidad en terapia nutricional (ICTN) permiten la evaluación práctica en el manejo de la terapia nutricional enteral (TNE).

**Objetivos:** controlar la calidad de la TNE en pacientes con cáncer en riesgo nutricional.

**Metodología:** estudio prospectivo, observacional, con pacientes oncológicos > 19 años y sobre TNE exclusiva > 72 h. Para la evaluación del riesgo nutricional fue utilizada la *Nutritional Risk Screening* y en presencia de riesgo nutricional fue aplicada la *Subjective Global Assessment (SGA)*. Fueron aplicados 6 ICTN.

**Resultados:** nuestro estudio incluyó 211 pacientes (edad promedio de 59 ± 10 años; 67,3% de sexo masculino). Los diagnósticos oncológicos más predominantes fueron: cáncer de cabeza y cuello (68,2%) y gastrointestinal (18%). El riesgo nutricional estaba presente en el 93,3% (n = 197) de los pacientes; la SGA identificó desnutrición en 84,2% (n = 166). La TNE fue aplicada por 9,7 ± 7 días y presentó un déficit diario de -243,1 ± 141 ml de volumen de dieta administrada, -363,3 ± 214,1 kcal y -14,2 ± 8,41 g de proteínas. Tres de los seis ICTN aplicados estuvieron de acuerdo con la meta: frecuencia de aplicación de la SGA; cálculo de las necesidades nutricionales y frecuencia de diarrea. En desacuerdo con la meta: volumen de la TNE administrada > 70% de lo prescrito; frecuencia de ayuno digestivo > 24 h y frecuencia de estreñimiento. La prescripción de medicamentos anticolinérgicos (p = 0,023) y diuréticos (p = 0,007) se asoció con la aparición de diarrea.

**Conclusión:** el riesgo nutricional y la desnutrición son frecuentes entre pacientes con cáncer que reciben TNE. El control de calidad en la TNE se afectó de una forma negativa por los episodios de ayuno y disturbios en el tránsito intestinal.

**Palabras clave:**

Cáncer. Indicadores de calidad. Nutrición enteral. Desnutrición. Diarrea. Estreñimiento.

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## INTRODUCTION

Prevalence rates of nutritional risk and malnutrition are high among cancer patients (1,2). Malnutrition prevalence at the time of diagnosis has been estimated to range from 15% to 40%, with this value increasing to 80% with cancer progression. Hospital malnutrition compromises surgical treatment outcomes and leads to more infectious complications, increased length of hospital stay, and mortality (1,3,4).

Cancer patients are at high nutritional risk. When malnourished and unable to meet their nutritional needs through the oral route alone, cancer patients are candidates for the early introduction of high-quality effective nutritional therapy. Enteral nutrition therapy (ENT) is considered to be the best route of nutrition when the gastrointestinal (GI) tract is structurally and functionally intact (5). Nutrients provided by the digestive system help to maintain the architecture of intestinal microbiota and to modulate the intestinal immune system. Thus, compared to parenteral nutritional therapy, ENT is associated with a lower incidence of infectious complications in surgical patients (6). However, benefits of ENT for cancer patients are only achieved if ENT is administered properly and efficiently.

The Task Force of Clinical Nutrition at the International Life Sciences Institute of Brazil (ILSI - Brazil) proposed indicators to assess the quality of ENT provided by hospitals. These quality indicators in nutritional therapy (QINTs) have been used for the practical assessment of the quality of ENT provided by various health services (7-11). Despite the availability of QINTs, however, only a few published studies have monitored the quality of using exclusive ENT (12), particularly in cancer patients (13). In this context, the present study aimed to analyze the adequacy and quality of ENT used in patients with cancer diagnoses and undergoing treatment at specialized public hospitals in São Paulo City, Brazil, by applying selected QINTs.

## MATERIAL AND METHODS

### ETHICAL CONSIDERATIONS

This research was previously approved by the Research Ethics Committee of the corresponding institutions (NP 315/12 and CEP125/13). The protocol was performed in accordance with the principles of the Declaration of Helsinki (1975).

### PATIENTS STUDIED

This prospective, observational, descriptive study included adult patients admitted to the Instituto do Câncer do Estado de São Paulo (ICESP), a tertiary public-referral hospital with expertise in cancer management in the city of São Paulo, Brazil. Cancer patients admitted to wards were aged 19 years or older, with exclusive ENT for at least 72 h. All patients were under treatment for cancer complications and/or chemotherapy and radiation therapy and provided their informed consent for inclusion in the study. Exclusion criteria were as follows: age less than 19 years; ENT use for less than 72 h; prescription for an oral diet, parenteral nutrition therapy, or parenteral and enteral nutrition; surgical treatment; palliative care; colostomy and/or ileostomy; and admission to the intensive care unit (ICU). All patients who did not fit the exclusion criteria were included in the study.

### NUTRITIONAL STATUS ASSESSMENT

Data related to patient demographics, clinical information, nutritional status, and ENT characteristics were collected by consulting the TASI© electronic medical records collected during the period from June to November 2013. The Nutritional Risk Screening (NRS) tool was used for nutritional risk assessment (14). In the presence of nutritional risk, Subjective Global Assessment (SGA) (15) was applied to evaluate nutritional status. NRS and SGA were carried out by nutritionists in different hospital wards. Caloric and protein needs were estimated on an individualize basis, according to the patient's initial clinical condition and nutritional status, and in compliance with the institutional protocol, which includes specific guidelines for cancer nutrition therapy (16).

### ENTERAL NUTRITION THERAPY

In all patients, ENT was administered into the stomach. Correct positioning of the enteral tube was confirmed by X-ray before introduction of ENT. After medical and diet prescriptions were established, enteral formulas (closed system) were administered by infusion pumps (Lifemed® Model LF 2001 Brazil), according to the institutional protocol (intermittently in six steps per day, during the period from 8:00 to 23:00 hours). We used three types of enteral formulas available at the institution: polymeric hypercaloric, normal protein with and without fiber, and oligomeric.

After data collection, percentages of caloric and protein adequacy were calculated as the ratio between the amount of calories and protein administered effectively and the amount of calories and protein prescribed each day. Then, the mean percentage of adequacy and the cumulative calorie and protein deficits for each patient were calculated. Outcome data for each patient were collected from electronic medical records.

### SELECTED INDICATORS OF ENTERAL NUTRITION

We applied six QINTs, which were related to the frequency of nutritional assessment, calorie/protein requirements, ENT administration, fasting and digestive motility complications caused by ENT (Table I). With regard to bowel habits, the patient was considered to have diarrhea when there were more than three episodes of watery stools per day. The patient was considered to have constipation in the absence of evacuation for three consecutive days (7,9,11,16,17).

**Table I.** Quality indicators in nutritional therapy applied to cancer patients with exclusive enteral nutritional therapy

| Indicator | Formula | Goal |
|---|---|---|
| I. Frequency of application of SGA in patients at nutritional risk | $\frac{100 \times \text{No. of patients at nutritional risk with SGA applied}}{\text{Number of patients at nutritional risk}}$ | > 80% |
| II. Frequency of estimated energy and protein needs in patients on ENT | $\frac{100 \times \text{No. of patients with measurement of energy expenditure/protein}}{\text{Number of patients on ENT}}$ | > 80% |
| III. Frequency of infused volume > 70% of prescribed volume in patients on ENT | $\frac{100 \times \text{No. of patients with ENT-infused volume >70\%}}{\text{Number of patients on ENT}}$ | > 80% |
| IV. Frequency of digestive fasting > 24 h in patients on ENT | $\frac{100 \times \text{No. of patients with fasting ENT > 24h}}{\text{Number of patients on ENT}}$ | < 10% |
| V. Frequency of diarrhea episodes in patients on ENT | $\frac{100 \times \text{No. of days with diarrhea}}{\text{Number of days on ENT}}$ | < 10% |
| VI. Frequency of episodes of constipation in patients on ENT | $\frac{100 \times \text{No. of patients with constipation}}{\text{Number of patients on ENT}}$ | < 20% |

*Source: Waitzberg, 2008 (7); Verotti et al., 2012 (9); Waitzberg et al., 2011 (11); Isosaki et al., 2015 (17). SGA: subjective global assessment; ENT: enteral nutrition therapy.*

## STATISTICAL ANALYSIS

Statistical analyses were performed using STATA® software. We used the Kolmogorov-Smirnov test ($p > 0.05$) to verify sample normality. For parametric variables, we used mean and standard deviation (SD) values. For nonparametric values, median values and interquartile ranges (IQRs, p25-p75) were used. To compare qualitative variables, we used the chi-square test ($\chi^2$). To compare quantitative variables, we used ANOVA and Student's t-test. For parametric variables, the Kruskal-Wallis test was used. For nonparametric variables, the Mann-Whitney test was used. A difference with $p < 0.05$ was considered statistically significant for all tests.

## RESULTS

The sample comprised 211 patients (mean age: 59 ± 10 years, 67.3% men). Head and neck (HN) was the most common cancer diagnosis, accounting for 68.2% of cancer diagnoses. Other cancer diagnoses encountered are presented in table II. Primary reasons for admission to the hospital were problems related to cancer or its treatment (97.6% of cases). Two patients were hospitalized to finalize chemotherapy cycles. And two others were hospitalized to receive concurrent chemotherapy and radiotherapy. At the time of admission, 93.3% (n = 197) of patients were at nutritional risk, including 84.2% (n = 166) who had moderate and severe malnutrition (SGA B+C). Prevalence of malnutrition was higher in patients with HN and GI tract cancer. Table III presents details related to nutritional status for all patients studied, stratified according to cancer diagnosis.

On average, patients used ENT exclusively for 9.7 ± 7 days. Daily amount of enteral diet prescribed was approximately 1 L (1,500 calories). However, the volume administered was lower than that prescribed; on average, this resulted in a reduced supply of calories and protein. The ratio of prescribed/infused enteral diet volume, calories and protein was 74.3% (Table IV). On average, the cumulative deficit for the entire sample was more than 3,000 kcal and 130 g protein. The cumulative energy and protein deficits for all patients (stratified for HN and GI cancer) are shown in figure 1.

**Table II.** Most common primary cancer diagnoses in patients treated exclusively with enteral nutritional therapy

| Primary cancer diagnosis | n (%) |
|---|---|
| Head and neck | 144 (68.2) |
| Gastroenterological | 38 (18) |
| Thoracic | 14 (6.6) |
| Gynecological | 10 (4.7) |
| Urological | 3 (1.5) |
| Lymphoma/leukemia/myeloma | 2 (1) |

Among the six applied QINTs, three (50%) were in line with goals established by the institution: QINT I, which evaluated the frequency of SGA application in patients at nutritional risk; QITN II, which verified the fulfillment of energy and protein requirements; and QITN V, which investigated the frequency of episodes of diarrhea. Three QINTs presented disagreement with the proposed goals: QINT III, which evaluated the frequency of patients with ENT-infused volume of greater than 70%; QINT IV, which addressed the frequency of digestive fasting for more than 24 h in patients using ENT; and QINT VI, which evaluated the frequency of constipation in patients on ENT (Table V).

**Table III.** Nutritional status in cancer patients with exclusive enteral nutritional therapy

| Cancer type | W/O nutritional risk (NRS, 2002 score < 3) | | AT nutritional risk (NRS, 2002 score ≥ 3) | | Malnutrition in patients at risk (SGA B+C) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Head and neck (n = 144) | 10 | 7 | 134 | 93.0 | 112 | 83.5 |
| Gastroenterological (n = 38) | 2 | 5.2 | 36 | 94.8 | 31 | 86.1 |
| Thoracic (n = 14) | 1 | 7.1 | 13 | 92.0 | 11 | 84.6 |
| Gynecological (n = 10) | 1 | 10 | 9 | 90 | 7 | 77.7 |
| Urological (n = 3) | 0 | - | 3 | 100 | 3 | 100 |
| Lymphoma, leukemia and myeloma (n = 2) | 0 | - | 2 | 100 | 2 | 100 |
| *Total (n = 211)* | *14* | *6.6* | *197* | *93.3* | *166* | *84.2* |

*Source: Serviço de Nutrição e Dietética. NRS: Nutritional Risk Screening; SGA: subjective global assessment; SGA B+C: moderate and severe malnourishment.*

**Table IV.** Characteristics of enteral nutritional therapy in cancer patients

| Variable | Value |
|---|---|
| Length of ENT (d) | 9.7 ± 7 |
| *Quantity of ENT prescribed* | |
| Median volume (ml) | 960 (IQ 720.6;1164) |
| Median calories (kcal) | 1440 (IQ 1080;1750) |
| Mean protein (g) | 56.2 ± 20.2 |
| *ENT received* | |
| Median volume (ml) | 698 (IQ 533.3;885) |
| Median calories (kcal) | 1047.5 (IQ 797;1327) |
| Mean protein (g) | 41.9 ± 8.4 |
| *Daily deficit of ENT* | |
| Mean volume (ml/day ) | -243.1 ± 141 |
| Mean calories (kcal/day) | -363.3 ± 214.1 |
| Mean protein (g/day ) | -14.2 ± 8.41 |
| *Percentage of ENT adequacy* | |
| Prescribed volume/infused (%) | 74.3 |

*Source: Serviço de Nutrição e Dietética. ENT: enteral nutrition therapy.*

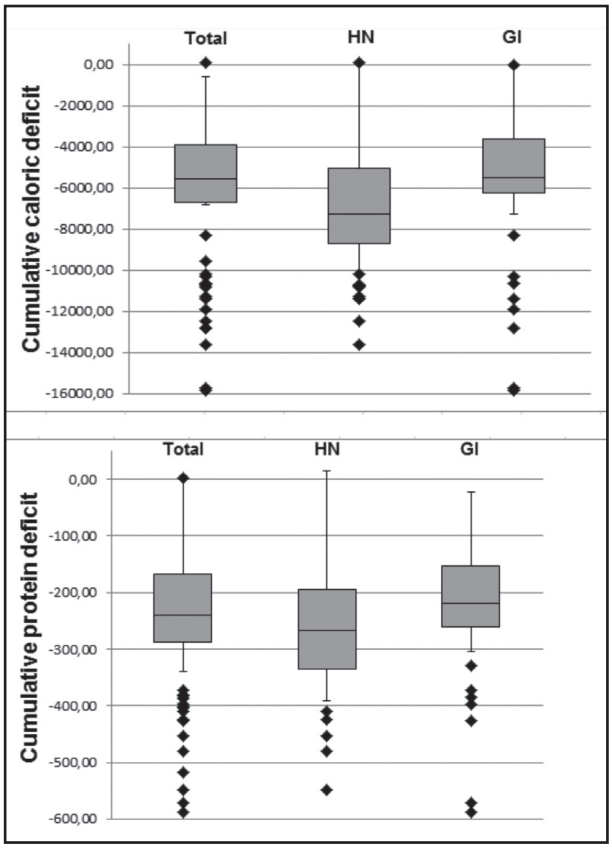


**Figure 1.**

Dispersion of cumulative caloric/protein deficit values in cancer patients treated exclusively with enteral nutritional therapy (Source: Serviço de Nutrição e Dietética. HN: head and neck cancer; GI: gastrointestinal cancer).

Most frequently prescribed drugs for patients with constipation or diarrhea were antibiotics (74.9%), opioids (76.3%), and anticholinergic drugs (53.1%). No relationship was found between prescription of these drugs and the presence of constipation. Use of anticholinergic drugs (p = 0.023) or diuretics (p = 0.007) was associated with diarrhea (Table VI). No relationship between the presence of constipation or diarrhea and chemotherapy was identified; however, patients who did not undergo chemotherapy tended to have more constipation (p = 0.059).

## DISCUSSION

Among cancer patients, malnutrition is associated with a high risk of infection and hospital admission, lower rate of survival, and

**Table V.** Quality indicators in nutritional therapy in cancer patients treated by exclusive enteral nutritional therapy

| Indicator | Result | Goal |
|---|---|---|
| I. Frequency of SGA application in patients at nutritional risk | 100% | > 80% |
| II. Frequency of estimated energy and protein needs in patients on ENT | 100% | > 80% |
| III. Frequency of patients with infused volume of ENT > 70% of prescribed | 71.5% | > 80% |
| IV. Frequency of digestive fasting > 24 h in patients on ENT | 13.2% | < 10% |
| V. Frequency of diarrhea episodes in patients on ENT | 8.1% | < 10% |
| VI. Frequency of episodes of constipation in patients on ENT | 28.6% | < 20% |

*Source: Serviço de Nutrição e Dietética. SGA: subjective global assessment; ENT: enteral nutrition therapy.*

**Table VI.** Percentage of prescribed medication use in clinical cancer patients with *vs.* without diarrhea among patients treated exclusively with enteral nutritional therapy

| Drug group | Patients W/ diarrhea (n = 17) | Patients W/O diarrhea (n = 194) | Total (n = 211) | p |
|---|---|---|---|---|
| Antibiotic | 16 (94.1) | 142 (73.2) | 158 (74.9) | 0.106 |
| Opioid | 13 (76.5) | 148 (76.3) | 161 (76.3) | 1 |
| Anticholinergic | 14 (82.4) | 98 (50.5) | 112 (53.1) | 0.023 |
| Antihistamine | 0 | 4 (2.1) | 4 (1.9) | 1 |
| Antiemetic | 9 (52.9) | 85 (43.8) | 94 (44.5) | 0.637 |
| Benzodiazepine | 0 | 11 (5.7) | 11 (5.2) | 0.66 |
| Diuretic | 10 (58.8) | 49 (25.3) | 59 (28) | 0.007 |
| Antipsychotic | 5 (29.4) | 51 (26.3) | 56 (26.5) | 1 |
| Nonsteroidal anti-inflammatory | 0 | 6 (3.1) | 6 (2.8) | 1 |
| Anticonvulsant | 3 (17.6) | 77 (39.7) | 80 (37.9) | 0.125 |
| Tricyclic antidepressant | 3 (17.6) | 39 (20.1) | 42 (19.9) | 1 |
| Antacid with aluminum | 0 | 2 (1) | 2 (0.9) | 1 |

*Source: Serviço de Nutrição e Dietética. Data are reported as n (%) or p-value.*

decreased quality of life (18). In our study, we found nutritional risk in 93.3% of cancer patients who were treated exclusively with ENT. In this group, 84.2% of patients had some degree of malnutrition (SGA B+C). These data were not in accordance with a report by Silander et al. (19), in which values of malnutrition varied from 26% to 66% among a group of 119 cancer patients.

In our study, HN and GI tract cancers were most prevalent; among this subgroup, greater than 80% of patients had malnutrition. Depending on tumor location and disease progression, these patients can suffer from anorexia and dysphagia, factors that contribute to malnutrition, which is exacerbated by a delayed cancer diagnosis and difficulty of accessing public treatment associated with low economic social status, which was prevalent amount our patient population (1-3,5,16,20).

Due to the difficulty of oral feeding in malnourished patients with HN and GI cancers, the use of ENT represents a useful alternative (3,16,18,20). However, use of ENT is not free of adverse effects, such as refeeding syndrome, high residual gastric volume, diarrhea, and constipation. In addition, successive periods of fasting for various tests or procedures result in reduced protein and calorie intakes (5,12,21). To attain the expected benefits of ENT, it must be administered properly and efficiently, in accordance with institutional guidelines (22).

To control the quality of ENT use, our hospital has applied the Brazilian QINTs (7,9,11,13) since 2008. In our study, nutritional status was assessed using the SGA (QINT I) in all patients at nutritional risk. Combined use of the NRS and SGA can predict negative clinical outcomes (23). We found 197 patients at nutritional risk and 166 with SGA B+C. Among this latter group, we calculated a mortality rate of 59%, according to the findings of Raslam *et al.* (23). These data reinforce the utility of systematic implementation of SGA in cancer patients at nutritional risk.

We estimated caloric and protein needs (QINT II) using "pocket formulas" (16) for all patients studied. Various tools can be used to estimate caloric needs in cancer patients, but indirect calorimetry

remains the gold standard in terms of performance. In clinical practice, the use of predictive equations and "pocket formulas" for estimating patient energy expenditure predominates (5,12,13,16,24).

It is assumed that patients receiving ENT volumes close to 100% of the prescribed volume will progress with lower rates of infectious complications, shorter hospital stays, and with a tendency to a lower mortality rate (25). However, discrepancies between prescribed and infused volume had been reported as an important factor for hypoalimentation including high nutritional risk patients (25-27,32). In 3390 patients at high nutritional risk at ENT, it was found poor adequacy in protein and energy supply (57.6% and 61.2%) and 74% of them did not receive at least 80% of their nutritional goal (32). In cancer patients at high nutritional risk at ENT it was found 89.1% of adequacy of the volume prescribed (28). However, in our study, 28.5% of patients received less than 70% of the prescribed volume of ENT (QINT III). Our findings were similar to those observed for critically ill patients at nutritional risk (12). This indicator can be interpreted in conjunction with the QINT IV (frequency of digestive fasting > 24 h in patients on ENT). In our group, this calculation yielded a value of 13.2% with respect to the established goal. This value is in accordance with observations for 93 critically ill patients at nutritional risk treated exclusively with ENT more than 72 h (12).

The total volume of the prescribed enteral diet that was not administered can be attributed to GI intolerance, due to abdominal distension, diarrhea, and/or vomiting, as well as fasting pauses for exams and surgical procedures (21,27-30). There are other reasons for pausing ENT, such as the absence of or noncompliance with specific ENT protocols (22,27) and failures in the logistics of ENT delivery to wards by the nutrition service (29). Successive delays in the delivery of ENT to wards, in addition to prolonged fasting times, can exacerbate the calorie and protein deficits in cancer patients treated exclusively with ENT (29).

Refusal of patients to participate in the last hours of enteral feeding at night was one reason that some did not receive full enteral nutrition (QINTs III). The unsuitability of a prescribed volume, administered effectively, resulted in a cumulative deficit of 3,000 calories and 130 g protein, which can impair the development and survival of patients (31). Given the results of QINTs III and IV, we opted to modify the ENT administration from intermittent to continuous over a period of 14 h per day. This approach resulted in improved results on QINT III (not shown).

Several barriers have been reported to prevent the full offer of the prescribed energy and protein amount to ENT patients (21,28-30). The prolonged time to achieve the nutritional goal, for example, was the main reason to contribute for energy-protein deficit in cancer patients at high nutritional risk (28). Also, GI intolerances may delay the attainability of nutritional goal in ENT patients (33). Recently we have shown that the average time to reach the nutritional target was 61.2 h for ENT cancer patients (28). The timing to advance to full nutritional goal on ENT is still unclear, but, when tolerated, enteral feeding should be advanced to full goal after 48-72 h of start. However, with reduced GI tolerance (diarrhea, constipation and/or abdominal distension) feeding should be advanced with caution to achieve full goal by 5 to 7 days (5).

Frequency of diarrhea associated with ENT varies from 9% to 41% (24,25,34). In our study, we observed a lower frequency of episodes of diarrhea in patients on ENT (QINT V). Among clinical cancer patients, diarrhea can be considered as an adverse effect of antineoplastic treatment (mucositis, enteritis) and/or associated with intensive antibiotic therapy, including *Clostridium difficile* infection (35). It is known that diarrhea can be attributed to the use of certain drugs, and we found that patients treated with anticholinergic drugs ($p = 0.023$) and diuretics ($p = 0.007$) presented diarrhea during follow-up.

We observed episodes of constipation in 28.6% of patients with ENT (QINT VI), which was beyond the desired value. Machado et al. (36) showed constipation in 58.5% of patients treated exclusively with ENT, while Bittencourt et al. (34) found constipation in 70% of patients with and without cancer, especially among those who received formula without fiber. At our institution, according to protocol, all patients with no evidence of diarrhea or GI discomfort received standard polymeric formula containing a fiber mix (soluble and insoluble; average, 20 g/d) and water as required. Drugs such as opioids have been associated with constipation (35,37); however, in our study, there was no relationship between drugs prescribed and the presence of constipation, as observed in severely ill patients in the ICU with ENT (37). Patients who did not undergo chemotherapy at our institution tended to have more episodes of constipation ($p = 0.059$).

We believe that the application of the QINTs is important and useful in evaluating the quality of nutritional care (7-13,17,24,38,39) and should be performed according to the guidelines provided by the Joint Commission on Accreditation of Health Care Organization (40) and The Task Force of Clinical Nutrition at the ILSI – Brazil (7). Evaluating the quality of nutritional care allows nutritionists to recognize deviations from established goals, which, when corrected, can ensure patient access to the very best nutritional therapy. This approach facilitates the recovery/maintenance of nutritional status at low cost and the medium- and long-term improvement of quality of life (7,9,11,17,38,39).

Many QINTs are available for use, and it is challenging for health professionals to define the QINTs to be applied at each hospital. There is no general rule for selecting a QINT. These decisions should be made based on the needs and experience at each particular institution (17).

Nutrition programs aiming improvement of ENT can be done with success, as shown by increased caring out of admission nutrition screening, implementing oral intake, ENT and parenteral nutrition, or by reducing involuntary withdrawal of enteral feeding tubes, and diarrhea episodes rates among hospitalized patients (12,24,34,38,39). In Brazil, Waitzberg and Correia (39) recently published the main implemented strategies that resulted in quality improvement of nutrition therapy. The authors pointed out that a rigorous monitoring by Nutrition Support Team is paramount, in addition to the creation/execution of continuous education projects to all members of the multidisciplinary team and the periodical selection and application of QINT.

Our study was the first to assess quality control of ENT, through the implementation and monitoring of QINTs in cancer patients treated exclusively with ENT. However, the study had certain lim-

itations. The study was developed in only one assistance referral hospital for cancer patients, had a reduced number of cancer diagnoses, and included a small number of patients. For better results, it will be necessary to carry out more studies to assess cancer patients on ENT, parenteral nutrition, and nutritional oral supplementation, and to relate QINT application to questionnaires assessing quality of life. Carrying out further studies may also allow for a reasonable comparison among health institutions and guide future strategic actions to improve nutrition therapy.

## CONCLUSION

Prevalence rates of nutritional risk and malnutrition are high among cancer patients treated exclusively with ENT. Application of ENT was moderately impaired by episodes of fasting and intestinal motility disorders. The QINTs implementation is important and useful to assess quality in the management of ENT among cancer patients at high nutritional risk.

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Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

# Estimación del coste de la nutrición parenteral domiciliaria en España

*Cost analysis of home parenteral nutrition in Spain*

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## Resumen

**Introducción:** la nutrición parenteral domiciliaria (NPD) mejora la calidad de vida de los pacientes permitiéndoles recibir nutrición en su domicilio y facilitando su integración social y laboral.

**Objetivo:** analizar el coste de la NPD en España.

**Métodos:** se realizó una revisión bibliográfica de los Registros de NPD en España (años 2007-2014), elaborados por el Grupo NADYA-SENPE. Se analizó la evolución de: pacientes que requerían NPD, episodios/paciente por los que se administró NPD, duración media de los episodios, vías de acceso y tasa de complicaciones. Se estimó el consumo y coste de la NPD. Los pacientes fueron agrupados según patología: benigna o maligna. Los costes directos (€, 2015) incluidos fueron: bolsas administradas, vías de acceso y complicaciones.

**Resultados:** el número de pacientes que recibió NPD aumentó a lo largo de los años (2007: 133 pacientes; 2014: 220 pacientes). El número medio de episodios/paciente osciló entre 1-2 episodios/año y su duración media disminuyó (2007: 323 días; 2014: 202,8 días). Las vías de acceso más utilizadas fueron los catéteres tunelizados y las complicaciones sépticas fueron las más comunes. El coste directo anual medio por paciente se estimó en 8.393,30 € y 9.261,60 € para patología benigna y maligna, respectivamente. Considerando que, en 2014, 220 pacientes requirieron NPD, el coste anual fue 1.846.524,96 € (1.389.910,55 € debidos a la fórmula de NPD) y 2.037.551,90 € (1.580.937,50 € debidos a la fórmula de NPD) para patología benigna y maligna respectivamente.

**Conclusiones:** estos resultados sirven de base para futuros análisis económicos de la NPD y para establecer estrategias de priorización eficiente de recursos disponibles.

**Palabras clave:**

Nutrición parenteral domiciliaria. Complicaciones. Vías de acceso. Análisis de costes.

## Abstract

**Introduction:** Home parenteral nutrition (HPN) improves quality of life, allowing patients to receive nutrition at home and providing a social and labor integration to these patients.

**Objective:** To assess the direct costs of HPN in adult population in Spain.

**Methods:** A literature review of the records of HPN in Spain, carry out by NADYA-SENPE Group (years 2007-2014), was performed. The analysis included the evolution of: patients requiring HPN, number of episodes/patient, mean duration of episodes, description of delivery routes and complications rate. HPN consumption and cost were estimated. Patients were grouped according to their pathological group: benign and malignant. Direct costs (€, 2015) included were: parenteral nutrition bags, delivery sets and costs due to complications.

**Results:** The number of patients who receive HPN has increased over years (2007: 133 patients; 2014: 220 patients). The average number of episodes per patient ranged from 1-2 episodes per year. The average duration of those episodes decreased (2007: 323 days; 2014: 202.8 days). Tunneled catheters were the most used and septic complications were the most common. The average annual cost per patient was estimated at € 8,393.30 and € 9,261.60 for benign and malign disease respectively. Considering that 220 patients required HPN in 2014, an annual cost of € 1,846.524.96 (€ 1,389,910.55 directly due to HPN) and € 2,037,551.90 (€ 1,580,937.50 directly due to HPN) was estimated for patients with benign and malignant pathologies respectively.

**Conclusions:** These results can be used to develop future economic evaluations on HPN and to establish efficient prioritization strategies to allocate available resources.

**Key words:**

Home parenteral nutrition. Complications. Venous access. Cost analysis.

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## INTRODUCCIÓN

La nutrición parenteral (NP) consiste en el aporte de nutrientes directamente al torrente circulatorio por vía intravenosa, a través de una vena central o periférica. Está indicada en aquellas situaciones en las que la alimentación oral o enteral es imposible, insuficiente, está contraindicada y el paciente sufre o puede sufrir un estado de desnutrición.

La desnutrición se asocia a un mayor número de complicaciones para el paciente, ocasionando un aumento de la necesidad de recursos médicos y un incremento de la inversión económica (1). Los pacientes desnutridos presentan un peor estado funcional por disminución de la masa muscular, y una disminución de la respuesta inmunitaria, lo que ocasiona un aumento de las complicaciones y una estancia hospitalaria más prolongada (2).

La NP es una terapia no exenta de complicaciones, tales como desequilibrios electrolíticos, hiperglucemia, hipertrigliceridemia, afectación hepatobiliar, complicaciones infecciosas y mecánicas asociadas al catéter venoso (3). Sin embargo, estudios recientes indican que la mayoría de las muertes acontecidas en pacientes con tratamiento de nutrición parenteral domiciliaria (NPD) estuvieron relacionadas con la enfermedad subyacente y no por una complicación en la administración de la NPD (4).

En los últimos años, ha habido un progreso en la industria farmacéutica (desarrollo de formulaciones nutricionales, catéteres) y en los sistemas sanitarios (equipos de soporte nutricionales muy especializados, mayor capacidad de seguimiento de los pacientes en el domicilio y mayor experiencia) que, junto con el desarrollo de nuevos equipos de asistencia domiciliaria (de hospitalización a domicilio y cuidados paliativos, entre otros), han puesto los medios necesarios para que estos pacientes puedan recibir NPD sin necesidad de aislarlos de su ambiente social y de asumir innecesariamente costosas hospitalizaciones (5,6).

La NPD consiste en la administración de soluciones de nutrición parenteral en el propio domicilio del enfermo, lo que permite a los pacientes estar en su entorno con mayor libertad de horarios, rodeados de su familia y de la confortabilidad de su hogar, mejorando su calidad de vida (7). Además, en ocasiones, cuando el estado funcional del paciente lo permite, se consigue incorporar al paciente a su vida social y laboral (8).

El coste de la NPD no está bien establecido en España. Por ello, el principal objetivo de este proyecto estudio fue estimar los costes directos asociados al manejo de los pacientes que requieren NPD en España, basado en los datos de los Registros de NPD, elaborados por el Grupo NADYA-SENPE (Nutrición Artificial Domiciliaria Y Ambulatoria – Sociedad Española de Nutrición Parenteral y Enteral).

## MÉTODOS

### DISEÑO DEL ANÁLISIS

El presente análisis del coste de la NPD incluyó una descripción previa de la evolución de los diferentes parámetros clínicos relacionados con el manejo de los pacientes que requieren NPD, desde el año 2007 hasta el 2014. Dicha evolución se obtuvo a través de los Registros de NPD en España en esos años, elaborados por el Grupo NADYA-SENPE (7-11).

El registro de pacientes se realiza a través de la página web del grupo NADYA. Cada Unidad de Nutrición Clínica tiene acceso al registro mediante una clave de acceso y contraseña individualizada que le permite introducir nuevos datos y visualizar los datos acumulados de su propio centro.

### POBLACIÓN DE REFERENCIA

El análisis consistió en una revisión de los registros de NPD en España, desde el año 2007 hasta el 2014, incluyendo una estimación del consumo de NPD y de su correspondiente coste. La población del análisis se compuso de pacientes registrados con tratamiento de NPD, desde el 1 de enero al 31 de diciembre de cada año evaluado, pertenecientes a los diversos centros españoles que colaboran en el registro.

### VARIABLES

Dentro de los parámetros clínicos, se analizó la siguiente información para los años 2007-2014: número de pacientes que requerían NPD en dicho año, número de episodios por paciente por los que se les administró NPD, duración media de dichos episodios al año, las diferentes vías de acceso por las cuales se administró la NPD y la tasa de complicaciones debidas a la administración de la NPD (Tabla I).

### COSTES

En este análisis se han incluido los siguientes costes: coste de las bolsas de NP administradas (bolsas elaboradas en el Servicio de Farmacia, bolsas tricamerales listas para usar y bolsas elaboradas por una empresa farmacéutica externa –*catering*–), coste de las diferentes vías de acceso venoso (catéteres tunelizados, reservorios y otras vías) y coste de las diferentes complicaciones sufridas debido a la NPD (metabólicas, mecánicas y sépticas).

No se ha considerado ningún otro coste sanitario asociado al manejo de los pacientes, como costes de ingreso hospitalario, pruebas o visitas médicas debido a la dificultad para obtener datos homogéneos. Tampoco se han tenido en cuenta los costes indirectos derivados de gastos de personal o instalaciones, ni los debidos a la enfermedad de base.

El coste de la NPD se calculó en función del tipo de enfermedad de base que requería NPD: patología benigna (definida como toda enfermedad no neoplásica activa) y maligna (definida como enfermedad neoplásica activa).

El coste anual promedio se estimó a partir de los datos obtenidos por cada uno de los miembros del panel, evaluando una muestra de los pacientes con NPD. Para ello, se tuvo en cuenta

**Tabla I.** Parámetros clínicos

| Año | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|---|---|---|
| Pacientes | 133 | 143 | 158 | 148 | 184 | 203 | 197 | 220 |
| Episodios/paciente | 1,05 | 1,03 | 1,06 | 1,07 | 1,01 | 1,04 | 1,03 | 1,04 |
| *Duración media episodio/año* | | | | | | | | |
| Días | 323,0 | 335,7 | 328,9 | 317,0 | 226,6 | 245,7 | 223,6* | 202,8* |
| Semanas | 46,1 | 48,0 | 47,0 | 45,3 | 32,4 | 35,1 | 31,9 | 29,0 |
| Vía de acceso | | | | | | | | |
| Tunelizado | 69,0% | 60,4% | 60,0% | 69,20% | 62,70% | 52,70% | 49,10% | 46,3% |
| Reservorio | 27,0% | 29,2% | 36,4% | 25,00% | 24,80% | 34,30% | 28,80% | 28,0% |
| Otras vías | 4,0% | 10,4% | 3,6% | 5,80% | 12,40% | 13,00% | 22,10% | 25,7% |
| *Complicaciones (paciente/año)* | | | | | | | | |
| Metabólicas | 0,09** | 0,05** | 0,04** | 0,01 | 0,36 | 0,31 | 0,08** | 0,07** |
| Mecánicas | 0,08** | 0,01** | 0,02** | 0,02 | 0,25 | 0,21 | 0,06** | 0,05** |
| Sépticas | 0,26 | 0,15 | 0,20 | 0,16 | 1,00 | 0,85 | 0,13** | 0,18** |

**A falta de datos, valores ajustados según recta de regresión de 2007-2012. **A falta de datos, valores ajustados en función de datos disponibles.*

**Tabla II.** Descripción de la NPD en función del tipo de patología (benigna o maligna)

| | Patología benigna | | Patología maligna | |
|---|---|---|---|---|
| | Nº medio de bolsas/semana | % de uso | Nº medio de bolsas/semana | % de uso |
| Bolsas elaboradas en Servicio de Farmacia | 4,31 | 43,33% | 6,50 | 30,00% |
| Bolsas tricamerales | 5,5 | 18,33% | 7 | 16,67% |
| Bolsas de *catering* | 3,44 | 38,33% | 2,94 | 53,33% |

el número de bolsas semanales y la duración media del episodio, así como el tipo de bolsas de NP empleadas (Tabla II).

El coste de los diferentes catéteres se obtuvo de la base de datos de costes sanitarios eSalud (12). Para estimar el coste de las complicaciones, se utilizaron costes medios de los grupos relacionados por el diagnóstico (GRD) (13). Los GRD constituyen un sistema de clasificación de pacientes que permite clasificar a los pacientes en grupos clínicamente similares y con consumo similar de recursos sanitarios. Para el coste de las complicaciones metabólicas, se utilizó un promedio de los costes de los GRD 296 (trastornos nutricionales y metabólicos misceláneos, edad mayor de 17 años con complicaciones), GRD 557 (trastornos hepatobiliares y de páncreas con complicación o comorbilidad mayor) y GRD 566 (trastornos endocrinos, nutricionales o metabólicos, excepto trastornos de la ingesta o fibrosis quística con complicación o comorbilidad mayor). Para el coste de las complicaciones sépticas se utilizó el coste del GRD 452 (complicaciones de tratamiento con complicación o comorbilidad). Para el coste de las complicaciones mecánicas se utilizó un promedio de los costes de los GRD 452 (complicaciones de tratamiento con complicación o comorbilidad) y 898 (infecciones y parasitosis con procedimiento quirúrgico).

En la tabla III se especifican los costes unitarios de los recursos incluidos en el análisis. Todos los costes incluidos en el análisis se expresan en euros (€) del año 2015.

**Tabla III.** Costes unitarios

| | |
|---|---|
| *Vía de acceso (€/vía)** | |
| Tunelizados | 614,19 € |
| Reservorios | 992,12 € |
| Otras vías | 860,76 € |
| *Complicaciones (€/episodio)*** | |
| Metabólicas | 5.257,68 € |
| Mecánicas | 6.069,02 € |
| Sépticas | 3.560,40 € |
| *Nutrición parenteral (€/bolsa)*** | |
| Bolsas elaboradas en Servicio de Farmacia | 35,21 € |
| Bolsas tricamerales | 34,68 € |
| Bolsas de *catering* | 82,50 € |

## ANÁLISIS ESTADÍSTICO

Los análisis estadísticos se desarrollaron con el programa Microsoft Excel 2013. El análisis descriptivo de los parámetros clínicos se realizó mediante gráficos de evolución de los datos del Registro NADYA a lo largo de los años 2007-2014. Las variables continuas se analizaron a partir de datos medios y tasas/año. Para la descripción de variables categóricas se utilizó el número o el porcentaje. Para el análisis de costes se utilizó la media de los diferentes costes unitarios incluidos.

## RESULTADOS

### VARIABLES CLÍNICAS

Según los datos del Registro NADYA (Tabla I), la población analizada incluyó un total de 133 pacientes que recibieron NPD en el año 2007, dato que ha ido en aumento hasta llegar a los 220 pacientes en el año 2014.

También se analizó la evolución del número medio de episodios que sufrió un paciente promedio al año. El número medio osciló entre 1 y 2 episodios, siendo el 2010, el año en el que hubo más episodios por paciente (1,7 episodios por paciente), y el año 2011, el que menos (1,1 episodios por paciente).

La duración media de los episodios disminuye con los años. En el año 2007, un episodio duraba una media de 323 días, sin embargo, en el año 2014, descendió 120 días (202,8 días por episodio).

El Registro NADYA también obtuvo información acerca de las vías de acceso por las cuales se administraba la NPD. Se observó que en los primeros años, el catéter tunelizado fue la opción más utilizada (en el 60%, 69%, 60% y 69% de los casos para los años 2007, 2008, 2009 y 2010, respectivamente). Sin embargo, a partir del año 2011, dicho porcentaje comienza a descender hasta llegar a un 46% en el año 2014. El porcentaje de pacientes que utilizaban otras vías -entre los que se encuentra el catéter venoso central de inserción periférica (PICC)-, fue incrementándose, desde un 4% en 2007, a un 26% en 2014. El porcentaje de utilización de catéter con reservorio se mantiene constante a lo largo de los años, oscilando entre el 20 y el 30% de pacientes.

La tasa de complicaciones debidas a la NPD también fue registrada por el grupo NADYA. Las complicaciones sépticas fueron las más comunes, seguidas de las metabólicas y, por último, las mecánicas. Sin embargo, la tasa por paciente y año, para los tres tipos de complicaciones, fue baja (0,18, 0,07 y 0,05 para las sépticas, metabólicas y mecánicas, respectivamente).

### COSTES DE LA NPD EN FUNCIÓN DEL TIPO DE PATOLOGÍA

El análisis de costes se desarrolló tomando como referencia dos perfiles de pacientes en función del tipo de patología: benigna o maligna.

El coste directo anual medio de un paciente con patología benigna que requiere NPD se estimó en 8.393,30 €. Para un paciente con patología maligna, ascendió a 9.261,60 € (Tabla IV).

Considerando que, para el año 2014, un total de 220 pacientes requirieron NPD, se estimó un coste total anual de 1.846.524,96 €, para el caso de pacientes con patologías benignas, incluyendo los 1.389.910,55 € debidos a la fórmula de la NPD. Para el caso de los pacientes con patologías malignas, el coste total anual, para el mismo número de pacientes, ascendería a 2.037.551,90 €, incluyendo 1.580.937,50 € debidos a la fórmula de la NPD.

Tanto en los pacientes con patologías benignas como en los que padecían patologías malignas, la NP fue el recurso que más contribuyó a dicho coste, suponiendo un 75% y un 78% del coste total considerado en este estudio, respectivamente. Por el contrario, los catéteres venosos, fueron las que supusieron un menor coste (un 9% y un 8% sobre el coste total, para patologías benignas y malignas, respectivamente).

**Tabla IV.** Costes totales de la NPD

| | Patología benigna | | Patología maligna | |
|---|---|---|---|---|
| | **Coste (€)** | **%** | **Coste (€)** | **%** |
| *Coste medio por paciente - año 2014* | | | | |
| Nutrición | 6.317,78 € | 75% | 7.186,08 € | 78% |
| Vías de acceso | 783,38 | 9% | 783,38 | 8% |
| Complicaciones | 1.292,14 € | 16% | 1.292,14 € | 14% |
| *Total* | *8.393,30 €* | | *9.261,60 €* | |
| *Coste total 220 pacientes - año 2014* | | | | |
| Nutrición | 1.389.910,55 € | | 1.580.937,50 € | |
| Vías de acceso | 172.343,44 € | | 172.343,44 € | |
| Complicaciones | 284.270,96 € | | 284.270,96 € | |
| *Total* | *1.846.524,96 €* | | *2.037.551,90 €* | |

## DISCUSIÓN

La NPD está indicada en aquellos pacientes, tanto niños como adultos, que no tienen un tracto gastrointestinal funcional o accesible, o bien, en los que son incapaces de mantener un estado nutricional adecuado con alimentación natural y artificial, oral o enteral, y no necesitan estar ingresados en un centro hospitalario para asegurar sus cuidados (14). Las ventajas que esto implica son: una mayor comodidad para el paciente y su reinserción en su entorno familiar y social, la oportunidad de mejora de la gestión de camas hospitalarias para el sistema sanitario y, por consecuencia, una mayor eficiencia económica. Todo ello hace prever que esta modalidad de NP se convierta progresivamente en una práctica consolidada en muchos hospitales de referencia (15).

En España, desde el año 1992, el registro del grupo NADYA de la Sociedad Española de Nutrición Enteral y Parenteral trata de cuantificar la dimensión de la Nutrición Artificial Domiciliaria, tipificar la distribución por patologías, vías y modos de infusión, además de otras variables. A pesar de las ventajas clínicas demostradas para los pacientes, y económicas para el Sistema Nacional de Salud, de sus informes se podría deducir que la NP en España es menos utilizada que en otros países de la Unión Europea (16-19). No obstante, es posible que exista un registro sesgado, ya que no todas las Unidades participan, al tratarse de un registro voluntario.

Sin embargo, tal y como se observa en dichos registros, el empleo de la NPD va en progresivo aumento. Esto es debido a diferentes avances como las bolsas listas para usar, los servicios de *catering* y la mayor experiencia de los diferentes equipos sanitarios (15). Otra causa de la progresión del uso de la NPD en España es el mayor número de pacientes considerados como candidatos a recibir NPD, sobre todo, pacientes oncológicos, que conforman el grupo patológico más numeroso desde 2003 (9).

A pesar de sus múltiples ventajas, es una técnica no exenta de complicaciones, aunque la mayoría de ellas están relacionadas con la enfermedad de base del paciente. Por ello, hay que ser estrictos en sus indicaciones y valorar en todo momento los beneficios y riesgos de su utilización, ya que suponen una elevada carga asistencial y un coste económico considerable (20). La incidencia de las complicaciones relacionadas con la NPD ha ido disminuyendo con el tiempo debido a la existencia de un equipo multidisciplinar experimentado, de protocolos de seguimiento clínico y analíticos y del empleo de técnicas de sellado del catéter con antisépticos o antimicrobianos, convirtiendo la NPD en un tratamiento cada vez más seguro (21-23). La estandarización de las bolsas de nutrición no modifica la calidad de la NP (3), y contribuye a minimizar el número de complicaciones, reduciendo el riesgo de error de cálculo para su formulación, así como el riesgo de infección, ya que se reduce el manejo de los constituyentes de la solución (6,24,25).

Según los resultados obtenidos en este análisis de costes directos, la NPD es un tratamiento que cuesta entre 8.393,30 € y 9.261,60 € por paciente y año, incluyendo los gastos atribuibles a las posibles complicaciones de la NPD. Diversos estudios en diferentes países examinaron diferentes aspectos económicos del tratamiento con NPD (26-34). La mayoría de estos estudios incluye únicamente costes directos sanitarios. Solo en algunos de ellos se incluyen los gastos atribuibles a las complicaciones de la NPD que requieren la hospitalización del paciente. Según sus resultados, el coste anual por paciente es de 75.000-150.000 $ en EE. UU. y 25.000 £ en Reino Unido, costes más altos que los obtenidos para España. Dichos estudios también muestran que la NPD es un 65-80% más barata que el tratamiento con nutrición parenteral en el hospital.

El presente análisis no está exento de una serie de limitaciones que deben tenerse en cuenta a la hora de interpretar los resultados obtenidos. Dado que los registros nacionales se realizan de forma voluntaria al no existir ninguna normativa que obligue a su declaración (35), es posible que las cifras registradas sean datos que infravaloren la realidad. De igual modo, al basarnos en la información reflejada en dichos registros, solo se han podido incluir costes directos sanitarios. Además, los resultados del presente análisis no conllevan la misma calidad metodológica que los que se podrían obtener mediante un estudio prospectivo, diseñado específicamente para recoger los recursos y costes asociados al manejo de los pacientes que requieren NPD. Sin embargo, sí que puede considerarse como una herramienta útil que proporciona información sobre la tendencia de costes para estos pacientes.

A pesar de las limitaciones descritas, conocer la magnitud y características de la NPD en España, puede facilitar la toma de decisiones, tanto clínicas como de gestión.

## CONCLUSIONES

La NPD es un tratamiento que en España tiene unos costes directos que oscilan entre 8.393,30 € (patología benigna) y 9.261,60 € (patología maligna) por paciente y año, incluyendo únicamente los gastos atribuibles a las formulaciones de NPD, los catéteres venosos y el manejo de las complicaciones de la NPD.

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ARÁN

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Trabajo Original

Paciente crítico

# Oral glutamine reduces myocardial damage after coronary revascularization under cardiopulmonary bypass. A randomized clinical trial

*La glutamina oral reduce el daño miocárdico tras revascularización coronaria bajo derivación cardiopulmonar. Un ensayo clínico aleatorizado*

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## Abstract

**Background:** Glutamine is the most abundant free amino acid in the body. It modulates immune cell function and is an important energy substrate for cells in critically ill patients. Reduction of injury cardiac markers had been observed in patients receiving intravenous glutamine and in a pilot study with oral glutamine. The aim of this study was to analyze the effect of preoperative oral supplementation of glutamine on postoperative serum levels of cardiac injury markers.

**Methods:** A randomized clinical trial was performed in 28 Mexican patients with ischemic heart disease who underwent cardiopulmonary bypass with extracorporeal circulation. Patients were randomly assigned to receive oral glutamine (0.5 g/kg/day) or maltodextrin 3 days before surgery. Cardiac injury markers as troponin-I, creatine phosphokinase, and creatine phosphokinase-Mb were measured at 1, 12, and 24 hours postoperatively.

**Results:** At 12 and 24 hours serum markers levels were significantly lower in the glutamine group compared with controls ($p = 0.01$ and $p = 0.001$, respectively) ($p = 0.004$ and $p < 0.001$, respectively). Overall, complications were significantly lower in the glutamine group ($p = 0.01$, RR = 0.54, 95% CI 0.31-0.93). Mortality was observed with 2 cases of multiple organ failure in control group and 1 case of pulmonary embolism in glutamine group ($p = 0.50$).

**Conclusion:** Preoperative oral glutamine standardized at a dose of 0.5 g/kg/day in our study group showed a significant reduction in postoperative myocardial damage. Lower cardiac injury markers levels, morbidity and mortality were observed in patients receiving glutamine.

**Key words:**

Glutamine. Cardiac surgery. Cardiopulmonary bypass. Troponin-I. CPK. CPK-Mb.

## Resumen

**Introducción:** la glutamina es el aminoácido libre más abundante en el cuerpo. Modula funciones celulares inmunológicas y es un sustrato importante de energía. Se observó reducción de los marcadores de daño cardiaco en pacientes que recibieron tanto glutamina intravenosa como oral en un estudio piloto. Nuestro objetivo fue analizar el efecto preoperatorio con suplementación de glutamina oral sobre los niveles postoperatorios de los marcadores de lesión cardiaca.

**Métodos:** ensayo clínico aleatorizado con 28 pacientes mexicanos con cardiopatía isquémica y sometidos a *bypass* cardiopulmonar con circulación extracorpórea. Los pacientes fueron asignados al azar para recibir glutamina oral (0,5 g/kg/día) o maltodextrina 3 días antes de ser operados. La troponina-I, creatinina fosfoquinasa y creatinina fosfoquinasa-Mb fueron medidas a la hora, 12 y 24 horas postoperatorias.

**Resultados:** a las 12 y 24 horas los niveles séricos de marcadores fueron menores en el grupo de glutamina comparado con los controles ($p = 0,01$ y $p = 0,001$, respectivamente) ($p = 0,004$ y $p < 0,001$, respectivamente). Las complicaciones fueron menores en el grupo de glutamina ($p = 0,01$, RR = 0,54, 95% IC 0,31-0,93). La mortalidad ocurrió en 2 casos con dos falla orgánica múltiple en el grupo control y 1 caso de tromboembolia pulmonar en el grupo de glutamina ($p = 0,50$).

**Conclusión:** la administración estandarizada de glutamina oral de manera preoperatoria (0,5 g/kg/día) en nuestro estudio demostró una reducción significativa del daño miocárdico postoperatorio. Los niveles séricos de marcadores cardiacos, la morbilidad y mortalidad fueron menores en los pacientes que recibieron glutamina.

**Palabras clave:**

Glutamina. Cirugía cardicaca. *Bypass* cardiopulmonar. Troponina-I. CPK. CPK-Mb.

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## BACKGROUND

Glutamine (GLN) is the most abundant free amino acid in the body and is commonly known as a nonessential amino acid, because of the ability of most cells to produce it. It has many essential metabolic functions in the organism, such as the transportation of nitrogen, and is the most important substrate for renal ammoniagenesis (1-3). GLN is also a beneficial substrate for metabolically stressed patients, especially during critical illness, where patients experience general nutritional depletion and augmented infectious complications, which are correlated with low plasma GLN concentrations (4-8). GLN has an important influence on the inflammatory response, oxidative stress, apoptosis modulation, and the integrity of the gut barrier (9-11) through the attenuation of multiple inflammatory pathways. It decreases nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) expression, protein kinases, and inhibits the increase in nitric oxide synthase expression (12).

Moreover, GLN has beneficial immune functions related to cardiac protection after ischemia/reperfusion (I/R) in cardiopulmonary bypass (CPB); it increases myocardial adenosine triphosphate-adenosine diphosphate (ATP-ADP) substrate, prevents intracellular lactate accumulation, and enhances the accumulation of myocardial glutathione (GSH), a major stress substrate for the stressed myocardium, post-I/R injury (13). Patients undergoing CPB are at increased risk of having abnormal inflammation in their body after surgery. Such inflammation can contribute to slower recovery from surgery, an increased risk of infection, an increased risk of damage to organs other than the heart, and a more complicated course (14).

Numerous experimental and clinical trials have demonstrated the cardioprotective effects of GLN, including dose-dependent enhanced myocardial functional recovery following acute normothermic ischemia in rats (15). GLN has also been shown to reduce infarct size to approximately 39% in a rabbit model following ischemia/reperfusion injury (16). GLN treatment also increased load tolerance in patients with ischemic heart disease (IHD) (13,17).

Enteral GLN is suggested to contribute to de novo synthesis of Arginine (ARG). ARG is an important regulator of protein synthesis and proteolysis, and is the sole precursor for nitric oxide generation, a signaling agent with a crucial role in immunity, inflammation, and organ perfusion. GLN supplementation is suggested to be a more physiologic way of correcting ARG concentrations and subsequently achieving both GLN and ARG benefits. GLN, by restoring ARG availability should improve tissue oxygenation and myocardial protection (18).

Despite various experimental data showing the cardioprotective effects of GLN, there is a lack of clinical trials with patients undergoing CPB. The finding that lower levels of cardiac injury markers are observed in patients treated with oral GLN prior to CPB can have major implications for these patients. The purpose of this study was to determine whether an oral supplementation of 0.5 g/kg GLN prior to heart surgery contributes to a reduction in cardiac injury markers, postoperative complications, and mortality in Mexican patients.

## METHODS

### PATIENTS

A randomized clinical trial was performed in 28 Mexican patients with a confirmed diagnosis of IHD who underwent CPB with extracorporeal circulation. The study was conducted between January 2014 and September 2015 in the Specialty Hospital of the Western National Medical Center, Mexican Institute of Social Security.

The present protocol included men and non-pregnant women aged 40-70 years with a confirmed diagnosis of IHD that required coronary revascularization under CPB. All surgical procedures were performed under the same anesthetic technique and the same group of cardiovascular surgeons.

Exclusion criteria included preexisting kidney or liver dysfunction, demonstrated with a creatinine level above 1.6 mg/dl and total bilirubin level above 2 mg/dl. Also, any comorbid condition, such as drug or alcohol abuse, human immunodeficiency virus infection, hepatitis B or C or suspicious of any active infection defined as presence of fever above 37.8 °C, leukocytosis with or without a positive culture. Also patients with known allergies to the components of GLN or maltodextrin as well as signs of ongoing ischemia (defined by a persistent elevation of troponin-I [TROP-I] and creatine phosphokinase-Mb [CPK-Mb] levels and ingestion of high-protein diet or a diet with any supplemental GLN) were not considered candidates for this study.

### TREATMENT

Following study enrollment, patients were randomly assigned (blinded envelopes were opened sequentially by a blinded study pharmacist) to receive oral GLN supplement (study group) or maltodextrin as an isocaloric complex carbohydrate as control group.

All investigators and clinical caregivers were blinded to the study intervention. All patients in the GLN group received an oral GLN supplement (Glutapack-10™ VICTUS, Miami, FL, USA). The total GLN/maltodextrin dose given to patients was standardized to 0.5 g/kg/day for the 3 days prior to CPB and one final dose of 0.25 g/kg/day of GLN/maltodextrin on the morning of surgery, 4 hours prior to initiation of anesthesia. Compliance with ingestion of the study drug was assessed via daily reminder calls from the study investigator and required empty package returns.

### PATIENT SAMPLE COLLECTION AND ANALYSIS

Blood was collected at baseline (one hour prior to surgery) and one hour after surgery, and then at 12 and 24 hours postoperatively. After collection, blood was processed for the analysis of the cardiac injury markers TROP-I, creatine phosphokinase (CPK), and CPK-MB, and analyzed using Meso Scale technology (Meso Scale

Discovery, Gaithersburg, MD, USA). These markers constituted the primary outcome variables.

## CLINICAL DATA COLLECTION

All essential demographic information was obtained of all patients. Preoperative cardiac evaluation included cardiac ejection fraction measured closest to the surgical procedure, and during surgery total pump time and aortic clamping time were included in the analysis.

Infectious complications were defined as follow: Systemic inflammatory response syndrome was defined as a systemic response to a variety of severe clinical insults manifested by at least 2 of the following conditions: a) temperature > 38 °C or < 36 °C; b) heart rate faster than 90 beats/min; c) respiratory rate faster than 20 breaths/min or an arterial partial pressure of carbon dioxide below 4.3 kPa; and d) white blood cell count larger than 12,000 cells/mm$^3$, less than 4,000 cells/mm$^3$, or more than 10% of immature forms. Sepsis was defined as the systemic response to infection and septic shock was defined as sepsis with hypotension despite adequate fluid resuscitation and the presence of perfusion abnormalities, including but not limited to lactic acidosis, oliguria, or an acute alteration in mental status. Multiple organ dysfunction syndrome was defined as the presence of altered organ function in an acutely ill patient such that homeostasis could not be maintained without intervention.

Other Infectious morbidity included pneumonia which was defined as a chest radiographic examination showing new or progressive infiltrate, consolidation, and cavitation (interpreted by a radiologist blinded to a patient's treatment assignment), and at least 2 of the following: a) temperature above 38.5 °C or below 35°C; b) a white blood cell count larger than $10 \times 10^3$/L or less than $3 \times 10^3$/L; and c) isolation of pathogens from the sputum, bronchial aspirates or bronchial brushing. Bacteremia was diagnosed when a pathogen was isolated from the blood with a temperature above 38.5 °C or below 35 °C or a white blood cell count larger than $10 \times 10^3$/L or less than $3 \times 10^3$/L, and it was not related to infection at another site. Urinary tract infection was defined as the isolation of at least $10^5$ colonies/mL of a pathogen from the urine.

Catheter-related sepsis was diagnosed if the patient had local signs of infection at the entry site, a temperature > 38.5 °C or < 35 °C, a white blood cell count > $10 \times 10^3$/L or < $3 \times 10^3$/L that resolved after catheter removal with no other infection site, the semi quantitative culture of the catheter tip showing more than 15 colony-forming units/mL, or isolation of a pathogen from blood cultures.

Inotropic support was defined as a requirement for infusion of an inotrope or vasopressor (dopamine, adrenaline, dobutamine, noradrenaline) equivalent to dopamine dosages (> 5 µg/kg per minute) or their combination for at least 8 hours after surgery.

Secondary efficacy parameters included durations of hospital stay, intensive care unit (ICU) stay, ventilatory support, and the incidence of mortality.

## SAMPLE SIZE

The sample size was predetermined. We consider the results obtained by Sufit et al. (12), in a pilot study, which evaluated markers of myocardial damage in patients undergoing cardiac surgery and who received or not received oral glutamine preoperatively. They showed a drop of more than 50% in the level of troponin I, 24 hours after the study compared to the control. Using a formula for mean differences, with a confidence level ($\alpha$) of 0.05 and a power ($\beta$) of 0.10, a total of 14 patients per group were established as sufficient.

## STATISTICAL ANALYSIS

Descriptive analyses for quantitative variables included the mean, standard deviation, and standard error of the mean (SEM) for values related to cardiac injury markers. Raw numbers and percentages were used for qualitative variables. Inferential statistical analyses included the parametric Student's *t* test for independent samples and the $\chi^2$ test and/or Fisher's exact test. Relative risk (RR) and 95% confidence intervals were also calculated. A p value < 0.05 was considered significant. Office Excel 2007 (Microsoft Corp., Redmond, WA, USA) and SPSS version 20 for Windows (IBM Corp., Armonk, NY, USA) were used for data processing and statistical analysis, respectively.

## ETHICAL CONSIDERATIONS

The study was conducted according to the principles of the Declaration of Helsinki of 1989 and the Mexican Health Guidelines for Human Research. The study protocol was approved by the Mexican Local Committee for Ethics and Research (2014-1301-76) and was registered at www.clinicaltrials.gov with the identifier number NCT02491931. All patients included gave their signed informed consent to participate in this study.

## RESULTS

During the period of study, 317 patients underwent cardiac surgery. Ninety-eight patients required valve replacement, 69 patients were treated without CPB (off-pump coronary revascularization), 55 required valve replacement and coronary revascularization, 29 patients presented with hepatitis B or C infection, kidney or liver insufficiency, or a history of a high-protein diet, and 21 were treated for tumors or congenital conditions. Forty-five patients were suitable for inclusion in the study, but 17 patients did not accept the invitation to participate. The remaining 28 patients agreed to participate. They were randomized into two groups: the GLN group (n = 14) and the control (CONT) group (n = 14). All patients were diagnosed with ischemic heart disease and underwent coronary revascularization with extracorporeal circulation. The gender distribution was equal in both groups, with 3 women

(21.4%) and 11 men (78.6%) in each group. The mean ages were 62.5 ± 7.4 and 63.2 ± 8.0 years for the GLN and CONT groups, respectively, with no statistical difference (p = 0.82). The results are illustrated in table I.

Anthropometric data revealed normal weight in 7 patients in the GLN group and overweight or obesity in the remaining 7. In contrast, the CONT group consisted of 5 patients of normal weight and 9 overweight or obese patients. However, the difference was not statistically significant (p = 0.73). The body mass index (BMI) was similar between groups, 25.7 ± 3.1 and 24.4 ± 2.3 for GLN and CONT groups, respectively (p = 0.23). Among the comorbid conditions, smoking, alcohol consumption, and dyslipidemia incidences were also similar between groups, as shown in table I. Preexisting type 2 diabetes mellitus was observed in a large proportion of our patients; however, the most common comorbid condition was arterial hypertension, with an incidence of 78.5% of the total sample (n = 22). The preoperative evaluation of cardiac function revealed a mean left ventricular ejection fraction of 52.5 ± 13.3 and 48.0 ± 28.3 L/min in the GLN and CONT groups, respectively (p = 0.60). The total pump time during surgery was 111.0 ± 40 min in the GLN group and 127.8 ± 38.1 min in the CONT group (p = 0.27). The total duration of aortic clamping was similar between groups.

## CARDIAC INJURY MARKERS

Troponin-I serum levels at 24 hours postoperatively were lower in the GLN group (1.9 ± 0.24) than in the CONT group (3.02 ± 0.25). This difference was statically significant (p = 0.004). At 12 hours postoperatively, their levels were also lower in comparison to the CONT group (2.07 ± 0.21 *vs.* 2.7 ± 0.26, p = 0.06); troponin-I levels were slightly lower after surgery, as shown in figure 1A.

Similarly, CPK levels were also found to be lower in the GLN group than in the CONT group at 12 hours postoperatively. The difference was statically significant (p = 0.01), as shown in figure 1B.

Regarding to CPK-Mb, serum levels were also lower in the GLN group than in the CONT group at 1, 12, and 24 hours postoperatively with significant differences, as shown in figure 1C.

## POSTOPERATIVE COURSE

The complications in both groups are described in table II. There were no differences in individual complications between groups. These included postoperative vasopressor requirement, postoperative arrhythmias (atrial fibrillation), myocardial infarction, postoperative bleeding requiring surgical reintervention for hemostasis, and infections, which included two episodes of pneumonia, one of which also developed purulent mediastinitis (CONT group), and a urinary tract infection in one patient (GLN group). The overall morbidity was significantly less frequent in the GLN group (p = 0.01, RR = 0.54, 95% CI 0.31-0.93) and the number of patients with complications was also lower in the GLN group (p = 0.02, RR = 0.50, 95% CI 0.20-0.95%).

Mortality was observed in 3 patients. Of these, multiple organ failure was observed in two cases (pneumonia and pneumonia plus purulent mediastinitis) in the CONT group (14.2%) and pulmonary embolism was observed in one case in the GLN group (7.1%); no significant difference was observed between the groups (p = 0.54). The mean length of hospital stay in the UCI

**Table I.** Baseline characteristics of patients

| | GLN group (n = 14) | CONT group (n = 14) | p value |
|---|---|---|---|
| *Gender (n, %)* | | | |
| Female | 3 (21.4) | 11 (78.6) | 1.0 |
| Male | 3 (21.4) | 11 (78.6) | |
| Age (years) | 62.5 ± 7.4 | 63.2 ± 8.0 | 0.82 |
| *BMI (kg/m²)* | 25.7 ± 3.1 | 24.4 ± 2.3 | 0.23 |
| Normal (n, %) | 7 (50) | 5 (35.7) | 0.73 |
| Owt/Ob* (n, %) | 7 (50) | 9 (64.2) | |
| Smoking (n, %) | 8 (57.1) | 8 (57.1) | 1.0 |
| Alcohol consumption (n, %) | 5 (35.7) | 5 (35.7) | 1.0 |
| Dyslipidemia (n, %) | 5 (35.7) | 6 (42.8) | 0.69 |
| Diabetes mellitus (n, %) | 8 (57.1) | 10 (71.4) | 0.43 |
| Arterial hypertension (n, %) | 11 (78.6) | 11 (78.6) | 1.0 |
| Preoperative left ventricular ejection fraction (%) | 52.5 ± 13.3 | 48.0 ± 28.3 | 0.60 |
| Aortic clamping time (min) | 71.4 ± 24.9 | 90.2 ± 34.1 | 0.10 |
| Extracorporeal circulation time (min) | 111.0 ± 40 | 127.8 ± 38.1 | 0.27 |

**Owt: overweight. Ob: obesity.*

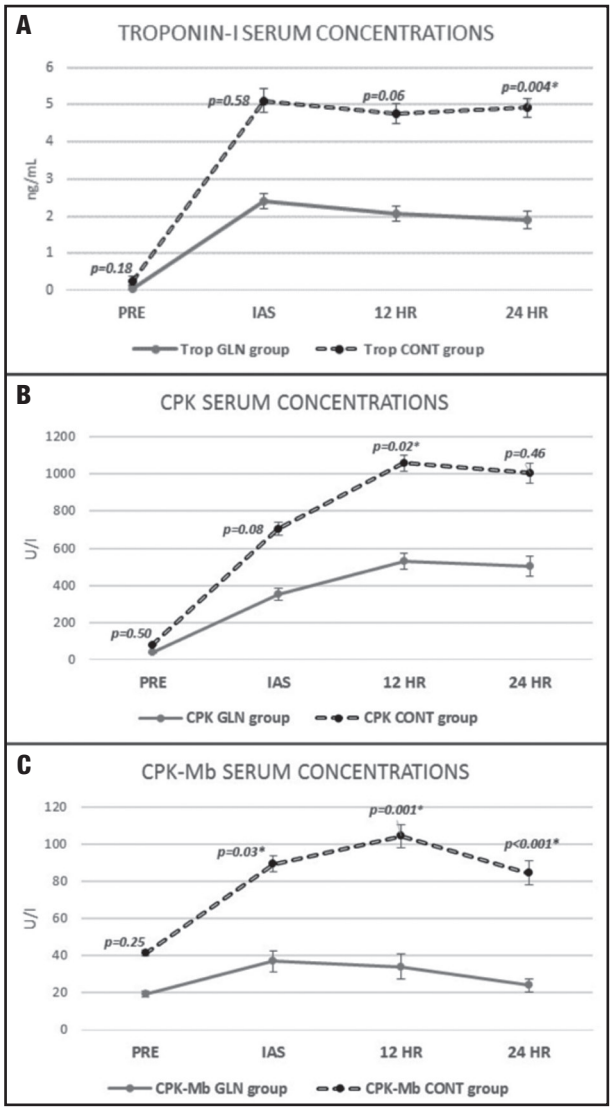


**Figure 1.**

Cardiac injury serum concentrations. Troponin-I, CPK and CPK-Mb levels in GLN and CONT groups at baseline (PRE), 1 hour after surgery (IAS), 12, and 24 hours.

was 4 ± 1.9 days for the GLN group and 4.7 ± 2.4 days for the CONT group, with no significant difference (p = 0.24).

## DISCUSSION

Preoperative oral supplementation of GLN at a standardized dose of 0.5 g/kg/day in our study group showed a significant reduction in postoperative myocardial damage. Lower TROP-I, CPK-Mb, and CPK levels were observed in patients receiving GLN, and the total morbidity and total number of patients with any complications was also lower in this group.

Elevated TROP-I levels are common in patients who undergo CPB. A close correlation between TROP-I concentration and mortality during postoperative follow-up has been recognized (19). Numerous mechanisms for the cardioprotective effects of GLN have been described in multiple studies (20).

GLN is also an indirect precursor of GSH, and is involved in antioxidant protection by increasing the ratio of reduced to oxidized GSH. The correlation between the perioperative use of GLN and plasma GSH concentrations in patients after CPB has been previously shown (21). Moreover, in cases of I/R injury, GLN increases the myocardial adenosine triphosphate- adenosine diphosphate ratio and prevents intracellular lactate accumulation (9).

The supplementation of GLN has contributed new and valuable information to allow clinicians to understand the mechanism associated with the reduction in myocardial damage after heart surgery. Lomivorotov et al. in 2011, demonstrated a significant reduction in TROP-I levels after CPB with coronary artery bypass grafting at 24 hours postoperatively (p = 0.035) in patients who received intravenous GLN (Dipeptiven, 0.4 g/kg per day; Fresenius Kabi, Bad Homburg, Germany); the median stroke index was also higher in the study group (p = 0.023), and there was decreased median systemic vascular resistance (p = 0.001). There were no significant differences in the postoperative complications or mortality between groups (13). Under that same line of investigation, in 2012, Sufit and colleagues also observed that GLN conferred cardiac protection when supplemented orally (37.5 g/per day) during the 3 days prior to surgery in patients who underwent CPB

**Table II.** Postoperative complications and mortality

| | GLN group | CONT group | p value | RR (95% CI) |
|---|---|---|---|---|
| Vasopressor requirement | 4 (28.5%) | 5 (35.7%) | 0.68 | 0.80 (0.22-2.37) |
| Auricular fibrillation | 1 (7.1%) | 3 (21.4%) | 0.28 | 0.33 (0.04-2.83) |
| Myocardial infarction | 0 | 1 (7.1%) | 0.30 | NC* |
| Bleeding | 1 (7.1%) | 1 (7.1%) | 1.0 | 1.0 (0.07-14.45) |
| Infection | 1 (7.1%) | 3 (21.3%) | 0.28 | 0.33 (0.04-2.83) |
| Total morbidity | 7 | 13 | 0.01 | 0.54 (0.31-0.93) |
| Total patients with complications | 6 | 12 | 0.02 | 0.50 (0.20-0.95) |
| Mortality | 1 (7.1%) | 2 (14.2%) | 0.50 | 0.50 (0.05-4.90) |

*Not calculable.*

without artery bypass grafting. TROP-I, CPK, and CPK-Mb levels were significantly lower at 24, 48, and 72 hours postoperatively ($p < 0.03$, $p < 0.05$, and $p < 0.04$), respectively, in the study group. This reduction in myocardial injury was associated with a reduction in clinical complications ($p = 0.03$). This pilot feasibility trial assessed the safety, tolerability, and patient compliance of preoperative supplementation of oral GLN therapy in patients undergoing CPB. Given the small sample size ($n = 10$), the potential for clinical efficacy must be confirmed in a larger, definitive multicenter trial of GLN therapy prior to cardiac surgery (22).

In comparison with previous studies of oral supplementation of GLN, we observed a stronger effect in the GLN group. Comorbidities were also observed in a large number of patients, at both study groups, as shown in table I. The determination of cardiac injury markers are indicative of myocardial damage and worse prognosis, that's why it was so important in our study to measure all the markers to relate our results, that also support those previously reported regarding the reduction of cardiac injury markers such as TROP-I, CPK-Mb, and CPK, suggesting a beneficial clinical effect in patients undergoing open heart surgery for multi-vessel ischemic disease, reducing myocardial I/R injury during CPB in Mexican patients with this exclusive condition (21). A convenient and practical administration regimen of preoperative GLN at safe doses (0.5 g/kg per day and cumulative) resulted in a robust benefit that is a favorable benefit-risk. This action resulted in a decrease in all cardiac injury CPB patients. There were no significant differences in clamp time or pump time between groups, and times were consistent with published normal and safe values. In our cohort, the comorbid conditions presented before surgery may have influenced postoperative morbidity but nevertheless they also had clear and robust benefit and was safe and well tolerated included in this patient population with multiple clinical conditions and different morbidities, glutamine was effective. Diabetes is a risk factor for cardiovascular disease and is associated with an elevated risk of coronary heart disease, hence the impaction glutamine on cardiac biochemistry and function may reflect in cardioprotection beyond purely ischemic events, but also in conditions of metabolic dysregulation that impact cardiac and cardiovascular function. More than 50% of our patients suffered diabetes mellitus in addition to another comorbid condition. Recently, Mansour et al. (23) demonstrated that 6 weeks of oral GLN supplementation (30 g/d) was safe and significantly reduced some cardiovascular risk factors such as fasting plasma glucose, HbA1c levels, blood pressure, and waist circumference in patients with type 2 diabetes. In addition, the oral GLN supplementation reduced the effect of a high-fat diet on the incidence of obesity, which is an important risk factor in the development of myocardial infarction.

In our study, the number of postsurgical complications, such as vasopressor requirement, atrial fibrillation, and myocardial infarction, was less frequent in the GLN group. The clinical population of this study had a lot of comorbidities and cardiovascular risk factors. The fact that GLN was consistently effective (and safe at the regimen dose used) in this clinical population, opens a new possibilities for more detailed and larger studies on GLN and cardioprotection, impact on cardiac and vascular function, and complications. Glutamine depletion occurs in critically injured patients, and may contribute to the high rate of infection. In our study we had 3 patients complicated with infection in the control (CONT) group and 1 in the GLN group. Although our sample was relatively small, a fourteen control clinical trials meta-analysis done by Wang et al., showed that the risk of infection was reduced in patients who received GLT parenteral nutrition compared with normal parenteral nutrition ($p = 0.02$) (24), other possible directions for further research of oral supplementation of glutamine in patients with multiple co-morbidities and different disease conditions and underlying pathophysiologies, like is a fact known that the myocardial concentration of glutamine changes during ischemia and reperfusion due to alterations in metabolic and ionic processes.

Because myocardial damage is directly related to the degree of cell damage by ischemia, deeper and wider intervention in more patients will clarify the cardioprotective effects of GLN in cardiac surgery. More complicated cases could be interesting, and may help to strengthen our results.

This form of oral supplementation may be a safe and practical way for the patient to lower the concentrations of TROP-I during the postoperative period without the need for medical assistance. Because both oral and intravenous administrations were shown to reduce the equally dependent perioperative variables in previous studies, it is recommended that a study of both interventions is conducted with the same type of patients during the pre/postoperative period.

The present study has some limitations that must be addressed. We were unable to study all of the mechanisms involved in the cardioprotective effects of GLN. Thus, it may be interesting to evaluate whether a correlation exists between GLN oral supplementation and myocardial HSP expression, as well as proinflammatory interleukins IL-1, IL-6, TNF-$\alpha$, and myoglobin, which have been found to contribute to cardiac injury (25). Another limitation was that the cohort included patients with a low ejection fraction (< 50%) and with comorbidities such as diabetes mellitus (64.2%) and hypertension (78.5%), which may explain the relatively high morbidity in both groups of patients, although it can be considered a limitation of the study, the observation of a beneficial effect of oral glutamine (at a safe regimen) in the clinical patient population of the present study (that is, with heterogeneous disease condition and comorbidities) also suggest that glutamine has effect in these complex population which then may benefit from preoperative oral supplementation of glutamine, this needs to be followed in larger clinical studies.

In summary, the majority of these findings may be related to GLN supplementation, suggesting that it has the ability to enhance cell survival during I/R, attenuate the systemic inflammatory response, oxidative stress, apoptosis modulation, and the integrity of cardiac cells by increasing myocardial ATP/ADP substrate, and enhance myocardial GSH (26).

## CONCLUSIONS

This study demonstrated that oral supplementation of GLN prior to cardiac surgery confers a protective effect on the heart by

decreasing the biochemical injury markers and clinical complications. These data indicate that a larger number of trials with GLN supplementation, whether orally or intravenously administered to patients undergoing cardiac surgery, are needed to confirm a clinical benefit. Future GLN dose-response studies are warranted in these areas.

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*Authors' contribution:* MCT, JARJ and VCCR carried out the enrollment of patients, collecting the data and drafted the manuscript. FCL and JGLT carried out all the surgeries and PEMG, AAR and AGO took care of the patients in the recovery ICU. AGO, CFO, JCVJ and LCM participated in the design of the study and performed the statistical analysis. JRF, LRME, LIJ and JGR participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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ARÁN

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Trabajo Original

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# Intestinal dysfunction in the critical trauma patients – An early and frequent event

*Disfunción intestinal en los traumatizados críticos. Un suceso precoz y frecuente*

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## Abstract

**Background:** Small-bowel dysfunction exerts a relevant prognostic impact in the critically ill patients. Citrullinemia has been used in the evaluation of the intestinal function and it is considered an objective parameter of the functional enterocyte mass. Present study proposes to determine the intestinal dysfunction prevalence and the citrullinemia kinetic profile in severe trauma patients and to investigate its correlation with severity indicators and clinical outcome.

**Methods**: A prospective study including 23 critical trauma patients was performed. Aminoacidemias were quantified, by ion exchange chromatography, at the admission and at the first and third days. Severity and outcome parameters were registered.

**Results**: In severe trauma patients, severe hypocitrullinemia (< 20 µmol/L) prevalence at admission was high (69.6%) and mean citrullinemia was low (19.5 ± 11.1 µmol/L). Baseline citrullinemia was inversely and significantly correlated with shock index ($r$ = -55.1%, $p$ = 0.008) and extent of invasive ventilation support ($r$ = -42.7%, p = 0.042). Citrullinemia < 13.7 µmol/L at admission, observed in 17.4% of patients, was associated with higher shock index (1.27 ± 0.10 *versus* 0.75 ± 0.18, p = 0.0001) and longer duration of invasive ventilation support (20.3 ± 7 *versus* 11.2 ± 7.1 days, p = 0.029) and intensive care unit stay (22 ± 5.9 *versus* 12.2 ± 8.8 days, p = 0.048). A citrullinemia decrease in the first day after admittance superior to 12.7% constituted a significant predictive factor of in-hospital mortality (75 *versus* 14.3%, p = 0.044; *odds* ratio = 7.8; accuracy = 65.2%; specificity = 92.3%; negative predictive value = 85.7%] and lower actuarial survival (69.8 ± 41.6 *versus* 278.1 ± 37.4 days, p = 0.034).

**Conclusions**: Those results confirm the high prevalence and the prognostic relevance of hypocitrullinemia, considered a biomarker of enterocyte dysfunction, in severe trauma patients.

**Key words:**

Citrulline. Intestinal dysfunction. Trauma. Mortality. Critically ill patients.

## Resumen

**Introducción:** la disfunción intestinal ejerce un importante impacto pronóstico en los pacientes críticamente enfermos. La citrulinemia se ha utilizado en la evaluación de la función intestinal. El presente estudio propone determinar la prevalencia de la disfunción intestinal y el perfil cinético de la citrulinemia en enfermos con trauma grave e investigar su correlación con la gravedad y la evolución clínica.

**Métodos:** se realizó un estudio prospectivo incluyendo 23 pacientes traumatizados críticos. Las aminoacidemias se cuantificaron, mediante cromatografía de intercambio iónico, en la admisión y en el primer y tercer días. Se registraron los parámetros de gravedad y evolución clínica.

**Resultados:** la prevalencia de la hipocitrulinemia grave (< 20 µmol/L) en la admisión fue alta (69,6%) y citrulinemia media fue baja (19,5 ± 11,1 µmol/L). La citrulinemia basal se correlacionó con el índice de choque ($r$ = -55,1%, p = 0,008) y la duración de asistencia ventilatoria invasiva ($r$ = -42,7%, p = 0,042). La citrulinemia < 13,7 µmol/L en la admisión se asoció con mayor índice de choque (1,27 ± 0,1 *versus* 0,75 ± 0,18, p = 0,0001) y mayor duración de ventilación invasiva (20,3 ± 7 *versus* 11,2 ± 7,1 días, p = 0,029) y hospitalización en la unidad de cuidados intensivos (22 ± 5,9 *versus* 12,2 ± 8,8 días, p = 0,048). La disminución de la citrulinemia en el primer día superior al 12,7% fue un factor predictor significativo de mortalidad hospitalaria (75 *versus* 14,3%, p = 0,044; *odds* ratio = 7,8; precisión = 65,2%; especificidad = 92,3%; valor predictivo negativo = 85,7%] y menor supervivencia actuarial (69,8 ± 41,6 *versus* 278,1 ± 37,4 días, p = 0,034).

**Conclusiones:** estos resultados confirman la alta prevalencia y la importancia pronóstica de la hipocitrulinemia, biomarcador de disfunción enterocitaria, en los pacientes con trauma severo.

**Palabras clave:**

Citrulina. Disfunción intestinal. Trauma. Mortalidad. Pacientes críticos.

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## INTRODUCTION

The small-bowel accomplishes complex and intricate absorptive, digestive, defense, neuromotor, endocrine and metabolic functions. It is the largest endocrine organ and produces peptides that regulate the metabolism of glucose; appetite and food ingestion; gastric, biliary and pancreatic secretions; gastrointestinal motility and immune function (1,2). The Gut-associated Lymphoid Tissue (GALT) is one of the largest lymphoid organs, containing up to 70% of the body's total number of immune cells, and the inductor for the mucosal-associated lymphoid tissue (MALT) (2,3). Furthermore, small-bowel plays a central role in pathophysiology of the systemic inflammatory response and multiple organ dysfunction syndromes in the critical illness (4).

The definition of acute gastrointestinal injury in the critically ill patients remains challenging (5,6). Nevertheless, small-bowel dysfunction is considered to exert a relevant adverse impact on the prognosis and to be frequently unrecognized in this context (6,7). As previously reported, 60.2% of critically ill patients evidenced one or more gastrointestinal symptoms during the first week of intensive care unit (ICU) admittance, including high gastric residual volumes, absent bowel sounds, vomiting or regurgitation, diarrhea, bowel distention and gastrointestinal bleeding (8); and 58.3% developed enteral nutrition intolerance (9). Reintam A et al. (8) verified that the gastrointestinal failure, defined by the association of three or more gastrointestinal symptoms on the first day in ICU, was present in 4.8% of the patients and was independently associated with a threefold increased risk of mortality. In their study, during the first week in ICU, gastrointestinal failure occurred in 6.4% of patients and was associated with higher 28-day mortality (62.5 *versus* 28.9%, $p = 0.001$) (8). According Reintam A et al. (9), the development of gastrointestinal failure, described by a five-grade scoring system based on food intolerance and intra-abdominal hypertension, in the first three days of the ICU stay, was an independent risk factor for ICU and 90-day mortality.

Citrulline is a non-protein amino acid that results from the enterocyte mitochondrial metabolism of glutamine, particularly in the proximal small bowel, at the upper and medium part of the villi (10,11). Citrulline participates in the adaptation to the variations of the protein ingestion and in the nitric oxide production (10,12). After its synthesis, regulated by pyrroline 5-carboxylate synthase, an enzyme almost exclusive of the enterocytes, citrulline is released in the portal circulation and converted to arginine in the kidneys. Therefore, the intestine represents the main source of circulating citrulline (10,11).

Citrullinemia has been recognized an objective, quantitative, reproducible and simple parameter of the functional enterocyte mass (10,12,13) and proposed as a biomarker of acute intestinal failure in the critically ill patients (6,12,13).

The present study intends to determine the prevalence of intestinal dysfunction and the kinetic profile of citrullinemia in severe trauma patients and to evaluate its correlation with the severity indicators and clinical outcome.

## METHODS

A prospective observational cohort study of adult critical trauma patients admitted in the Intensive Care Unit (ICU) of a tertiary university hospital was accomplished between October 2013 and April 2014. Recruitment of trauma patients was based on the Intensive Care Society definition of critically illness (14) and the prediction of an ICU length of stay not inferior to three days. Rejection factors were pregnancy, lactation, acquired immunodeficiency syndrome, renal insufficiency (creatininemia $\geq 2$ mg/dL), acute liver failure (conforming to previous definitions) (15,16), amino acid metabolism diseases, chronic gut disorders and previous enterectomy.

Study was ratified by the institution's ethics committee and adhered to the principles of the Helsinki's declaration (17).

Patients' age, gender and type of admission (primary or after initial treatment on other hospital) were registered. Severity scores were recorded at the admittance, including Acute Physiology and Chronic Health Evaluation II (APACHE II) score (18), Simplified Acute Physiology Score II (SAPS II) (19), Sequential Organ Failure Assessment (SOFA) score (20), Injury Severity Score (21), Revised Trauma Score (22) and Shock Index (23). Mechanical ventilation, erythrocytes transfusions, catecholamines support, renal substitution therapy, surgical interventions and artificial feeding were listed, as well as, glutamine exogenous supplementation. Regular regimens were used in enteral nutrition; glutamine (0.2-0.4 mg/kg/day) was provided intravenously in patients on parenteral nutrition.

Assessment was undertaken at the time of admittance in the ICU, at the first and the third days, with measurement of amino acid plasma levels (citrulline, ornithine, proline, arginine, glutamine, alanine, glutamic acid, leucine and isoleucine) and routine laboratory tests (including blood gases analysis and arterial lactate level).

Plasma levels of amino acids were quantified by ion exchange chromatography in a high-pressure system (Biochrom 30 analyzer). Plasma was obtained from blood drawn in ethilenediaminotetraacetic acid, by centrifugation at 4,000 g, during 10 minutes, and refrigerated at 4 °C; samples were prepared with 12% ditiotreitol, five to 10 minutes, deproteinized with sulfosalicilic acid, 60 minutes at room temperature and, after separation of the sediment by centrifugation, were filtered and stored at -20 °C for posterior processing.

Primary targets included in-hospital mortality rate and actuarial survival. Secondary goals were health care-associated infections rate (24), extent of invasive ventilation support, hospital and ICU lengths of stay and performance *status* at the last examination (as stated by the Karnofsky index) (25). The criteria of the health care-associated infections in the acute care setting of the National Healthcare Safety Network (NSHN), Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA were considered (24).

Statistical analysis was completed with SPSS Software version 18.0 for Windows (SPSS Inc., Chicago, IL, USA) applying Qui-square, Student's *t,* Kaplan Meier and log rank tests, Pearson's correlations and Receiver Operating Characteristic

(ROC) curves. Significant differences were regarded for *p* value < 0.05. Data were expressed as n (%) or mean ± standard deviation (SD).

## RESULTS

Twenty-three critical trauma patients were included, 78.3% of male gender, with a mean age of 48.8 ± 17.8 (21-82) years-old and 78.3% primarily admitted. Mean values of APACHE II, SAPS II and SOFA scores were 19.4 ± 5.5 (10-32), 41.3 ± 12.2 (20-78) and 6.9 ± 3.2 (2-10), respectively; Shock Index, Injury Severity Score and Revised Trauma Score were 0.82 ± 0.25 (0.31-1.4), 47.9 ± 18.5 (27-75) and 5.9 ± 1.3 (3.6-7.6). All the patients were submitted to invasive ventilation and enteral nutrition, 16 to cathecolamines support, 14 to erythrocytes transfusion, 14 to surgical interventions and one to parenteral nutrition. ICU, hospital and global mortality rates were 17.4%, 26.1% and 43.5%, respectively. Health care-associated infections rate was 87%. Mean duration of ventilation support was 12.7 ± 7.8 (2-27) days; ICU and hospital extent of stay were 13.9 ± 9.1 (3-52) and 29.4 ± 21.9 (5-95) days. After a mean follow-up of 7.4 ± 3.1 (2.3-12.2) months, actuarial survival was 229.2 ± 32.9 (95%CI 164.7-293.8) days. Karnofsky's index at the moment of the last examination was 69 ± 17.3 (40-90).

Analysis of plasma amino acid profile was completed in all patients at the ICU admission; in 18 both at the admission and the first day; 12 patients fulfilled the three points of assessment.

In critical trauma patients, mean value of citrullinemia at the moment of admission was low [19.5±11.1 (4-60.3) µmol/L] and increased, although not significantly, during the first three days in the ICU [20.2 ± 10.6 (5.6-49.2) µmol/L in the first day and 24.8 ± 15.2 (13.8-56.6) µmol/L in the third day] (Fig. 1). Severe hypocitrullinemia (< 20 µmol/L) prevalence was high (n = 16; 69.6%). At admittance, citrullinemia was not significantly correlated with the plasma concentrations of other amino acids, including glutamine, arginine, ornithine and proline. Baseline citrullinemia was inversely and significantly correlated with shock index [Pearson's correlation coefficient *(r)* = -55.1%, p = 0.008] and length of invasive ventilation support (*r* = -42.7%, p = 0.042) (Fig. 2). No significant connection was observed between citrullinemia and severity indexes. Citrullinemia < 13.7 µmol/L at admission, documented in 17.4% of patients, was associated with higher shock index (1.27 ± 0.10 *versus* 0.75 ± 0.18, p = 0.0001) and longer duration of invasive ventilation support (20.3 ± 7 *versus* 11.2 ± 7.1 days, p = 0.029) and of intensive care unit stay (22 ± 5.9 *versus* 12.2 ± 8.8 days, p = 0.048) (Table I). In univariate analysis, a citrullinemia reduction at the first day after admission (ΔCitrullinemia1) superior to 12.7%, verified in 17.4% of patients, constituted a significant predictive factor of in-hospital mortality [75 *versus* 14.3%, p = 0.044; *odds* ratio = 7.8 (95%CI 1.04-58.8); accuracy = 65.2%; sensitivity = 60%; specificity = 92.3%; positive predictive value = 75%; negative predictive value = 85.7%] and lower actuarial survival (69.8 ± 41.6 *versus* 278.1 ± 37.4 days, p = 0.034) (Figs. 3 and 4).

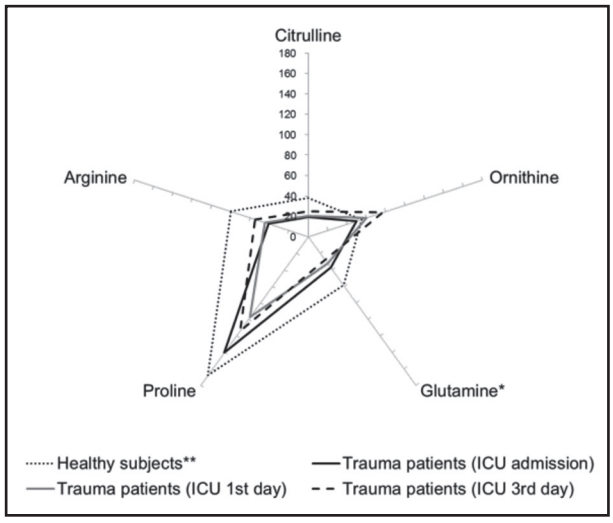


**Figure 1.**

Mean plasma concentrations of citrulline, glutamine, ornithine, proline and arginine in critical trauma patients (n = 23) at the moment of admission in the intensive care unit (ICU), at the first and the third days. *Plasma levels × $10^{-1}$; **Mean values of a cohort of fasting healthy individuals (n = 100) were used for comparison (26).

## DISCUSSION

In present series, acute intestinal dysfunction, defined as the reduction of enterocyte function and quantified by the citrulline plasma concentration, developed frequently and early after severe trauma. Approximately 69.6% of patients demonstrated citrullinemia levels under 20 µmol/L at the time of ICU admission, in consonance with the observed by other authors (50 to 68%) (6). Mean citrulline plasma levels of critical trauma patients at the admission on the ICU were lower than those of described in the literature for fasting healthy individuals (26).

Baseline citrullinemia demonstrated a significant inverse and moderate correlation with the shock index, in agreement with the pathophysiology of gut failure in critically ill patients; in fact, ischemia is one of the leading mechanisms of loss of enterocyte integrity in this context (6). Intestinal mucosa is extremely sensitive to ischemia-reperfusion injury with induction of epithelial apoptosis, disruption of barrier integrity and increase of permeability (27).

According present data and in agreement with other studies (6), an association between citrullinemia values and outcome parameters was demonstrated. Citrullinemia was inversely related with duration of invasive ventilation and baseline levels of citrulline below 13.7 µmol/L were significantly associated with prolonged mechanical ventilation and ICU stay. Furthermore, a reduction of citrulline levels higher than 12.7% during the first day after admission constituted a risk factor of in-hospital mortality, with high specificity and negative predictive value, and of lower actuarial survival. Citrullinemia threshold observed in present study is in consonance with those referred in the literature (6).

Intestinal mucosal barrier integrity is compromised in the critical illness, with increase of epithelial apoptosis and permeability.

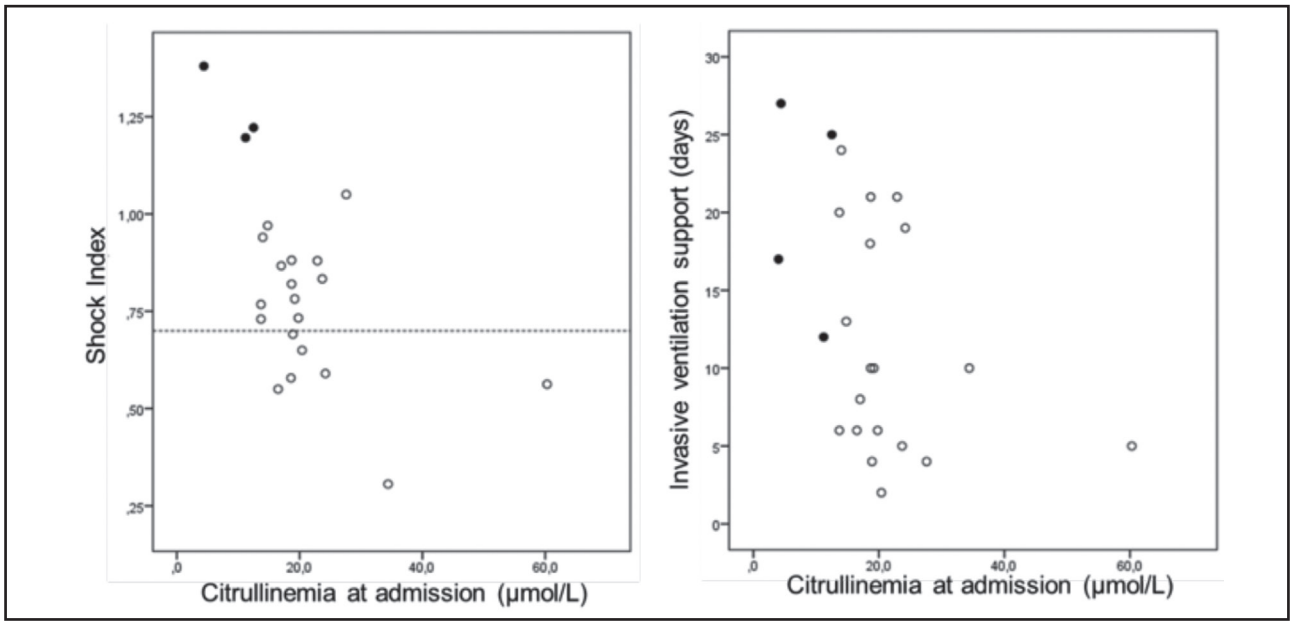


**Figure 2.**

Correlations between citrullinemia at the admission and Shock Index (r = -55.1%, p = 0.008) and invasive ventilation support duration (r = -42.7%, p = 0.042) in severe trauma patients (n = 23). Pearson's correlation test and coefficient (r) were used. Shock index was calculated as the ratio between the first recorded heart rate and systolic blood pressure and its normal value is considered 0.7 or less (23). ○ Citrullinemia ≥ 13.7 µmol/L, • Glutaminemia < 13.7 µmol/L.

**Table I.** Relation between citrullinemia at the admission and critical trauma patients' characteristics, severity scores and outcome parameters (n = 23)

| | Citrullinemia | | P[a] |
|---|---|---|---|
| | < 13.7 µmol/L | ≥ 13.7 µmol/L | |
| Male gender (%) | 75 | 78.9 | n.s. |
| Age (years-old) | 47.8 ± 14.4 | 49.1 ± 18.7 | n.s. |
| Non-primary admittance (%) | 25 | 21.1 | n.s. |
| SAPS II | 41.7 ± 11 | 41.3 ± 12.7 | n.s. |
| APACHE II | 20.7 ± 4.9 | 19.2 ± 5.7 | n.s. |
| SOFA | 7 ± - | 6.9 ± 3.3 | n.s. |
| Shock index | 1.27 ± 0.10 | 0.75 ± 0.18 | 0.0001 |
| Injury Severity Score | 60.8 ± 22.9 | 45.2 ± 16.9 | n.s. |
| Revised Trauma Score | 5 ± 1.3 | 6 ± 1.2 | n.s. |
| Erythrocytes transfusion (%) | 75 | 57.9 | n.s. |
| Catecholamines perfusion (%) | 75 | 68.4 | n.s. |
| In-hospital mortality (%) | 0 | 31.6 | n.s. |
| Health CA infections (%) | 100 | 84.2 | n.s. |
| Ventilation support (days) | 20.3 ± 7 | 11.2 ± 7.1 | 0.029 |
| ICU stay (days) | 22 ± 5.9 | 12.2 ± 8.8 | 0.048 |
| Hospital stay (days) | 48 ± 31.6 | 25.5 ± 18.1 | n.s. |
| Mean actuarial survival (days) | 204.3 ± 65.4 | 231.1 ± 36.8 | n.s. |
| Performance status (Karnofsky) | 85 ± 7.1 | 65 ± 16.9 | n.s. |

*Data expressed as number (%) or mean ± standard deviation. APACHE II: Acute Physiology and Chronic Health Evaluation II; Health CA infections: health care-associated infections; SAPS II: Simplified Acute Physiology Score II; SD: standard deviation; SOFA: Sequential Organ Failure Assessment;* vs.: versus; *statistically n.s.: statistically not significant.* [a]*t-Student and Qui-square tests.*

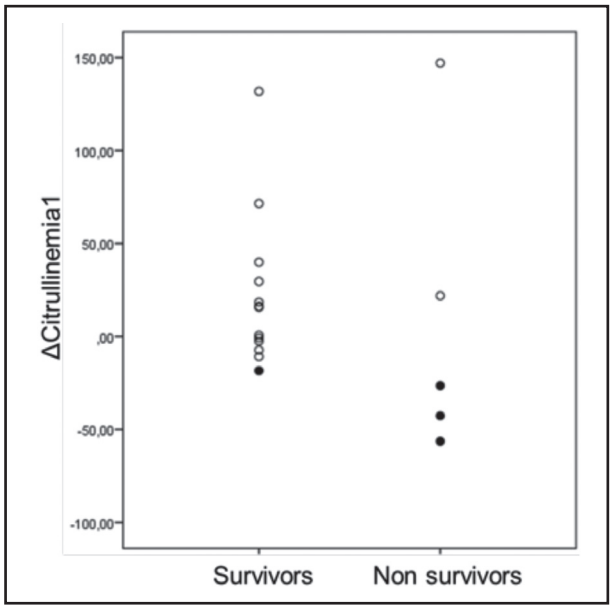


**Figure 3.**

Variation of citrullinemia between the moment of admission and the first day at the intensive care unit (ΔCitrullinemia1) in critical trauma patients (n = 23) according in-hospital mortality. ○ ΔCitrullinemia1 ≥ -12.7%, ● ΔCitrullinemia1 < -12.7%

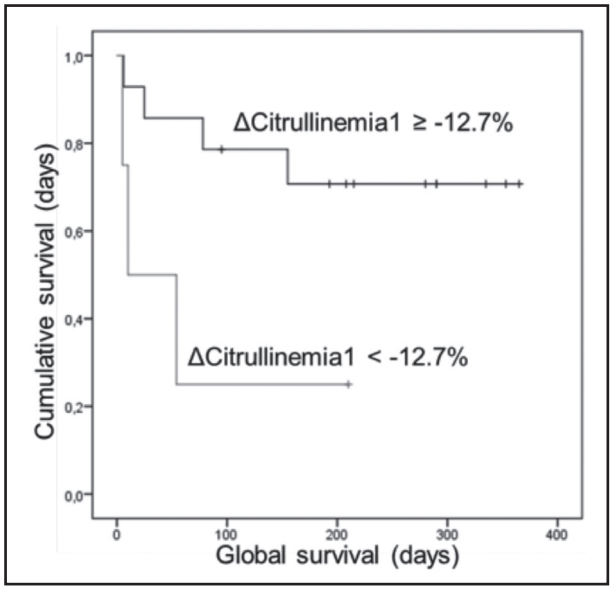


**Figure 4.**

Actuarial survival curves in critical trauma patients (n = 23) admitted in the intensive care unit according the variation of citrullinemia between the moment of admission and the first day at the intensive care unit (ΔCitrullinemia1) (Kaplan-Meyer curves and log rank test).

Autodigestion and release of toxic intestine-derived mediators through the mesenteric lymphatics induces inflammatory, cytotoxic and proteolytic injuries in distant organs, including the lung (28).

Citrullinemia has been related with objective intestinal dysfunction, including histological evidences of damage (29), systemic inflammation parameters (7,30-33), bacterial translocation (30,34) and clinical manifestations of intestinal dysfunction, such as ileus, diarrhea and bleeding (6,35).

Piton G et al. (31) verified that citrullinemia plasma concentrations ≤ 10 µmol/L at the first 24 hours, present in 44% of critically ill patients, were associated with higher nosocomial infection rates and constituted independent risk factors of 28 days-mortality. In another study, citrullinemia levels ≤ 12.2 µmol/L and plasma concentrations of intestinal-fatty acid binding protein (an enterocyte damage marker) ≥ 355 pg/mL at the moment of ICU admission were independently related with higher 28 days-mortality in multivariate analysis (7). Plasma citrulline concentration less than or equal to 10 µmol/L at admission to the ICU was associated with higher intra-abdominal pressure, higher plasma C-reactive protein concentration, and more frequent antibiotic use (7).

Hypocitrullinemia < 15 µmol/L was connected with the development of clinical manifestations of intestinal dysfunction, including higher residual gastric volume, ileus, among others (35).

Although citrullinemia has been proposed for the evaluation of the intestinal function in the critically illness, its prognostic value requires further validation. In fact, in this context, limitations of citrullinemia include the susceptibility to the interferences of renal insufficiency, the reduced glutamine bioavailability and the increase of extra-intestinal synthesis of citrulline from arginine in the systemic inflammatory syndrome (6,12,13).

Limitations of present series included the single-center character, small number of studied patients and high severity scores.

Present findings confirm the precocious development, high prevalence and prognostic relevance of hypocitrullinemia, considered a biomarker of intestinal dysfunction, in severe trauma patients. Evaluation of intestinal function may allow the implementation of prophylactic and therapeutic strategies of intestinal integrity preservation with potential impact on prognosis. Additional studies are necessary to determine the citrullinemia value in this context.

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*Ethics approval and consent to participate: All experimental procedures were performed in accordance with the ethical standards of the Helsinki Declaration and were approved by the Institutional Ethics Committee of the Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal (Official Letter nº CHUC00115), Coimbra, Portugal.*

*All subjects (or their representatives) were fully informed of the nature and purpose of the investigation and gave their consent to participate.*

*Authors' contributions: BPC: Conception and design of the study; acquisition, analysis and interpretation of data and writing the article. PM: Acquisition, analysis and interpretation of data; revision of the article. MG, CV, MS and MT: Acquisition of data and revision of the article. FCS and JP: Interpretation of data and revision of the article. All authors: Reading and approval of the final version of the manuscript.*

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Nutrición Hospitalaria

Trabajo Original

Pediatría

# Aporte de hierro y zinc bioaccesible a la dieta de niños hondureños menores de 24 meses

## *Contribution of bioavailable iron and zinc to the diet of Honduran children under 24 month*

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## Resumen

**Objetivo:** en el presente estudio se han analizado 18 alimentos infantiles (10 elaborados con recetas tradicionales hondureñas y 8 papillas industriales comercializadas en ese país), que suponen la base de la alimentación de los lactantes hondureños excluida la leche materna y las fórmulas infantiles.

**Material y métodos:** se determinó el contenido y bioacesiblidad (fracciones solubes y dializables) de Fe y Zn. Para ello se simuló una digestión *in vitro* gastrointestinal con una primera fase de digestión gástrica (con pepsina), seguida de una segunda fase de digestión intestinal (con pancreatina y sales biliares). La espectrometría de absorción atómica midió el contenido mineral en las fracciones soluble y dializable.

**Resultados:** las papillas tradicionales hondureñas (PTH) mostraron baja densidad de los micronutrientes estudiados, siendo las PTH elaboradas con base de "arroz con frijoles y hojas verdes", "arroz con frijol molido" y "frijoles con plátano" las que presentaron un contenido superior con valores de 1,96, 1,56, y 1,46 mg Fe/100 g, respectivamente, aunque con valores de disponibilidad *in vitro* inferiores al 50% de su contenido. Para el Zn en estas recetas, los valores encontrados fueron muy bajos y están por debajo del límite de detección. En relación a las papillas industriales (PIH), las de "arroz", "trigo con leche" y "5 cereales" presentaron un mayor contenido de Fe (9,4, 8,53 y 7,56 mg Fe/100 g, respectivamente). Su disponibilidad *in vitro* fue mayor del 70% en todos los casos. Las PIH mostraron valores de Zn de 1,36, y 0,99 mg Zn/100 g en las muestras de "trigo con leche" y "trigo con miel", respectivamente, y una disponibilidad mayor del 75%.

**Conclusión:** queda demostrado que las PTH poseen algunas limitaciones en su formulación que hace que los micronutrientes seleccionados se encuentren en menor cantidad e incluso menos bioaccesibles, frente a los PIH, por lo que se recomienda su revisión para evitar la suplementación de estos micronutrientes y ayudar a mejorar el estado nutricional de la población infantil hondureña como país modelo de la región centroamericana.

**Palabras clave:**

Deficiencia. Micronutrientes. Honduras. Disponibilidad *in vitro*. Alimentos infantiles.

## Abstract

**Objective:** In the present study we analyzed 18 baby food (10 made from traditional Honduran recipes, and 8 industrial baby food sold in that country) involving the staple food of Honduran excluded infants breast milk and infant formulas.

**Material and methods:** The content and bioaccesibility (soluble and dialysable fractions) of Fe and Zn were determined. For this *in vitro* gastrointestinal digestion in a first phase of gastric digestion (pepsin) followed by a second phase of intestinal digestion (with pancreatin and bile salts) was simulated. The atomic absorption spectrometry mineral content measured in soluble and dialyzable fractions.

**Results:** Traditional porridges from Honduras (PTH) showed low density of micronutrients being the PTH prepared based on "rice with beans and greens", "rice with ground beans" and "beans with banana" which had a higher content values of 1.96, 1.56, and 1.46 mg Fe/100 g, respectively, although *in vitro* availability values below 50% of its content. For Zn in these recipes, the values found were very low being below the detection limit. In relation to industrial porridges (PIH), those of "rice", "wheat with milk" and "5 cereals" they had a higher content of Fe (9.4, 8.53 and 7.56 mg Fe/100 g, respectively). Its availability in vitro was greater than 70% in all cases. PIH Zn showed values of 1.36, and 0.99 mg Zn/100 g samples of "wheat with milk" and "wheat with honey", respectively, and increased availability of 75%.

**Conclusions:** It is shown that PTH have some limitations in its formulation that makes the selected micronutrients are in fewer and even less bioaccessible, compared with PIH, so review is recommended to avoid supplementation of these micronutrients and help improve the nutritional status of the child population as Honduran model country in Central America.

**Key words:**

Deficit. Micronutrients. Honduras. Availability *in vitro*. Meal for children.

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## INTRODUCCIÓN

Honduras presenta uno de los índices más altos de desnutrición infantil en Mesoamérica, según el informe más reciente del Programa Mundial de Alimentos (WPF), la organización para la Alimentación y la Agricultura (FAO) y el Fondo Internacional de Desarrollo Agrícola (FIDA) (1). Ocupa el segundo lugar en la región por detrás de Guatemala, con un 31% de desnutrición infantil, lo que significa que algo más de 1 de cada 4 niños menores de 5 años sufre desnutrición en distinto grado. A este problema global hay que añadir que dentro de los nutrientes esenciales se producen carencias significativas. Así, 3 de cada 10 niños de entre 6 meses y 5 años padecen de anemia, siendo mayor la incidencia de anemia ferropénica en poblaciones rurales con una tasa del 40% (2). Aunque el rango de edad en el que se puede manifestar la anemia es muy amplio, la mayor parte aparece en Honduras durante el llamado "periodo de diversificación de la dieta del lactante", comprendido entre los 6 y 9 meses de edad, llegando a ser la incidencia de anemia por déficit de Fe de un 60% en la población infantil (3). Evidentemente este problema nutricional tiene su causa en la disponibilidad de alimentos y en las pautas alimentarias que siguen los responsables de la alimentación de los lactantes. Es una pauta extendida, especialmente en grupos de población rurales, indígenas o de bajos ingresos, que elaboren estos alimentos con los recursos disponibles y basados en recetas tradicionales que en muchas ocasiones pueden aportar alimentos que no sean los adecuados a los periodos de iniciación a la alimentación sólida de los niños, siendo quizás la causa, entre otros factores, de la anemia observada en la población infantil de este país. Junto con los alimentos tradicionales se emplean para alimentar a los lactantes los alimentos infantiles producidos por la industrial alimentaria, principalmente cereales infantiles y alimentos complementarios homogeneizados, que están limitados en países como Honduras a estratos sociales de mayores recursos económicos, mientras que en otros países (europeos o Estados Unidos de Norteamérica) son de consumo más generalizado.

No existe una recomendación específica sobre qué tipo de alimentos para lactantes deben ser introducidos para iniciar la alimentación complementaria, si bien casi todos los organismos internacionales coinciden en que estos deberían cumplir un principio fundamental: proveer alta cantidad de energía de fácil utilización en el mínimo volumen posible (4). El ajuste de energía aconsejable para el lactante es de 650 calorías al día, es decir, 108 kcal/kg/día en los primeros 6 meses y 96 kcal/kg/ día, lo que supone 850 calorías al día entre los 6 a 12 meses (5). Es posible que los requerimientos energéticos de lactantes en poblaciones de riesgo (con infecciones frecuentes o condiciones ambientales adversas) como en Honduras varíen en virtud de las situaciones de estrés que se produzcan. De los tres grupos de alimentos que es posible administrar a partir del 6.º mes (cereales, frutas, y verduras), no existen razones sólidas para recomendar el inicio con uno u otro tipo, pudiendo adaptarse el esquema alimentario al contexto sociocultural de cada país (6). Como complemento a este objetivo principal mencionado, los alimentos para lactantes de entre 9 y 12 meses de edad deben servir para cubrir además el 97% de la ingesta diaria recomendada de Fe, y el 86% del Zn (7).

Los procesos metabólicos de absorción de nutrientes son muy complejos, especialmente los del Fe, ya que depende de factores clave como su forma hémica o no, y en este último caso de su estado oxidado o reducido, así como de otros factores dietéticos que determinan que no todo el Fe presente en el alimento sea absorbido y accesible para el organismo (8). De modo general podemos considerar que el coeficiente de absorción del Fe oscila entre el 7 y el 15%, lo que significa que el niño necesita aproximadamente una concentración igual o superior a 10-11 mg/día para cubrir los requerimientos diarios de Fe biodisponible en el periodo de 6-12 meses, que son del orden de 0,9 mg/día, demandados esencialmente para el rápido crecimiento, y también para las pequeñas pérdidas producidas por la descamación celular y las hemorragias. No obstante, el Fe posee un estrecho margen en sus recomendaciones dietéticas para esta edad, ya que si su recomendación de ingesta dietética de Fe en el lactante es de 10 mg/día (9), tampoco se recomienda que exceda de los 15 mg/día (4) (Tabla I).

En el caso del Zn las necesidades durante la lactancia son de 12-13 mg/día y su absorción intestinal varía ampliamente entre el 5 y el 95%, dependiendo de que las reservas tisulares estén disminuidas o no, y, principalmente, de la presencia de factores dietéticos que pueden actuar como antinutrientes, tales como los fitatos, o mediante efecto competitivo por los canales de absorción con el Fe (12). También modifica la absorción de minerales la presencia de aminoácidos (sobre todo de origen animal) o ácidos orgánicos propios del alimentos y que actúan favoreciendo dicha absorción (13). La disponibilidad también varía en los lactantes

**Tabla I.** Ingesta recomendada de Fe y Zn según el tipo de dieta

| Grupo I | Absorción de Fe necesario | IDR (mg) | | *Ingesta recomendada de Fe (mg) según tipo de dieta* | | |
|---|---|---|---|---|---|---|
| | | Fe | Zn | Alimentos origen animal que aportan menos del 10% de calorías | Alimentos origen animal que aportan del 10-20% de calorías | Alimentos origen animal que aportan más del 25% de calorías |
| Lacte 0-4 meses | 0,5 | 0,27 | 2 | --- | --- | --- |
| Lacte 5-12 meses | 0,7 | 11 | 3 | 7 | 5 | 4 |

*(2) WHO/UNICEF/UNU 2001; (10) 2007; (24) 2005.*

según el modo de alimentación, ya que los alimentos con biberón presentan un requerimiento más alto debido a la menor disponibilidad de Zn que han demostrado tener las formulas infantiles (14). A diferencia del Fe, el Zn no figura como micronutriente deficitario dentro de la población pediátrica en Honduras, aunque sí que está sujeto a iniciativas de enriquecimiento de la dieta (Plan de Nación y el Plan Nacional de Salud 2010-2014, SM2015), como el suministro de Zn en polvo a niños de entre 6 y 23 meses para el tratamiento de las diarreas (15). Por todo lo anteriormente mencionado, el contenido de Fe y Zn son señalados como "nutrientes críticos" durante esta etapa de la vida, por lo que se hace necesaria la búsqueda de una optimización en la absorción de los mismos (16).

En materia de salud materno-infantil las recomendaciones internacionales establecen que la lactancia materna se realice al menos hasta los 6 meses desde el nacimiento (10). La alimentación de transición entre la lactancia materna exclusiva y la alimentación complementaria elaborada en los hogares en Honduras presenta unos patrones alimentarios que parecen estar relacionados con el deterioro del estado nutricional en el lactante. La evaluación del indicador de desnutrición crónica (talla/edad) muestra una deficiencia energética crónica del 23% de los menores de 5 años hondureños, además a partir del 4.º mes de vida, el 29% de la población infantil de entre 6 y 23 meses ha padecido diarrea (3). Este problema viene también determinado en Honduras por factores como una escasa disponibilidad de alimentos en ciertos grupos de población, una mala praxis nutricional (como indican resultados anteriores con solo un 59% de los lactantes hondureños alimentados correctamente con leche materna), una introducción muy temprana de los alimentos y no siempre con los alimentos más adecuados basados en la tradición hondureña, y que las pautas sobre la alimentación complementarían en ciertos estratos socioeconómicos se basan en elaboraciones tradicionales que presentan errores (17). El ejemplo más acusado se observa en las áreas rurales, donde un alto porcentaje de madres (51,9%) dan a sus hijos café en el 1.er mes de vida; y entre el 3.er y 4.º mes de vida se introducen bebidas carbonatadas con azúcar, diversos tipos de leche no materna, caldos o sopas de sobre (con alto contenido en sal), agua, tortillas de maíz, arroz, papa, pan y algunas frutas y verduras (18). Diversos estudios (19,20) concluyen que estas prácticas de alimentación no solo podrían estar relacionadas con la deficiencias de uno o más micronutrientes al presentar en su composición fitatos, oxalatos o taninos, inhibidores de la absorción de Fe y Zn, sino que también estarían relacionadas con una mayor frecuencia de diarreas y otros procesos patológicos.

Ante la ausencia de información documentada de la ingesta de los micronutrientes esenciales de Fe y Zn en la población infantil hondureña en los primeros dos años de vida, y del contenido y disponibilidad de dichos minerales en alimentos tradicionales e industriales comercializados en el país, en el presente estudio se plantean dos objetivos principales:

- Evaluar el contenido de Fe y Zn en recetas locales hondureñas y en diferentes alimentos para lactantes (papillas a base de cereales y harinas infantiles de industriales) de amplia implementación en los hábitos alimentarios seguidos por las madres hondureñas con niños lactantes.
- Evaluar la cantidad de Fe y Zn bioaccesibles (disponibles para ser absorbidos a nivel intestinal) procedentes de su dieta complementaria (recetas tradicionales y alimentos para lactantes) hondureños menores de 24 meses.

## MATERIALES Y MÉTODOS

### ALIMENTOS PARA LACTANTES DE RECETAS TRADICIONALES HONDUREÑAS E INDUSTRIALES COMERCIALIZADOS EN HONDURAS

Para el estudio se elaboraron 10 recetas tradicionales hondureñas siguiendo las recomendaciones de la guía de alimentación infantil desarrollada por el Ministerio de Salud del país (21) para lactantes en edades comprendidas entre 6-12 meses. Los platos seleccionados fueron todos purés elaborados de forma casera identificados como los alimentos de mayor consumo entre la población infantil hondureña (18):

- De arroz con frijol y hojas verdes.
- De arroz con frijol molido.
- De ayote (calabaza) con cuajada.
- De ayote con mantequilla.
- De banano asado con azúcar.
- De camote (batata) anaranjado.
- De frijol (habichuela) con plátano.
- De papa (patata) con mantequilla
- De plátano con mantequilla.
- De zanahoria, crema y leche

A estos platos y a sus muestras las denominaremos a lo largo del trabajo como PTH (platos tradicionales hondureños).

Los ingredientes fueron adquiridos en distintos mercados y supermercados de Tegucigalpa, y la elaboración de las mismas se realizó en el laboratorio de preparación de alimentos de la Universidad Pedagógica Nacional Francisco Morazán (Tegucigalpa, Honduras). Para completar la visión de la dieta de los niños hondureños en este periodo de vida, se seleccionaron 8 productos infantiles con base de cereales y frutas comerciales destinados a alimentación complementaria y que tienen alta presencia en el mercado nacional en Honduras. Estos fueron cereales cuyos ingredientes mayoritarios determinan su denominación:

- Arroz.
- Avena.
- 5 cereales (trigo, arroz, avena, cebada y centeno).
- Harina de trigo.
- Masa de maíz.
- Trigo y leche.
- Trigo y miel.
- Vainilla y canela.

En este caso los denominaremos como PIH (platos industriales hondureños) para su identificación en el trabajo.

## REACTIVOS

Los reactivos utilizados fueron de grado analítico salvo que se indique lo contrario. El agua fue doblemente destilada y desionizada para la realización de todos los análisis de determinación de minerales. Todo el material de cristal y botellas de polietileno empleadas para simular la digestión gastrointestinal fueron lavados con agua destilada y desionizada, mantenidas durante 24 horas en una solución de $HNO_3$ 10 N 10 N, y de nuevo lavadas con agua doblemente destilada y desionizada antes de su uso a fin de eliminarles cualquier residuo que pudiera interferir en la determinación de minerales. Para la digestión gastrointestinal *in vitro* (ver siguiente apartado) la suspensión de pepsina se preparó con 16 g de pepsina (pepsina de mucosa de estómago porcino P6887; Sigma Chemical Co., St. Louis, MO) en 100 ml con una solución de HC1 0,1 N. La mezcla del extracto pancreatina-bilis se preparó con 4 g de pancreatina (pancreatina de páncreas porcino P3292; Sigma Chemical Co., St. Louis, MO) y 25 g de extracto de bilis porcino (Sigma Chemical Co., St. Louis, MO) que fueron dispersados hasta 1 litro con solución de $NaHCO_3$ 0,1 M.

## DIGESTIÓN GASTROINTESTINAL *IN VITRO*

Antes de comenzar el proceso, los alimentos fueron preparados conforme a las indicaciones comerciales (PIH) y siguiendo la receta tradicional en el caso de los alimentos hondureños (PTH). El alimento fue homogeneizado con una Osterizer® (Cycle blend 10 pulse matic) en posición "blend" durante 3 min para asegurar conseguir una textura lo más parecida en todos los casos y semejante a la que los niños ingieren. De cada homogeneizado se tomaron aleatoriamente 10 g de muestra para su valoración analítica, y cada analítica se realizó por triplicado. Las papillas infantiles (PTH y PIH) fueron digeridas siguiendo el método de digestión gastrointestinal *in vitro* descrito por Miller y cols. (22), con modificaciones (23) dirigidas a reducir las cantidades de enzimas utilizadas y simular las condiciones del proceso digestivo infantil, ya que el tracto gastrointestinal en las primeras etapas de la vida aún no está completamente desarrollado. El proceso de digestión *in vitro* consistió en una etapa gástrica con una primera fase gástrica que se desarrolló a 37 °C y pH 2 en agitación en presencia de una solución de pepsina, tal y como se describe en el apartado "Reactivos", seguida de una fase de digestión intestinal a 37 °C a pH 5.5 en agitación con pancreatina y sales biliares (obteniendo ensayos de solubilidad y diálisis). Al final de la etapa intestinal, se seleccionaron alícuotas para obtener la fracción soluble en la que se encuentran los minerales solubilizados o accesibles para ser absorbidos. Para ello, 30 g de cada alícuota se centrifugaron a 3500 x g durante 1 hora a 4 °C, empleando una centrifugadora refrigerada (Eppendorf 5804-R Centrífuga, Hamburgo, Alemania). El sobrenadante (fracción soluble) se utilizó para determinar el contenido mineral según la metodología descrita en el siguiente apartado. La fracción dializable se define como la que contiene los minerales que son absorbidos, y para su determinación se realizó un proceso de dializado usando tripas de diálisis semipermeable (tamaño de poro de la membrana 6.000-8.000 Da y un diámetro de 29 mm, Spectra/Por, Spectrum, Houston, TX, USA) que contenía 50 ml de agua destilada desionizada y una cantidad de $NaHCO_3$ 0,1M equivalente a la acidez titulable. La fracción biodisponible de los minerales totales presentes en la muestra (expresado en porcentaje) se considera al Fe y al Zn se dializan a través de la membrana.

## DETERMINACIÓN DEL CONTENIDO DE Fe Y Zn

La concentración de Fe y Zn en las diferentes muestras y en ambas fracciones, solubles y dializables, se determinó mediante espectrofotometría de absorción atómica (AAS) (Thermo Scientific AA Espectrómetro S Series; Thermo, Waltham, MA). Antes del análisis la materia orgánica fue destruida por incineración en un horno mufla de temperatura programada (Nabertherm, Lilienthal, Alemania) a 525 °C durante 32 horas (velocidad de 50 °C/h). Una vez incinerada la materia orgánica, se añadieron a las cenizas 3 ml de $HNO_3$ 10 N, y las muestras se calentaron en placas calefactoras a 100 °C hasta sequedad. Tras su enfriamiento a temperatura ambiente el residuo se disolvió con 1 ml de HCl 0.1N, y la solución se transfirió a un matraz aforado de 50 ml y se enrasó con agua doblemente destilada y purificada. El análisis se realizó mediante un espectrómetro de llama de aire-acetileno y un quemador de 10 cm, siendo las longitudes de onda 248,8 nm Fe y de 213 nm para el Zn. Las curvas de calibración obtenidas se establecieron entre 0,25 y 5 ppm para ambos minerales, y mostraron una linealidad aceptable, con coeficientes de correlación mayor que 0,995. Siendo sus ecuaciones ([$y = 2{,}86.10^{3}$-+ $4.76.10^{-2}x$] [$y = 3{,}58 \times 10^{3}$-+ $0{,}18.0{,}10^{2}$-x]) para el Fe y para el Zn respectivamente.

## ANÁLISIS ESTADÍSTICO

Los resultados se expresaron como media ± desviación estándar a partir de tres determinaciones independientes de cada muestra. Diferencias entre las muestras se examinaron para la significación estadística ($p < 0{,}05$) por el análisis de la varianza (ANOVA) de una vía y t de Student para comparar los valores con un control apropiado.

## RESULTADOS

Las muestras objeto de estudio estuvieron formadas por 18 papillas infantiles hondureñas: 10 de elaboración casera (PTH) y 8 de elaboración industrial (PIH). Es preciso señalar que en el caso de los PTH y PIH que fueron elaborados en el estudio se siguieron las recomendaciones indicadas en cuanto a cantidades y a proporciones tanto por los fabricantes. En las tablas II y III se describen los ingredientes empleados en la elaboración de las

**Tabla II.** Ingredientes empleados en la elaboración los purés tradicionales (PTH) y su valor nutricional

| PTH ingredientes | | Valor nutricional de la receta (por ración) | | |
|---|---|---|---|---|
| 1 | Arroz con frijol y hojas verdes (45 g arroz, 15 g frijol, 15 g hojas verdes) | Ración 37,5 g | Kilocalorías<br>Proteínas (g)<br>Hierro (mg) | 0,2<br>7,3<br>2,2 |
| 2 | Arroz con frijol molido (30 g arroz, 15 g frijol, 15 ml agua hervida) | Ración 37,5 g | Kilocalorías<br>Proteínas (g)<br>Hierro (mg | 0,07<br>2,4<br>0,7 |
| 3 | Ayote (calabaza) con cuajada (45 g ayote, 30 g cuajada) | Ración 37,5 g | Kilocalorías<br>Proteínas (g)<br>Hierro (mg) | 0,08<br>4<br>0,6 |
| 4 | Ayote con mantequilla (75 g ayote, 5 g mantequilla) | Ración 37,5 g | Kilocalorías<br>Proteínas (g)<br>Hierro (mg) | 0,06<br>0,5<br>0,5 |
| 5 | Banano asado con azúcar (2,5 g azúcar, 100 g banano) | Ración 37,5 g | Kilocalorías<br>Proteínas (g)<br>Hierro (mg) | 0,04<br>0,4<br>0,1 |
| 6 | Camote (batata) anaranjado (5 g mantequilla, 15 ml leche materna, 100 g camote) | Ración 37,5 g | Kilocalorías<br>Proteínas (g)<br>Hierro (mg) | 0,17<br>1,6<br>1 |
| 7 | Frijol (habichuela) con plátano (70 g plátano, 15 g frijol colado, 5 g manteca) | Ración 37,5 g | Kilocalorías<br>Proteínas (g)<br>Hierro (mg) | 0,1<br>1,9<br>0,7 |
| 8 | Papa (patata) con mantequilla (1 papa media, 5 g de mantequilla, 34 g leche materna) | Ración 37,5 g | Kilocalorías<br>Proteínas (g)<br>Hierro (mg) | 0,1<br>1,2<br>0,5 |
| 9 | Plátano con mantequilla (35 g plátano maduro, 5 g de mantequilla) | Ración 37,5 g | Kilocalorías<br>Proteínas (g)<br>Hierro (mg) | 0,07<br>0,6<br>0,2 |
| 10 | Zanahoria, crema y leche (5 g mantequilla,100 g zanahoria, 15 ml leche materna) | Ración 37,5 g | Kilocalorías<br>Proteínas (g)<br>Hierro (mg) | 0,08<br>0,9<br>0,5 |

papillas tradicionales PTH y PIH de mayor cuota de consumo en Honduras y su valor nutricional, en relación a la ingesta dietética de referencia (IDR) para niños de 1 a 3 años.

Los resultados obtenidos se han agrupado en las tablas IV y V. En ellas se muestran el contenido mineral, y la disponibilidad *in vitro* de Fe y Zn en la alimentación complementaria Hondureña de elaboración casera PTH, en comparación con las papillas industriales PIH.

El contenido de Fe en las diferentes PTH osciló entre 0,26 y 1,95 mg Fe/100 g (Tabla IV). Como elemento común en las recetas de las PTH encontramos que las recetas que presentaron promedios significativamente más elevados en el contenido en Fe, independientemente del método de cocinado de los alimentos (cocido, triturados, asado), fueron aquellas que presentaban entre sus ingredientes leguminosas frijoles (pintos), tal y como ocurre en las recetas de "arroz con frijol y hojas verdes", "arroz con frijol molido" y "frijol con plátano" las de mayor contenido de Fe (1,96, 1,56 y 1, 46 mg Fe/100 g, respectivamente). En los PIH observamos que todas las papillas comerciales analizadas presentaron un contenido total en Fe superior a 4 mg/100 g, destacando la de "arroz", la de "trigo y leche" y la de "5 cereales" (9,04, 8,53 y 7,56 mg/100 g, respectivamente). En cuanto a las dos muestras de harinas industriales empleadas en la elaboración de alimentos infantiles, destaca la "masa de maíz" con 6,96 mg Fe/100 g, que duplica el contenido total de Fe de la "harina de trigo" (3,16 mg Fe/100 g).

En cuanto contenido de Zn para las PTH encontramos que los valores se hallaban por debajo de los limites detectables (0,25 ppm). Sin embargo, en las muestras PIH analizadas se obtuvo un contenido total de Zn en un rango de entre 1,80 y 2,85 mg Zn/100 g, que correspondían a las papilla de "trigo y miel" y de "trigo y leche", respectivamente. Las muestras de "harina de trigo" presentaron un valor ínfimo en cuanto a contenido total de Zn (0,63 mg Zn/100 g).

[Nutr Hosp 2017;34(2):290-300]

**Tabla III.** Ingredientes empleados en la elaboración los papillas industriales (PIH), valor nutricional (% en relación con la ingesta dietética de referencia [IDR] para niños de 1 a 3 años)

| Papillas tradicionales (PIH) | | Valor nutricional de la receta | | | % IDR que cubren los 30 g |
|---|---|---|---|---|---|
| 1 | Arroz:<br>harina de arroz, carbonato de calcio (1,20% como estabilizador), fosfato disódico (0,72% estabilizador), lecitina de soya, vitamina C, ácido ascórbico), vainilla (0,02% como aroma idéntico al natural), fumarato ferroso, niacina (nicotinamida), sulfato de zinc, vitamina E, pantotenato de calcio, vitamina $B_1$ (tiamina), vitamina $B_6$ (piridoxina), ácido fólico, biotina, vitamina $D_3$ (colecalciferol), vitamina $B_{12}$ (cobalamina), probióticos *(Bifidobacterium lactis)* | Ración 30g | Kilocalorías<br>Hidratos de Carbono (g)<br>Fibra dietética (g)<br>Proteínas (g)<br>Grasas totales (g) | 111<br>25,3<br>0,57<br>1,98<br>0,3 | |
| | | | Hierro (mg) | | 14% |
| | | | Zinc (mg) | | 16% |
| 2 | Avena:<br>(harina de avena, azúcar, almidón de maíz, carbonato cálcico 1,27% como estabilizador), fosfato disódico (0,58% estabilizador), vitamina C (ácido ascórbico), vainilla (0,02% como aroma) fumarato ferroso, niacina (nicotinamida), Sulfato de zinc, vitamina E, pantotenato de calcio , vitamina $B_1$ (tiamina), vitamina $B_6$ (Piridoxina), ácido fólico, Biotina, vitamina $D_3$ (Colecalciferol), vitamina $B_{12}$ (cobalamina), probióticos *(Bifidobacterium lactis)* | Ración 30g | Kilocalorías<br>Hidratos de carbono (g)<br>Fibra dietética (g)<br>Proteínas (g)<br>Grasas totales (g) | 111<br>2,9<br>1,56<br>21,2<br>1,4 | |
| | | | Hierro (mg) | 1,59 | 16% |
| | | | Zinc (mg) | 1,02 | 38% |
| 3 | 5 cereales (trigo, arroz, avena, cebada y centeno):<br>harinas (trigo, cebada, avena, arroz y maíz) (83,19%%), azúcar, extracto de malta (cebada), sales minerales (carbonato cálcico, fosfato de sodio, fumarato ferroso, sulfato de zinc) vitaminas (C niacina (PP), E, pantotenato de calcio, A $B_a$ (tiamina), $B_2$ (riboflavina), $B_6$, ácido fólico, $D_3$, biotina y $B_{12}$) probióticos *(Bifidobacterium lactis).* Saborizante idéntico al natural de vainilla) | Ración 30 g | Kilocalorías<br>Hidratos de carbono (g)<br>Fibra dietética (g)<br>Proteínas (g)<br>Grasas totales (g) | 110<br>23,4<br>0,9<br>3<br>0,45 | |
| | | | Hierro (mg) | 3,0 | 14% |
| | | | Zinc (mg) | 0,9 | 16% |
| 4 | Harina de trigo | Ración 100 g | Kilocalorías<br>Hidratos de carbono (g)<br>Fibra dietética (g)<br>Proteínas (g)<br>Grasas totales (g) | 360<br>77<br>3<br>11<br>1 | |
| | | | Hierro (mg/kg de harina) | 55 | |
| | | | Zinc (mg) | – | |

*(Continúa en la página siguiente)*

**Tabla III (Cont.).** Ingredientes empleados en la elaboración los papillas industriales (PIH), valor nutricional (% en relación con la ingesta dietética de referencia [IDR] para niños de 1 a 3 años)

| Papillas tradicionales (PIH) | | Valor nutricional de la receta | | | % IDR que cubren los 30 g |
|---|---|---|---|---|---|
| 5 | Masa de maíz | Ración 100 g | Kilocalorías<br>Hidratos de carbono (g)<br>Fibra dietética (g)<br>Proteínas (g)<br>Grasas totales (g) | 371,5<br>76,6<br>2,0<br>7,7<br>3,6 | |
| | | | Hierro (mg) | 5,5 | |
| | | | Zinc (mg) | – | |
| 6 | Trigo y miel:<br>harinas de trigo, azúcar, miel de abejas, carbonato de calcio (fosfato disódico, vitamina C, fumarato ferroso, sulfato de zinc, saborizante idéntico al natural de vainilla, probióticos *(Bifidobacterium lactis)*. Vitaminas E, niacina (nicotinamida), vitamina A, $B_1$ (tiamina), $B_2$ (pantotenato de calcio), $B_6$ (piridoxina), ácido fólico (folacina), $D_3$ (colecalciferol), biotina y $B_{12}$ | Ración 50 g | Kilocalorías<br>Hidratos de carbono (g)<br>Fibra dietética (g)<br>Proteínas (g)<br>Grasas totales(g) | 208<br>33,8<br>0,6<br>–<br>4,8 | |
| | | | Hierro (mg) | 8 | 36% |
| | | | Zinc (mg) | 5 | 83% |
| 7 | Trigo y leche:<br>harinas de trigo (40%), leche parcialmente descremada azúcar, aceite de maíz (con antioxidantes: palmitato de ascórbico), aceite de canola, aceite de palma, dextrosa, sales minerales (carbonato cálcico, fosfato de sodio, fumarato ferroso, sulfato de cobre, yoduro de potasio y sulfato de zinc), probióticos *(Bifidobacterium lactis* $10^6$ ufc/g), vitaminas (C niacina (PP), E, pantotenato de calcio, A, $B_1$ (tiamina), $B_2$ (riboflavina ), $B_6$, ácido fólico, $K_1$ (floquinona), $D_3$, biotina y $B_{12}$), aromatizante natural idéntico al de vainilla, maltodextrina de maíz | Ración 30 g | Kilocalorías<br>Hidratos de carbono (g)<br>Fibra dietética (g)<br>Proteínas (g)<br>Grasas totales (g) | 112<br>25,3<br>0,8<br>2,2<br>0,3 | |
| | | | Hierro (mg) | 3,0 | 14% |
| | | | Zinc (mg) | 0,9 | 16% |
| 8 | Vainilla y canela:<br>harinas (trigo, cebada, maíz, arroz, avena) (71%), azúcar, extracto de malta (cebada), sales minerales (carbonato cálcico, fosfato de sodio, fumarato ferroso, sulfato de zinc), canela (0,3%), extracto de vainilla (vainilla) (0,02%), probióticos *(Bifidobacterium lactis* $10^6$ ufc/g), vitaminas (C niacina, E, pantotenato de calcio, A, $B_1$ (tiamina), $B_2$ (riboflavina ), $B_6$, ácido fólico, $D_3$, biotina y $B_{12}$), aromatizante natural idéntico al de vainilla, maltodextrina de maíz | Ración 8 g + 200 ml de leche | Kilocalorías<br>Hidratos de carbono (g)<br>Fibra dietética (g)<br>Proteínas (g)<br>Grasas totales (g) | 146<br>15,2<br>–<br>6,9<br>6,4 | |
| | | | Hierro (mg) | 0,3 | 5% |
| | | | Zinc (mg) | 0,15 | 31% |

**Tabla IV.** Contenido de Fe y Zn expresado en mg/100 g en 10 purés tradicionales hondureños para lactantes (PTH) de elaboración casera frente a 8 papillas industriales (PIH) consumidos por el lactante hondureño

| PTH | | Contenido (mg/100 g) | | PIH | | | Contenido (mg/100 g) | |
|---|---|---|---|---|---|---|---|---|
| | | Fe total | Zn total | | | | Fe total | Zn total |
| 1 | Arroz con frijol y hojas verdes | 1,955 ± 0,06 [a] | ND | | | | | |
| 2 | Arroz con frijol molido | 1,555 ± 0,03 [a] | ND | | | | | |
| 3 | Ayote (calabaza) con cuajada | 1,551 ± 0,00 [a] | ND | 1 | Arroz | | 9,41 ± 0,63 [b] | 1,86 ± 0,31 [a] |
| 4 | Ayote con mantequilla | 0,527 ± 0,02 [c] | ND | 2 | Avena | | 4,13 ± 0,20 [c] | 2,14 ± 0,44 [b] |
| 5 | Banano asado con azúcar | 1.42 ± 0,11 [a] | | 3 | 5 cereales (trigo, arroz, avena, cebada y centeno) | | 7,56 ± 0,14 [a] | 2,63 ± 0,08 [b] |
| 6 | Camote (batata) anaranjado | 1,110 ± 0,21 [b] | ND | 4 | Harina de trigo | | 5,61 ± 0,26 [c] | 0,63 ± 0,04 [c] |
| 7 | Frijol (habichuela) con plátano | 1,456 ± 0,06 [a] | ND | 5 | Masa de maíz | | 6,97 ± 0,17 [a] | 0,91 ± 0,03 [c] |
| 8 | Papa (patata) con mantequilla | 0,685 ± 0,02 [c] | ND | 6 | Trigo y leche | | 8,53 ± 0,10 [b] | 2,85 ± 0,27 [b] |
| 9 | Plátano con mantequilla | 0,264 ± 0,01 [d] | ND | 7 | Trigo y miel | | 7,15 ± 0,19 [a] | 1,79 ± 0,26 [a] |
| 10 | Zanahoria, crema y leche | 0,821 ± 0,03 [b] | ND | 8 | Vainilla y canela | | 6,09 ± 0,12 [a] | 2,33 ± 0,26 [b] |

*Los resultados se expresaron como la media DE ± desviación estándar de 3 determinaciones en 3 muestras distintas. ND: por debajo del límite de detección (mg/100 g). Diferentes letras en la misma columna indican diferencias estadísticamente significativas ($p < 0,05$).*

En la tabla V se muestra la bioaccesiblidad (o disponibilidad *in vitro*) de Fe y Zn para las muestras de PTH y PIH determinado como fracciones solubles y dializables. Para la fracción soluble, que simula la parte principal del proceso de digestión gástrica, se obtuvieron valores inferiores a 0,60 mg de Fe/100 g en las muestras de PTH, a excepción de la muestra de "ayote con cuajada", para las que se obtuvieron valores medios ligeramente superiores (0,9 mg/100 g). Para las muestras elaboradas con "frijoles" se obtuvieron valores más elevados que los anteriores, en un rango entre 1,09-1,60 mg Fe/100 g. En la fracción de la digestión intestinal (fracción dializable o pancreática) los valores de Fe se situaron en dos niveles: inferiores a 0,58 mg/100 g para las muestras de "puré de camote anaranjado", "arroz con frijol molido", "arroz con frijol y hojas verdes", y entre 0,76-0,59 para los de "puré de frijol con plátano", "ayote con cuajada" y "banano asado con azúcar". Los valores obtenidos se situaron en niveles bajos en todos los purés (< 0,8 mg/100 g), con pérdidas superiores al 50% para todas ellas (con respecto al contenido de Fe inicial), y alcanzando en algunos casos mermas del 70% y 84% para el puré de "arroz con frijol molido" y para el de "arroz con frijoles y hojas verdes". Por otra parte, en cuanto a disponibilidad *in vitro* de Zn para las papillas de elaboración tradicional hondureñas (PTH) encontramos que los valores encontrados, son inferiores a los índices de detección.

En el caso de los PIH (Tabla V) se observó que el porcentaje de Fe presenta valores relativamente similares en cuanto a disponibilidad *in vitro* para la fracción soluble en 4 de las 8 papillas, con pérdidas inferiores al 71% del Fe, además, 3 de las 8 papillas de cereales presentaron diferencias significativas en la fracción soluble con el resto de muestras, con valores superiores a 5 mg de Fe/100 g, concretamente 5,68, 5,64, 5,26 mg Fe/100 g para las muestras de "trigo y miel" y "arroz, vainilla y canela", respectivamente. Asimismo, en la fracción dializable los valores observados mostraron diferencias significativas para 2 de las 8 PIH estudiadas, con valores cercanos a 2 mg de Fe/100 g en la papilla de "5 cereales" y la de "vainilla y canela". En el caso de las fracciones solubles y dializables encontramos que las muestras de "trigo y miel", "5 cereales" y la de "arroz" son las que se mantienen más estables en ambas fracciones, con valores de disponibilidad *in vitro* de entre 100-75%, 52-50,9% y 62-44,9%, respectivamente. Por otro lado, las muestras de papillas infantiles que presentan una menor disponibilidad en la fracción dializable son las papillas "avena" y la de "vainilla y canela", mostrando una absorción *in vitro* inferior al 27% del contenido inicial. Además, entre las harinas, debemos destacar que la "masa de maíz" presentó una disminución de casi el 90% en la fracción dializable, que es equivalente a la fracción que es absorbida a nivel intestinal. Al comparar entre sí los PIH y PTH, se observan en ambas fracciones muestran diferencias estadísticamente significativas.

Finalmente, la disponibilidad *in vitro* del Zn en los preparados PIH presentó baja disponibilidad de este mineral con valores inferiores a 0,5 mg/100 g en todas las muestras salvo en la "papilla de arroz" y la de "trigo y leche" (1,36 mg/100 g y 0,99 mg/100 g, respectivamente, lo que supone una disminución en su disponibilidad *in vitro* superior al 75%, y en algunos casos alcanzando el 96%, como sucede en la papilla de "avena".

**Tabla V.** Disponibilidad *in vitro* de Fe en 10 recetas de purés tradicionales hondureños (PTH) y disponibilidad *in vitro* de Fe y Zn en 8 papillas industriales para lactantes hondureños (PIH)

| PTH | | % Fe (mg/100 g) | | PIH | | % Fe (mg/100 g) | | % Zn (mg/100 g) |
|---|---|---|---|---|---|---|---|---|
| | | Soluble | Dializable | | | Soluble | Dializable | Dializable |
| 1 | Arroz con frijol y hojas verdes | 1,60 ± 0,05 [c] | 0,32 ± 0,00 [a] | 1 | Trigo y miel | 5,683 ± 0,45 [a] | 1,337 ± 0,03 [a] | 0,423 ± 0,00 [a] |
| 2 | Arroz con frijol molido | 1,12 ± 0,04 [a] | 0,41 ± 0,00 [a] | 2 | 5 cereales | 3,962 ± 0,18 [b] | 1,931 ± 0,04 [b] | 0,109 ± 0,00 [b] |
| 3 | Ayote (calabaza) con cuajada | 0,89 ± 0,01 [a] | 0,67 ± 0,01 [b] | 3 | Arroz | 5,639 ± 0,20 [a] | 1,155 ± 0,02 [a] | 1,364 ± 0,03 [c] |
| 4 | Ayote con mantequilla | 0,41 ± 0,01 [b] | 0,26 ± 0,00 [a] | 4 | Avena | 3,859 ± 1,34 [b] | 1,094 ± 0,05 [a] | 0,483 ± 0,00 [a] |
| 5 | Banano asado con azúcar | 0,60 ± 0,01 [a] | 0,16 ± 0,03 [a] | 5 | Vainilla y canela | 5,264 ± 0,01 [a] | 1,973 ± 0,08 [b] | – |
| 6 | Camote (batata) anaranjado | ND | 0,33 ± 0,00 [a] | 6 | Trigo y leche | 3,511 ± 0,01 [b] | – | 0,990 ± 0,01 [c] |
| 7 | Frijol (habichuela) con plátano | 1,09 ± 0,21 [a] | 0,59 ± 0,02 [a] | 7 | Harina de trigo | 3,966 ± 0,02 [b] | 1,353 ± 0,01 [a] | 0,436 ± 0,00 [a] |
| 8 | Papa (patata) con mantequilla | 0,37 ± 0,00 [b] | – | 8 | Masa de maíz | 4,186 ± 0,03 [b] | 0,870 ± 0,00 [a] | – |
| 9 | Plátano con mantequilla | 0,08 ± 0,00 [b] | – | | | | | |
| 10 | Zanahoria, crema y leche | 0,58 ± 0,00 [b] | 0,24 ± 0,00 [a] | | | | | |

*Los resultados se expresaron como la media de ± desviación estándar de 3 determinaciones en 3 muestras distintas. ND: por debajo del límite de detección (mg/100 g). Diferentes letras en la misma columna indican diferencias estadísticamente significativas ($p < 0,05$).*

## DISCUSIÓN

En una etapa como la lactancia y los primeros meses de vida en la que los requerimientos nutricionales son superiores a los de cualquier otro grupo de edad y situación fisiológica, resulta necesario conocer del modo más preciso posible la composición de los alimentos y aquellos factores asociados a la absorción, especialmente de los micronutrientes esenciales como son el Fe y el Zn. La bioaccesibilidad juega un papel clave para que no solo el aporte cuantitativo sino el cualitativo sea el adecuado para el desarrollo físico, cognitivo e inmunológico del lactante. Igualmente la búsqueda de estrategias para mejorar dicha absorción en el periodo de diversificación de la dieta son esenciales, teniendo en cuenta que existen factores determinantes, que intervienen en la biodisponibilidad de los minerales ingeridos como son los procesos digestivos o de absorción, la unión con la matriz alimentaria, la alteraciones de pH, la naturaleza de los minerales (componentes propios del alimento o añadidos como fortificantes) o estado fisiológico del individuo. Factores que adquieren especial relevancia en países en los que existen grupos de población de mayor riesgo por sus condiciones económico-culturales o de desarrollo como es el caso Honduras. Además, este país de la región centroamericana es considerado por la FAO como de ingresos medios-bajos, y presenta un índice de desnutrición crónica del 23% con una incidencia de anemia ferropenica en preescolares superior al 29% (17), lo que indica que ciertos grupos de población rural, indígena o de bajos ingresos se encuentran en riesgo de desnutrición especialmente infantil.

Los resultados de nuestro estudio muestran en general cómo la dieta del lactante hondureño alimentado con alimentos disponibles a nivel local (PTH) presenta una baja densidad de los micronutrientes analizados (Fe y Zn) identificados como uno de los problemas de nutrientes en el país (24). Coincidiendo de este modo con numerosos estudios que relacionan una alimentación complementaria basada en alimentos de origen vegetal o mayoritariamente vegetal con una absorción disminuida de estos micronutrientes (25,26,11). Fundamentalmente por su baja biodisponibilidad (1-6%), y por la presencia de alimentos ricos en inhibidores, como los taninos, ácido oxálico, ácido fitico (cereales integrales y legumbres), calcio y la presencia de fosfoproteínas (11). Además, una dieta predominantemente vegetariana también decrece la secreción de ácido del estómago, interfiriendo en la absorción a nivel intestinal del Fe (26).

En las muestras analizadas la ración diaria de PTH proporciona valores inferiores a las PIH, con un contenido menor en todas las PTH de 2 mg Fe/día por 100 g y valores de disponibilidad *in vitro* para las PTH que se sitúan en niveles esencialmente bajos en todas las muestras analizadas. Nuestros resultados son similares a los que muestran estudios anteriores en México y Chile en cuanto al contenido total de Fe en alimentos (27,28). El porcen-

taje de Fe que presentan los alimentos típicos empleados para la elaboración de las PTH se muestra como una dieta monótona, fundamentalmente de origen vegetal, que no contiene cantidades significativas de otros alimentos que mejoren la absorción del Fe contribuyendo a la baja disponibilidad *in vitro*. Las muestras de PTH que proporcionan un porcentaje más alto son las elaboradas con "frijoles pintos y cuajada", con valores entre el 44%-65% de la IDR por 100 g, valores cercanos a los que presenta la dieta complementaria de los lactantes indonesios, donde su alimentación complementaria no proporciona IDR superior al 63% de Fe (29) en los alimentos de elaboración casera.

Otro de los factores a tener en cuenta es que las frutas o vegetales que se adicionan a los preparados están cocinadas, por lo que vitamina C, que actúa como potenciador puede aparecer inhibida en las PTH, ya que el cocinado de la papilla acelera la velocidad de degradaciones debido a las altas temperaturas durante la cocción (30). En ninguno de los PTH se detectó Zn, posiblemente por encontrarse por debajo del límite de detección. La evidencia de un efecto del Ca sobre la biodisponibilidad de Zn en los seres humanos ha sido contradictoria, ciertos estudios sugieren un posible efecto inhibidor del Ca, y otros sugieren que incrementan la disponibilidad uniéndose el Fe y Ca al ácido fitico y permitiendo una mejor absorción de Zn (31). Asimismo, el consumo paralelo de suplementos o alimentos enriquecidos con Ca, Cu o Fe puede dificultar la absorción del Zn (11).

Estos valores, relativamente bajos en las PTH, pueden indicar que este tipo de alimentos de consumo mayoritario (18) contribuyan a una inadecuada ingesta de Fe y Zn, y a ser un factor que contribuya a una mayor incidencia de anemia entre los lactantes hondureños, muy especialmente en el momento que comienza la introducción de la alimentación complementaria en los meses 6-9 (3,32). Además, tal y como hemos mencionado, en Honduras también encontramos una alta incidencia de diarrea entre su población infantil, incrementado su susceptibilidad al déficit de determinados nutrientes y al incremento en el riesgo de infecciones. Esto justifica la puesta en práctica de pautas de salud pública como las empleadas en este país en las que se recomienda el suplemento en Zn, ya que se ha observado cómo su aporte como suplemento reduce la duración y la gravedad de la diarrea y previene episodios posteriores (33). Por ello, una mayor bioaccesiblidad en la alimentación de Zn y de Fe sería una estrategia alimentaria y nutricional con claras repercusiones positivas para la salud infantil.

En cuanto a los PIH en Honduras, observamos que presentan valores más elevados en disponibilidad *in vitro* en ambos minerales frente a las PTH, ya que todas se mantenían relativamente estables en ambas fracciones con valores de disponibilidad *in vitro* de entre el 75% y el 50% como las muestras del "trigo y miel" y "5 cereales", respectivamente, destacando la de "avena" como la menos bioaccesible con pérdidas superiores al 90%. Destacar que las muestras fueron reconstituidas con agua, por lo que no participaban los inhibidores de la leche como el Ca que puede competir con Zn, Mg, Cu, y Fe para la absorción en el intestino (34), y se elaboraron en la proporción indicada por el fabricante ya que en ocasiones se ha observado como práctica habitual una dilución de los cereales en mayor proporción de lo indicado, ocasionado una merma en el consumo de ambos minerales y por ende una ingesta inadecuada (35). Tampoco se sometieron a las muestras a largos periodos de almacenamiento, que pudieran ocasionar pérdidas (36).

## CONCLUSIÓN

Queda evidenciado que, aunque el empleo de ingredientes locales sea una de las vías de sostenibilidad nutricional en determinados grupos de población en los países de ingresos medios o bajos como Honduras, la incorporación de ciertos alimentos como legumbres o vegetales puede conferir ciertos quelantes de los minerales esenciales como el Fe y el Zn, que reduce significativamente su absorción en comparación con los mismo alimentos de origen industrial. Sin embargo, se necesitan enfoques que combinen intervenciones para proporcionar Fe con otras medidas en entornos donde su carencia no es la única causa de la anemia.

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Nutrición Hospitalaria

Trabajo Original

Pediatría

# Lactancia materna para control del dolor agudo en lactantes: ensayo clínico controlado, ciego simple

*Breastfeeding for acute pain control on infants: a randomized controlled trial*

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## Resumen

**Objetivo:** determinar la eficacia de la lactancia materna (LM) para el manejo del dolor agudo después de la vacunación en lactantes menores de 6 meses al compararse con el sucedáneo de la leche (SL) y no aplicar ninguna maniobra.

**Métodos:** se realizó un ensayo clínico controlado aleatorizado, ciego simple en fase III en lactantes menores de 6 meses de edad. Se incluyeron 3 grupos: LM, SL y sin aplicar analgesia (control). El dolor se midió a través del tiempo de llanto y una escala de dolor pediátrico. En el análisis estadístico se utilizaron las pruebas de Kruskal Wallis y U de Mann Whitney para variables cuantitativas y para variables cualitativas se aplicó la prueba de $Chi^2$. Se utilizó Kaplan Meier para analizar el tiempo de llanto total.

**Resultados:** se analizaron un total de 144 pacientes, 48 por grupos. El grupo de LM tuvo menor tiempo de llanto ($p = 0,007$) y menor calificación de dolor a los 90 ($p = 0,006$) y 120 ($p = 0,003$) segundos comparado con los otros 2 grupos. Mientras que entre el grupo SL y el grupo control no hubo diferencia significativa en la duración del llanto ni la escala de dolor.

**Palabras clave:**

Lactancia materna. Dolor. Lactantes.

**Conclusiones:** la lactancia materna es efectiva para el manejo del dolor agudo después de la vacunación en lactantes menores de 6 meses de edad en comparación al sucedáneo de leche y no aplicar analgesia.

## Abstract

**Objective:** To determine the effectiveness of breastfeeding (BF) for the management in acute pain after vaccination in infants under 6 months of age when compared to the milk substitute (MS) and not to apply any maneuver.

**Methods:** A controlled, single-blind phase III clinical trial was conducted on infants under 6 months old to evaluate the effectiveness of BF in acute pain by vaccination. Divided in 3 groups: BF, milk substitutes (MS), and without applying any analgesic maneuver (control). Pain was measured by crying time and pediatric pain scale. Statistical analysis was performed using the Kruskal Wallis and Mann-Whitney U for quantitative variables. For qualitative data, $Chi^2$ was applied Kaplan Meier was used to analyze the total time crying.

**Results:** A total of 144 patients were recruited, divided in groups of 48 patients. The group of BF had fewer crying time ($p = 0.007$) and pain rating at 90 ($p = 0.006$) and 120 ($p = 0.003$) seconds compared with other groups. There was no significant difference in the crying time ($p = 0.396$) and the pain scale between the group receiving MR and control.

**Key words:**

Breastfeeding. Pain. Infants.

**Conclusions:** Breastfeeding is effective in management of acute pain by vaccination in infants under six months of age compared to milk substitute and control.

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## INTRODUCCIÓN

Por sus múltiples beneficios, la leche humana es el mejor alimento que se puede otorgar desde el nacimiento a todo recién nacido; por supuesto, contiene los nutrientes (vitaminas, minerales, proteínas, hidratos de carbonos y grasas de fácil digestión) necesarios el crecimiento y desarrollo para los lactantes, pero además los lactantes amamantados presentan una menor morbilidad y mortalidad por infecciones gastrointestinales y respiratorias (1). También el amamantamiento se ha relacionado con mayor coeficiente intelectual, así como menor riesgo de enfermedades crónicas como diabetes, obesidad, asma y leucemia (2,3). Además la leche humana posee hormonas, factores de crecimiento, anticuerpos, acción antimicrobiana y estimula el desarrollo del sistema inmune (4). Otro punto a destacar es que en años recientes la lactancia materna (LM) se ha utilizado para el manejo no farmacológico del dolor agudo provocado por procedimientos médicos en recién nacido y lactantes (5). Por todo lo anterior, a la LM no solamente se le considera como alimento, sino como un "tejido líquido" que no tiene comparación con los sucedáneos de la leche (SL) humana. A pesar de todos sus beneficios, en México, la lactancia materna exclusiva en menores de seis meses mostró un descenso porcentual del 22,3% al 14,4%, entre el año 2006 al 2012, respectivamente (6).

Con respecto al dolor, se ha reconocido que los neonatos expuestos a repetidos procedimientos (venopunciones, punciones capilares y aplicación subcutánea o intramuscular de medicamentos) en las primeras horas de vida, aprenden a anticipar el dolor y presentan respuestas más intensas durante estos procedimientos en comparación a los neonatos no expuestos a los mismos (7). Mientras que en lactantes cuando no se les brinda algún tratamiento para el dolor, pueden ocurrir efectos a largo plazo, como alteraciones en el desarrollo cognoscitivo, incluyendo memoria y lectura, así como aumento de la somatización, ansiedad, e hipersensibilidad en futuros procedimientos dolorosos (8-10).

Específicamente, para el manejo del dolor en la aplicación de vacunas, el uso de fármacos es poco recomendado (11,12), prefiriéndose intervenciones no farmacológicas puesto que los efectos adversos son casi nulos (13). Dentro de estas últimas, tanto la administración de alimentos dulces, que el bebé esté succionando durante y después de la aplicación (por ejemplo, con chupones), así como ofrecer SL o LM han demostrado ser efectivas y seguras (14-17). Se piensa que estas maniobras reducen el dolor indirectamente por la disminución de los estímulos nocioceptivos y, en forma directa, por bloqueo de la transmisión nocioceptiva, activación de vías descendientes inhibitorias y por activación del sistema modulador del dolor (18,19).

Con respecto a la LM, en los últimos años se han realizado ensayos clínicos controlados para determinar su eficacia para disminuir el dolor después de la vacunación. Por ejemplo, Dilli y cols. incluyeron 162 lactantes menores de 6 meses de edad; a 77 se les administró LM antes y durante la aplicación de la vacuna de hepatitis B y a 85 no se les dio analgesia (20). Efe y cols. incluyeron a 66 lactantes entre 2 a 4 meses de edad; se dividieron en 2 grupos, uno recibió LM antes y durante la vacunación de difteria-tosferina-tétanos y el otro grupo sin analgesia (21). Moddares y cols. incluyeron a 130 recién nacidos; 65 recibieron LM durante y después de la vacunación de hepatitis B y los otros 65 recién nacidos fueron grupo control (22). Abdel Razek y cols. incluyeron a 120 lactantes de 1 a 12 meses de edad, divididos en 2 grupos; uno que recibió LM durante y después de la aplicación de la vacuna de hepatitis B, y otro grupo no recibió ninguna maniobra analgésica (23). En todos los casos, el dolor fue medido a través del tiempo de llanto obteniéndose una adecuada eficacia de la LM para el control de dolor; sin embargo, por la técnica en que se aplicó la LM, no hubo forma de cegar la maniobra en ninguno de los estudios.

El objetivo del presente estudio fue determinar la eficacia de la lactancia materna, para el manejo del dolor agudo después de la vacunación en lactantes menores de 6 meses al compararse con el SL y no aplicar ninguna maniobra.

## MÉTODOS

Se realizó un ensayo clínico controlado y aleatorizado con tres ramas: LM, SL y un tercer grupo al cual no se les dio alguna intervención (control). Durante el periodo de marzo a agosto de 2015 se reclutaron niños con edades comprendidas de 2 a 6 meses, quienes eran atendidos en dos unidades de atención primaria en la consulta de niño sano.

Antes del inicio del estudio, el protocolo fue aprobado por la Comisión Nacional de Investigación y Ética del Instituto Mexicano del Seguro Social (IMSS); para ingresar al estudio, todos los padres firmaron carta de consentimiento informado.

Se incluyeron niños que tuvieron peso al nacimiento > 2,5 kg, con adecuada tolerancia a la vía oral, y que estuvieran alimentados en ese momento tanto con LM como con SL (es decir, con alimentación mixta). Se excluyeron pacientes con alguna cardiopatía, con problemas neurológicos, con antecedentes de intubación endotraqueal, con contraindicaciones para la aplicación de la vacuna pentavalente acelular, quienes hubieran recibido algún analgésico en las últimas 48 horas, o bien, cuando el lactante no fuera acompañado por la madre en el momento de la vacunación o que no llevara SL.

## ALEATORIZACIÓN

La asignación a cualquiera de los brazos de intervención fue aleatoria; el proceso de aleatorización se realizó antes del inicio del estudio, mediante la generación de números aleatorios por computadora. Para mantener oculta la secuencia de la aleatorización para la aplicación de la intervención (LM, SL o control), se conservó en sobres cerrados y opacos hasta que cada paciente fue seleccionado y se firmó el consentimiento informado. Uno de los investigadores (JNZC) entregó, de manera subsecuente, a los padres el sobre opaco. A su vez, los padres entregaban el sobre a otro investigador (RRR) quien lo abría y aplicaba la maniobra de acuerdo a lo indicado.

## INTERVENCIONES

Fueron dos: manejo del dolor con el uso de LM, SL o nada y la segunda fue la vacunación que ocasiona el dolor. Para el grupo de LM la maniobra consistió en ofrecer al niño/a lactancia materna, dos minutos antes de vacunación. En el caso del grupo que recibió SL, también dos minutos antes de la vacunación se ofreció en un biberón 0,6 ml de SL por kilo de peso (17). Mientras que los niños del tercer grupo no recibieron maniobra alguna. Posteriormente, una enfermera capacitada y estandarizada aplicó una dosis de vacuna pentavalente acelular, de acuerdo a las recomendaciones establecidas (24).

## EVALUACIÓN DE LA EFECTIVIDAD DE LAS INTERVENCIONES

Cada niño o niña que ingresó al estudio se videograbó desde del término de la LM o SL, durante la aplicación de la vacuna y hasta 120 segundos posterior a la vacunación. Cabe señalar que para mantener el cegamiento de las intervenciones utilizadas, se corroboró que durante la grabación no se observara si había recibido LM o SL.

Cada vídeo fue enviado a dos observadores independientes. Uno de ellos (MAVK) cuantificó el tiempo de llanto desde la aplicación de la vacuna hasta el término del llanto. La duración del llanto se clasificó como la duración del primer llanto *(vibraciones vocales armónicas, escuchadas en el primer lanzamiento de llanto después de la aplicación de la vacuna)* y la duración del llanto total *(llanto persistente desde la aplicación de la vacuna, incluyendo múltiples frecuencias moduladas periódicamente con periodos de 1 segundo entre cada intervalo de llanto emitido (25,26). Cuando el intervalo entre cada llanto fue mayor de 2 segundos se consideró finalizado el llanto).*

El otro observador (VGA) calificó la intensidad del dolor con la escala del Hospital Universitario Pediátrico de Wisconsin (HUPW) inmediatamente tras la vacunación, y posteriormente a los 30, 60, 90 y 120 segundos. Antes del inicio del estudio, ambos observadores fueron estandarizados. La escala del dolor del HUPW está validada para pacientes menores de 3 años de edad (27).

## ANÁLISIS ESTADÍSTICO

Los datos se presentan como frecuencias absolutas y porcentajes; las variables cuantitativas se presentan como mediana y valores mínimo (min.) y máximo (máx.), en virtud que no tuvieron una distribución normal. Para la comparación de variables cuantitativas de tres grupos se utilizó Kruskal Wallis y U de Mann Whitney como prueba *post-hoc.* Mientras que la comparación de las variables cualitativas entre los grupos fue con prueba de Chi-cuadrado. Por último, se calcularon curvas de Kaplan-Meier a fin de comparar el tiempo para que terminara el llanto posterior a la vacunación entre los grupos; la comparación de las curvas fue con el estadístico Log-rank. Los análisis se realizaron tomando en cuenta el principio de intención de tratar.

El tamaño muestral se calculó considerando una disminución del tiempo de llanto de 40% en los niños que reciben LM en comparación de aquellos que no la reciben. Se asumió que el recibir SL era equivalente a la LM. Así, y tomando en cuenta error alfa de 0,05 y error beta de 0,80, se obtuvo un tamaño de muestra de 45 pacientes por grupo.

Todos los análisis se realizaron con el software SPSS versión 17.0 (IBM).

## RESULTADOS

Se incluyeron un total de 144 lactantes de dos a seis meses de edad, con una mediana de cuatro meses; 74 fueron de sexo masculino (51,4%), la mediana del peso fue de 6 kg (mín. 3,8, máx. 8,3) y la mediana de la talla de 59 cm (mín. 51 cm, máx. 69 cm). En la tabla I se comparan las características generales de los lactantes entre los tres grupos de intervención, observando que los tres grupos fueron similares, lo cual se comprobó estadísticamente ($p > 0,05$) para cada una de las cinco variables descritas.

En la figura 1 se describe el flujo de los pacientes desde su selección hasta la conclusión del estudio, incluyendo los eventos que condicionaron que los lactantes fueran excluidos. Como se observa, el motivo principal de exclusión fue relacionado a que no se pudo concretar el cegamiento apropiadamente. No hubo

**Tabla I.** Comparación de las características generales de los lactantes de acuerdo al grupo de intervención

| | Lactancia materna n = 48 | Sucedáneo de la leche n = 48 | Control n = 48 |
|---|---|---|---|
| | Mediana (min-max) | | |
| *Sexo** | | | |
| Masculino | 24 (50) | 23 (54,7) | 22 (51,2) |
| Femenino | 24 (50) | 25 (45,3) | 26 (48,8) |
| Edad (meses) | 4 (2-6) | 4 (2-6) | 4 (2-6) |
| Peso (kg) | 6,05 (4-8,3) | 5,2 (4-8) | 6,5 (4-8) |
| Talla (cm) | 59,5 (51-69) | 56 (52-67) | 59 (51-69) |
| Peso al nacer (kg) | 2,9 (2,5-3,9) | 3 (3-4) | 3 (3-4) |

**n (%).*

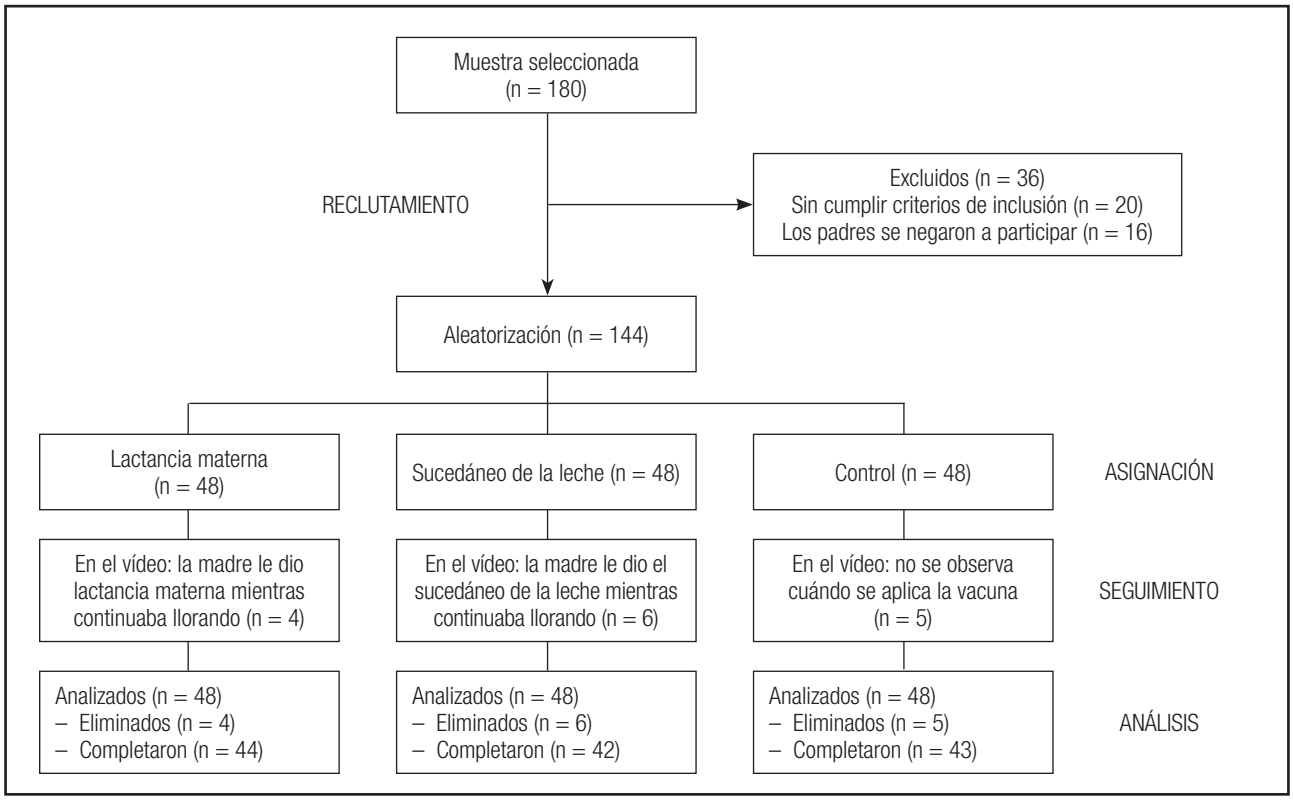


**Figura 1.**

Proceso de selección, aleatorización y seguimiento de los participantes en el estudio.

diferencia estadística en el porcentaje de pacientes que completaron de manera adecuada el estudio: 91,6% de LM, 87,5% de SL y 89,5% del grupo control.

En la figura 2 se comparan las calificaciones de la intensidad del dolor mediante la escala del HUPW a través del tiempo entre los tres grupos de estudio. Como se observa, desde la calificación inmediatamente tras la vacunación existe una tendencia a que la LM controla mejor el dolor en los lactantes en los cinco tiempos evaluados; pero únicamente para los 90 y 120 segundos posterior a la vacunación se determinó diferencia estadísticamente significativa entre los tres grupos (p = 0,006 y 0,003, respectivamente). En el análisis *post-hoc* se estableció que esta diferencia fue debida a que en el grupo LM la calificación del llanto fue estadísticamente menor que las obtenidas en el grupo SL y del grupo control, tanto a los 90 y a los 120 segundos**.** Mientras que no hubo diferencia significativa entre las calificaciones del llanto el grupo SL y el grupo control en ninguno de los momentos evaluados.

El tiempo de llanto entre los grupos se describe en la tabla II. La mediana de tiempo (en segundos) para el inicio del llanto tras la vacunación fue similar entre los tres grupos. Sin embargo, la duración total del llanto (desde el inicio del llanto hasta que el bebé dejó de llorar) fue menor en el grupo que recibió LM (mediana 19 segundos), en comparación con los 41 segundos del grupo SL y del grupo control (LM *vs.* SL p = 0,027, LM vs control p = 0,003). No hubo diferencia significativa en la duración del llanto entre el grupo que recibió sucedáneo de la leche y el control (p = 0,396).

Por último, en la figura 3 se presenta la comparación del tiempo en segundos para que el llanto desaparezca, entre los grupos. Como se observa, en el grupo LM el tiempo fue estadísticamente menor que el de los otros dos grupos (p = 0,014).

## DISCUSIÓN

Los resultados de este estudio demuestran que la LM es efectiva para el control del dolor agudo ocasionado por la vacunación en lactantes menores de seis meses. Si bien esta observación ya ha sido descrita en otros estudios en los que se demuestra la eficacia de la LM previa, durante y después de la aplicación de la vacuna, comparado con un grupo control, es conveniente mencionar que dichos estudios tienen problemas metodológicos, por ejemplo, en el estudio de Dilli y cols. y Abdel Razek y cols. los observadores no estuvieron cegados al momento de calificar el dolor (20,23). Harrison y cols. (28) publicaron un metaanálisis del manejo del dolor posterior a la vacunación en menores de 1 año de edad, en el que incluyeron 10 estudios con un total de 1.066 lactantes. Se demostró la eficacia de la lactancia materna en comparación con cualquiera de las siguientes intervenciones: agua oral, caricias, glucosa oral, anestésico tópico o masaje. Sin embargo, los estu-

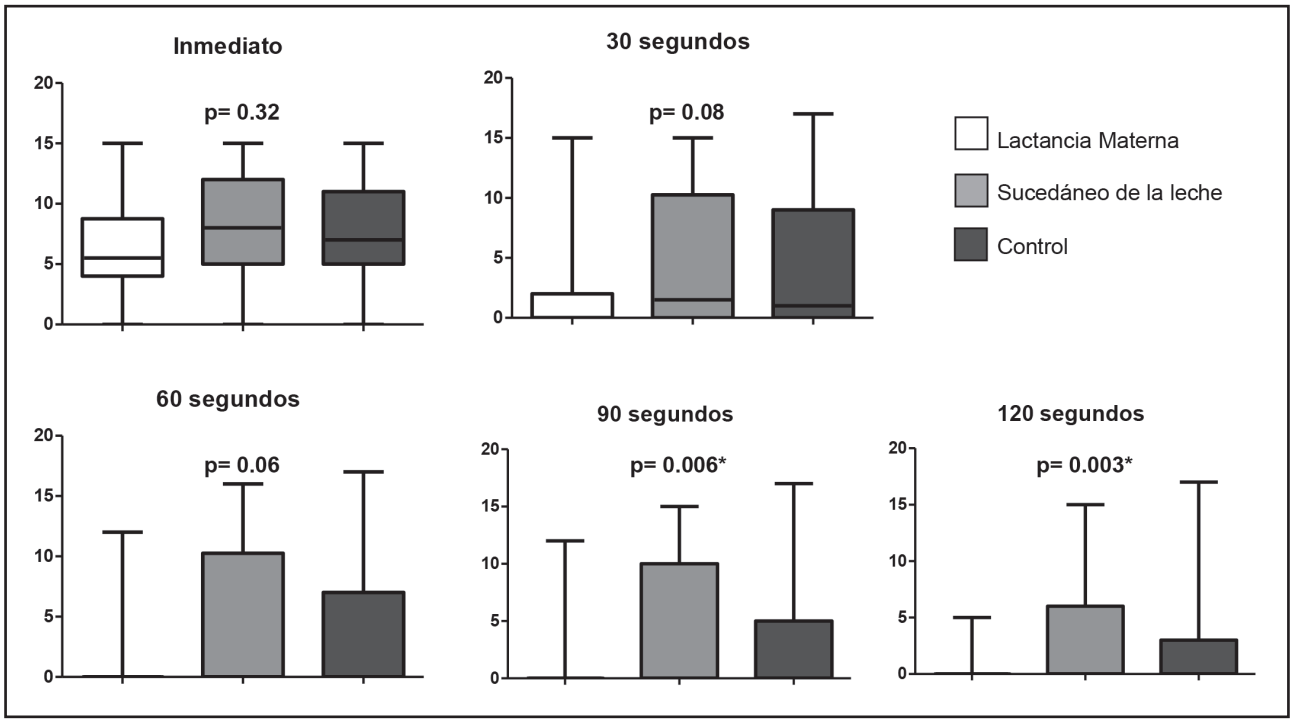


**Figura 2.**

Comparación de las medianas del puntaje de dolor con la escala del Hospital Universitario Pediátrico de Wisconsin (HUPW) entre los grupos, en diferentes momentos posteriores a la vacunación.

**Tabla II.** Tiempo de llanto de los lactantes de acuerdo al grupo de intervención

| | Lactancia materna n = 44 | Sucedáneo de la leche n = 42 | Control n = 43 | p |
|---|---|---|---|---|
| | Mediana (min-max) | | | |
| *Tiempo (seg)* | | | | |
| Primer llanto | 2 (0-10) | 1,5 (0-9) | 2 (0-8) | 0,229 |
| Llanto total | 19 (0-136)* | 41,5 (0-184) | 41 (0-161) | 0,007* |

**Tiempo de llanto significativamente menor, p < 0,05.*

*Primer llanto: vibraciones vocales armónicas, escuchadas en el primer lanzamiento de llanto después de la aplicación de la vacuna.*

*Duración del llanto total: llanto persistente desde la aplicación de la vacuna, incluyendo múltiples frecuencias moduladas periódicamente con periodos de 1 segundo entre cada intervalo de llanto emitido. Cuando el intervalo entre cada llanto fue mayor de 2 segundos se consideró finalizado el llanto.*

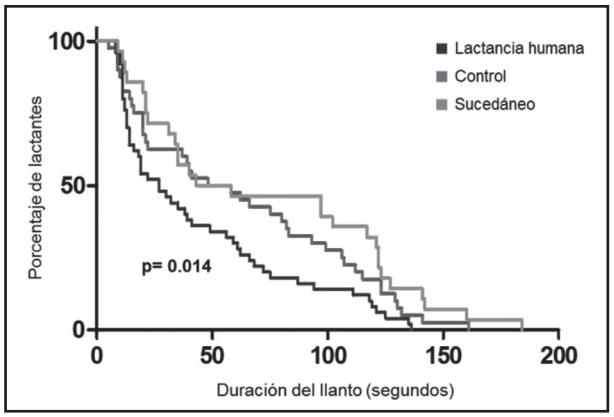


**Figura 3.**

Duración del llanto.

dios fueron clasificados como de alto riesgo de sesgo, ya que no se realizó cegamiento a participantes o al personal. La fortaleza de nuestro estudio es que la maniobra aplicada en los grupos fue cegada para los investigadores que evaluaron la escala del dolor y el tiempo de llanto, y los resultados son más fiables.

Se ha descrito que la LM tiene efectos analgésicos, dentro de los que se incluyen la presencia de una persona reconfortante (madre), la sensación física de contacto piel a piel, la distracción de la atención y la dulzura de la leche materna (29). Además, la LM contiene triptófano (30), un precursor de la melatonina que tiene propiedades analgésicas y antiinflamatorias, y estimula la producción de endorfinas (31). Ramenghi y cols., en recién nacidos pretérmino, comparó el manejo del dolor a través de la administración de sacarosa por succión y por sonda gástrica, teniendo efecto analgésico solo en el grupo que se le administró por succión (32). Esto apoya a que la succión promueve la produc-

ción de endorfinas, siendo otro mecanismo que confiere analgesia en los lactantes que reciben lactancia materna.

El manejo del dolor agudo en pediatría ha ido evolucionando (33) y, a pesar de que desde el 2001 se han implementado recomendaciones por especialistas (34), hasta el momento existen limitantes por lo cual algunos profesionales de la salud continúan sin utilizar de forma rutinaria tratamiento farmacológico o no farmacológico cuando se realiza algún procedimiento médico que provoque dolor agudo en el paciente. Las barreras que hasta el momento continúan presentando son que el manejo del dolor es más tardado que el procedimiento que se va a realizar, preocupación por los efectos adversos de los medicamentos, tiempo insuficiente para premedicar o preparar al paciente antes del procedimiento, falta de personal y espacio para aplicación de la analgesia y la baja prioridad que se da al manejo del dolor por el personal médico (35,36). La mayoría de las limitaciones descritas pueden ser salvadas con el uso de la LM antes de algún procedimiento doloroso en lactantes, ya que no se requiere de una preparación ni personal extra para realizar esta maniobra, a diferencia del resto de las medidas no farmacológicas que se emplean. Este efecto analgésico, pudiera ser otro estimulante para promover el uso de la LM.

No hubo diferencia estadística entre el grupo control y el grupo que recibió SL. Por ejemplo, Skogsdal y cols. (37) compararon el SL con glucosa al 10% y 30%, donde se demostró que ni la glucosa al 10% ni el SL eran efectivos para el control del dolor en neonatos. Por otro lado, Shah y cols. (38) realizaron un metaanálisis donde incluyeron 11 estudios que comparaban la LM o SL con glucosa/sacarosa o no aplicar ninguna maniobra; los resultados no fueron suficientes para demostrar la eficacia del SL en el manejo agudo del dolor en lactantes. Esto apoya a los resultados obtenidos en nuestro estudio.

A la luz de los resultados obtenidos, también se deben reconocer ciertas limitaciones. La que parece destacar más es la ausencia de un grupo de lactantes en quienes se les administrara leche humana en biberón, a fin de identificar si la leche humana por sí sola tiene el mismo efecto analgésico que durante el amamantamiento.

En conclusión, se puede afirmar que la LM es efectiva para el manejo del dolor provocado por la vacunación en lactantes al compararse con sucedáneos de la leche o sin alguna medida analgésica.

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Nutrición Hospitalaria

Trabajo Original

Pediatría

# Factors associated with body mass index in Brazilian children: structural equation model

## *Factores asociados con el índice de masa corporal en niños brasileños: modelo de ecuaciones estructurales*

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## Abstract

**Introduction:** Overweight and obesity in children is an important global problem. Its prevalence is increasing in developed and developing countries.

**Objective:** The aim of this study was to evaluate the association between socioeconomic conditions, maternal body mass index (BMI), food security, and intake of obesogenic foods on excess body weight in children.

**Methods:** A cross-sectional study was conducted, using the data of 3,676 children from the latest National Demographic and Health Survey in Brazil. The children's BMI was the study outcome. Socioeconomic condition, maternal BMI, food security, and intake of obesogenic foods were use as predictors. structural equation models were used for analysis.

**Results:** Socioeconomic conditions directly influenced the children's BMI ($\beta = 0.102$; $p = 0.02$), mediated by intake of obesogenic foods ($\beta = 0.018$; $p = 0.04$). A direct association was observed between maternal and child BMIs ($\beta = 0.169$; $p < 0.001$) and intake of obesogenic foods and child BMI ($\beta = 0.114$; $p < 0.001$).

**Conclusions:** Favorable socioeconomic conditions, increased maternal BMI, and intake of obesogenic foods contributed to increased child BMI.

**Key words:**

Risk factors. Nutritional status. Child. Structural equation modeling. Brazil.

## Resumen

**Introducción:** el sobrepeso y la obesidad en los niños es un importante problema de salud global, habiéndose verificado aumento de la prevalencia en las poblaciones de los países desarrollados y en desarrollo.

**Objetivo:** el objetivo de este estudio fue estimar la asociación entre las condiciones socioeconómicas, el consumo y el exceso de peso corporal en los niños.

**Métodos:** estudio transversal de una muestra probabilística representativa de la población brasileira que incluyó 3.676 niños provenientes de la última Encuesta Nacional de Demografía y Salud. El índice de masa corporal (IMC) de los niños fue la variable desenlace. El nivel socioeconómico, IMC materno, inseguridad a la hora de alimentarles y el consumo de alimentos obesogénicos fueron consideradas variables independientes. Las ecuaciones estructurales fueron usadas como método de análisis.

**Resultados:** las condiciones socioeconómicas influyeron directamente el IMC de los niños ($\beta = 0{,}102$; $p = 0{,}02$), mediado por la ingesta de alimentos obesogénicos ($\beta = 0{,}018$; $p = 0{,}04$). Se observó asociación directa entre el IMC de la madre y del niño ($\beta = 0{,}169$; $p < 0{,}001$) y entre el consumo de alimentos obesogénicos y el IMC del niño ($\beta = 0{,}114$; $p < 0{,}001$).

**Conclusiones:** la condición socioeconómica favorable, el IMC materno y la ingesta de alimentos obesogénicos pueden potencialmente contribuir para el aumento del IMC del niño.

**Palabras clave:**

Factores de riesgo. Estado nutricional. Niños. Modelos de ecuaciones estructurales. Brasil.

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## INTRODUCTION

Overweight and obesity is an important global problem. Its prevalence is increasing in developed and developing countries (1,2), not only in adults, but also in children. This has been observed in North American (3), European (4), and Latin American (5) populations, including in Brazil (6). Its persistence throughout life can lead to several comorbidities (7) such as postural impairment, psychosocial problems (8), and metabolic disorders (dyslipidemia, arterial hypertension, insulin resistance, hyperinsulinemia, and diabetes) (9).

Genetic and postnatal factors (such as social, economic, cultural, psychosocial, and behavioral factors) are related to excess weight, making this a complex and multifaceted condition (8,10). The association between socioeconomic conditions and weight outcomes in children is controversial (2,11). Income and education are associated with food choices and food availability (12,13). Less economically privileged families are more susceptible to food and nutritional insecurity (12). Families with food insecurity adopt compensatory eating practices such as an increased consumption of low-cost, high-calorie, low-nutrient foods (14). Although several studies have indicated a positive association between food insecurity and excess weight (15,16), other studies found no such association (17,18).

Several studies have also indicated that parental, particularly maternal, overweight/obesity status influences excess weight in children, owing to genetic and family-behavioral components and life habits, including food intake and the unrestricted availability of high-calorie, low-nutrient foods at home (19,20).

Determinants of body weight gain in childhood have been investigated through models in which linear regression analysis, logistic analysis, and meta-analysis are commonly performed. However, few studies have applied structural equation modeling (SEM), which limits the simultaneous analysis of explanatory relationships between multiple variables, whether latent or observed.

In this context, the aim of this study was to evaluate the association between socioeconomic conditions, maternal body mass index (BMI), food security, and intake of obesogenic foods on excess body weight in children and how these interrelate to trigger this nutritional outcome. To evaluate these correlations, we used a theoretical model and consulted other studies as references (21).

For the present study, the following hypotheses were established *a priori:* a) increased child BMI is directly associated with unfavorable socioeconomic conditions, mediated by increased maternal BMI, food insecurity, and intake of obesogenic foods by the child, which are, in turn, directly associated with increased child BMI; b) increased child BMI is directly associated with increase in maternal BMI, mediated by the intake of obesogenic foods by the child; and c) increased child BMI is directly associated with food insecurity, mediated by the child's intake of obesogenic foods. Thus, we expected to obtain information that might support preventive and control programs against this nutritional phenomenon, particularly in children.

## MATERIALS AND METHODS

This cross-sectional study analyzed data from the latest National Demographic and Health Survey of Children and Women conducted between 2006 and 2007 in Brazil (PNDS) (22). The PNDS was designed to provide estimates representative of the Brazilian population living in private households (including slums), who were selected in 10 sampling strata that comprised a combination of all five major geographical Brazilian regions and both urban and rural areas. The sampling units were selected in two stages as follows: the primary units were composed of census tracts, and the secondary units were composed of households (22). Detailed sampling plans, data collection information and data quality assurance are available in the PNDS/DHS 2006 survey final reports at http://bvsms.saude.gov.br/bvs/pnds/index.php.

Anthropometric measurements of the mothers and children were performed according to internationally standardized procedures (23), where two measures were obtained for each anthropometric indicator (weight and height) and the mean value was used. Mothers whose children were alive and living with them at the date of the interview were included in this analysis. If the mother had more than one child (approximately 22% of participants), the eldest child was chosen for this study. This choice was due to older children having had a longer duration of exposure to excess weight (24). The final number of child observations was 3,676. No statistically significant differences in socioeconomic and demographic characteristics were observed between the excluded and included children (data not shown). In addition, the amount of missing data was minimal (maternal education level, n = 44; maternal BMI, n = 16; household condition, n = 124; food insecurity, n = 109). Substitution of mean variable values was used for imputation of missing data (25).

BMI in children was expressed as a z-score in a continuous form and was considered the outcome variable. It was calculated as the weight (kg) divided by the square of the height ($m^2$). The category excess weight, including overweight and obesity, measured by the z-score of the body mass index/age (BMIz) indicator was greater and equal than 1 z-scores. BMI z-scores were calculated using the standardized reference curves of the World Health Organization (26).

For the analysis via the SEM from the defined conceptual model, the latent variables considered and represented by an ellipse were as follows:

*A. Intake of obesogenic foods by the child (foodobes):* latent variable composed of the observed variables (represented by a rectangle): A.1. Intake of fried foods (friefood); A.2. Snacks (pretzels); and A.3. Sweets within the week preceding the interview. These three foods best represented the obesogenic foods. The frequency questionnaire of food consumption used to assess dietary intake of children consisted of a list of twenty foods, food groups, or preparations. The frequency of consumption was in reference to the seven days prior to the interview, and the following answers could be chosen: not consumed, consumed on one day, consumed on two or three days, consumed on four to six

days, consumed every day, and do not know (27). To transform the categories of weekly frequencies into daily intake, a weight (Sn) was assigned to each food, in accordance with the intake frequency category as follows: Sn = (1/7)[(a + b)/2], where *a* and *b* correspond to the numbers of days of weekly intake frequency (27). A zero value was assigned to the "does not consume" or "rarely" frequency categories. The remaining categories of weekly frequency were the following: once, 2 or 3 times, 4-6 times, and daily (category to which a maximum weight of 1 was allocated).

*B. Socioeconomic conditions(ses):* latent variables composed of the following observed variables: B.1. Possession of household goods (hholdg), based on the economic classification criteria of Brazil of the Brazilian Association of Research Companies (28), considering the sum of goods, used as a continuous variable; B.2. Household conditions (housecon) and the presence (assigned the value of 0) or absence (assigned the value of 1) of piped water, linkage to a sewage network, electricity, and type of construction (masonry or other), were assessed. Then, a variable composed of the sum of the points of all items, ranging from zero (domicile that possessed all items) to three (domicile that had none of the items), was created; and B.3. Maternal education level (mateduc): years of study of the mother, used as a continuous variable.

The possible mediating observed variables were as follows:

*A. Food insecurity (foodsec):* assessed using the Brazilian Food Insecurity Scale, represented by scores (0: food security; 1: mild food insecurity; 2: moderate food insecurity; 3: severe food insecurity). This scale was adapted and validated for the non-institutionalized Brazilian population (29) and measures families' perceptions regarding food access. B. Maternal BMI (matbmi): calculated as weight (kg) over the square of height ($m^2$), used as a continuous variable.

The SEM was used to assess the relationship between the study variables. Estimation of the direct and indirect effects of theoretical risk factors on child BMI provided more-realistic model tests and potentially greater statistical power than traditional multistep methods. In addition, under complex sampling, both point and variance estimators derived under independently and identically distributed observation assumptions are well known to potentially produce biased and inconsistent estimates. The model specified for SEM was built in Mplus 7.0 software by using robust maximum likelihood, where the strategy for replacing inverse Fisher information with a sandwich estimator of variance is useful for non-normality and non-independence of observations (30). To consider the complex survey design of the data, we used the "Type = Complex" statement, which included sampling weights and clustering of the PNDS data.

In relation of model fitness information, we choose to use relative (TLI- Tucker-Lewis Index) and the no centrality parameter (CFI- Bentler's Comparative Fit Index, RMSEA- Root Mean Square Error of Approximation) fit indices that are relatively unaffected by sample size. Values > 0.95 are suggested as cut-offs for these indices (31).

Regarding the ethical aspects, PNDS (2006) received the approval from the Ethics Research Committee (CEP) of the Center of Reference and Training DST/AIDS of the State Department of Health (SP). All individuals who agreed to participate in the study signed the informed consent form.

## RESULTS

The mean age of the children was 2 years (standard deviation [SD] = 0.03), with similar frequency between sexes. The mean maternal age was 27 years (SD = 0.21), maternal BMI was 25 $kg/m^2$ (SD = 0.16), and number of years of schooling was 8 years (SD = 0.11). Among the study children, 54.4% (95% confidence interval [CI] 0.51-0.58) lived in excellent housing conditions, 34.1% (95% CI 0.30-0.38) were among those whose possessions were within the first third of household goods, 6.4% (95% CI 0.05-0.08) had severe food insecurity, 4.9% (95% CI 0.04-0.06) consumed fried foods, 16.8% (95% CI 0.01-0.03) consumed snacks and 19.7% (95% CI 0.17-0.23) consumed sweets daily. The prevalence of excess weight, including overweight and obesity, was 7.3% (95% CI 0.06-0.09): 4.1% (95% CI 0.03-0.05) among boys and 3.2% (95% CI 0.03-0.04) among girls (data not shown).

Significant correlations were observed between certain variables and child BMI, such as maternal education ($r = 0.05$; $p < 0.001$), household goods ($r = 0.11$; $p < 0.001$), intake of fried foods ($r = 0.05$; $p = 0.04$), intake of sweets ($r = 0.07$; $p = 0.01$), and maternal BMI ($r = 0.18$; $p < 0.001$). Other correlations are shown in table I.

The factorial loads (FL) for the latent variable socioeconomic conditions ranged from -0.05 to 0.80, with the possession of household goods being the component that contributed most in this model of measurement (FL = 0.80), followed by maternal education (FL = 0.59; Fig. 1). The latent variable intake of obesogenic foods by the child (foodobes) was represented by the indicators of intakes of fried foods, snacks, and sweets within the week preceding the interview. The factorial loads ranged from 0.27 to 0.67, with the intake of snacks (FL = 0.67; Fig. 1) contributing most to this model, followed by the intake of sweets (FL = 0.59; Fig. 1).

The direct and indirect effects (with their respective estimates) of socioeconomic conditions on child BMI, via maternal BMI, food security, and intake of obesogenic foods and how these variables are interrelated in triggering the outcome, are presented in table II and figure 1. We noted a direct association between socioeconomic conditions and child BMI ($\beta = 0.102$; $p = 0.02$) and an indirect effect mediated by the intake of obesogenic foods ($\beta = 0.018$; $p = 0.04$). This association was not mediated by maternal BMI ($\beta = 0.006$; $p = 0.37$) or food security ($\beta = -0.030$; $p = 0.84$). A direct positive association between socioeconomic conditions and intake of obesogenic foods was observed ($\beta = 0.155$; $p = 0.02$), along with an inverse association with food security ($\beta = -0,544$; $p < 0.001$). The data also indicated a direct association between maternal and child BMI ($\beta = 0.169$; $p < 0.001$) and intake of obesogenic foods ($\beta = 0.114$; $p < 0.001$). No other associations were statistically significant. The results of the SEM analysis attained acceptable values for adjustment indexes of the models (Table III).

**Table I.** Mean, standard deviation, and correlation coefficient of each study variable (Brazil, National Demographic and Health Survey of Children and Women, 2006-2007)

| Variable | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| **Mean (SD)** | 7.9 (0.12) | 13.8 (0.26) | 0.4 (0.02) | 0.1 (0.01) | 0.4 (0.01) | 0.4 (0.01) | 25.0 (0.17) | 0.7 (0.03) | 0.45 (0.03) |
| 1. Maternal education | 1.00 | | | | | | | | |
| 2. Possession of household goods | 0.48* | 1.00 | | | | | | | |
| 3. Housing conditions | -0.04* | -0.02* | 1.00 | | | | | | |
| 4. Intake of fried foods | -0.02 | 0.03* | 0.01 | 1.00 | | | | | |
| 5. Intake of sweets | 0.02* | 0.11* | -0.02* | 0.17* | 1.00 | | | | |
| 6. Intake of snacks | -0.01 | 0.12* | -0.03** | 0.18* | 0.39* | 1.00 | | | |
| 7. Maternal BMI | -0.04* | 0.06 | -0.04 | 0.02 | 0.03** | 0.05 | 1.00 | | |
| 8. Food security | -0.33* | -0.43* | 0.08* | -0.01 | 0.07* | -0.09* | -0.03 | 1.00 | |
| 9. BMI in children (z-score) | 0.05* | 0.11* | -0.04 | 0.05** | 0.07** | 0.10 | 0.18* | -0.07 | 1.00 |

**p < 0.001; **p < 0.05; BMI: body mass index; SD: standard deviation.*

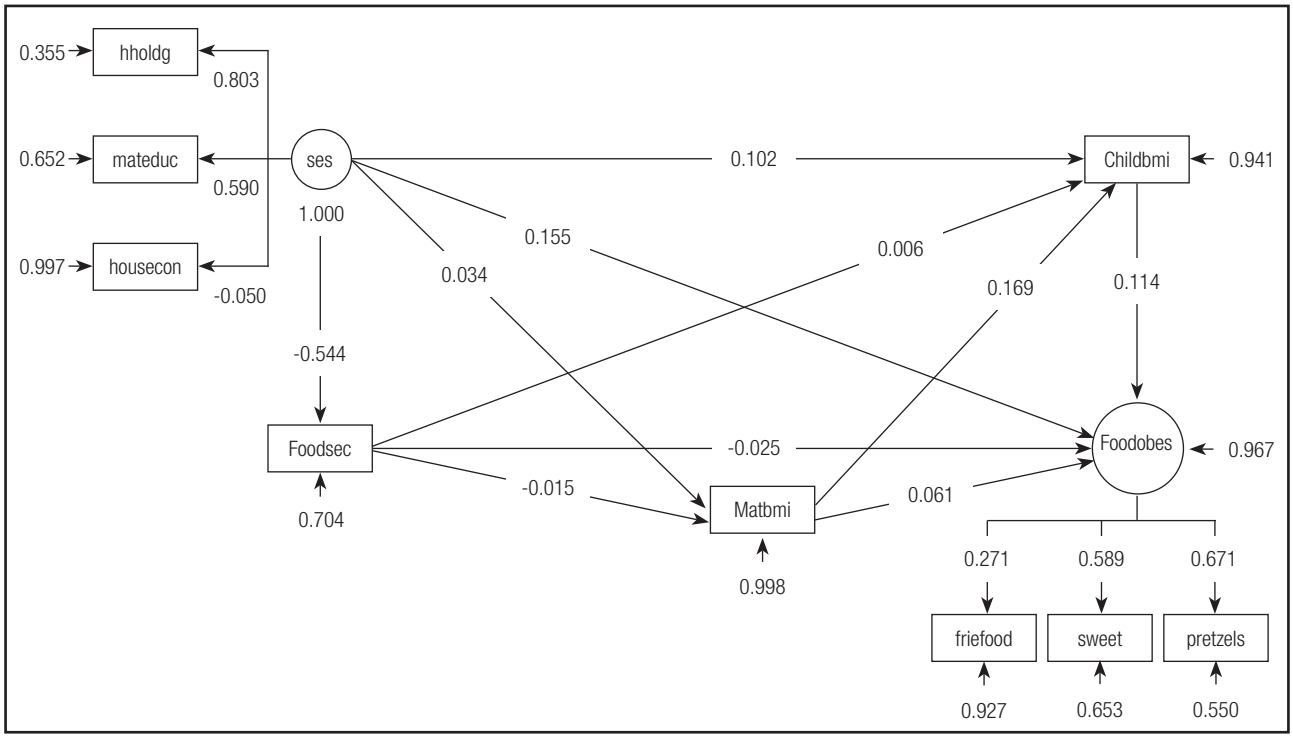


**Figure 1.**

Standardized estimates from structural equations modeling: measurement model and analysis of direct and indirect effects (note: hholdg: possession of household goods; mateduc: maternal education level; housecon: household conditions; ses: socioeconomic conditions; foodsec: food insecurity; matbmi: maternal body mass index; foodobes: intake of obesogenic foods by the child; childbmi: body mass index of child; fried food: intakes of fried foods).

Socioeconomic conditions were observed to play an important role, affecting child BMI both directly (82.9% of the total effect; not mediated by other variables) and indirectly through maternal BMI (4.9% of the total effect) and the intake of obesogenic foods (14.6% of the total effect). The direct effect was 17 and 6 times greater than the indirect effect of maternal BMI and intake of obesogenic foods, respectively (Table IV). A similar effect was observed for maternal BMI (results not shown), although the indirect effect was not statistically significant.

**Table II.** Direct and indirect effects of factors associated with child BMI (Brazil, National Demographic and Health Survey of Children and Women, 2006-2007)

| Effects | β | SD | p |
|---|---|---|---|
| *Socioeconomic conditions on child BMI* | | | |
| Direct | 0.102 | 0.04 | 0.02 |
| Via maternal BMI | 0.006 | 0.01 | 0.37 |
| Via food insecurity | -0.003 | 0.02 | 0.84 |
| Via intake of obesogenic foods | 0.018 | 0.01 | 0.04 |
| *Socioeconomic conditions on maternal BMI* | | | |
| Direct | 0.034 | 0.04 | 0.37 |
| *Socioeconomic conditions on food insecurity* | | | |
| Direct | -0.544 | 0.03 | < 0.001 |
| *Socioeconomic conditions on intake of obesogenic foods* | | | |
| Direct | 0.155 | 0.07 | 0.02 |
| *Maternal BMI on child BMI* | | | |
| Direct | 0.169 | 0.03 | < 0.001 |
| Via food intake | 0.007 | 0.01 | 0.16 |
| *Maternal BMI on intake of obesogenic foods* | | | |
| Direct | 0.061 | 0.04 | 0.14 |
| *Food security on child BMI* | | | |
| Direct | 0.006 | 0.03 | 0.84 |
| Via intake of obesogenic foods | -0.003 | 0.01 | 0.62 |
| *Food security on maternal BMI* | | | |
| Direct | -0.015 | 0.03 | 0.67 |
| *Food security on intake of obesogenic foods* | | | |
| Direct | -0.025 | 0.05 | 0.61 |
| *Intake of obesogenic food on child BMI* | | | |
| Direct | 0.114 | 0.04 | < 0.001 |

*BMI: body mass index; β: standardized beta coefficient; SD: standard deviation.*

**Table III.** Adjustments of the final model for the factors associated with child BMI (Brazil, National Demographic and Health Survey of Children and Women, 2006-2007)

| Tests | Values | Reference |
|---|---|---|
| Comparative fit index (CFI) | 0.98 | > 0.95 |
| Tucker-Lewis index (TLI) | 0.97 | > 0.95 |
| Root Mean Square Error of Approximation (RMSEA) | 0.02 | < 0.05 |

## DISCUSSION

From a nationally representative survey, the interrelations (direct and indirect) of socioeconomic conditions, maternal BMI, food security, and intake of obesogenic foods with the BMI z-scores of Brazilian children were tested using SEM.

Socioeconomic conditions positively influenced the increase in child BMI z-scores; this direct relationship (82.9%) was the most important association observed. It was further noted that a part of this total effect (14.6%) was mediated by the intake of obesogenic foods, indicating that as the socioeconomic level increases, food choices can lead to increased intake of unhealthy foods, which are predictors of increasing child BMI (32).

The association between an improved socioeconomic situation and unhealthy intake patterns may be indication of the changes in the modern lifestyle experienced by Brazilian families in the last few decades. In today's hectic world, the demand for practical and easy foods such as industrialized/processed foods, has increased. This increasingly contributes to the introduction of unhealthy intake patterns in families, including children's eating habits (33).

Results contrary to those observed in the present study showed that higher socioeconomic levels are associated with the adoption of consuming adequate and healthy foods (34). Evidence shows that higher maternal schooling and higher family income contribute positively to healthy food choices for children, as they allow parents to assimilate messages of nutritional education programs and understand the importance of diet as a way to promote health, leading to a reduced risk of excess weight in this age group (14). Nonetheless, the overestimation of the registry of healthy food intake, which occurs mainly among individuals with higher education levels, must not be disregarded. Having greater knowledge about healthy foods can lead them to exaggerate their report on their food intakes, thus concealing their actual food intakes (35). Therefore, this controversial correlation still needs to be clarified.

The findings of this study also revealed the direct and positive influence of obesogenic food intake on child BMI. Studies have analyzed the correlation between food intake patterns and excess weight, especially in children, and have shown that intake patterns based on junk food, characterized by a high intake of sweets, chocolate, ice cream, foods with added sugar, fried foods, and sugar-sweetened soft drinks, are related to excess weight. The effect of the intake of fatty foods on BMI gain is due to the high energy density associated with low levels of micronutrients that can result in an excessive passive intake, in which excess calories are unintentionally ingested (36,37). Most studies on this topic remain limited to cross-sectional studies, allowing investigation of the associations between variables only. However, several randomized and controlled intervention studies concluded that changes in eating practices to promote healthy eating positively influenced body weight reductions in all age groups (38).

Another important result of this study is the positive influence of maternal BMI on child BMI, reiterating findings from other studies that maternal obesity is one of the main predictors of excess weight in children (11,12). Although in the present study no direct positive association was observed between maternal BMI and the

**Table IV.** Proportion of direct and indirect effects contributing to the total effect of socioeconomic conditions on child BMI (Brazil, National Demographic and Health Survey of Children and Women, 2006-2007)

| Socioeconomic conditions on child BMI | β | 95% CI | Proportion of direct and indirect effects (%) |
|---|---|---|---|
| Total | 0.123 | - | - |
| Direct | 0.102 | 0.018 - 0.187 | 82.9 |
| Indirect - via maternal BMI | 0.006 | -0.007 - 0.018 | 4.9 |
| Indirect - via food safety | -0.003 | -0.036 - 0.029 | -2.4 |
| Indirect - via intake of obesogenic foods | 0.018 | 0.001 - 0.035 | 14.6 |

*BMI: body mass index; CI: confidence interval; β: standardized beta coefficient.*

child's intake of obesogenic foods, the parents' influence on the development of their child's eating habits according to their preferences and attitudes toward diet could not be ignored, as it can interfere with the availability of food in households and can shape the child's nutritional status (22). One must also consider the role of genetics associated with obesity, which has been pointed out as an explanation for the occurrence of excess weight among individuals of the same family (10).

As expected, a reduction in food insecurity was directly associated with an increase in socioeconomic conditions. Despite the absence of statistical significance, food insecurity was negatively associated with child BMI, corroborating the results of another Brazilian study (17). However, our findings differ from those of studies in other underdeveloped and developing countries (39,40). In those studies, increased food insecurity was associated with increased body weight. According to the authors, the lack of financial resources often led families to adopt compensatory feeding practices, such as increasing the intake of high-calorie diets rather than foods with better nutritional quality. This may result in increased body weight in this segment of the population (16,17). These findings must be interpreted with caution, as socioeconomic status does not represent a direct or sufficient indicator of food security, because it does not take into account existing intra-family differences or specific problems such as maternal depression and parental dietary practices, which interfere with the food choices offered to the child (14).

As limitations, we highlight that the cross-sectional design of this study only allowed us to estimate associations between exposure and nutritional outcome; it cannot establish causal relationships. Another aspect that must be considered is that important factors associated with excess weight, such as children's physical activity level, hours of sleep, assisted use of television, and genetic factors were not considered in the models, as such information was not obtained by PNDS (2006-2007). On the other hand, the data from DHS are considered of high quality, as they follow strict standardization procedures and, in most cases, are the only sources of data on maternal and infant health to which several countries refer, especially those with developing or transitioning economies.

In conclusion, the results of this study confirm findings already reported in the literature, that favorable family socioeconomic conditions, increased maternal BMI, and intake of obesogenic foods contribute positively to increased child BMI. These data confirm the complexity of the interrelations between variables involved in determining child BMI and the need to mobilize several sectors of society to promote healthy habits and maintain healthy body weights in children.

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Nutrición Hospitalaria

Trabajo Original

Pediatría

# Assessment of anthropometric indicators in children with cerebral palsy according to the type of motor dysfunction and reference standard

## *Evaluación de indicadores antropométricos en niños con parálisis cerebral de acuerdo con el tipo de disfunción motora y estándar de referencia*

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## Abstract

**Aim**: The study aimed to demonstrate that the assessment of the anthropomorphic measurements of children with cerebral palsy (CP) varies according to the type of motor dysfunction and references standard used for comparison.

**Method:** In a cross-sectional design, 108 children 2 to 16 years were classified according to the type of motor dysfunction by gender and age group. Weight, mid-upper-arm-circumference (MUAC), and alternative measures for height were performed. Height/age and weight/age indexes and BMI were evaluated with percentiles and/or Z-scores with reference to a number of previously published references of growth, including those of the World Health Organization (WHO).

**Results**: Fifty-three (49.1%) were females and 55 (50.9%) males. Spastic type was predominant (73.1%) and 26.9% were other types of dysfunction. Most of the children were located on level IV (14.6%) and level V (73.1%) of the Gross Motor Function Classification System (GMFCS). Significant differences were found, suggesting that weight ($p = 0.002$), height ($p = 0.001$), and MUAC ($p = 0.05$) are higher in the spastic group than in other groups.

**Conclusions:** The anthropometric indicators were significantly higher in the spastic group than in other groups. Upper-arm length (UAL) seemed less appropriate than knee height (KH) and lower-leg length (LLL) for measuring height. The WHO reference standard was not useful to evaluate the majority of anthropometric indexes in children with CP, other references as the growth charts of Day and Brooks have been more suitable.

**Key words:**

Cerebral palsy. Children. Spastic quadriplegia.

## Resumen

**Objetivo:** demostrar que la evaluación de las mediciones antropomórficas de los niños con parálisis cerebral (PC) varía según el tipo de disfunción motora y la referencia estándar utilizada.

**Método:** en un diseño transversal se incluyeron 108 niños de 2 a 16 años clasificados de acuerdo con el tipo de disfunción motora por sexo y grupos de edad. Se obtuvieron el peso, circunferencia media de brazo y mediciones alternas para la talla. Los índices talla/edad, peso/edad y el IMC fueron evaluados con los percentiles y/o puntuaciones Z con referencia a estándares de crecimiento previamente publicados, incluyendo los de la Organización Mundial de la Salud (OMS).

**Resultados:** cincuenta y tres (49.1%) eran mujeres y 55 (50.9 %) hombres. Predominó la PC tipo espástico (73.1%) y 26.9% otros tipos de disfunción. La mayoría de los niños se encontraron en el nivel IV (14.6%) y en el nivel V (73.1 %) de la Gross Motor Function Classification System (GMFCS). Se encontraron diferencias significativas, lo que sugiere que el peso ($p = 0,002$), talla ($p = 0,001$), y la circunferencia media del brazo CMB ($p = 0,05$) son mayores en el grupo espástico que en otros grupos.

**Conclusiones:** los indicadores antropométricos fueron mayores en el grupo espástico. La longitud del brazo pareció menos apropiada que la altura de la rodilla y la longitud de la pierna para la medición de la talla. El estándar de crecimiento de la OMS no resultó útil para evaluar los índices antropométricos en niños con parálisis cerebral; otras referencias como las tablas de crecimiento de Day y Brooks fueron más adecuadas.

**Palabras clave:**

Parálisis cerebral. Niños. Cuadriplejia espástica.

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## INTRODUCTION

Infantile cerebral palsy (CP) is the most common cause of motor disability in children and refers to the syndrome caused by injuries to the central nervous system in early stages of development (1). Food shortage is a common problem that causes multiple nutritional deficiencies that ultimately lead to protein-energy malnutrition, especially in patients with more severe neurological conditions (2,3). This syndrome of malnutrition is associated with poor growth, which generally depends on the type and distribution of dysfunction and its severity; however exist non nutritional factors that can be associated to malnutrition (4). It has also been observed that overweight and obesity are common comorbidities in children with neurological damage (5-6).

The assessment of nutritional status in children with CP is hard because of the difficulty in obtaining reliable measurements of basic data such as weight, height, and body mass index (BMI), which may cause an incorrect interpretation and analysis of data to identify children with nutritional risk and prevent a proper diagnosis. This difficulty is due to the presence of joint contractures, muscle atrophy, and movement disorders common in these patients (7). Furthermore, anthropometric data obtained should be compared with special reference standards for this population. Apparently, the problem of measurement of height in this group of patients has been overcome by the use of alternative measures (8,9).

There are different growth charts for assessing the nutritional status of children with CP. Day et al. (10) published these for weight and linear growth of children and adolescents 2 to 20 years of age with CP. Anthropometric indicators included weight for age, height for age, and body mass index. Growth curves for each indicator were prepared separately for different levels of disability (according to gross motor skills and feeding ability). There are others growth charts that have also been used such as specialized growth curves (11), using the Gross Motor Function Classification System (GMFCS) (8,12-17) and the use of percentiles for growth assessment with alternative measures (18); and, there are studies evaluating children with CP by using reference standards for healthy children (2,4,16,19,20). However, it has been recognized that children with CP cannot be evaluated with reference standards for healthy children because most of them have linear growth retardation and/or an altered body composition (21). For example, using the reference of the National Center for Health Statistics of the Centers for Disease Control and Prevention (NCHS/CDC), the probable malnutrition becomes excessively elevated to 80% (2). The aforementioned CP-specific growth charts by Day et al. and Brooks et al., as well as the others utilizing non-standard growth parameters, shed much light on this, and on the fact that level of disability plays a significant role in determining growth patterns for children and adolescents with CP. However, the question of whether type of motor dysfunction might also play a role has not been considered. Therefore, the purpose of this study was to demonstrate that the assessment of the anthropomorphic measurements of children with cerebral palsy (CP) varies according to the type of motor dysfunction and references standard used for comparison.

## METHODS

A cross-sectional design included 108 children (53 females and 55 males) from 2 years to 16 years, nine months (7y 9m ± 4y 3m), who attended the outpatient pediatric clinic at the Civil Hospital of Guadalajara "Dr. Juan I. Menchaca." They were divided into three age groups: preschoolers (24-71 months), schoolchildren (72-119 months), and adolescents (≥ 120 months). CP patients with any type of dysfunction were included, diagnosed and classified by a pediatric neurologist according to the GMFCS (22). The sample size was determined and calculated with a confidence level of 95% ($\alpha$ 0.05) $[(Z_{\alpha}/_{2}^{2})\ (p(1\text{-}p)]/d^2$ assuming a probability of 50% malnutrition (20).

## PARTICIPANTS

Patients with diagnoses unrelated to CP (Down syndrome, autism, degenerative disorders); use of medications that could alter body composition (steroids, thyroxine, anti-retrovirals); and those with CP of postnatal origin (traumatic injuries, accidents, tumors, other injuries) were not included. Three cases, two incomplete files, and one with CP secondary to an accident were excluded. Informed consent from the parents or legal caregivers of the children for participation in this study was obtained.

## ANTHROPOMETRIC MEASUREMENTS

The weight of the children with CP was obtained with clean diaper and as little clothing as possible on a SECA scale (model 700, Hamburg, Germany), to the nearest 50 g. The child was weighed in the arms of a family member or observer, after which only the adult was weighed, and the difference of the weights was obtained. For the measurement of the length two observers were previously standardized. The length was estimated using the Lower-leg length (LLL) and was obtained with a tape (Seca 206, Hamburg, Germany); it was measured from the line of the inner knee joint to the lower border of the malleolus of the tibia at an angle of 90°; knee height (KH) and upper-arm length (UAL) were obtained with a segmometer (Rosscraft segmometer, Canada) according to the techniques proposed by Stevenson (9). KH measurement was performed with the knee flexed to 90° in a straight line with the heel. It was measured from the proximal end of the patella to the bottom of the heel; UAL was measured with the arm relaxed at the side of the trunk. It was measured from the lateral edge of the acromion to the radial head. The alternative measurements equations are shown next: LLL = (3.26 × LLL) + 30.8; KH = (2.68 × KH) + 24.2; UAL = (4.35 × UAL) + 21.8.

A flexible tape (Seca 206, Hamburg, Germany) was used to measure the mid-upper-arm circumference (MUAC) and was measured at the midpoint of the length of the arm from the acromion to the olecranon. The Lange caliper (Cambridge, Maryland), which has a sensitivity of 1 mm, was used for the measurement of skin folds. The triceps skinfold (TSF) was obtained at the midpoint

of the left arm in its internal backside. The measurement was performed in triplicate and the average of the three measurements was obtained. The subscapular skinfold (SSF) was obtained from the bottom corner of the left scapula; this measurement was performed in triplicate and the average was obtained. Anthropometric indexes weight/age (W/A), height/age (H/A), and BMI according to the growth charts of Day (10), Brooks (17) and WHO reference (23,24) were estimated. Subjects were considered normal when indicators were found between the 10th and 90th, malnourished below the 10th percentile, and overweight above the 90th percentile according to the BMI growth charts of Day. Z scores with the WHO reference standard were also obtained (23,24).

## STATISTICAL ANALYSIS

Student's t-test, Mann-Whitney U, single-factor ANOVA for comparison of averages, and post hoc comparisons for multi-quantitative variables were performed. Chi-square test and Fisher's exact test for qualitative variables were performed. Significant results were expressed as odds ratios to identify the likelihood of epidemiological meaning. For statistical analysis, SPSS version 20 (SPSS Inc., Chicago, IL, USA) was used.

## ETHICAL CONSIDERATIONS

The protocol does not put at risk the participant of study and adhered to the guidelines of the Declaration of Helsinki and principles of beneficence, non-maleficence, justice, and autonomy of decision. The protocol was approved by the ethics committee of the Hospital Civil de Guadalajara "Dr. Juan I. Menchaca" No. 1344/14.

## RESULTS

The first part of table I shows the frequency of the type of dysfunction in children with CP; spastic type predominated with 73.1% of cases. The second part of the table shows the classification with the growth charts of Day (10). Most children belonged to group 3 (46.3%), which have important brain dam-

**Table I.** Distribution according to the type of motor dysfunction, Day and GMFCS Classifications

| Type of dysfunction | n | % | | | | |
|---|---|---|---|---|---|---|
| Spastic | 79 | 73.1 | | | | |
| Ataxic | 1 | 0.9 | | | | |
| Dyskinetic | 3 | 2.8 | | | | |
| Hypotonic | 11 | 10.2 | | | | |
| Mixed | 14 | 13 | | | | |
| | Spastic | | Others | | Total | |
| Day Classification[1,3] | n | % | n | % | n | % |
| Day 1 | 7 | 8.9 | 1 | 3.4 | 8 | 7.4 |
| Day 2 | 6 | 7.6 | 0 | 0 | 6 | 5.6 |
| Day 3 | 33 | 41.8 | 17 | 58.6 | 50 | 46.3 |
| Day 4 | 6 | 7.6 | 5 | 17.2 | 11 | 10.2 |
| Day 5 | 27 | 34.2 | 6 | 20.7 | 33 | 30.6 |
| GMFCS Classification[2,3] | n | % | n | % | n | % |
| GMFCS I | 4 | 5.1 | 1 | 3.4 | 5 | 4.6 |
| GMFCS II | 6 | 7.6 | 0 | 0 | 6 | 5.6 |
| GMFCS III | 2 | 2.5 | 0 | 0 | 2 | 1.9 |
| GMFCS IV | 10 | 12.7 | 6 | 20.7 | 16 | 14.8 |
| GMFCS V | 57 | 72.2 | 22 | 75.9 | 79 | 73.1 |
| Total | 108 | 100 | 108 | 100 | 108 | 100 |

*[1]Day classification (10): Group 1. Walks well alone at least 20 feet, balances well; Group 2. Walks with support or unsteadily alone at least 10 feet; Group 3. Crawls, creeps, or scoots but does not walk; Group 4. Does not walk, creep, or scoot, does not feed self, no feeding tube; Group 5. Does not walk, creep, or scoot, does not feed self, feeding tube. [2]GMFCS Classification (17): I. Walks without limitations; II. Walks with limitations; III. Walks using a hand-held mobility device; IV. Self-mobility with limitations, may use powered mobility; V. Transported in a manual wheelchair. [3]Fisher's exact test; Day classification by spastic vs. others p = 0.124; and GMFCS classification by spastic vs. others p = 0.479.*

age; and group 5 (30.6%) refers to children with severe neurological deterioration and who require the use of gastrostomy. Both levels included 76.9% of cases. The third part of the table shows the distribution with the GMFCS classification (22). More than 70% of the children belonged to level V. Table II shows the comparison of anthropometric data in children with spastic CP versus other types of dysfunction. Significant differences in favor of spastic type to have higher weight (p = 0.002) and greater height estimated by LLL (p = 0.001), KH (p = 0.001), UAL (p = 0.002), and MUAC (p = 0.05) were observed. Table III shows

**Table II.** Anthropometric indicators of children with spastic CP and other CPs

| | Spastic (n = 79) | | | Others (n = 29) | | | |
|---|---|---|---|---|---|---|---|
| | Mean (SD) | Limit | | Mean (SD) | Limit | | p[1] |
| Age in months | 101.4 (50.3) | 24 | 201 | 79.8 (51.6) | 27 | 203 | 0.011 |
| Weight (kg) | 17.4 (7.3) | 7 | 37 | 13.7 (7.0) | 7 | 35.5 | 0.002 |
| [2]Height by LLL (cm) | 110.5 (18.7) | 72.2 | 168.4 | 98.4 (18.0) | 78.1 | 157.9 | 0.001 |
| [2]Height by KH (cm) | 111.2 (18.6) | 78 | 169.5 | 98.3 (18.8) | 77.2 | 158.7 | 0.001 |
| [2]Height by UAL (cm) | 124.7(21.7) | 85.3 | 192.3 | 110.9 (19.4) | 85.7 | 167.1 | 0.002 |
| KH (cm) | 32.3 (6.9) | 20 | 54 | 27.5 (7.0) | 19.7 | 50 | < 0.001 |
| LLL (cm) | 24.4 (5.7) | 12.7 | 42.2 | 20.7 (5.5) | 14.5 | 39 | 0.001 |
| UAL (cm) | 23.7 (5.0) | 14.6 | 39.2 | 20.5 (4.5) | 14.7 | 33.4 | 0.002 |
| BMI by LLL | 13.7 (2.6) | 8.3 | 22.0 | 13.5 (3.1) | 8.9 | 23.8 | 0.449 |
| BMI by KH | 13.5 (2.5) | 8.8 | 23.7 | 13.5 (3.3) | 9.0 | 22.5 | 0.665 |
| BMI by UAL | 10.7 (1.8) | 6.8 | 16.0 | 19.6 (2.5) | 7.3 | 18.2 | 0.378 |
| MUAC (cm) | 15.4 (2.9) | 11 | 23 | 14.6 (4.4) | 8.5 | 28.8 | 0.05 |
| TSF (mm) | 6.6 (3.5) | 2 | 18 | 6.2 (4.7) | 2 | 22 | 0.152 |
| SSF (mm) | 5.2 (2.9) | 2 | 17 | 4.6 (3.1) | 1 | 16 | 0.113 |

*KH: Knee height; LLL: Lower leg length; UAL: Upper arm length; BMI: Body mass index; MUAC: Mid-upper-arm circumference; TSF: Triceps skinfold; SSF: Subscapular skinfold; [1]Mann-Whitney U. [2]Student t test: spastic vs. others with LLL, KH, UAL p < 0.005. Spastic: LLL vs. UAL p < 0.001; KH vs. UAL p < 0.001; others: LLL vs. UAL p < 0.001; KH vs. UAL p < 0.001; when compared LLL vs. UAL and KH vs. UAL by gender p < 0.001.*

**Table III.** Anthropometric data by age group

| | Age group | | | |
|---|---|---|---|---|
| | 24-71 m n = 46 | 72-119 m n = 30 | ≥ 120 m n = 32 | p[1] |
| | Mean (SD) | Mean (SD) | Mean (SD) | |
| Weight (kg) | 11.9 (4.0) | 17.5 (6.2) | 21.8 (8.2) | < 0.001 |
| Height by LLL (cm) | 92.3 (9.2) | 110.6 (12.4) | 125.5 (18.0) | < 0.001 |
| Height by KH (cm) | 93.1 (9.8) | 110.6 (13.5) | 126.0 (18.0) | < 0.001 |
| Height by UAL (cm) | 104.3 (12.0) | 125.5 (14.8) | 140.7 (20.3) | < 0.001 |
| BMI by LLL (kg/cm$^2$) | 13.6 (2.4) | 14.0 (3.4) | 13.4 (2.5) | 0.731 |
| BMI by KH (kg/cm$^2$) | 13.4 (2.7) | 14.0 (3.2) | 13.3 (2.3) | 0.582 |
| BMI by UAL (kg/cm$^2$) | 10.7 (1.8) | 10.8 (2.4) | 10.7 (1.9) | 0.952 |
| MUAC (cm) | 14.2 (3.2) | 15.9 (3.2) | 16 (3.3) | 0.025 |
| TSF (mm) | 6.1 (3.2) | 8.1 (4.7) | 5.6 (3.3) | 0.024 |
| SSF (mm) | 4.5 (2.6) | 5.8 (3.6) | 5.1 (2.7) | 0.176 |

*[1]One-way ANOVA. LLL: Lower-leg length; KH: Knee height; UAL: Upper-arm length; BMI: Body mass index; MUAC: Mid-upper-arm circumference; TSF: Triceps skinfold; SSF: Subscapular skinfold. Post Hoc test (T3 Dunett): weight between age groups 24-71* vs. *72-119 and 24-71* vs. *≥ 120 months p = 0.001; 72-119* vs. *≥ 120 months p = 0.059; height estimated by alternative measures between groups 24-71* vs. *72-119 and 24-71* vs. *≥ 120 months, 72-119* vs. *≥ 120 months p < 0.005; MUAC 24-71* vs. *120 p = 0.060; TSF 72-119* vs. *≥ 120, p = 0.064.*

significant differences among the three age groups for weight; height estimated by LLL, KH, and UAL ($p < 0.001$); and MUAC ($p = 0.025$) and TSF ($p = 0.024$). Post hoc tests showed significant differences in weight between the age groups of 24-71 and 72-119 months and 24-71 and ≥ 120 months and in height estimated by alternative measures among the three age groups. The MUAC was lower in the 24-71 months age group than in the ≥ 120 months ($p = 0.060$) group, although the thickness of TSF was higher in the 72-119 group than in the ≥ 120 months group ($p = 0.064$).

Table IV shows according to the BMI, using the Day reference standard, 31.5% of the total population was below the 10th percentile. It was observed that the group of children with "other types" of dysfunction showed a significantly higher frequency of BMI below the 10th percentile than the spastic group (41.4% *vs.* 27.8%, respectively) [OR 20.1 (4.1, 98.4), $p < 0.001$]. Females (35.8%) were more affected (were below the 10th percentile) than males (27.3%) and, when we compared the age groups, children of 72-119 months of age were more affected (43.3%) than the other two age groups, 24-71 (26.1%) and ≥ 120 months of age (28.1%), [OR 2.07 (0.86, 4.99), $p = 0.10$]. The same table shows the height/age index of the total population. It shows that 88.9% are between the 10th and 90th percentiles. No significant association was observed between height/age index deficit and females ($p = 0.058$). Likewise, a significantly increased probability of deficit appears in the height/age index in children older than 120 months compared with children of 24-71 and 72-119 months of age [OR = 6.9 (1.2-37.4), $p = 0.023$]. Figure 1A shows the anthropometric indexes of height/age, weight/age, and BMI according to the WHO reference standard (23,24). It is noted that the vast majority of cases is below -2 SD regardless of sex, age, and the type of dysfunction.

**Table IV.** BMI and height/age according to the Day growth charts by type of dysfunction, sex and age group

| Variable | Percentile < 10 | Percentile 10-90 | Percentile > 90 |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| *Body mass index* | | | |
| *Type of dysfunction* | | | |
| Spastic (n = 79) | 22 (27.8) | 56 (70.9) | 1 (9.3) |
| Others (n = 29) | 12 (41.4) | 15 (51.7) | 2 (6.9) |
| *Sex* | | | |
| Female (n = 53) | 19 (35.8) | 32 (60.4) | 2 (3.8) |
| Male (n = 55) | 15 (27.3) | 39 (70.9) | 1 (1.8) |
| *Age group* | | | |
| 24-72 months (n = 46) | 12 (26.1) | 33 (71.7) | 1 (2.2) |
| 72-119 months (n = 30) | 13 (43.3) | 16 (55.3) | 1 (3.3) |
| ≥ 120 months (n = 32) | 9 (28.1) | 22 (68.8) | 1 (3.1) |
| Total (n = 108) | 34 (31.5) | 71 (65.7) | 3 (2.8) |
| *Heigth/age* | | | |
| *Type of dysfunction*[1] | | | |
| Spastic (n = 79) | 3 (3.8) | 73 (92.4) | 3 (3.8) |
| Others (n = 29) | 4 (13.8) | 23 (79.3) | 2 (6.9) |
| *Sex*[2] | | | |
| Female (n = 53) | 6 (11.3) | 46 (86.8) | 1 (1.9) |
| Male (n = 55) | 1 (1.8) | 50 (90.9) | 4 (7.3) |
| *Age group*[3] | | | |
| 24-71 months (n = 46) | 1 (2.2) | 43 (93.5) | 2 (4.3) |
| 72-119 months (n = 30) | 1 (3.3) | 28 (93.3) | 1 (3.3) |
| ≥ 120 months (n = 32) | 5 (28.1) | 25 (68.8) | 2 (3.1) |
| Total (n = 108) | 7 (6.5) | 96 (88.9) | 5 (4.6) |

*Day, 2007; BMI: Others vs. spastic [OR 20.1 (4.1, 98.4), $p < 0.001$]; children of 72-119 months vs. other two age groups, 24-71 and ≥ 120 months [OR 2.07 (0.86, 4.99), $p = 0.10$]; Day, 2007; Height/age. Fisher's exact test; [1]Type of dysfunction: Others vs. spastic [OR 4.0 (0.85, 19.3), $p = 0.08$]; [2]Sex: Female vs. male [OR 6.9 (0.8, 53.3), $p = 0.058$]; [3]Age group: ≥ 120 months vs. < 120 months [OR 6.9 (1.25, 37.4), $p = 0.023$].*

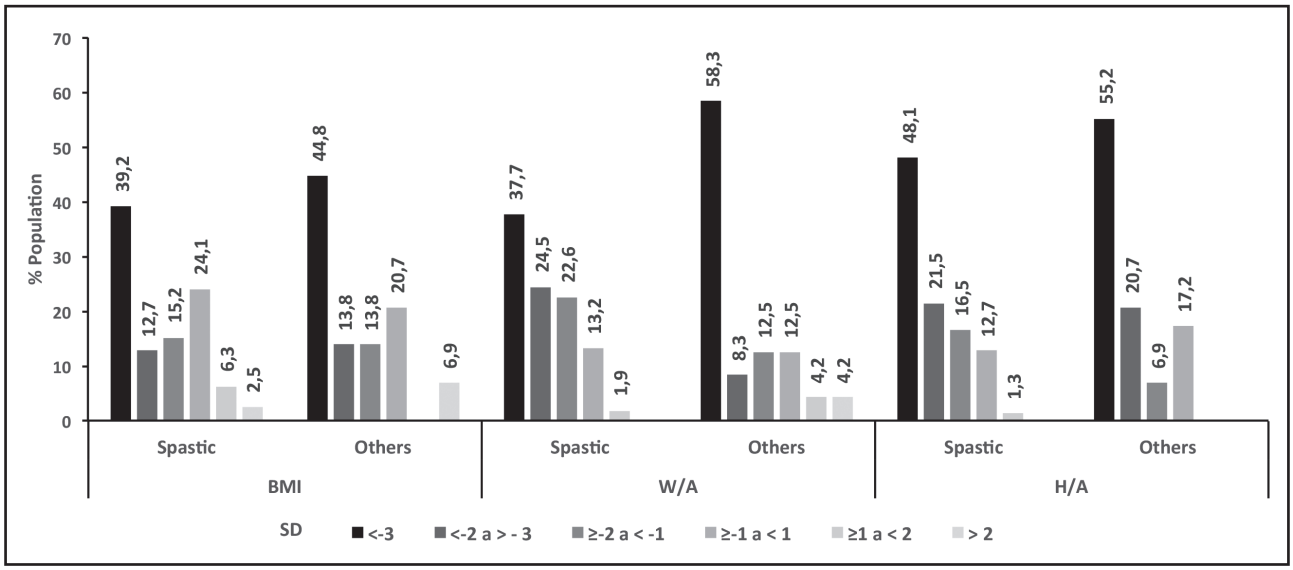


**Figure 1A.**

Anthropometric indexes: BMI, weight/age (W/A), and height/age (H/A) according to WHO standard references (2006, 2007).

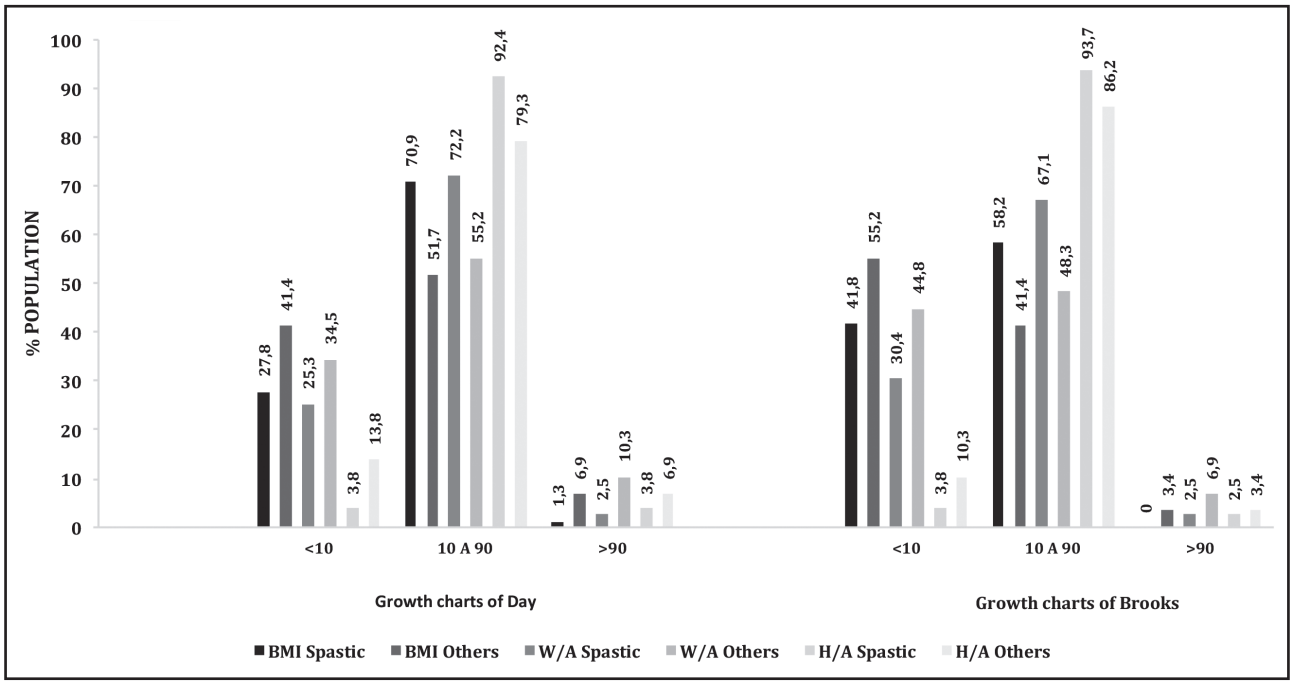


**Figure 1B.**

Anthropometric indexes: BMI, weight/age (W/A), and height/age (H/A) according to Day (10) and Brooks (17) growth charts Spastic group, BMI < 10 percentile, Brooks vs. Day: OR 1.86 (CI 95% 0.96, 3.6), p = 0.067. Others vs. spastic group, height/age: OR 4.0 (CI 95% 0.85, 19.3), p 0.08.

Figure 1B shows the same indexes according to Day and Brooks growth charts. When we compared the BMI between both references of the children who were below the 10$^{th}$ percentile and between the spastic group *vs.* others, no significant differences were observed.

## DISCUSSION

To our knowledge, this is the first study in Mexico that evaluates the nutritional status of children with cerebral palsy according to the type of motor dysfunction and uses the growth charts of Day

and Brooks et al. (10,17). As observed in previous studies (20), the spastic dysfunction predominated and occurred in 79 of the 108 cases that completed the study, so the other types (ataxic n = 1, dyskinetic n = 3, hypotonic n = 11, and mixed n = 14) occurred in 29 cases. According to the Day classification, most of the children belonged to group 3, which have a severe brain dysfunction and to group 5, which comprises children with serious deterioration that forces them to remain bedridden and live with gastrostomy.

The differences in weight and height favoring children with spastic CP *versus* the other types of dysfunction were manifest. One might speculate that these differences in weight are explained by the greater lean mass in children with spastic CP due to the constant muscle spasms that characterize it. However, the height was also significantly higher in the spastic group. Perhaps the age of the spastic group (101.4 ± 78.9 months) *versus* other types of dysfunction (79.8 ± 51.6 months) had influenced these differences, p = 0.011. The growth retardation has been associated with the type of dysfunction and topographical distribution of this. Patients with more severe CP tend to weigh less and be smaller in stature than children with less severe disabilities (4,10). When anthropometric indicators among male and female children were compared, a non-significant trend toward greater weight, height, and alternative measures of height was observed in males. We supposed that this anthropometric pattern is explained by the difference between the sexes as it is in children without CP. With regard to the different age groups, it is reasonable suppose that as age advanced, most of the anthropometric indicators increased. The MUAC was lower in children 24-71 months and was similar in the 72-119 and ≥ 120 months' groups. Perhaps the reason correlates with the small increase in lean mass between schoolchildren and adolescents, which would indicate the presence of hypotrophy in both age groups. It was interesting that the TSF seemed significantly greater in the group of 72-119 months compared to the other two groups. A decrease is observed in TSF in the ≥ 120 months group compared with the 72-119 group. It is likely that the onset of adiposity that happens physiologically in healthy children between five and six years of age may have influenced this result (25).

Measuring the length and height in children with spastic CP is difficult and imprecise due to contractures, spasticity, and spinal deformities these children present; therefore, alternative measurements have been used for several years for height, using different body segments, particularly LLL, UAL, and KH (8,9,26,27). In our study, we show that the estimation of height by the measurement of LLL and KH was very similar, and both differed significantly from the height estimated by UAL as it was showed in previous studies (27). When alternative measures were separated from the type of spastic dysfunction *versus* other types of dysfunction, similar outcomes were observed.

We observed that 31.5% of the total population was below the 10$^{th}$ percentile on BMI with the Day growth charts. In addition, children with other types of dysfunction showed a high frequency of BMI below the 10$^{th}$ percentile (41.4%) compared with children of the spastic group (27.8%); this occurred particularly with the mixed-dysfunction type. It is possible that the mixed-type dysfunction is more affected by nutritional status than by increased brain damage. Schoolchildren of 72-119 months showed higher frequency of BMI below the 10$^{th}$ percentile. One possible explanation is that parents have more difficulties feeding and caring for this group.

Araujo and Silva (16) showed that 13% and 36% of children with CP had a BMI below the 10$^{th}$ percentile curves, using Brooks's charts and CDC references, respectively. However, there is controversy about using alternative measures for height to calculate BMI because they include a degree of error associated with the prediction equation, and the evaluation of BMI would magnify the error when squaring the estimated height (26).

Our data was similar to those found by Araujo and Silva (16) with respect to the height/age index but no with respect to BMI. With the growth charts of Brooks, one percent of the cases were below the 10$^{th}$ percentile; 90% between the 10$^{th}$ and 90$^{th}$ percentile; and 9% above the 90$^{th}$ percentile (16). In addition, when we were using the Day growth charts, 6.5% were below the 10$^{th}$ percentile; 88.9% were between the 10$^{th}$ and 90$^{th}$ percentile; and 4.6% were above the 90$^{th}$ percentile.

A smaller deficit was observed in the height/age index in children with spastic CP (3.8%) versus children who had other types of dysfunctions (13.8%). Even when we double the number of observations per cell of the contingency table, it is more likely that deficit will appear in the group with other dysfunctions than in the group of children with spastic CP. We have no clear explanation for this finding. A frank tendency to higher deficit in the height/age index in girls (p = 0.058) is apparent. In studies of children without CP, an increased risk of severe primary malnutrition is observed in girls over boys, especially in populations of the very low socioeconomic stratum or indigenous areas (28). This raises the possibility of potential gender discrimination in that chronic malnutrition, expressed as the deficit in the height/age index, would be more common in girls with CP.

When the indicator height for age is analyzed by age group, it shows that children older than 120 months have seven times more likely [OR = 6.8 (1.2-37.4), p = 0.023] a deficit than children 24 to 120 months. This finding could be explained by considering that by the time the child with CP becomes older, he or she would have endured a longer period of food insufficiency, which consequently would have adversely affected his or her growth.

The results obtained with anthropometric data confirm that the gold standard of WHO (23,24) is not suitable for the anthropometric evaluation of children with CP. As observed, the indexes of weight/age, height/age, and BMI of the majority of the children studied were between -3 and -2 standard deviations regardless of the type of dysfunction, sex, and age group. In recent years, studies have been conducted to define the most appropriate methods and reference patterns to assess the growth and development of children with CP (16). Although several growth charts for this population have been published, there is debate about the use of such charts because they are not recommended by the CDC (26). Using the same growth charts for children with neurological impairment as for the population of healthy children is questionable because it tends to overestimate malnutrition and growth and development

in children with CP, which is different from the growth and development of children without this condition (8,16,17). In addition, Day et al. (10) reported that the measurement of height of children with CP at groups 3 y 5 is more difficult; therefore, the estimated final height should be accepted with caution.

Further studies are needed, an important step would be to identify direct markers of malnutrition supported by clinical, bio physical and laboratorial data, which are clearly more frequent among those children below the 10th percentile (or whatever percentile used to define malnutrition), so we could have real clinical evidence of malnutrition, not only by anthropometric assessment.

## CONCLUSION

Our study showed that the nutritional status of children with CP differs, depending on the sex, age, and type of motor dysfunction, and can be adequately evaluated through alternative measures of the height such as knee height and lower-leg length. We consider the Day et al. (10) and Brooks et al. growth charts (17) are useful for evaluating nutritional status of the specific population. The most affected age groups in the index height/age and BMI were schoolchildren 72-119 months of age and the adolescent group of ≥ 120 months old, with a higher proportion of girls more affected than boys. In spite of the difficulties and controversies that persist, more studies and anthropometric growth charts are necessary for proper estimation of different anthropometric indicators, especially for height, for their use in clinical practice and investigative settings.

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Trabajo Original

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# Association between vitamin D levels and cardiovascular risk factors in obese children and adolescents

## *Asociación entre los niveles de vitamina D y factores de riesgo cardiovascular en niños y adolescentes obesos*

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## Abstract

**Background and aim:** Childhood obesity is associated with an increased risk of chronic disease. We aimed to determine the association between vitamin D deficiency and cardiovascular risks in obese children.

**Method:** The studied children were selected from obese children who were followed up at obesity clinic, aged 6-17 years. Basic demographic information and laboratory data were collected retrospectively from hospital records.

**Results:** A total of 310 students (178 [57.4%] girls) were evaluated for 25-hydroxyvitamin D (25[OH] D) levels in late winter/spring. The prevalence rates of vitamin D deficiency, insufficiency, and sufficiency were 62.3%, 34.5%, and 3.2%, respectively. Insulin resistance was observed in 146 (47.1%) children; the frequencies of dyslipidemia and hypertension were 31% and 19.4%, respectively. The mean atherogenic dyslipidemia ratio was higher in the deficient group ($p = 0.049$). Inverse correlations of 25(OH) D levels were observed with homeostasis model assessment of insulin resistance values ($r = -0.146$, $p = 0.010$). The mean values of 25(OH) D (ng/mL) were lower in girls ($12.15 \pm 6.60$) than in boys ($16.48 \pm 8.69$) ($p < 0.05$) and in children with hypertension ($11.92 \pm 5.48$) than in those without ($14.50 \pm 8.24$) ($p < 0.05$).

**Conclusions:** Vitamin D deficiency is observed more frequently than expected in obese children and adolescents. Our findings indicate that low 25(OH) D levels are associated with insulin resistance. Vitamin D deficiency could contribute to the morbidities associated with childhood obesity, such as insulin resistance or diabetes mellitus, increased cardiovascular/cardiometabolic risks, atherogenic dyslipidemia, and hypertension.

**Key words:**

Vitamin D.
Obesity. Child.
Cardiovascular risk.
Insulin resistance.
Hypertension.

## Resumen

**Introducción y objetivo:** la obesidad infantil se asocia a un riesgo aumentado de enfermedades crónicas. El objetivo de este estudio es determinar la relación entre la deficiencia en vitamina D y el riesgo cardiovascular en niños obesos.

**Método:** se seleccionaron niños tratados en la clínica de obesidad, con edades entre 6 y 17 años. Los datos de laboratorio y la información demográfica básica se recogieron de forma retrospectiva a partir de las historias clínicas.

**Resultados:** se evaluaron 310 estudiantes (178, 57,4% mujeres) midiendo los niveles de vitamina D a finales de invierno y en primavera. La prevalencia de deficiencia en vitamina D, insuficiencia y suficiencia fueron 62,3%, 34,5% y 3,2% respectivamente. Se encontró resistencia insulínica en 146 niños (47,1%); mientras que la frecuencia de dislipemia e hipertensión fue de 31% y 19,4%, respectivamente. La razón de aterogenicidad debida a dislipemia fue mayor en el grupo deficiente ($p = 0,049$). Se encontró una correlación inversa entre los niveles de 25-OH-D y los valores de HOMA ($r = -0,146$; $p = 0,01$). Los valores medios de vitamina D (ng/Ml) fueron inferiores en niñas ($12,15 \pm 6,60$) que en niños ($16,48 \pm 8,69$) ($p < 0,05$) y en niños con hipertensión ($11,92 \pm 5,48$ *vs.* $14,50 \pm 8,24$ en normotensos) ($p < 0,05$).

**Conclusiones:** se encontró una prevalencia de deficiencia en vitamina D en niños y adolescentes obesos superior a lo esperado. Nuestros hallazgos indican que los niveles bajos de vitamina D se asocian con resistencia insulínica. La deficiencia en vitamina D podría contribuir a las morbilidades que se asocian a la obesidad infantil, como la resistencia insulínica o la diabetes mellitus, el aumento del riesgo cardiovascular, la dislipemia y la hipertensión.

**Palabras clave:**

Vitamina D. Obesidad.
Niño. Riesgo cardiovascular.
Resistencia insulínica.
Hipertensión.

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## INTRODUCTION

The global prevalence of childhood obesity has increased considerably over the past 3 decades (1). Ten percent of school-aged children worldwide are estimated to have excess body fat, which is associated with an increased risk of chronic disease. Of these overweight children, a quarter are obese and thus have a significant likelihood of possessing multiple risk factors for the development of type 2 diabetes, heart disease, and various other co-morbidities before or during early adulthood. The increasing incidence of disorders in children, such as type 2 diabetes, is a consequence of the obesity epidemic (1,2).

Although the main physiologic role of vitamin D is the regulation of calcium and phosphorus homeostasis, it plays a variety of nonskeletal roles, such as the pathogenesis of several endocrine diseases, modification of immune competence, regulation of blood pressure, and modulation of cancer and infectious disease risks, and propensity for autoimmune diseases (3-5). However, cynicism surrounds the lack of randomized controlled trials to support association studies concerning the nonskeletal health benefits of vitamin D (5).

To date, many studies have observed low 25-hydroxyvitamin D (25[OH] D) levels in overweight and obese populations (6-8). In US children, the prevalence of vitamin D deficiency is nearly 21% among normal-weight population, 29-34% in overweight and obese populations, and 49% in a severely obese population (9).

Evidence from many studies indicates the existence of a strong association between vitamin D and cardiovascular risks, particularly blood pressure. Vitamin D deficiency might be linked to the pathophysiology of hypertension through its influence on the renin-angiotensin system (10). Vitamin D receptor (VDR) null mice exhibit significantly elevated renin activity and circulating plasma angiotensin II concentrations, as well as increased activity of the local cardiac tissue renin-angiotensin system (11).

Vitamin D has also been shown to modulate insulin synthesis and secretion (12). An analog of the active metabolite of vitamin D, $1,25(OH)_2$ D, has been found to directly enhance glucose-stimulated insulin release by increasing intracellular calcium levels in pancreatic β-cells (13).

In this study, we aimed to determine the associations between vitamin D deficiency and cardiovascular risks, such as hypertension, dyslipidemia, and insulin resistance (IR), in obese children and adolescents.

## MATERIALS AND METHODS

### PARTICIPANTS AND STUDY AREA

A total of 872 obese children who were followed up at the hospital of the Gaziosmanpasa University School of Medicine between January 2012 and February 2016 were retrospectively investigated, and we enrolled only children who were tested between February and May (i.e., in late winter and spring). Subjects were diagnosed with obesity according to a body mass index (BMI) value > 95$^{th}$ percentile in accordance with the sex-specific growth curves and cut-off levels proposed by Neyzi et al. (14). We excluded 562 obese children because of missing data, syndromic obesity, renal or hepatic disorders, metformin or vitamin D derivative usage, testing season, and age. Finally, 310 obese children aged 6-17 years were included in this study.

Subjects' demographic and clinical data, basic demographic information (age and sex), and physical data (body height, body weight, BMI, and systolic and diastolic blood pressure [BP]) were collected retrospectively from hospital records.

### LABORATORY TESTS

Laboratory tests, including 25(OH) D, glucose, and insulin levels and lipid profiles, were conducted using fasting blood samples drawn from each participant. Laboratory and BP details were collected retrospectively from the electronic medical records used at the hospital.

Serum fasting glucose, triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC) levels were detected using reagent kits adapted to the COBAS 6000 Autoanalyzer (Roche Diagnostics, Indianapolis, IN, USA). Vitamin D levels were analyzed using chemiluminescence immunoassay methods and a COBAS C-501&E-601 analyzer (Roche Diagnostics).

### DEFINITIONS OF OBESITY, IR, AND ATHEROGENIC RISK

Children were weighed on a digital scale (Seca Corp., Chino, CA, USA) and subjected to height measurement with a portable stadiometer (Seca Corp.) while they were barefoot and wearing light clothing. If BMI was > 95$^{th}$ percentile, the children was recorded as obese. BP was measured using a digital sphygmomanometer (OMRON 705IT; Omron Healthcare Co., Kyoto, Japan); if the measured BP was high with respect to age and sex, the mean of two measurements was recorded. Hypertension was defined as a BP ≥ 95$^{th}$ percentile according to age, sex, and height.

The homeostasis model assessment of IR (HOMA-IR) index was calculated using the following equation: HOMA-IR = (fasting insulin [mIU/mL] × fasting glucose [mmol/L])/22.5. Positive IR was defined as a HOMA-IR > 2.67 in boys and > 2.22 in girls during the prepubertal period or > 5.22 in boys and > 3.82 in girls during the pubertal period (15).

Dyslipidemia was defined as the presence of any of the following criteria: TGs > 105 mg/dL in children < 10 years of age and > 136 mg/dL in children ≥ 10 years of age, HDL-C < 35 mg/dL, and TC > 95$^{th}$ percentile (16). We calculated the atherogenic dyslipidemia (AD) ratio (log [TGs/HDL-C]) (17,18) to determine the effect of 25(OH) D on the cardiovascular atherogenic risk.

Vitamin D groups were determined according to measured levels. Vitamin D deficiency, insufficiency, and sufficiency were defined as a 25(OH) D level < 15 ng/mL (19), 15-29 ng/mL, and ≥ 30 ng/mL, respectively (20).

Study children were divided into healthy obese and non-healthy obese groups. Non-healthy obesity was defined as the presence of metabolic disturbances, such as IR according to HOMA-IR, dyslipidemia, and hypertension. Children without any such disturbances were considered healthy obese.

## STATISTICAL ANALYSIS

Descriptive analyses were performed to obtain information about the general characteristics of the study population. A one-way analysis of variance was used to compare continuous data among the groups. For multiple comparisons, Tukey's honest significant difference (HSD) test was used. Continuous data are presented as means ± standard deviations. Categorical variables are presented as numbers and percentages. The chi-square test was used to compare categorical variables between groups. A p-value < 0.05 was considered significant. Analyses were performed using SPSS 19 (IBM SPSS Statistics 19, SPSS Inc., an IBM Co., Somers, NY, USA).

## RESULTS

There were 310 obese children aged 6-17 years (178 [57.4%] females and 132 [42.6 %] males) who met the aforementioned inclusion criteria. In this cohort, the prevalence rates of vitamin D deficiency, insufficiency, and sufficiency were 62.3%, 34.5%, and 3.2%, respectively.

IR was observed in 146 (47.1%) obese children. Dyslipidemia and hypertension were found in 96 (31%) and 60 (19.4%), respectively. Only 109 (35.2%) children were classified as healthy obese. Table I summarizes the distributions of qualitative variables in the entire cohort according to vitamin D status.

The means of subject age (p = 0.008), BMI (p = 0.010), and AD ratio (p = 0.049) were higher in the vitamin D deficient group.

Non-healthy obese children were more frequently recorded as vitamin D deficient than healthy obese children (p = 0.023). Otherwise, no statistically significant differences were observed between 25(OH) D groups with respect to hypertension frequency (p = 0.074).

The mean age of the cohort was 12.10 ± 2.82 years, and the mean BMI was 29.21 ± 4.71. The mean HOMA-IR value was 3.78 ± 2.23. Table II summarizes the mean values of laboratory and clinic quantitative variables in the cohort according to vitamin D status.

No correlations of 25(OH) D levels were observed with lipid levels (TC, r = -0.032 and p = 0.571; TGs, r = -0.041 and p = 0.472; HDL, r = -0.01 and p = 0.858) or systemic BP (systolic, r = -0.099 and p = 0.082; diastolic, r = -0.065 and p = 0.256) (p > 0.01). Otherwise, weak but significant inverse correlations of 25(OH) D levels were observed with BMI (r = -0.167, p = 0.003) and HOMA-IR values (r = -0.146, p = 0.010). Figures 1 and 2 present scatter plots of 25(OH) D with BMI and HOMA-IR values, respectively.

The mean 25(OH) D values (ng/mL) were lower in girls (12.15 ± 6.60) *vs.* boys (16.48 ± 8.69) (p < 0.05), in children with hypertension (11.92 ± 5.48) *vs.* non-hypertensive children (14.50 ± 8.24) (p < 0.05), and in the nonhealthy obese group (13.29 ± 6.90) *vs.* the healthy obese group (15.30 ± 9.24) (p < 0.05). Table III summarizes the mean 25(OH) D levels according to sex and cardiovascular risk status.

## DISCUSSION

Hypovitaminosis D (both insufficiency and deficiency) was observed more frequently than expected in obese children and

**Table I.** Distribution of qualitative variables in entire participant cohort according to vitamin D status (n = 310)

| Variables | | Total n = 310 | Group of 25(OH) D status n (%) | | | p |
|---|---|---|---|---|---|---|
| | | | Deficient 193 (62.3) | Insufficient 107 (34.5) | Sufficient 10 (3.2) | |
| Sex | Female | 178 (57.4) | 126 (70.8) | 49 (27.5) | 3 (1.7) | 0.001 |
| | Male | 132 (42.6) | 67 (50.8) | 58 (43.9) | 7 (5.3) | |
| Insulin resistance (IR) | No | 164 (52.9) | 98 (50.8) | 58 (54.2) | 8 (80) | 0.185 |
| | Yes | 146 (47.1) | 95 (49.2) | 49 (45.8) | 2 (20) | |
| Dyslipidemia | No | 214 (69) | 130 (67.4) | 76 (71) | 8 (80) | 0.602 |
| | Yes | 96 (31) | 63 (32.6) | 31 (29) | 2 (20) | |
| Hypertension | No | 250 (80.6) | 149 (77.2) | 91 (85) | 10 (100) | 0.074 |
| | Yes | 60 (19.4) | 44 (22.8) | 16 (15) | 0 (0) | |
| Obesity group | Non-healthy | 201 (64.8) | 133 (68.9) | 65 (60.7) | 3 (30) | 0.023 |
| | Healthy obese | 109 (35.2) | 60 (31.1) | 42 (39.3) | 7 (70) | |

*Data are shown as n(%). Chi-square test was used. Deficient: 25(OH) D level < 15 ng/Ml; insufficient: 25(OH) D level = 15-29 ng/mL; sufficient: 25(OH) D level ≥ 30 ng/mL.*

**Table II.** The mean values of quantitative variables in the cohort according to vitamin D status

| Variables | Total n = 310 | Group of vitamin D status (Mean) | | | p |
|---|---|---|---|---|---|
| | | Deficient (n = 193) | Insufficient (n = 107) | Sufficient (n = 10) | |
| Age | 12.10 ± 2.82 | 12.48 ± 2.68[a] | 11.43 ± 2.9[b] | 12.1 ± 3.51[a] | 0.008 |
| BMI | 29.22 ± 4.71 | 29.82 ± 4.87[a] | 28.1 ± 4.34[b] | 29.62 ± 3.48[a] | 0.010 |
| Systolic BP (mmHg) | 115.93 ± 13.74 | 116.73 ± 14.32 | 114.83 ± 12.61 | 112.2 ± 13.69 | 0.357 |
| Diastolic BP (mmHg) | 73.74 ± 10.67 | 73.88 ± 11.28 | 73.64 ± 9.65 | 72 ± 9.36 | 0.859 |
| Glucose (mg/dL) | 86.80 ± 10.84 | 86.87 ± 11.49 | 87.16 ± 9.32 | 81.7 ± 12.82 | 0.312 |
| Insulin (ulU/mL) | 17.45 ± 10.00 | 18.45 ± 10.58 | 16.01 ± 8.84 | 13.56 ± 7.82 | 0.059 |
| HOMA-IR | 3.78 ± 2.23 | 3.99 ± 2.37 | 3.5 ± 1.95 | 2.8 ± 1.78 | 0.067 |
| HDL-C (mg/dL) | 47.99 ± 12.09 | 47.63 ± 10.95 | 48.03 ± 13.46 | 55.12 ± 16.88 | 0.192 |
| LDL-C (mg/dL) | 102.21 ± 27.47 | 104.52 ± 28.07 | 98.41 ± 26.46 | 97.77 ± 23.19 | 0.166 |
| Total cholesterol (mg/dL) | 160.82 ± 30.70 | 161.97 ± 31.05 | 158.66 ± 30.77 | 161.81 ± 23.81 | 0.669 |
| Triglycerides (mg/dL) | 109.46 ± 53.74 | 111.1 ± 50.94 | 108.73 ± 59.24 | 85.53 ± 41.95 | 0.337 |
| 25 (OH) D (ng/mL) | 14.00 ± 7.84 | 9.34 ± 3.25[a] | 20.01 ± 3.5[b] | 39.56 ± 11.02[c] | < 0.001 |
| AD ratio | 0.33 ± 0.25 | 0.34 ± 0.23[a] | 0.32 ± 0.29[ab] | 0.14 ± 0.28[b] | 0.049 |

*Data are shown as mean ± standard deviation. Different superscripts in the same row (one way ANOVA) indicate statistical significant difference. BMI: body mass index; BP: blood pressure; HOMA-IR: the homeostasis model assessment of insulin resistance index; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; 25 (OH) D: 25-hydroxyvitamin D. AD ratio: atherogenic dyslipidemia ratio, p = 0.045 for AD ratio between deficient and sufficient groups.*

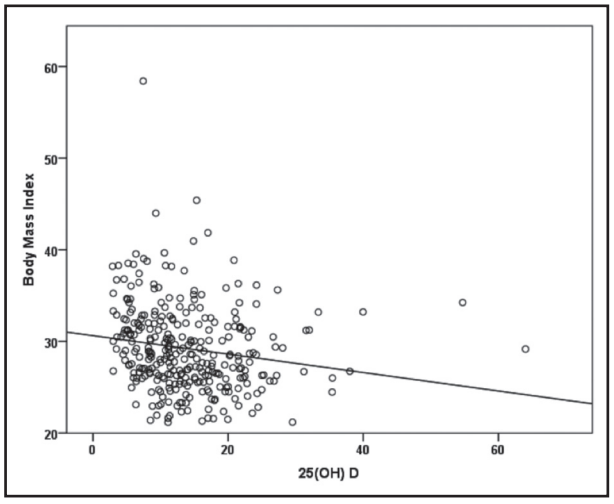


**Figure 1.**
Scatter plot of 25(OH) D (ng/mL) and body mass index (r = -0.167; p = 0.003).

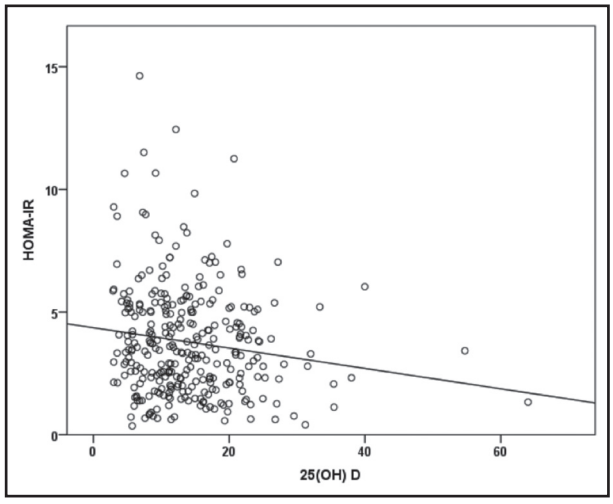


**Figure 2.**
Scatter plot of 25(OH) D (ng/mL) and HOMA-IR (r = -0.146; p = 0.010).

adolescents. In a previous meta-analysis, the prevalence of vitamin D deficiency was 24% in obese adults and 14% in obese children and adolescents (21). In another study, hypovitaminosis D was identified in 74% of obese subjects, whereas vitamin D deficiency was observed in 32.3% of the cohort (22). The higher prevalence of vitamin D deficiency observed in our study might be attributable to decreased exposure of these obese children to sunlight, as testing was conducted in late winter and spring, and might also be a consequence of a low intake of vitamin D-rich foods. However, we did not have access to dietary data for these children. This should be considered a limitation of this study. Nevertheless, our findings with consistent with those of Buyukinan et al. who reported vitamin D deficiency and insufficiency values of 62.2% and 34.0%, respectively, in obese children (23).

Previously, obese children were reported to have a greater risk of developing vitamin D deficiencies. The association between

**Table III.** The mean values of the 25(OH) D levels according to qualitative variables

| Variables | | 25(OH) D | | p |
|---|---|---|---|---|
| | | Mean | Standard deviation | |
| Sex | Female | 12.15 | 6.60 | < 0.001 |
| | Male | 16.48 | 8.69 | |
| IR | No | 14.69 | 8.82 | 0.093 |
| | Yes | 13.22 | 6.52 | |
| Dyslipidemia | No | 14.11 | 7.83 | 0.710 |
| | Yes | 13.75 | 7.91 | |
| Hypertension | No | 14.50 | 8.24 | 0.004 |
| | Yes | 11.92 | 5.48 | |
| Obesity group | Non-healthy obese | 13.29 | 6.90 | 0.047 |
| | Healthy obese | 15.30 | 9.24 | |

obesity and 25(OH) D deficiency is complex because in addition to the sequestration of vitamin D in adipose tissue (24), obese children might also have more sedentary, indoor lifestyles. In addition, obese children might obtain lower levels of vitamin D than non-obese children from food sources (22); however, a combination of the above factors, as well as other potential factors, is most likely.

In our study, vitamin D levels were lower in girls, consistent with the findings of previous studies (20,25); girls also more frequently exhibited vitamin D deficiency. These findings were consistent with an earlier study that reported a higher prevalence of vitamin D insufficiency among girls relative to boys (26).

As in previous studies (3,27), we observed a weak but significant inverse relationship between BMI and 25(OH) D levels. This finding has been attributed to the sequestration of vitamin D within adipose tissue (24) and the reduced hepatic synthesis of 25(OH) D in obese individuals with nonalcoholic fatty liver disease (28). In contrast, another study found no significant association between BMI and 25(OH) D (25).

In an analysis of multiple cohorts, Vimaleswaran et al. calculated that each 10% increase in BMI would lead to a 4.2% decrease in the 25(OH) D concentrations. The authors concluded that the efforts of vitamin D deficiency monitoring and treatment in obese individuals would alleviate the adverse influences of excess adiposity on health; in addition, attempts to reduce BMI are expected to reduce the prevalence of vitamin D deficiency (29).

Inconsistent with a recent report (25), our study did not observe any correlation of 25(OH) D levels with TG, LDL-C, or HDL-C levels. However, Dolinsky et al. suggested that there was insufficient evidence to support an association between vitamin D and lipid levels, which is consistent with our findings (30).

In recent years, the AD ratio, derived from a log transformation of the ratio of fasting TG to HDL-C levels, has gained importance as an indicator of atherosclerosis, an established cardiovascular risk factor (17,18). In the present study, the AD ratio was higher in the vitamin D-deficient group, consistent with many other reported findings (20). Vitamin D deficiency causes an increase in AD, a component of cardiovascular risk factors, and thus leads to worse long-term consequences (20).

In our study, hypertensive children exhibited lower 25(OH) D levels. Accordingly, and consistent with many recent studies, hypertension in obese patients was associated with reduced vitamin D levels; in an earlier study, a lower HDL-C level and higher systolic BP were associated with lower levels of 25(OH) D (31). In addition, 25(OH) D deficiency in children and adolescents has been associated with hypertension as a cardiovascular risk factor (20).

As we specified earlier, vitamin D deficiency has been linked to the pathophysiology of hypertension through its augmenting influence on renin–angiotensin system activity (10) both in obese individuals (32) or independently of obesity (33). On the other hand, VDRs are present in vascular smooth muscle, which suggests that vascular smooth muscle is a target organ of vitamin D (34). Furthermore, studies have linked vitamin D deficiency with low levels of adiponectin (35), a protein associated with hypertension.

An inverse correlation was observed between 25(OH) D levels and HOMA-IR values. In other words, 25(OH) D levels affect insulin sensitivity, consistent with previous research (22). Hypovitaminosis D has been implicated in the pathogenesis of IR, β-cell dysfunction, and both type 1 and type 2 diabetes mellitus (36,37). Furthermore, obese children and adolescents with low levels of vitamin D might have an increased risk of glucose metabolism impairment, independent of body adiposity (22).

A previous study found a significant positive association between vitamin D and β-cell function, as well as significant relationships of vitamin D with IR and β-cell function in a multi-ethnic sample at risk for type 2 diabetes (12). In addition, vitamin D has been implicated in the development of type 1 diabetes mellitus through its modulatory effects on the immune system (38).

Multiple factors, such as the levels of vitamin D and reactive oxidative species, might have a synergistic effect on the pathogenesis of obesity-related morbidities. In recent decades, some studies have demonstrated that similar to vitamin D, oxidative stress, which increases in the context of obesity, is directly and indirectly associated with IR pathogenesis via the respective inhibition of insulin signals and dysregulation of adipocytokines/adipokines (39). We believe that other factors, in addition to vitamin D, affect and contribute to IR in obese children.

Over time, oxidative stress in several other cells or tissues (e.g., pancreatic β-cells, myocytes, vascular endothelial cells, and some types of tumors) has been implicated in the pathogenesis of diabetes, hypertension, atherosclerosis, and cancer (40).

Metabolic disturbances and/or hypertension would be expected to occur more frequently in the context of vitamin D hypovitaminosis. We observed lower 25(OH) D levels in non-healthy obese children than in healthy obese children. Accordingly, we can suggest that some of the long-term morbidities associated with obesity might be prevented by improving vitamin D levels.

The main limitations of our study involved the lack of data regarding dietary habits and physical activity. Therefore, we could not exclude lifestyle factors, such as dietary habits and social

status, that might have affected vitamin D metabolism and the other laboratory variables measured in our study participants. In addition, because the children were evaluated retrospectively, we could not incorporate methods to measure adiposity. Furthermore, we did not observe statistical significance in the comparisons of some variables with respect to vitamin D status, possibly because of the very small number of vitamin D sufficient children.

## CONCLUSION

Vitamin D deficiency is observed more frequently than expected in obese children and adolescents. Lower 25(OH) D levels are associated with a high BMI, and this relationship might be attributable to the increased adiposity of obese individuals. In addition, low 25(OH) D levels might be associated with IR. Vitamin D deficiency might therefore be prevented by reducing the BMI and incorporating some simple lifestyle precautions. Vitamin D deficiency might contribute to obesity-related morbidities, such as IR or diabetes mellitus, increased cardiovascular/cardiometabolic risk, atherogenic dyslipidemia, and hypertension. The long-term morbidities associated with obesity could be reduced by improving vitamin D levels.

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Pediatría

# Infant growth and early adiposity depending on immigrant background and anthropometric standards; the CALINA Study

## *Crecimiento y adiposidad durante la primera infancia dependiendo del origen de la familia y de los estándares antropométricos; Estudio CALINA*

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## Abstract

**Objective:** To compare infant growth and adiposity pattern up to 2 years of age in Spanish infants, depending on maternal origin and anthropometric standards.

**Methods:** Longitudinal study of a representative cohort of infants born at term in Aragon (Spain) (n = 1.430). Mean z-scores of weight, length, body mass index, triceps and subscapular skinfolds were calculated until 24 months of age using World Health Organization (WHO), Euro-Growth and Spanish growth standards and categorized by maternal origin (Spanish *vs.* immigrant).

**Results:** Infants of immigrant mothers had higher weight, length, body mass index, triceps and subscapular skinfolds than Spanish maternal origin infants during the first months of life. Mean z-scores significantly varied depending on growth standards used. At 18 months of age, all anthropometric differences between both groups disappeared, but only when using WHO growth standards. Mean triceps and subscapular skinfold z-scores substantially and progressively increased from 3 months to 24 months of age in both groups compared to WHO standards. At 24 months, the prevalence of infants at risk of overweight and overweight were similar in both groups (Spanish: 15.1% and 3.8%; immigrant: 14.7% and 4.9%, respectively).

**Conclusions:** Infant growth, adiposity patterns and prevalence of overweight depend on maternal origin, showing initial differences which progressively disappeared at 24 months of life when WHO growth standards were used. Differences in infant mean anthropometric measurements depend on anthropometric standard used.

**Key words:**

Infant. Growth. Adiposity. Immigration.

## Resumen

**Objetivo:** comparar el patrón de crecimiento infantil y adiposidad temprana hasta los 2 años en los niños españoles, según el origen materno y los estándares antropométricos.

**Métodos**: estudio longitudinal en una cohorte representativa de niños nacidos a término en Aragón (España) (n = 1.430). Se calcularon z-scores de peso, longitud, índice de masa corporal, pliegue tricipital y subescapular hasta los 2 años usando estándares de crecimiento de la Organización Mundial de la Salud (OMS), Euro-Growth y nacionales, y se categorizaron según el origen materno (español *vs.* inmigrante).

**Resultados:** los niños de madre de origen inmigrante presentaron mayor peso, longitud, índice de masa corporal y pliegues tricipital y subescapular que los de origen español durante los primeros meses de vida. Los valores medios de z-score variaron significativamente según el estándar de crecimiento utilizado. A los 18 meses, las diferencias entre ambos grupos desaparecieron solo al emplear los estándares de la OMS. Los valores de z-score de pliegues tricipital y subescapular se incrementaron de manera sustancial y progresiva desde los 3 a los 24 meses comparándolos con los estándares de la OMS. A los 24 meses, la prevalencia de niños con riesgo de sobrepeso y sobrepeso fue similar en ambos grupos (español: 15,1% y 3,8%; inmigrante: 14,7% y 4,9%, respectivamente).

**Conclusiones:** el patrón de crecimiento y la adiposidad durante la primera infancia, así como la prevalencia de sobrepeso mostraron diferencias según el origen de la madre que desaparecieron progresivamente a los 24 meses de vida al emplear los estándares de la OMS. Se objetivaron diferencias en los valores antropométricos según el estándar de crecimiento utilizado.

**Palabras clave:**

Infantil. Crecimiento. Adiposidad. Inmigración.

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## INTRODUCTION

Infant growth during the first months of life is a sensitive indicator of early health status. Optimal nutrition during childhood provides adequate support for immediate growth and development as well as long-term health. Intrauterine environment, infant feeding practices, family lifestyle habits and socio-cultural characteristics are the main environmental determinants of postnatal growth, as well as predictive variables of later adiposity and metabolic risk (1-4).

At the present moment in most countries, migration is a key factor influencing nutritional, health, social and growth determinants (5,6). In the last decade, Spanish population has considerably increased mainly due to the migration phenomenon. Spain is nowadays the second country in Europe regarding foreign population amounts. Immigrants reach 5.7 millions in our country, being more than 12% of the total population. This social change, among other aspects, has induced the increase of our national birth rates, being 17.4% of them children with migrant background in the year 2011 when this study was conducted (7).

It is a well-accepted phenomenon that recent immigrants are on average even healthier than the native-born population which is known as "The Healthy Migrant Effect". It has been reported that newborns of immigrant mother have higher birth-weight, lower risk to be born small for gestational age (SGA), and higher rates of breastfeeding maintenance than newborns of Spanish mother (8,9). However, there is no enough information about how migration may influence nutritional status and obesity risk later in life, as it has been observed in other countries (10-12).

Several growth standards can be used for evaluating growth and adiposity patterns in Spanish infants: a) World Health Organization (WHO) standards (13), performed from longitudinal study data of 1.737 children born in Brazil, Ghana, India, Norway, Oman and the United States during 1997-2000 and fed with exclusive breastfeeding; b) Euro-Growth standards (14), performed from an European longitudinal study on 2.245 children born in Spain, Austria, Germany, France, Greece, United Kingdom, Hungary, Italy, Ireland, Croatia, Portugal and Sweden during 1990-1996; and c) Spanish Growth Study 2010 (15), from a cross-sectional study on 38.461 children born in five different Spanish regions from 2000 to 2010. It has been reported differences in growth and adiposity infant patterns depending on the growth standard used (16,17). In addition, some of them are not designed for a mixed population of native and migrant background children. Therefore, the aim of this study is to compare growth and adiposity patterns from birth to 24 months of age in Spanish infants, depending on maternal origin and considering the previously mentioned growth standards.

## MATERIALS AND METHODS

### GENERAL DESIGN AND STUDY POPULATION

Participant population belonged to the CALINA Study (Spanish acronym of Growth and Feeding in Infants from Aragón, Spain) (18), a longitudinal study in a representative cohort of infants from Aragón (Spain), from birth to 24 months of age.

The main objective of the CALINA study was to assess growth patterns, body composition and feeding aspects in this population, as well as, to examine prenatal, postnatal and socio-cultural factors which may influence them. It was developed in a random sample of Primary Care Centers of Aragón, meeting the following inclusion criteria: to have permanent trained pediatric staff conducting the Spanish Child Health Program at least in the last 2 years and with compliance and attendance over 80% of the population living in this area. Infants included in this study were those born between March 2009 and February 2010 (both inclusive), whose parents signed the written consent at the first scheduled health examination in the selected centers. Infants with malformations, diseases, physical disabilities or other important conditions which could affect growth or nutritional status were excluded. The sample initially recruited (1.602 newborns) was representative of the population born over this period in Aragón (18). For the present analysis we only included infants born at term (gestational age ≥ 37 weeks) (n = 1,430). They were divided into 2 groups according to maternal origin: Immigrant group: infants born to immigrant mothers (n = 331) and Spanish group: infants born to Spanish mothers (n = 1,099). The study was performed following the ethical guidelines of the Declaration of Helsinki 1961 (revision of Edinburgh 2000), the Good Clinical Practice, and the legislation about clinical research in humans and was approved by the Clinical Research Ethics Committee of Aragón (CEICA).

### VARIABLES AND MEASUREMENTS

Birth weight and length were obtained from hospital records. Anthropometric measurements were registered by the pediatric trained staff at the Primary Care Centers selected at 3, 6, 9, 12, 18 and 24 months of age following standard protocols (18).

Body weight was measured in kilograms (kg) with an infant scale (sensitivity of 10 g); length was measured in meters (m) with a homologated measuring telescopic board for this use (sensitivity of 1 millimeters); body mass index (BMI) was calculated by dividing weight by the squared length (kg/m$^2$); triceps and subscapular skinfolds thickness measurements were assessed at the left body size with a Holtain® skinfold Caliper (sensitivity of 0.1 mm).

Parents completed a questionnaire about maternal origin and women born outside Spain were considered to be immigrants.

Data analyses were performed with IBM Statistical Package for Social Science (SPSS), version 19.0 (IMB Corp., New York, USA, 2010). Data normality was verified using the Kolgomorov-Smirnov test and the residue variance homogeneity was verified using the Levene test. Anthropometric measurements were converted into z-scores using Euro-Growth (14) and Spanish Growth Study 2010 (15) standards for each age and sex as follows:

z-score = measured value - mean population / standard deviation

WHO growth standard (13) z-scores were calculated using WHO growth macros for SPSS Syntax File for PC (19). Z-score values ≤ 4 or ≥ 4 were considered implausible and excluded. Infants at risk of overweight, overweight and obesity at 24 months of life were defined as +1, +2 and +3 BMI z-scores, respectively (13,20). Mean z-scores differences between both groups (immigrant *vs.* Spanish maternal origin) where examined by student´s t-test, and mean z-scores calculated using the three different growth population standards by analysis of variance (ANOVA). A significance level of $p < 0.05$ was adopted.

## RESULTS

Mean weight, length, BMI and skinfold z-scores of the sample, calculated by the selected growth standards and stratified by maternal origin, are shown in tables I and II. Mean infant z-scores significantly vary depending on growth standards used.

According to WHO standards, mean weight, length and BMI z-scores were higher in immigrant group up to 12 months ($p < 0.001$). Differences decreased progressively and at 18 and 24 months they were not significant (Figs. 1-3). Mean Z-score for triceps skinfold only showed statistical differences at 3 months with higher values in immigrant group ($p < 0.05$) (WHO standards) (Fig. 4). Mean Z-score for subscapular skinfold were significantly higher in immigrant group from 3 months to 18 months, while non-significant differences were found at 24 months of age (WHO standards) (Fig. 5). We did not observe statistically significant difference in the prevalence of infants at risk of overweight and overweight at 24 months of age between Spanish (15.1% and 3.8%, respectively) and immigrant group (14.7% and 4.9%, respectively) when using WHO standards. Nevertheless, differences between both groups remained using Spanish and European standards during the studied period. We did not found obese infants in either group (Tables I and II).

Mean weight z-score values of Spanish group were all negative except for those calculated using the WHO standards that became positive from 9 to 24 months of age. In contrast, weight z-scores in immigrant group were always positive at all ages independently of the growth standard used (non significant differences at 6 and 24 months) (Tables I and II). Length z-scores were weak positive in Spanish group except for those from Euro-growth standards. Length z-scores were always positive in immigrant group, although decreased progressively up to 24 months of age. BMI Z-scores of Spanish group are negative except for those from WHO standards, that became positive from 12 months. Immigrant group showed negative BMI Z-scores from 9 to 24 months compared to Spanish and Euro-growth standards but they have positive Z-scores compared to WHO growth standards from 6 to 24 months (Tables I and II). Mean triceps and subscapular skinfold z-scores substantially and progressively increased from 3 months (negative Z-score) to 24 months of age in both groups compared to WHO standards (Tables I and II).

## DISCUSSION

Spanish population has undergone an important demographic change in the last decade due to immigration. According to the published data by the Statistical Office of the European Communities (EUROSTAT) (21), immigrant population increased considerably in our country from 923,879 in 2000 to 5,730,667 in 2011. Foreign population living in Spain comes mainly from Africa (both Maghreb and Sub-Saharan countries), Latin-America and East Europe. This social change has influenced the increase of Spanish birth rates, being the 17.4% children with migrant background in the year 2011 (7). The anthropometric data in our study were obtained longitudinally in a large and representative sample of the population born over this period in Aragón (North of Spain) (18), showing even higher percentage (23.1%) compared with national data but similar to official immigration rate in Aragón (20,4%) and other bordering areas (7). The obtained results could be extrapolated to the rest of Spain and to countries with similar demographic characteristics.

It is well known that immigrant mothers in our country are younger, have lower educational level, greater parity, longer duration of breastfeeding, less smoking consumption rates and higher weight gain during pregnancy (23-26). Many of these factors and other perinatal and nutritional characteristics make that their infants had lower risk to be born small for gestational age (9.2% in Spanish origin mothers *vs.* 3.8% in immigrant origin mothers), less morbidity and higher birth anthropometric measurements (27-29).

Spanish newborn anthropometric characteristics depending on maternal origin have been already described (23,30), however, there is no enough information about how migration may influence infant nutritional status, growth patterns and obesity risk later in life in our country. Carrascosa et al. (31) published cross-sectional studies conducted on populations from African (The Maghreb and Sub-Saharan regions) and South American (Inca and Mayan regions) origin infants born in Spain. Both populations were separately assessed, and showed similar values to those found in the native Caucasian population during the first years of postnatal life (31). CALINA study reported data on postnatal infant growth characteristics in children born to immigrant mother in our country and compared growth patterns from birth to 24 months of life between infants born to Spanish and immigrant origin mother. Differences in infant growth and adiposity patterns depending on anthropometric standard used, has also been showed. Results showed that weight, length and BMI z-scores were higher in immigrant background group up to 12 months, but at 18 and 24 months there were not significant differences according to WHO growth standards (13). However, differences between both groups remained in our sample when using European and Spanish growth standards (15).

New immigrants in developed countries have significant health advantages that contribute to facilitate an adequate perinatal health status and good postnatal growth, either comparable or even better than native-born population conditions, according to some studies published in other countries (24).

[Nutr Hosp 2017;34(2):330-337]

**Table I.** Mean infant z-scores for weight, length, body mass index and skinfolds z-score up to 2 years of age in Spanish maternal origin group

| | Spanish maternal origin group | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Birth** | **3 months** | **6 months** | **9 months** | **12 months** | **18 months** | **24 months** |
| | **Mean (95% CI)** | **Mean (95% CI)** | **Mean (95% CI)** | **Mean (95% CI)** | **Mean (95% CI)** | **Mean (95% CI)** | **Mean (95% CI)** |
| *Weight* | | | | | | | |
| n | 1099 | 962 | 950 | 903 | 911 | 989 | 974 |
| WHO z-score (13) | -0.12 (-0.17; 0.07) | -0.35 (-0.41; -0.28) | -0.06 (-0.12; 0.00) | 0.07 (-0.01; 0.12) | 0.19 (0.13; 0.25) | 0.35 (0.29; 0.41) | 0.32 (0.26; 0.38) |
| Euro-Growth z-score (14) | -0.30 (-0.35; -0.24) | -0.09 (-0.17; -0.01) | -0.12 (-0.18; -0.06) | -0.24 (-0.30; -0.18) | -0.29 (-0.36; -0.23) | -0.22 (-0.28; -0.16) | -0.17 (-0.23; -0.11) |
| Spanish Growth Study 2010 z-score (15) | -0.01 (-0.05; 0.10) | -0.08 (-0.13; -0.02) | -0.14 (-0.19, -0.09) | -0.30 (-0.35; -0.24) | -0.45 (-051; -0.38) | -0.39 (-0.44; -0.33) | -0.26 (-0.32; -0.20) |
| *p* | *< 0.001* | *< 0.001* | *< 0.001* | *< 0.001* | *< 0.001* | *< 0.001* | *< 0.001* |
| *Length* | | | | | | | |
| n | 1091 | 960 | 942 | 933 | 909 | 989 | 975 |
| WHO z-score (13) | 0.15( 0.08; 0.20) | 0.12 (0.02; 0.24) | 0.05 (-0.01; 0.11) | 0.12 (0.06; 0.18) | 0.15 (0.09; 0,21) | 0.17 (0.11; 0.23) | 0.18 (0.12; 0.24) |
| Euro-Growth z-score (14) | 0.04 (-0.01; 0.10) | 0.00 (-0.08; 0.08) | -0.18 (-0.24; -0.12) | -0.02 (-0.08; 0.03) | -0.04 (-0.10; 0.02) | -0.24 (-0,31; -0.18) | -0.13 (-0.19; -0.06) |
| Spanish Growth Study 2010 z-score (15) | 0.04 (-0.02; 0.10) | 0.10 (0.04, 0.15) | 0.08 (0.03; 0.13) | 0.05 (0.02; 0.11) | 0.06 (0.00; 0.12) | 0.04 (-0.02; 0.10) | 0.05 (-0.10; 0.11) |
| *p* | *< 0.001* | *< 0.001* | *< 0.001* | *< 0.001* | *< 0.001* | *< 0.001* | *< 0.001* |
| *BMI* | | | | | | | |
| n | 1091 | 960 | 940 | 888 | 907 | 989 | 974 |
| WHO z-score (13) | -0.30 (-0.35; -0.24) | -0.38 (-0.45; -0.31) | -0.12 (-0.19; -0.06) | -0.01 (-0.08; 0.05) | 0.15 (0.08; 0.21) | 0.36 (0.29; 0.42) | 0.29 (0.22; 0.35) |
| Euro-Growth z-score (14) | -0.27 (-0.32; 0.21) | -0.16 (0.24; -0.09) | -0.09 (-0.15; -0.03) | -0.30 (-0.36; -0.24) | -0.37 (-0.43; 0.31) | -0.69 (-0.75; -0.63) | -0.69 (-0.75; -0.63) |
| Spanish Growth Study 2010 z-score (15) | -0.01 (-0.06; 0.05) | -0.20 (-0.27, -0.13) | -0.26 (-0.31; -0.20) | -0.38 (-0.43; -0.33) | -0.61 (-0.67; -0,55) | -0.93 (-0.98; -0.87) | -0.83 (-0.89; -0.77) |
| *p* | *< 0.001* | *< 0.001* | *< 0.001* | *< 0.001* | *< 0.001* | *< 0.001* | *< 0.001* |
| *Skinfolds* | | | | | | | |
| n | | 521 | 753 | 653 | 586 | 586 | 475 |
| WHO triceps z-score (13) | Not available | -0.42 (-0.58; -0.34) | 0.28 (0.18; 0.37) | 0.36 (0.26; 0.46) | 0.69 (0.58; 0.79) | 0.88 (0.78; 0.99) | 0.87 (0.75; 0.99) |
| WHO subescapular z-score (13) | Not available | -0.20 (-0.13; 0.83) | 0.38 (0.28; 0.45) | 0.37 (0.27; 0.46) | 0.58 (0.47; 0.67) | 0.57 (0.56; 0.75) | 0.57 (0.45; 0.70) |

*BMI: body mass index; CI: confidence interval; WHO: World Health Organization; z-score: Standard deviation score. *p-value from ANOVA between mean infant z-scores calculated by different growth standards for the same anthropometric measure.*

**Table II.** Mean infant z-scores for weight, length, body mass index and skinfolds z-score up to 2 years of age in immigrant maternal origin group

| | Immigrant maternal origin group | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Birth** | **3 months** | **6 months** | **9 months** | **12 months** | **18 months** | **24 months** |
| | **Mean (95% CI)** | **Mean (95% CI)** | **Mean (95% CI)** | **Mean (95% CI)** | **Mean (95% CI)** | **Mean (95% CI)** | **Mean (95% CI)** |
| *Weight* | | | | | | | |
| n | 331 | 303 | 243 | 215 | 227 | 250 | 217 |
| WHO z-score (13) | 0.21 (0.10; 0.30)[a] | 0.02 (-0.10; 0.16)[a] | 0.35 (0.23; 0.48)[a] | 0.45 (0.32; 0.58)[a] | 0.57 (0.44; 0.69)[a] | 0.37 (0.25; 0.50)[ns] | 0.33 (0.20; 0.46)[ns] |
| Euro-Growth z-score (14) | 0.07 (-0.04; 0.18)[a] | 0.36 (0.21; 0.52)[a] | 0.33 (0.20; 0.48)[a] | 0.16 (0.02; 0.30)[a] | 0.11 (-0.03; 0.25)[a] | 0.14 (-0.01; 0.28)[a] | 0.20 (0.05; 0.36)[a] |
| Spanish Growth Study 2010 z-score (15) | 0.38 (0.27; 0.49)[a] | 0.26 (0.14; 0.38)[a] | 0.24 (0.13, 0.36)[a] | 0.05 (-0.07; 0.17)[a] | 0.05 (-0.18; 0.09)[a] | 0.07 (-0.05; 0.19)[a] | 0.12 (-0.04; 0.28)[a] |
| *p* | *< 0.001* | *0.002* | *0.432* | *< 0.001* | *< 0.011* | *< 0.001* | *0.118* |
| *Length* | | | | | | | |
| n | 329 | 258 | 236 | 225 | 226 | 250 | 217 |
| WHO z-score (13) | 0.53 (0.43; 0.63)[a] | 0.24 (0.11; 0.37)[a] | 0.42 (0.30; 0.54)[a] | 0.38 (0.25; 0.51)[a] | 0.48 (0.36; 0,60)[a] | 0.18 (0.05; 0.32)[ns] | 0.14 (0.02; 0.27)[ns] |
| Euro-Growth z-score (14) | 0.40 (0.30; 0.50)[a] | 0.36 (0.23; 0.49)[a] | 0.19 (0.07;-0.30)[a] | 0.22 (0.09; 0.35)[a] | 0.28 (0.15; 0.41)[a] | 0.06 (-0,07; 0.19)[a] | 0.13 (-0.02; 0.28)[b] |
| Spanish Growth Study 2010 z-score (15) | 0.43 (0.33; 0.55)[a] | 0.36 (0.27, 0.46)[a] | 0.39 (0.29; 0.49)[a] | 0.19 (0.07; 0.31)[a] | 0.37 (0.25; 0.49)[a] | 0.32 (0.21; 0.44)[a] | 0.30 (0.15; 0.44)[b] |
| *p* | *0.200* | *0.256* | *0.008* | *0.078* | *0.091* | *0.019* | *0.190* |
| *BMI* | | | | | | | |
| n | 329 | 298 | 236 | 210 | 226 | 250 | 217 |
| WHO z-score (13) | -0.09 (-0.20; 0.01)[a] | -0.14(-0.28; 0.00)[a] | 0.14 (0.00; 0.28)[a] | 0.32 (0.18; 0.46)[a] | 0.40 (0.29; 0.53)[a] | 0.39 (0.27; 0.50)[ns] | 0.34 (0.27; 0.47)[ns] |
| Euro-Growth z-score (14) | -0.05 (-0.16; 0.05)[a] | 0.11 (-0.04; 0.26)[a] | 0.19 (0.05; 0.33)[a] | 0.04 (-0.10; 0.17)[a] | -0.11 (-0.24; 0.01)[a] | -0.47 (-0.61; -0.34)[b] | -0.38 (-0.53; -0.22)[a] |
| Spanish Growth Study 2010 z-score (15) | 0.21 (0.10; 0.33)[a] | 0.07 (-0.08, 0.21)[a] | 0.00 (-0.13; 0.14)[a] | -0.08 (-0.21; 0.05)[a] | -0.36 (-0.48; -0,24)[a] | -0.73 (-0.86; -0.61)[b] | -0.50 (-0.67; -0.34)[a] |
| *p* | *< 0.001* | *0.006* | *0.326* | *< 0.001* | *< 0.001* | *< 0.001* | *< 0.001* |
| *Skinfolds* | | | | | | | |
| n | | 148 | 183 | 163 | 142 | 185 | 151 |
| WHO triceps z-score (13) | Not available | -0.32 (-0.46; 0.08)[c] | 0.39 (0.14; 0.51)[ns] | 0.48 (0.31; 0.64)[ns] | 0.75 (0.61; 0.97)[ns] | 0.95 (0.78; 1.12)[ns] | 0.81 (0.68; 1.10)[ns] |
| WHO subescapular z-score (13) | Not available | -0.12 (-0.17; 0.09)[c] | 0.80 (0.59; 0.95)[a] | 0.94 (0.75; 1.10)[a] | 0.91 (0.76; 1.11)[a] | 0.73 (0.54; 0.92)[c] | 0.58 (0.37; 0.79)[ns] |

*BMI: body mass index; CI: confidence interval; WHO: World Health Organization; z-score: standard deviation score. *p-value from ANOVA between mean infant z-scores calculated by different growth standards for the same anthropometric measure. **p-value from t-student between mean infant z-scores of Spanish maternal origin group* vs. *immigrant maternal origin group for the same anthropometric measure ([a]p <0.001; [b]p <0.01, [c]p <0.05, ns: non significant).*

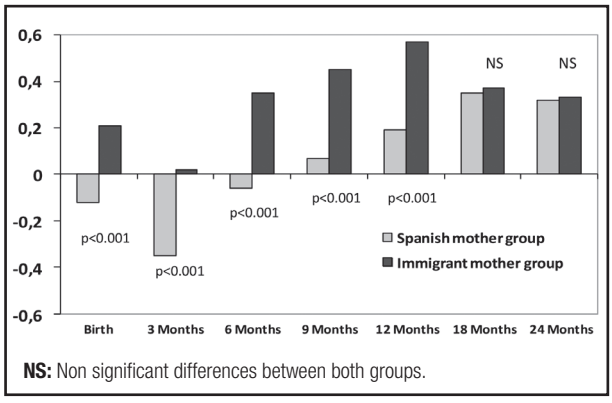


**Figure 1.**

Mean infant z-scores for weight up to 2 years of age depending on maternal origin by World Health Organization growth standards.

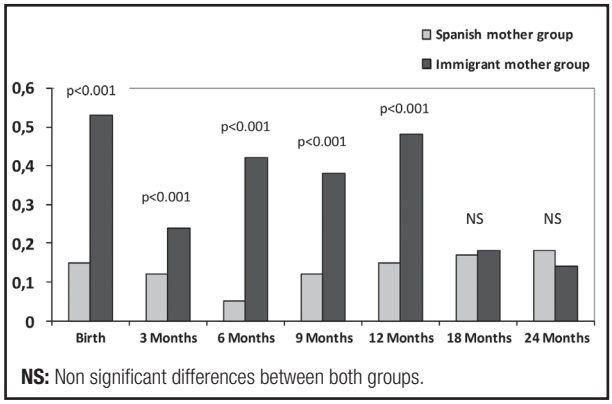


**Figure 2.**

Mean infant z-scores for length up to 2 years of age depending on maternal origin by World Health Organization growth standards.

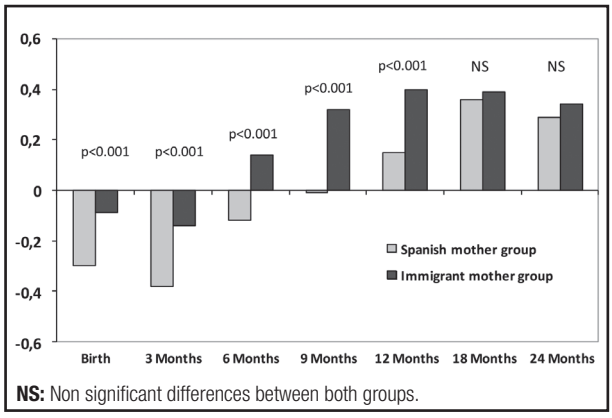


**Figure 3.**

Mean infant z-scores for BMI up to 2 years of age depending on maternal origin by World Health Organization growth standards.

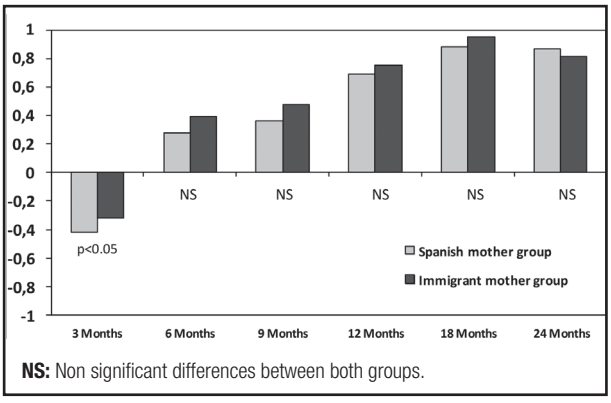


**Figure 4.**

Mean infant z-scores for triceps skinfold up to 2 years of age depending on maternal origin by world Health Organization growth standards.

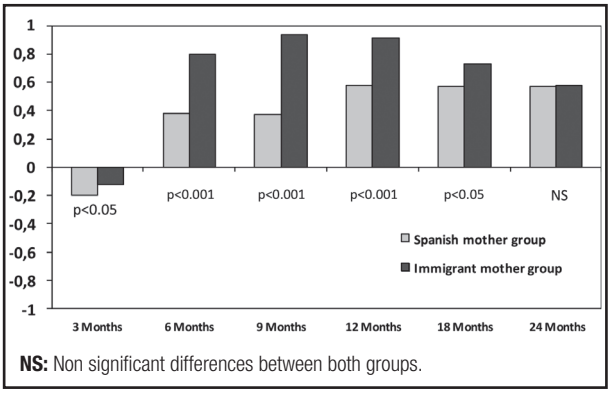


**Figure 5.**

Mean infant z-scores for subescapular skinfold up to 2 years of age depending on maternal origin by world Health Organization growth standards.

In spite of the Healthy Migrant Effect theory, socio-cultural characteristics of this population group give an explanation for the loss of health advantages over the time in the host country (10,32,33). A process of acculturation may cause that immigrants gradually adopt habits and lifestyles of the country where they live. Sedentary patterns, dietary habits or consumption of tobacco and alcohol those are deleterious to maintain health status (11). For example, in a study conducted in Canada, the probability of being overweight in adult immigrants on arrival was lower than in comparable native-born Canadians, but increased gradually with additional years in their new country and met or exceeded native-born levels after approximately 20-30 years (10). Similar patterns for adult immigrants have been observed in UK or in the United States of America (USA) (11,12).

This increased risk of overweight has been widely described also in children born to migrant population and in their following generations in USA (33); as well as more recently, in European countries

(UK, Sweden or Netherlands) (32,34-36) and Australia (37). In Spain, there is still no conclusive data about family migration and risk of adiposity in their descendants. In our sample, using the WHO growth standards (13), neither the prevalence of overweight nor subcutaneous adiposity measures showed statistical significant differences at 24 months of age depending on maternal origin. However, we observed higher subcutaneous adiposity levels in both groups, so skinfolds z-scores substantially and progressively increased from 3 months to 24 months of age compared to WHO standards. Perhaps this fact depends on WHO sample that was selected from exclusive breastfed infants (for at least 4 months) in emergent countries where the availability of food and nutritional status could be different. Prospective study of a Spanish cohort will be necessary to describe growth patterns and to assess obesity development and body composition differences depending on migrant background later in life.

We have previously reported that wide differences in the assessment of infant growth and nutritional status can be found depending on the growth standard used in the same population (16,17). It might be the case that a child met criteria to be considered at nutritional risk with one growth standard, but not with others (16). The characteristics of the population selected and the methodology applied to perform growth standards could explain differences among them. This fact has been demonstrated in our study sample by calculating z-scores for several anthropometric variables using WHO (13), Euro-Growth (14) and national (Spanish Growth Study 2010) growth standards (15). Mean infant z-scores significantly vary depending on growth standards used, so differences between Spanish and immigrant maternal origin groups remained using Spanish and European standards. WHO growth standards have been elaborated in a normative cohort of children from 7 countries with optimal environmental and nutritional conditions; meanwhile, Spanish and European growth standards are from observational studies, showing the current trend of infant nutritional status, higher values of BMI and an overestimation of undernutrition. So there are differences in BMI at 24 months but no in height. This is important because healthy children in low percentiles from WHO growth standards should be under the third percentile in the others, and they might be classified as malnourished causing unnecessary nutritional support.

In addition, considering socio-cultural and demographic changes produced by immigration, it seems recommendable to periodically review the growth standards. Cross-sectional and longitudinal growth studies conducted on the native Caucasian population and growth data of the immigrant population are currently available in Spain (30,31).

In conclusion, infant growth and adiposity patterns depending on maternal origin showed initial differences but they progressively disappear at 24 months of life. At birth, immigrant maternal origin infants have higher weight, length, body mass index and triceps and subscapular skinfolds than Spanish maternal origin infants. After 18 months of age, anthropometric differences between both groups disappear when WHO (13) standards are used. At 24 months, the prevalence of overweight is similar in both groups. Further studies are needed to confirm or refute these findings as well as to assess long-term effects of immigrant background.

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## CALINA COLLABORATIVE GROUP (CRECIMIENTO Y ALIMENTACIÓN DURANTE LA LACTANCIA Y LA PRIMERA INFANCIA EN NIÑOS ARAGONESES)

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Nutrición Hospitalaria

Trabajo Original

Nutrición en el anciano

# Adherence to the Mediterranean diet pattern, cognitive status and depressive symptoms in an elderly non-institutionalized population

*Adherencia al patrón de dieta mediterránea, estado cognitivo y síntomas depresivos en una población no institucionalizada de edad avanzada*

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## Abstract

**Introduction:** Scientific evidence indicates that adherence to the Mediterranean diet protects against the deterioration of cognitive status and depressive symptoms during aging. However, few studies have been conducted in elderly non-institutionalized subjects.

**Objective:** This study evaluated the relation between the adherence to the Mediterranean dietary pattern and cognitive status and depressive symptoms in an elderly population over 75 years.

**Methods:** A cross-sectional study was conducted in a Mediterranean city (Garrucha, Spain) in 79 elderly people over 75 (36 men and 41 women). Adherence to the Mediterranean dietary pattern was determined using the Mediterranean Diet Adherence Screener (MEDAS). Cognitive function was determined by the Mini Mental State Examination (MMSE), and depressive symptoms were assessed by the Geriatric Depression Scale (GDS).

**Results:** Most of population showed a very high adherence to the Mediterranean diet pattern and optimal cognitive and affective status. They consumed olive oil as their main source of fat, high levels of fish and fruit, low levels of foods with added sugars, and a low consumption of red meat. A significant relation between the MEDAS and MMSE scores was found. However, no relationship was observed between the MEDAS and GDS.

**Conclusions:** The Mediterranean diet pattern was positively related with the cognitive function, although the influence of a healthy dietary pattern on the symptomatology of depression was unclear. However, an effective strategy against cognitive function and depression would be to improve physical activity rates, establish lifelong healthy eating habits, and consume a nutritionally-rich diet in order to enhance quality of life of the elderly.

**Key words:**

Older adult. Mediterranean dietary pattern. Cognitive function. Depression. Aging.

## Resumen

**Introducción:** la evidencia científica indica que la adherencia al patrón de dieta Mediterránea protege contra el deterioro del estado cognitivo y los síntomas depresivos durante el envejecimiento. Sin embargo, se han realizado pocos estudios en ancianos no institucionalizados.

**Objetivo:** este estudio evaluó la relación entre la adhesión al patrón de dieta mediterránea, el estado cognitivo y los síntomas depresivos en una población anciana de 75 años de vida independiente.

**Métodos:** el estudio transversal se llevó a cabo en una ciudad mediterránea (Garrucha, Almería, España) en 79 adultos mayores de más de 75 años (36 hombres y 41 mujeres). La adhesión al patrón de dieta mediterránea se determinó utilizando el test *Mediterranean Diet Adherence Screener (MEDAS).* La función cognitiva se determinó con el test *Mini Mental State Examination (MMSE),* y los síntomas depresivos se evaluaron con la Escala de Depresión Geriátrica (GDS).

**Resultados:** la mayoría de la población mostró una alta adhesión al patrón de dieta mediterránea y un estado cognitivo y afectivo óptimos. Consumían aceite de oliva como principal fuente de grasa, un elevado consumo de pescado y fruta, y un bajo consumo de carne roja y de alimentos con azúcares añadidos. Se encontró una relación significativa entre las puntuaciones del MMSE y MEDAS. Sin embargo, no se observó relación entre los resultados de MEDAS y GDS.

**Conclusiones:** el patrón de dieta mediterránea se relacionó positivamente con la función cognitiva, pero la influencia de un patrón de dieta saludable en la sintomatología de la depresión no resultó claro. Sin embargo, una estrategia eficaz para mantener la función cognitiva y disminuir la sintomatología de depresión podría ser mejorar las tasas de actividad física, establecer hábitos alimenticios saludables durante la vida y consumir una dieta saludable con el fin de mejorar la calidad de vida de las personas mayores.

**Palabras clave:**

Ancianos. Patrón de dieta mediterránea. Función cognitive. Depresión. Envejecimiento.

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## INTRODUCTION

There is a high prevalence of depression in older adults, either clinically diagnosed or with a recognized depressive symptomatology, reportedly between 7 and 49% (1). Despite this incidence, it has been estimated that 70-90% of depression in old age is undiagnosed, misdiagnosed, or dismissed as a normal part of aging.

The objective is to increase the state of wellbeing and quality of life of the population, and especially the elderly. Quality of life is influenced by numerous factors, including certain food habits such as the consumption of fruits, vegetables, olive oil, fish and wine (in moderation), all distinguishing features of the Mediterranean diet, which has been associated with the ability to prevent cognitive deterioration, lower cardiovascular risk and decreased mortality from all causes (2). There is growing evidence that diet –a modifiable lifestyle factor– could be one component of an effective prevention strategy against depression, although no firm conclusion can be drawn at this point (3). A healthy Mediterranean dietary pattern appears to be associated with lower odds of depression and favourable mental and physical health outcomes (4). The Mediterranean dietary pattern refers not only to the type of food consumed, but also to lifestyle and the social customs associated with the way of eating. It therefore seems reasonable to assume that this pattern of healthy eating can modify cognitive status (4,5) and reduce the prevalence of depression in the elderly population (6).

There is a wealth of observations and experimental knowledge showing that effective brain function depends on an adequate and constant supply of nutrients, and that nutrition –particularly of micronutrients and ω-3 polyunsaturated fatty acids– is key for cognitive performance and mental wellbeing (7). The Mediterranean dietary pattern is rich in plant foods and fish. Plant foods have a high content in minerals, vitamins and natural antioxidants, and fish is a good source of ω-3 polyunsaturated fatty acids (2). The elderly population is at higher risk of receiving insufficient levels of these micronutrients that are essential for proper brain functioning, and whose deficiency negatively influences cognitive performance and is associated with age-related cognitive decline (5) and depressive symptoms (6).

Interest in old-age depression has increased due to the ageing population and the increasing demographic importance of elderly people. The study of these variables is interesting at any age, but it has a greater impact on the prevalence of morbidity and mortality when studied in older people. However, there are very few studies in the over-75 y.

## OBJECTIVE

The aim of this study was to determine the adherence to the Mediterranean dietary pattern, and its protective role against cognitive decline and depression in a population aged over 75.

## METHODS

### STUDY DESIGN

A cross-sectional survey, the Garrucha Old Age Health Study, was conducted in very old men and women living in Garrucha (8,626 registered inhabitants), Almería (Spain), located on the Mediterranean coast. All non-institutionalised inhabitants aged 75 and over (n = 464) registered in the municipal census in 2014 were invited by letter delivered personally to participate in the study. The final sample comprised 79 participants (43 women and 36 men). Participants were divided into four age groups: 75-80; 81-85; 86-89; ≥ 90.

Data were collected by interview using comprehensive geriatric and nutritional assessment. Interviews were conducted by trained researchers. Informed written consent was obtained from all participants.

The study was the result of a collaboration agreement between the Universidad Complutense de Madrid (Madrid, Spain) and the Garrucha City Council (Almería, Spain), and conducted according to Declaration of Helsinki guidelines. All procedures were approved by the Ethics Review Board of the Universidad Complutense de Madrid.

### FOOD CONSUMPTION

Food consumption data were collected by trained dietitians using three non-consecutive 24-hour diet recalls collected in face to face. In some cases, caregiver assistance was necessary to confirm the correct intake pattern. From three 24-hour diet recalls was calculated the grams of food per day and per person, and subsequently grams were transformed to serving according to recommendations of the food pyramid of Mediterranean diet (8).

### ADHERENCE TO THE MEDITERRANEAN DIET

Adherence to the Mediterranean diet was determined by the MEDAS that was developed in PREDIMED study (9). A face-to-face interview with each participant was conducted to complete a questionnaire consisting of 14 questions. The 14-item screener of MEDAS includes 12 items with targets for food consumption and another two items with targets for food intake habits characteristics of the Mediterranean diet focused to know if the surveyed consumes olive oil and if so, to know the amount daily ingested.

Each question was scored 0 or 1. One point was given for each target achieved. One point was given for using olive oil as the principal source of fat for cooking, preferring white meat over red meat, or for consuming: a) four or more tablespoons (1 tablespoon = 13.5 g) of olive oil/d (including that used in frying, salads, meals eaten away from home, etc.); b) two or more servings of vegetables/day; c) three or more pieces of fruit/day; d) < 1 serving of red meat or sausages/day; e) < 1 serving of animal fat/day; f) < 1 cup (1 cup = 100 mL) of

sugar-sweetened beverages/day; g) seven or more servings of red wine/week; h) three or more servings of legumes/week; i) three or more servings of fish/week; j) fewer than two commercial pastries/week; k) three or more servings of nuts/week; or l) two or more servings/week of a dish with a traditional sauce of tomatoes, garlic, onion, or leeks sautéed in olive oil. If the condition was not met, 0 points were recorded for the category. The total MEDAS score ranges from 0 to 14, with a higher score indicating better Mediterranean diet accordance. MEDAS score ≥ 7 (mid-range value) represented a modest accordance, and a score ≥ 9 represented strict accordance with the healthy dietary pattern (10).

## COGNITIVE STATUS

Cognitive status was evaluated using the Mini-Mental State Examination (MMSE) (11), which is used for screening for mild cognitive impairment. It consists of a series of questions grouped into six categories that represent significant aspects of intellectual function: time-space orientation, memory loss and attachment, attention, calculation, capacity for abstraction, language and praxis (naming, repetition, reading, order, graphics and copy). A maximum of 35 points is awarded. Scores below 24 indicate cognitive limitations. Participants with a physical or mental disability that prevented them performing the tests were excluded.

## DEPRESSIVE SYMPTOMS

Depressive symptoms were evaluated using the short version of the Geriatric Depression Scale (GDS) (12). The GDS was used to screen for any elements of depression. This scale was developed to assess many of the problems associated with depression, and to identify depressive symptoms in older adults (life outlook, mood, feelings of abandonment, predisposition for activities, fear of disease and death). Total scores were obtained by adding one point for each response which was symptomatic of depression, giving a score range of 0-15. This score was then classified into three categories of affective state: no depression (0-5), slight depression (6-9) and severe depression (> 9). Participants with a physical or mental disability that prevented them performing the tests were excluded.

## OTHER MEASUREMENTS

The baseline examination included other questionnaires designed to collect information on leisure time physical activity, body mass index (BMI), health conditions, smoking habits, history of illness, use of medication, and educational level.

## STATISTICAL ANALYSIS

A descriptive analysis was conducted on the frequencies, averages and percentages of the population segmented by sex and age groups. The results were stratified into categorical variables as the scoring criteria for each determination. The results for the categories were compared using contingency tables. Differences between categorical variables were analysed with the Chi-square Pearson test. The average score in each category in terms of sex and age was compared using analysis of variance (ANOVA). p-values ≤ 0.05 were considered statistically significant. V22 SPSS statistical software was used for data analysis and processing.

## RESULTS

The characteristics of the participants are shown in table I. The dispersion of data was very high and the differences between men and women were not significant in most of the parameters measured. However, there were significant differences in physical activity, and women showed poorer outcomes than men.

The mean age of the subjects in the study was 81.0 ± 4.6 years, with the most numerous group aged between 75 and 80. Most of population had a primary education level, less six diseases, a daily consumption of less five drugs and they were non-smokers, only one subject was smoker. The mean BMI was 27.9 ± 4.1 kg/m$^2$. They had a moderate level of physical activity, with an average of over 69 minutes of activity a day, particularly walking, cycling, swimming and gymnastics adapted to the elderly (Table I).

Regarding food consumption, most subjects routinely used olive oil for cooking and salads and frequently ate fresh fish.

Table II shows the percentage of senior citizens who met the MEDAS targets and adhere to the Mediterranean diet. All the participants used olive oil as their main cooking fat, almost 90% met the targets for using olive oil as their frying fat, and 94.9% consumed dished seasoned with tomato sauce, onion or leek with olive oil. The majority met the target for low consumption of red meat (92.4%), carbonated/sweetened beverages (79.7%), animal fat (77.2%), and commercial sweets and pastries (62%). In addition, more than 69% of the sample consumed more than three servings of fish per week. The population tended to consume vegetables, fruits and legumes. In contrast, consumption of wine and nuts was low. Less than 21% of individuals meet the targets.

Table III shows the relationship between consumption of foods of the study population and their adherence to the Mediterranean dietary pattern. Study population consumed similar serving of fruit, vegetables, and fish corresponding with the serving recommended of the food pyramid of Mediterranean Diet (Table III).

The mean MEDAS score was 9.4 ± 1.6, denoting strict adherence to the Mediterranean diet. 69.6% of individuals attained a MEDAS score of over 9, while 27.9% had a MEDAS score of 7 to 8, representing modest adherence to the Mediterranean diet. Only 2.5% showed values of low adherence to the Mediterranean diet pattern. No differences were found due to sex but there were significant differences due age. Group aged over 90 showed a lower MEDAS (8.3 ± 1.2) (Table IV).

MMSE values were high for all participants, especially for men and subjects aged over 90. Significant gender differences were

**Table I.** Characteristics of study population[a]

| | Total | Women | Men | p-value[b] |
|---|---|---|---|---|
| Age (years) | 81.0 ± 4.6 | 81.4 ± 4.7 | 80.6 ± 4.5 | 0.452 |
| Mediterranean Diet Adherence Screener | 9.4 ± 1.6 | 9.4 ± 1.5 | 9.3 ± 1.6 | 0.913 |
| Cognitive function (Mini Mental State Examination) | 29.2 ± 5.2 | 28.8 ± 4.2 | 29.6 ± 6.3 | 0.498 |
| Depression (Geriatric Depression Scale) | 3.2 ± 2.9 | 3.5 ± 3.1 | 2.8 ± 2.8 | 0.294 |
| Body mass index (kg/m$^2$) | 27.9 ± 4.1 | 27.8 ± 3.1 | 27.9 ± 3.1 | 0.817 |
| Number of diseases | 5.5 ± 3.8 | 6.2 ± 3.9 | 4.8 ± 3.6 | 0.130 |
| Number of drugs | 4.6 ± 2.8 | 4.4 ± 2.4 | 4.8 ± 3.2 | 0.602 |
| Physical activity (min/person/day) | 69.1 ± 50.9 | 48.5 ± 37.7 | 89.7 ± 54.6 | 0.001 |
| *Educational level* | | | | |
| None | 14 (17.7) | 6 (7.6) | 8 (10.1) | 0.754 |
| Primary studies | 16 (20.3) | 9 (11.4) | 7 (8.9) | |
| Secundary studies | 23 (41.7) | 18 (22.8) | 15 (18.9) | |
| University studies | 16 (20.3) | 10 (12.7) | 6 (7.6) | |
| Tobacco consumption | 1 (1.3) | 1 (1.3) | 0 | 0.006 |

*[a]Values were expressed as mean ± standard deviation and number of subject and percentage respect to total sample, n(%). [b]ANOVA and Chi-square Pearson test, $p \leq 0.05$ corresponds to significant differences between women and men.*

**Table II.** Participants who achieve each target of the MEDAS[a] score, and accordance of food consumption with the Mediterranean diet[b]

| | | Achievement of MEDAS target | |
|---|---|---|---|
| Questions | Target | Women (%) | Men (%) |
| 1. Do you use olive oil as main culinary fat? | Yes | 100 | 100 |
| 2. How much olive oil do you consume in a given day? (including frying, salads, etc.) | ≥ 4 tablespoon/d (1 tablespoon: 13.5 g) | 83.7 | 94.4 |
| 3. How many vegetable servings do you consume per day? (consider side dishes as a half a serving) | ≥ 2 servings/d (1 serving: 200 g) | 44.2 | 47.2 |
| 4. How many fruit units do you consume per day? (including natural fruit juices) | ≥ 3 | 55.8 | 52.8 |
| 5. How many servings of red meat, hamburger or meat products do you consume per day? | < 1 | 93 | 91.7 |
| 6. How many servings of butter, margarine, or cream do you consume per day? | < 1 | 76.7 | 77.8 |
| 7. How many sweetened and/or carbonated beverages do you drink per day? | < 1 | 87.7 | 75 |
| 8. How much wine do you drink per week? | ≥ 7 glasses | 16.3 | 25 |
| 9. How many servings of legumes do you consume per week? (1 serving 150 g) | ≥ 3 | 41.9 | 41.7 |
| 10. How many servings of fish or shellfish do you consume per week? (1 serving 100-150 g of fish or 4-5 units or 200 g of shellfish) | ≥ 3 | 69.8 | 69.4 |
| 11. How many times per week do you consume commercial sweets or pastries | < 3 | 62.8 | 61.1 |
| 12. How many servings of nuts do you consume per week? (1 servings 30 g) | ≥ 1 | 20.9 | 16.7 |
| 13. Do you preferentially consume chicken, turkey or rabbit meat instead of veal, pork, hamburgers or sausage? | Yes | 95.3 | 83.3 |
| 14. How many times per week do you consume vegetables, pasta, rice or other dished seasoned with sauce of tomato, onion, garlic, or leek with olive oil? | ≥ 2 | 93 | 97.2 |

*[a]MEDAS, Mediterranean Diet Adherence Screener. [b]Accordance of food consumption with Mediterranean diet is defined as achieving ≥ 9 targets of MEDAS (10).*

**Table III.** Relationship between consumption of foods and the Mediterranean diet adherence

| Food | Serving recommended in Mediterranean diet Serving (g or ml) (8) | Servings of the sample Serving (g or ml) |
|---|---|---|
| *Daily consumption* | | |
| Fruits (g) | ≥ 3 (≥ 450) | 2.3 (347.1) |
| Vegetables (g) | ≥ 2 (≥ 400) | 1.8 (354.2) |
| Olive oil (g) | ≥ 4 (≥ 40) | 2.2 (22.3) |
| Red wine (ml) | ≥ 1 (≥ 125) | 0.3 (40.5) |
| Cereals (g) | 4-5 (320) | 2.2 (138.6) |
| *Weekly consumption* | | |
| Fish (g) | ≥ 3 (≥ 450) | 2.5 (373.4) |
| Legumes (g) | ≥ 3 (≥ 450) | 0.9 (139.4) |
| Nuts (g) | ≥ 3 (≥ 90) | 0.5 (16.2) |

not found. 87.5% of people –especially men– showed no cognitive limitations, while 9.7% of women and 2.8% of men had cognitive limitations (Table IV).

The number of individuals with cognitive problems increased with age. It is worth noting that no cognitive limitation was detected in the group aged over 90, although this result is only indicative and cannot be generalized, as there were few participants in the study.

The average value of GDS indicated that the population had no depressive problems. No differences due to sex and age were found. Seventy-five per cent of population showed no depressive problems. However, 23.6% of study population showed symptoms of slight depression (15.3% women and 8.3% men). Only 1.4% reached values of severe depression. In terms of age, the group aged 81-85 years presented slightly higher values than the other age groups (Table IV).

We studied the relation between MMSE and GDS values with the three categories of degree of adherence to the Mediterranean diet: low degree of adherence (MEDAS score < 6), moderate degree of adherence (MEDAS score 7-8) and strict adherence (MEDAS score > 9) (Table V). As the degree of adherence rose, the percentage of individuals that had no cognitive limitations also increased, $p < 0.05$.

In terms of depression, it was observed that none of the subjects suffered severe depression; a few individuals had values indicating mild depression, but these do not appear to be related to the quality of the diet.

## DISCUSSION

The Mediterranean diet is an eating pattern that is culturally rooted and transmitted by eating habits learned from previous

**Tabla IV.** Adherence to Mediterranean diet, cognitive status and depressive symptoms of a population over 75 year non-institutionalized[a]

| Test | Gender | | | Age (year) | | | | |
|---|---|---|---|---|---|---|---|---|
| | Women n (%) | Men n (%) | p-value | 75-80 n (%) | 81-85 n (%) | 86-89 n (%) | ≥ 90 n (%) | p-value |
| *MEDAS* | 9.4 ± 1.5 | 9.3 ± 1.6 | 0.913[b] | 9.3 ± 1.6 | 9.7 ± 1.4 | 9.5 ± 1.8 | 8.3 ± 1.2 | 0.029[b] |
| Low adherence (≤ 6) | 2 (2.5) | 0 | 0.072[c] | 1 (1.3) | 0 | 1 (1.3) | 0 | 0.562[c] |
| Moderate adherence (7-8) | 8 (10.1) | 14 (17.7) | | 15 (18.9) | 2 (2.5) | 4 (5.1) | 1 (1.3) | |
| High adherence (≥ 9) | 33 (41.8) | 22 (27.8) | | 28 (35.4) | 15 (18.9) | 10 (12.7) | 2 (2.5) | |
| *MMSE* | 28.8 ± 4.2 | 29.6 ± 6.3 | 0.498[b] | 29.3 ± 5.9 | 29.3 ± 4.9 | 28.5 ± 3.7 | 30 ± 1.4 | 0.955[b] |
| Severe limitations (< 24) | 7 (9.7) | 2 (2.8) | 0.129[c] | 4 (5.6) | 3 (4.2) | 2 (2.8) | 0 | 0.683[c] |
| No cognitive limitations | 32 (40.5) | 31 (43.1) | | 38 (52.8) | 12 (16.7) | 11 (15.3) | 2 (2.8) | |
| *GDS* | 3.5 ± 3.0 | 2.8 ± 2.8 | 0.294[b] | 2.9 ± 2.9 | 3.5 ± 2.9 | 3.4 ± 3.0 | 3.0 ± 0 | 0.940[b] |
| No depression (0-5) | 27 (37.5) | 27 (37.5) | 0.371[c] | 32 (44.4) | 10 (13.9) | 10 (13.9) | 2 (2.8) | 0.589[c] |
| Slight depression (6-9) | 11 (15.3) | 6 (8.3) | | 10 (13.9) | 4 (5.6) | 3 (4.2) | 0 | |
| Severe depression (> 9) | 1 (1.4) | 0 | | 0 | 1 (1.4) | 0 | 0 | |

*[a]Data are presented as mean ± standard deviation; MEDAS (Mediterranean Diet Adherence Screener); MMSE (Mini-Mental State Examination); GDS (Geriatric Depression Scale). [b]ANOVA; p ≤ 0.05 were considered to be statistically significant. [c]Chi-square Pearson test; p ≤ 0.05 were considered to be statistically significant.*

**Table V.** Distribution of cognitive status and depressive symptoms according to the Mediterranean Diet Adherence Screener (MEDAS)

| | MEDAS score[a] | | | |
|---|---|---|---|---|
| | Low n (%) | Medium n (%) | High n (%) | p-value[b] |
| *Mini-Mental State Examination* | | | | |
| Severe limitations | 1 (1.4) | 4 (5.6) | 4 (5.6) | 0.034 |
| No cognitive limitations | 1 (1.4) | 15 (20.8) | 47 (65.3) | |
| *Geriatric Depression Scale* | | | | |
| No depression | 2( 2.8) | 15 (20.8) | 37 (51.4) | 0.364 |
| Depressive slight | 0 | 3 (4.2) | 14 (19.4) | |
| Depressive severe | 0 | 1 (1.4) | 0 | |

*[a]MEDAS SCORE: low (≤ 6), medium (7-8), high (≥ 9). [b]Chi-square Pearson test, p ≤ 0.05 were considered to be statistically significant.*

generations. The older population have followed these customs throughout their lives and been less influenced by the Westernization of their diet. This may be an important reason to explain the high MEDAS score found in this population, when currently the score for the Spanish population stands at around 6.3 (9). León-Muñoz et al. (9) considered that the MEDAS score using cutoffs > 9 defines a strict adherence to the Mediterranean diet, while the use of cutoffs > 7 denotes a modest adherence. The elderly population in the study had very high mean MEDAS scores (> 9). However, the results were quite different when the cutoff used in the MEDAS was modified to 7. It is interesting to note that some results observed in the answers to the 14 MEDAS questions may not reflect the real situation. For example, only 41.8% of older people met the goal of consuming legumes at least three times a week. However, the more detailed answers on food consumption indicated that most of the population frequently consumed legumes (twice a week). A similar situation occurred with the results for wine consumption. Most participants considered wine consumption to be beneficial for the health and had routinely consumed wine throughout their adult lives. However, they had abandoned or reduced their intake in recent years due to the greater prevalence of disease and the increased necessity of consuming medicines, some of which interacted with alcohol. In both examples it can be said that the consumption of legumes and wine were two eating habits that were deeply-rooted in this population.

In summary, oldest people still adhere to the main features of the Mediterranean diet pattern, such as high consumption of olive oil as the main source of fat, a high consumption of fish, low glycemic fruits and foods with added sugars, a moderate wine intake, and low consumption of red meat.

Cognition involves a variety of domains, and age-related decline varies considerably across these cognitive domains and between individuals. The cognitive functions that are most affected by ageing –independently of Alzheimer's and other dementias– often relate to attention, memory, perception, and executive function (13). Most of the population studied did not present cognitive limitations evaluated with the MMSE. These results were similar (14) –and in some cases higher (15-17)– to those found in other studies. It is worth noting that the over 90y were the age group without cognitive limitations. Similar results were found in the Octabaix study (14).

The population study had no depressive problems measured with the GDS. Depression during aging is an important public health problem, and causes suffering to many who go undiagnosed (6). Often neither the elderly themselves nor the healthcare providers recognize the symptoms in the context of the multiple physical problems affecting many elderly people (6). Certain depressive symptoms like low mood may be less prominent than others such as loss of appetite, sleeplessness, lost of interest and so on. Studies of depressed adults report that those with depressive symptoms –with or without a depressive disorder– have poorer functioning than non-depressed adults, and could function similarly to or worse than adults with chronic medical conditions (6,18). Depression is common in later life, but methodological differences between studies preclude firm conclusions about cross-cultural and geographic variation (19).

Depression, decline in cognitive function and problems in nutritional status are common in aging (19). In this study of the relationship between cognitive status and depressive symptoms and the degree of adherence to the Mediterranean diet pattern, we observed that the cognitive function and quality of the diet were positively related. However, no relation was observed with the depressive symptomatology.

Numerous studies have found a relationship between reduced cognitive decline (20) and lower risk of clinical depression with a greater adherence to the Mediterranean diet (18) and a higher quality of life (21). Skarupski et al. (6) reported that greater consumption of the characteristic food groups in a Mediterranean-based diet was associated with a lower likelihood of depressive symptoms in older adults over time. Diet influences the physiological processes that may be involved in the development of depression in different ways, such as inflammation, oxidative stress or hormonal factors (6). In contrast to several other non-communicable diseases, the preventive potential of diet in regard to depression is a relatively new research area (5). A recent review study (3) determines that dietary patterns may have an influence on the onset of depression, although the relationship is unclear.

The possible role of lifestyle-related factors has been proposed for age-related changes in cognitive function, pre-dementia syndromes and cognitive decline of degenerative or vascular origin. Among these factors, the type of diet (amount and type of food) and the socio-cultural habits related to eating habits could be important in the impairment of the cognitive and affective state (19). Féart et al. (2) reported that stricter adherence to a Mediterranean diet was associated with slower MMSE cognitive decline,

but not consistently with other cognitive tests; and not with risk for incident dementia (2).

The Mediterranean diet combines several foods and micro- and macronutrients already proposed separately as potential protective factors against dementia and pre-dementia syndromes. The Mediterranean diet can be linked to mental health outcomes via a high number of dietary constituents such as B-vitamins, antioxidants (nutrients and bioactive compounds) and fat composition –namely a high content in unsaturated fatty acids (mono- and poly-). Several foods such as legumes, nuts and fish are important contributors to polyunsaturated fatty acids, which may be involved in the neurodegenerative process (22-24). A clear reduction of risk for cognitive decline has been found in population samples with elevated fish and olive oil consumption and a high intake of monounsaturated and polyunsaturated fatty acids, but not when the disease has already taken over (7).

Epidemiological studies indicate a higher risk of cognitive decline in people with low ω-3 fatty acid intake, although the available evidence does not prove that polyunsaturated fatty acid supplements can protect against cognitive decline or dementia (25). These issues still require clarification. Nonetheless, there is much experimental evidence pointing to the beneficial role of consuming ω-3 fatty acids on the development of cognitive and emotional impairment.

Legumes, vegetables and fruits are an important source of vitamins and natural antioxidants. The limited epidemiological evidence available on fruit and vegetable consumption and cognition has generally highlighted the protective role of these foods against cognitive decline and dementia.

In summary, most people of this elderly group showed a very high adherence to the Mediterranean diet pattern, and did not present cognitive limitations. According to this study dietary habits appeared to be related with cognitive limitations but not with depressive symptomatology; however, efforts to decrease the prevalence of depression in the elderly should target risk factors. Prevention appears to require improvements in physical activity, diet and other lifestyle factors. The Mediterranean diet pattern includes a balanced combination of foods and a healthy lifestyle that positively affects the quality of life of the elderly.

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ARÁN

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Trabajo Original

Nutrición en el anciano

# Factors associated with sarcopenia in institutionalized elderly

*Factores asociados con la presencia de sarcopenia en ancianos institucionalizados*

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## Abstract

**Introduction:** The sarcopenia is a negative aspect for the health of the elderly, increased the risk for disease and mortality. Additionally can contributes greatly to functional reducing capacity and quality of life.

**Objective:** To identify the prevalence and factors associated with sarcopenia in institutionalized elderly.

**Methods:** This is a cross-sectional study, conducted with 216 elderly people, aged ≥ 60 years, of both sexes, residents in long-term care facilities in Salvador-Bahia, Brazil. To identify sarcopenia was used the skeletal muscle Index. Covariates were considered: gender, age, time of institutionalization, type of institution, body mass index and functional capacity. The Association between sarcopenia and covariates was evaluated using the Poisson regression model with robust variance.

**Results:** The prevalence of sarcopenia in the elderly was 72.2% and this condition was associated with male sex (PR = 1,33; CI 95% = 1,08-1,65), thinness (PR = 1,29; CI 95% = 1,16-1,43) and obesity (PR = 0,37; CI 95% = 0,23-0,61).

**Conclusion:** The prevalence of sarcopenia was high among the elderly living in long-term institutions, especially among men. Elderly with thinness showed greater impairment of muscle reserves, while the state of obesity was protective.

**Key words:**

Sarcopenia. Elderly. Institutionalization.

## Resumen

**Introducción:** la sarcopenia es un aspecto negativo para la salud de las personas mayores, aumenta el riesgo de enfermedad y mortalidad. Además puede contribuir en gran medida a la reducción de la capacidad funcional y calidad de vida.

**Objetivo:** identificar la prevalencia y los factores asociados con la sarcopenia en los ancianos institucionalizados.

**Métodos:** se trata de un estudio transversal, realizado con 216 personas de edad avanzada (≥ 60 años), de ambos sexos, residentes en centros de atención a largo plazo en Salvador-Bahia, Brasil. Para identificar la sarcopenia se utilizó el índice musculoesquelético. Se consideraron covariables: género, edad, tiempo de institucionalización, tipo de institución, índice de masa corporal y la capacidad funcional. La asociación entre la sarcopenia y covariables se evaluó utilizando el modelo de regresión de Poisson con varianza robusta.

**Resultados:** la prevalencia de la sarcopenia en los ancianos fue de 72,2% y esta condición se asocia con el sexo masculino (RP = 1,33; IC del 95% = 1,08-1,65), la delgadez (RP = 1,29; IC del 95 % = 1,16-1,43) y la obesidad (RP = 0,37; IC del 95% = 0,23-0,61).

**Conclusión:** la prevalencia de la sarcopenia fue alta entre los ancianos que viven en instituciones de larga duración, especialmente entre los hombres. Los ancianos con delgadez mostraron un mayor deterioro en las reservas musculares, mientras que los obesos mostraban una mayor protección muscular.

**Palabras clave:**

Sarcopenia. Anciano. Institucionalización.

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## INTRODUCTION

Sarcopenia is a complex and serious geriatric syndrome in the life of the elderly triggering functional impairment and increasing the risk of falls, fractures and dependence. It has the potential to reduce quality of life leading to higher spending on health and increased mortality (1,2). Its prevalence can reach 5-13% in the elderly between 60-70 years and 11-50% in those over 80 years old depending on the criteria used for diagnosis (1). In Brazil in 2006, a prevalence of 15.4% was found among the elderly population living in São Paulo (3).

Currently sarcopenia can be diagnosed taking into account the reduction of muscle mass and function including the evaluation of strength and physical fitness (1,4). However, some studies have shown that the isolated use of the skeletal muscle mass (SMM) is an appropriate parameter in the identification of sarcopenia (5-8).

The evaluation of SMM can be carried out using methods such as computerized tomography, magnetic resonance imaging and dual-energy X-ray absorptiometry (2). However, the high cost and the use of radiation in such methods have limited their applicability in clinical practice (9). Therefore, bioelectrical impedance is increasingly used to evaluate sarcopenia due to its low cost, ease of use and absence of radiation as well as being a method that has been validated for the diagnosis of this syndrome (10). Given the consequences of sarcopenia and lack of research in the Brazilian population, especially those who are institutionalized, this study assesses the prevalence and factors associated with sarcopenia in long-term care facilities (LTCF) in the city of Salvador Bahia, Brazil.

## METHODS

### STUDY DESIGN

This cross-sectional study is part of a larger project entitled "Multidimensional evaluation of the elderly living in long-term care facilities in Salvador, Bahia", developed by the Aging-Related Research and Intervention Center (CEIAE) at the Nutrition School the Federal University of Bahia (ENUFBA).

### SAMPLE

The sample of the larger study was performed in three stages. In the first stage, was identified a total of 29 LTCFs which were located in 10 Health Districts of the 12 existing in the urban area. In the second stage, the number of elderly subjects by Health District that would participate in the study was determined. This number was proportional to the total elderly population living in each Health District, thus ensuring 80% power in representing the institutionalized elderly of the city. At a significance level of 5%, this number totaled 412 elderly subjects of both genders. In the third stage, LTCFs and elderly subjects were selected by simple random sampling. The final sample information available bioelectrical impedance and anthropometric measures was 216 elderly evaluated.

### ELIGIBILITY CRITERIA

Those eligible to participate in the study were individuals of both sexes, aged over 60 years living in LTCF (public, philanthropic and private) located in the urban area of Salvador and who agreed to participate in the research.

Non-eligibility criteria for the examination of bioelectrical impedance were: limb amputation, presence of edema and/or ascites, cardiac defibrillator or pacemaker use and inability of weight measurement (11). Those who were unable to move and/or position themselves for gauging the anthropometric measures did not participate.

### DATA COLLECTION

Data collection took place from November 2012 to October 2013 by a multidisciplinary team who had been previously trained to use standardized techniques.

### VARIABLES

#### Outcome

Sarcopenia was identified according to the SMI (SMM (kg) / height ($m^2$) (6). The whole body SMM was estimated using the equation proposed by Janssen et al. (10) where SMM (kg) = [(height in centimeters$^2$/resistance of the bioelectrical impedance in ohms × 0.401) + (sex × 3.825) + (-0.071 × age in years)] + 5,102. For this calculation, the values considered were 1 and 0 for male and female, respectively.

The resistance measurement was carried out by a tetrapolar body composition analyzer Biodynamics (BF-450 model). The pretest care protocol used was that proposed by Kyle et al. (11): fasting for at least four hours prior to emptying of the bladder, alcohol abstention for 48 hours before the test and no intensive physical activity in the last eight hours.

SMI was classified by the following cut-off points proposed by Janssen et al. (6): severe sarcopenia ≤ 8.5 kg/m², moderate sarcopenia 8.51-10.75 kg/m², normal muscle ≥ 10.76 kg/m² for men and severe sarcopenia ≤ 5.75 kg/m², moderate sarcopenia 5.76- 6.75 kg/m², normal muscle ≥ 6.76 kg/m² for women.

#### Covariates

Covariates measured were sex, age, time at the institutionalization, type of institution, body mass index (BMI) and functional capacity.

The BMI was classified according to the Nutrition Screening Initiative (12). Weight and height were obtained according to standards established by Jellife (13).

For the assessment of functional capacity the 'Activities of Daily Living' scale proposed by Mahoney and Barthel (14) was used and the cutoff points proposed by Azeredo and Matos (15) were adopted.

## STATISTICAL ANALYSIS

The Kolmogorov-Smirnov test was used to analyze the data normality. Descriptive statistics were used (mean, standard deviation, median, interquartile range and percentile values), the Mann-Whitney tests, t student and Chi square Pearson test.

To investigate the relationship between sarcopenia and covariates, we used the Poisson regression model with robust variance, estimating the prevalence ratios and their respective confidence intervals at 95%. We opted for the multilevel modeling because of a possible clustering effect relating to the aggregation of individuals in institutions. Regression models were constructed by stepwise backward.

A 5% significance level was adopted for all analyses, which were carried out with the aid of the software STATA version 10.0 (STATA Corp, College Station, TX).

## ETHICAL ASPECTS

This project was approved by the Ethics Committee at ENUFBA (protocol number 11/2012). Prior authorization was sought from the LTCF and the elderly participants gave their informed consent using a signature or fingerprint. At the end of the study, the results from the evaluations were presented to the LTCFs in a report.

## RESULTS

The population characteristics are shown in table I. It can be observed in table II that the average values of SMM and SMI were higher for males in all age groups. Comparing gender and age group, the average values of the SMI and SMM were lower in women who were 80 and older and men aged between 70 and 79 years. It is noteworthy that 75% of elderly men of all the age groups analyzed had some degree of sarcopenia (SMI < 10.76 kg/m²) (Table II).

Most of the elderly people presented sarcopenia (72.2%) with the highest percentages observed among men (87.7%), in elderly people 60-69 years (77.3%), those who had been institutionalized for one to five years (75.8%). Those who resided in philanthropic LTCF (76.4%) showed thinness (92.4%) and moderate dependence (89%). Sarcopenia was associated only with sex (p = 0.006) and BMI (p < 0.001) (Table III).

The gross prevalence ratio also showed a statistically significant association between sarcopenia and BMI with a prevalence of sarcopenia which was 28% higher among elderly people with thinness (PR = 1.28, 95% CI: 1.14 to 1.43) compared to normal and 31% higher in men (PR = 1.31, 95% CI: 1.08 to 1.60) when compared to women. For these elderly people overweight and obesity were demonstrated to be sarcopenia protection factors (Table III).

In table IV multivariate Poisson model can be seen. This considers the possible cluster effect due to the aggregation of the elderly in LTCF. In model 1, adjusted for all variables, only males (PR = 1.34, 95% CI: 1.10 to 1.65), thinness (PR = 1.38, 95% CI: 1.19 to 1 60) and obesity (PR = 0.38, 95% CI: 0.20 to 0.73) were significantly associated with sarcopenia.

In model 2, the same variables remained significantly associated with sarcopenia, adjusted for other variables in the model, with prevalences of 33% and 29% higher from sarcopenia, respectively, in the men (OR = 1.33, 95% CI: 1 , 08 to 1.65) compared to females, and thinness (PR = 1.29, 95% CI: 1.16 to 1.43) compared to normal weight. On the other hand, obese elderly people had a 63 % lower prevalence of sarcopenia (PR = 0.37, 95% CI: 0.23 to 0.61) compared to those with adequate nutritional status, revealing obesity to be a protective factor for sarcopenia.

**Table I.** Characteristics of institutionalized elderly according to sex. Salvador Bahia

| Variables | Female (n = 159) | Male (n = 57) | p-value* |
|---|---|---|---|
| Age (years) | 81.68 (8.40) | 72.35 (8.86) | < 0.0001 |
| Weight (kg) | 54.7 (45.8-64.9) | 61.5 (54.2-73.9) | 0.0001 |
| Height (m) | 1.53 (1.49-1.57) | 1.67 (1.63-1.70) | < 0.0001 |
| Length of institutionalization (years) | 6.42 (8.85) | 4.23 (8.76) | 0.1197 |
| SMI (kg/m²) | 6.24 (5.59-7.04) | 8.64 (8.09-9.73) | < 0.0001 |
| SMM (kg) | 15.16 (3.33) | 25. 19 (4.65) | < 0,0001 |
| BMI (kg/m²) | 23.78 (5.19) | 22.82 (4.06) | 0.2108 |
| Score in the Barthel Scale | 95 (70-100) | 95 (85-100) | 0.5719 |

*SMI: Skeletal muscle index; SMM: Skeletal muscle mass; BMI: Body mass index. Weight (kg), height (m), SMI (kg/m²) and the Barthel Scale Score are expressed as median (interquartile range). The other variables are expressed as mean (standard deviation). *Mann-Whitney test and t student test.*

**Table II.** Mean values, standard deviations, percentiles of the SMM and SMI of institutionalized elderly according to sex and age group. Salvador Bahia

| Variables | | | | Percentil | | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | n | 10 | 25 | 50 | 75 | 90 |
| *SMM (kg)* | | | | | | | | |
| *Female* | | | | | | | | |
| 60-69 years | 16.68 | 3.39 | 18 | 12.95 | 14.67 | 16.41 | 18.60 | 20.97 |
| 70-79 years | 16.82 | 2.86 | 34 | 13.69 | 14.54 | 16.32 | 18.88 | 20.68 |
| ≥ 80 years | 14.39 | 3.21 | 107 | 11.03 | 12.15 | 14.06 | 15.93 | 18.21 |
| *Male* | | | | | | | | |
| 60-69 years | 25.49 | 5.42 | 26 | 20.57 | 21.31 | 24.31 | 26.63 | 32.24 |
| 70-79 years | 24.71 | 4.17 | 17 | 20.32 | 21.34 | 23.84 | 25.58 | 30.99 |
| ≥ 80 years | 25.23 | 3.84 | 14 | 20.57 | 21.29 | 25.01 | 28.77 | 39.61 |
| *SMI (kg/m$^2$)* | | | | | | | | |
| *Female* | | | | | | | | |
| 60-69 anos | 6.65 | 1.11 | 18 | 5.38 | 5.84 | 6.47 | 7.21 | 8.17 |
| 70-79 years | 6.95 | 1.03 | 34 | 5.77 | 6.12 | 6.81 | 7.75 | 8.05 |
| ≥ 80 years | 6.24 | 1.18 | 107 | 4.88 | 5.43 | 6.12 | 6.86 | 7.77 |
| *Male* | | | | | | | | |
| 60-69 years | 8.91 | 1.44 | 26 | 7.62 | 8.09 | 8.66 | 9.05 | 10.41 |
| 70-79 years | 8.83 | 1.23 | 17 | 7.62 | 7.86 | 8.56 | 9.70 | 10.91 |
| ≥ 80 years | 9.07 | 1.40 | 14 | 7.30 | 8.25 | 8.78 | 10.09 | 10.99 |

*SD: standard deviation; SMM: skeletal muscle mass; SMI: skeletal muscle index.*

## DISCUSSION

The prevalence of sarcopenia in this population was high (72.2%) and higher than that found in studies of institutionalized elderly in other countries (16,17). This is probably a result of the different methods used in the studies and the different living conditions of such populations.

This result highlights the vulnerability of the elderly because sarcopenia can affect the quality of life, functional capacity, health and morbidity of this population (2).

More than half of the elderly men of all age groups showed SMI values below the recommended, or had some degree of sarcopenia. The findings of a higher prevalence of sarcopenia in men (87.7%), corroborate those of other studies with institutionalized elderly (18,19). Bahat et al. (18) who investigated elderly men in LTCF in Turkey reported a prevalence similar to that found in our study (85%).

Although the present study did not find an association between sarcopenia and type of institution, the high prevalence of sarcopenia found in philanthropic institutions justifies more research on the impact of the characteristics of these LTCF on the nutritional status of the elderly. The work of Camarano et al. (20) shows that most of the expenses of running Brazilian LTCF are on staff costs (52.5%) and only 14.1% is spent on food. Perhaps this is one reason for the impairment of the nutritional status these elderly people.

Malnutrition implies loss of muscle and fat and this is a major problem in the institutionalized elderly population (21) and this may explain the higher prevalence of sarcopenia found in the elderly with thinness in this study. Similar results have been found by other authors (16,17,22). On the other hand, the protective effect of obesity for sarcopenia, despite being considered a risk factor for comorbidities in the case of the elderly, has been linked to a lower risk of death, complications during hospitalization and the development of sarcopenia (8,23).

Physical inactivity, insulin resistance, chronic diseases, hormonal changes, inflammation and nutritional deficiencies (protein, calories, vitamin D and antioxidants) stand out as major causes of sarcopenia in the elderly (24). Therefore, better research on these factors may help to understand this reality.

The severity of the clinical and nutritional status, and functional impairment made it impossible to gauge the weight of many elderly people living in the LTCF investigated and that may have caused an underestimation of the prevalence of sarcopenia found. Although SMI has been used for the diagnosis of sarcopenia in this study, further research is required into the sensitivity of the isolated use of this index for this purpose.

**Table III.** Prevalence, gross prevalence ratio and confidence intervals at 95% for association between sarcopenia and covariates in institutionalized elderly in Salvador Bahia

| Covariables | n /N | % | PR† | 95% CI | p-value |
|---|---|---|---|---|---|
| *Sex** | | | | | |
| Female | 106/159 | 66.7 | 1 | - | - |
| Male | 50/57 | 87.7 | 1.31 | 1.08-1.60 | 0.006 |
| *Age group* | | | | | |
| 60-69 years | 34/44 | 77.3 | 1 | - | - |
| 70-79 years | 31/51 | 60.8 | 0.78 | 0.60-1.02 | 0.076 |
| ≥ 80 years | 91/121 | 75.2 | 0.97 | 0.82-1.15 | 0.756 |
| *Length of institutionalization* | | | | | |
| < 1.0 year | 36/52 | 69.2 | 1 | - | - |
| 1.0-5.0 year (s) | 72/95 | 75.8 | 1.09 | 0.87-1.36 | 0.421 |
| 5.1-10.0 years | 21/28 | 75 | 1.08 | 0.81-1.44 | 0.589 |
| > 10.0 years | 21/33 | 63.6 | 0.91 | 0.76-1.11 | 0.385 |
| *Type of institution* | | | | | |
| Private | 81/115 | 70.4 | 1 | - | - |
| Public | 20/29 | 69 | 0.97 | 0.87-1.09 | 0.703 |
| Philanthropic | 55/72 | 76.4 | 1.08 | 0.89-1.31 | 0.409 |
| *BMI** | | | | | |
| Eutrophic | 58/80 | 72.5 | 1 | - | - |
| Thinness | 79/85 | 92.4 | 1.28 | 1.14-1.43 | 0.000 |
| Overweight | 13/28 | 46.4 | 0.64 | 0.41-0.99 | 0.049 |
| Obesity | 6/23 | 26.1 | 0.35 | 0.22-0.56 | 0.000 |
| *Functional capacity* | | | | | |
| Independence | 40/58 | 69 | 1 | - | - |
| Mild dependence | 36/45 | 80 | 1.16 | 0.96-1.39 | 0.118 |
| Moderate dependence | 40/52 | 89 | 1.11 | 0.84-1.46 | 0.432 |
| Severe dependence | 21/31 | 67.7 | 0.98 | 0.72-1.33 | 0.908 |
| Total dependence | 7/10 | 70 | 1.01 | 0.60-1.70 | 0.955 |

*PR: prevalence ratio; CI: confidence interval; BMI: body mass index. *Statistically significant association by the Chi-square test (gender: p-value = 0.002; BMI: p-value = 0.001). †Poisson regression model with gross prevalence ratio for association between sarcopenia and other variables.*

## CONCLUSION

The prevalence of sarcopenia was high among elderly residents in LTCF, especially among males. Elderly people with thinness showed greater impairment of their muscle reserves while obesity was shown to be a protective factor for the development of sarcopenia.

**Table IV.** Poisson regression model with adjusted prevalence ratio for association between sarcopenia and covariates in institutionalized elderly. Salvador Bahia

| | Model 1 | | Model 2 | |
|---|---|---|---|---|
| **Covariables** | **$PR_{aj}$** | **95% CI** | **$PR_{aj}$** | **95% CI** |
| *Sex* | | | | |
| Female | 1 | - | - | - |
| Male | 1.34 | 1.10-1.65 | 1.33 | 1.08-1.65 |
| *Age group* | | | | |
| 60-69 years | 1 | - | - | - |
| 70-79 years | 0.99 | 0.80-1.23 | 0.91 | 0.75-1.11 |
| ≥ 80 years | 1.19 | 0.99-1.42 | 1.17 | 0.98-1.40 |
| *Length of institutionalization* | | | | |
| < 1.0 year | 1 | - | - | - |
| 1.0-5.0 year (s) | 1.10 | 0.89-1.36 | - | - |
| 5.1-10.0 years | 0.95 | 0.79-1.13 | - | - |
| > 10.0 years | 1.10 | 0.92-1.31 | - | - |
| *Type of institution* | | | | |
| Private | 1 | - | - | - |
| Public | 0.94 | 0.82-1.09 | - | - |
| Philanthropic | 1.02 | 0.90-1.15 | - | - |
| *BMI* | | | | |
| Eutrophic | 1 | - | 1 | - |
| Thinness | 1.38 | 1.19-1.60 | 1.29 | 1.16-1.43 |
| Overweight | 0.72 | 0.50-1.03 | 0.67 | 0.45-1.00 |
| Obesity | 0.38 | 0.20-0.73 | 0.37 | 0.23-0.61 |
| *Functional capacity* | | | | |
| Independence | 1 | - | - | - |
| Mild dependence | 1.02 | 0.86-1.20 | - | - |
| Moderate dependence | 1.00 | 0.77-1.30 | - | - |
| Severe dependence | 0.84 | 0.60-1.19 | - | - |
| Total dependence | 0.89 | 0.59-1.33 | - | - |

*$PR_{aj}$: adjusted prevalence ratio; CI: confidence interval; BMI: body mass index. Model 1: adjusted by gender, age, length of institutionalization, type of institution, BMI and functional capacity. Model 2: adjusted by gender, age and BMI.*

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Nutrición Hospitalaria

Trabajo Original

Nutrición en el anciano

# Influencia del aceite de coco en enfermos de alzhéimer a nivel cognitivo

*How does coconut oil affect cognitive performance in alzheimer patients?*

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## Resumen

**Introducción:** la enfermedad de Alzheimer es a día de hoy la demencia neurodegenerativa con mayor prevalencia en el primer mundo. Este hecho, unido a la falta de tratamiento farmacológico que cure la enfermedad, hace que se estudien nuevas estrategias terapéuticas no farmacológicas como es la administración de nutrientes. En este sentido, destaca la posible influencia del aceite de coco como fuente energética alternativa, capaz de frenar la muerte neuronal que se produce de modo progresivo en esta enfermedad.

**Objetivos:** valorar el impacto del aceite de coco a nivel cognitivo en pacientes de alzhéimer, y concretamente en las áreas de orientación, lenguaje-construcción, fijación, cálculo-concentración y memoria.

**Métodos:** estudio prospectivo, longitudinal, cualitativo, analítico y experimental a través de un ensayo clínico, donde se seleccionaron a 44 pacientes con alzhéimer de la zona de la Ribera (Comunidad Valenciana), de los cuales a la mitad se le administró durante 21 días, 40 ml diarios de aceite de coco repartidos entre desayuno (20 ml) y comida (20 ml). Antes y después de la administración del aceite, se les valoró a través del test cognitivo Mini-Examen Cognoscitivo, para determinar los posibles cambios.

**Resultados:** en los enfermos que tomaron el aceite de coco se observó una mejora cognitiva tras finalizar la intervención, siendo estadísticamente significativa en las áreas de orientación y lenguaje-construcción.

**Conclusiones:** el aceite de coco parece mejorar la capacidad cognitiva de los enfermos de alzhéimer, variando la intensidad de la misma en función del área cognitiva.

**Palabras clave:**

Enfermedad de Alzhéimer. Triglicéridos. Aceite de coco. Cuerpos cetónicos.

## Abstract

**Introduction:** Alzheimer's disease is one of the most prevalent neurodegenerative dementia in developed world. This fact, coupled with the lack cure, makes new no pharmacological therapeutic strategies such as nutrient management to investigate. In this regard, it stresses the possible influence of coconut oil as alternative energy source capable of stopping the progressively neuronal death that occurs in this disease.

**Objectives:** To assess the cognitive impact of coconut oil in Alzheimer's patients, and specifically in orientation, language-building, fixing, calculation-concentration and memory areas.

**Methods:** Prospective, longitudinal, qualitative, analytical and experimental study through a clinical trial where 44 patients with Alzheimer's in region of Ribera (Valencia), of which half was selected to receive during 21 days, 40 ml coconut oil daily divided between breakfast (20 ml) and food (20 ml). Before and after administration of the oil, they were evaluated through cognitive test Mini-Mental State Examination to determine possible changes.

**Results:** It was observed in patients who received coconut oil, that cognitive improvement after completion of the intervention, statistically significant improved in the orientation and language-construction areas.

**Conclusions:** Coconut oil appears to improve cognitive abilities of Alzheimer's patients, with different intensity depending on the cognitive area.

**Key words:**

Alzheimer's disease. Triglycerides. Coconut oil. Ketone bodies.

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## INTRODUCCIÓN

Según la Organización Mundial de la Salud (OMS) la demencia afecta a unos 47,5 millones de personas en todo el mundo. Cada año se registran 7,7 millones de nuevos casos, por lo que se prevé que el número total de personas con demencia pase de 75,6 millones en 2030 a 135,5 millones en 2050 (1). De entre todas las demencias, la enfermedad de Alzheimer (EA) es la más frecuente (2) representando entre un 60% y un 70% de los casos (3). Se trata de una entidad clínico-patológica de naturaleza degenerativa, de inicio insidioso y evolución progresiva, crónica e irreversible que se caracteriza clínicamente por deterioro cognitivo (DC) y demencia, y neuropatológicamente por la presencia de ovillos neurofibrilares y placas neuríticas (2).

En cuanto al deterioro cognitivo, este se expresa a través de síntomas bien definidos. En etapas iniciales existe un trastorno de la memoria episódica anterógrada de inicio insidioso y de curso progresivo y también se observa afectada la memoria de trabajo (*working memory*), basada en la capacidad de mantener temporalmente la información en la mente para poder trabajar con ella, que se va a manifestar en las actividades de la vida diaria, tales como el cálculo simple y la resolución de problemas (4). También se observa una afectación gradual de la orientación, alterándose inicialmente la temporal, después la espacial y finalmente la personal (5). Asimismo se aprecia en la función lingüística, una afectación semántica, expresada como una dificultad en la evocación de palabras y alteración de la denominación (6). Y a medida que avanza la neurodegeneración en la corteza cerebral van a detectarse diferentes síntomas como déficits en las capacidades práxicas visoconstructivas (incapacidad de reproducir construcciones con bloques o dibujos), agnosia visual y disfunción ejecutiva (7).

La etiología del alzhéimer es heterogénea y compleja, manejándose diferentes causas. Inicialmente se apuntó la falta del neurotransmisor acetilcolina (8,9), y la causa genética (10-13). A estas dos habría que sumarle la fuerte influencia en el inicio y desarrollo de la enfermedad que tiene por una parte la acumulación de placas de proteínas beta-amiloide, y por otra la hiperfosforilación de la proteína tau, en el cerebro del paciente de alzhéimer (14,15). Y finalmente, otra alternativa etiológica que se presenta en prácticamente todas las demencias es la de los desórdenes metabólicos, especialmente los relacionados con la resistencia a la insulina a nivel cerebral (16), que impide la correcta utilización de la glucosa por parte de las neuronas, que por tanto mueren. En este sentido, los triglicéridos de cadena mediana (TGCM) formados por ácidos grasos saturados de cadena media (AGCM) como ácido capróico, ácido caprílico, ácido cáprico y ácido laúrico (17), parecen una buena estrategia terapéutica como fuente de energía alternativa a la glucosa ya que son los que más rápidamente se metabolizan y en mayor cantidad (18-20), dando lugar a cuerpos cetónicos que han mostrado beneficios en pacientes con alzhéimer en los diferentes grados de demencia, mejorando especialmente los más graves (21). En relación a esto se considera que el aceite de coco es el nutriente con mayor cantidad de TGCM, ya que en su composición, aproximadamente el 90%, son grasas saturadas, siendo la mayoría de ellas de cadena media. Dentro de estas, el ácido laúrico es el más presente (aproximadamente 45%) aunque también encontramos ácido palmítico, esteárico, mirístico y oléico en menores proporciones (22).

De este modo la ingesta de aceite de coco, puede ser una alternativa muy importante a la terapia con fármacos (23), y de gran seguridad para el paciente por la ausencia de efectos secundarios.

El objetivo del estudio es profundizar sobre la influencia de los TGCM en la EA a nivel cognitivo, analizando los posibles cambios en las áreas de la orientación, memoria, calculo-concentración, lenguaje-construcción y fijación.

## MATERIAL Y MÉTODOS

### DISEÑO DEL ESTUDIO

El diseño se basó en un estudio prospectivo, longitudinal, cualitativo, analítico y experimental.

Para obtener la población muestral, los criterios de inclusión que se aplicaron fueron: pacientes de alzhéimer de entre 65 y 85 años, institucionalizados en centros de la Asociación de Familiares y Amigos del Alzheimer (AFA) localizadas en la Comunidad Valenciana. Mientras que los de exclusión fueron: pacientes con una edad menor de 65 años o mayor de 85 años, que no estuvieran institucionalizados en estas asociaciones, que presentaran otro tipo de deterioro cognitivo, o que tuvieran discapacidad verbal por lo que no pudieran responder a los ítems del cuestionario. Tras aplicar estos criterios de selección se obtuvo una población de 44 pacientes que fueron divididos en dos grupos de 22 enfermos cada uno. Estos dos grupos se obtuvieron aplicando aleatorización estratificada equilibrada (estratos por grado de demencia) mediante el selector de casos del SPSS, siendo homogéneos en cuanto a media de edad, medicación recibida y porcentaje de los diferentes grados de demencia (5 enfermos leves, 3 moderados, y 14 graves, en cada grupo).

El grupo que recibió el aceite de coco virgen extra durante 21 días consecutivos fue el grupo experimental. La administración del aceite de coco la llevaron a cabo trabajadores de los centros, mediante jeringa milimetrada y directamente a la boca. El otro grupo se denominó grupo control, y durante esos 21 días mantuvieron la misma pauta alimentaria que el grupo experimental, pero sin la administración de aceite de cualquier tipo. Por tanto para este estudio no se empleó grupo placebo.

Antes de la intervención, todos los enfermos participantes del estudio fueron valorados cognitivamente a nivel individual mediante el test Mini-Examen Cognoscitivo (MEC-Lobo) (24) que es una traducción validada al español del Mini-Mental State Examination (MMSE) (25). Se trata de un test sencillo, rápido y muy fácil de administrar, empleado habitualmente para la detección del deterioro cognitivo (4), que valora la situación mental a través de la medida de distintas áreas (orientación, calculo-concentración, fijación, memoria, lenguaje-construcción).

Esta valoración la realizaron los mismos trabajadores del centro que administraron el producto, asesorados y apoyados por miembros cualificados de nuestro grupo de investigación. La valoración

se realizó a su vez, en un clima de relax, y con el paciente en sedestación. Tras la intervención, se llevó a cabo nuevamente la misma valoración cognitiva, siguiendo el proceso descrito anteriormente, a la misma hora, el mismo día de la semana, y repitiendo el mismo evaluador para cada enfermo.

## TRATAMIENTO ESTADÍSTICO DE LOS DATOS

Una vez obtenidos los resultados, estos fueron adecuadamente registrados en bases de datos. A continuación se les aplicó el tratamiento estadístico que consistió en un contraste de hipótesis, valorándose las diferencias observadas antes y después de la intervención, para lo cual se aplicó el programa SPSS 24, EPIDAT vs.4.1.

Para este análisis se asumió la misma desviación típica en las dos poblaciones, y se utilizó la diferencia estandarizada de medias obteniendo un $\delta = 0,632$ que está dentro de los valores de oscilación (donde el coeficiente de la razón entre las muestras fue 1). A partir de este modelo, se realizó el cálculo del valor de significación y de potencia, obteniendo que con confianza al 90% y potencial entre el 60%-70%, se validó el objetivo principal del estudio. Se ha realizado la prueba U de Mann-Whitney para el cálculo de la significación para $\alpha = 0,05$.

## CONSIDERACIONES ÉTICAS

Todos los participantes en el estudio fueron informados detalladamente de las bases de la investigación, tanto en las reuniones previas que se mantuvo con ellos y los representantes legales, como por escrito a partir de la hoja de información al paciente y consentimiento informado. Por otro lado, el estudio se llevó a cabo cumpliendo en todo momento con lo que promulga la Declaración de Helsinki (1975) y el informe Belmont (1983), previa aprobación del protocolo empleado, por el Comité de Investigación en Humanos de la Comisión de Ética en Investigación Experimental de la Universidad de Valencia.

**Tabla I.** Análisis descriptivo de la muestra (n = 44)

| Variable | Recuento |
|---|---|
| Edad (años). Media (DE) | 79.32 (4,47) |
| Sexo femenino, n (%) | 36 (81,82%) |
| *Estadio de demencia previo* | |
| *Boderline*, n (%) | 2 (4,55%) |
| Leve, n (%) | 8 (18,18%) |
| Moderado, n (%) | 6 (13,64%) |
| Grave, n (%) | 28 (63,64%) |

*n: muestra; DE: desviación típica.*

## RESULTADOS

Los 44 pacientes seleccionados presentaron una media de edad de 79,18 años, con una desviación típica de ± 4,546 años, siendo el 81,82% mujeres. El estadio de alzhéimer más prevalente fue el grave con un 63,64% (Tabla I).

Una vez obtenidos los resultados de las puntuaciones globales del test en los dos grupos de estudio, estos se dividieron según las áreas de funciones cognitivas valoradas en el test MEC-Lobo: orientación, calculo-concentración, fijación, memoria y lenguaje-construcción (Tabla II) pudiéndose observar que tras la terapia las funciones

**Tabla II.** Evolución de las funciones cognitivas a través del test MEC-LOBO antes y después de la intervención

| | Función (MAX) | Inicio estudio | | Fin estudio | | Diferencia | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Media | (DE) | Media | (DE) | Media | (DE) | I.C. (90%) | % Mejora | p |
| Grupo experimental | Orientación (10) | 2,36 | (2,42) | 3,90 | (2,58) | 1,55 | (1,22) | [1,10;1,98] | 65,38 | 0,000 |
| | Cálculo-concentración (8) | 1,36 | (1,43) | 2,05 | (2,61) | 0,32 | (1,32) | [-0,16;0,80] | 50,00 | 0,961 |
| | Fijación (3) | 2,27 | (1,16) | 2,59 | (0,80) | 0,68 | (2,15) | [-0,11;1,47] | 14,00 | 0,067 |
| | Memoria (3) | 0,18 | (0,59) | 0,23 | (0,69) | 0,05 | (0,58) | [-0,16;0,26] | 25,00 | 0,312 |
| | Lenguaje-construcción (11) | 5,43 | (2,83) | 7,05 | (2,80) | 1,62 | (1,89) | [0,93;2,31] | 29,77 | 0,003 |
| | Total (22) | 11,61 | (6,85) | 16,13 | (7,59) | 4,25 | (3,26) | [3,05;4,45] | 38,92 | 0,000 |
| Grupo control | Orientación (10) | 2,77 | (2,20) | 2,77 | (2,50) | 0,00 | (1,15) | [-0,42;0,42] | 0,00 | 0,000 |
| | Cálculo-concentración (8) | 1,23 | (2,00) | 1,59 | (2,17) | 0,36 | (2,04) | [-0,38;1,10] | 29,63 | 0,961 |
| | Fijación (3) | 2,14 | (1,36) | 1,82 | (1,26) | -0,32 | (0,84) | [-0,62;-0,01] | -14,89 | 0,067 |
| | Memoria (3) | 0,14 | (0,35) | 0,14 | (0,35) | 0,00 | (0,44) | [-0,16;0,16] | 0,00 | 0,312 |
| | Lenguaje-construcción (11) | 5,25 | (3,42) | 5,12 | (2,65) | -0,13 | (1,44) | [-0,66;0,40] | -2,42 | 0,003 |
| | Total (22) | 11,42 | (7,39) | 11,56 | (7,12) | 0,05 | (2,07) | [-0,71;0,81] | 1,22 | 0,000 |

*DE: desviación típica.*

orientación y lenguaje-construcción mejoran significativamente, y en las áreas cálculo-concentración, fijación y memoria la tendencia también es de mejora aunque no estadísticamente significativa.

## DISCUSIÓN

Una vez analizados los resultados obtenidos tras ingestaw de aceite de coco, estos están en la línea de los obtenidos por otros estudios en los que se observó el beneficio cognitivo tras administración de ácido caprílico, determinado tras entrevista con los enfermos utilizando los tests MoCA y MMSE (26,16). Sin embargo, hasta ahora se desconocía la influencia real en cada una de las funciones cognitivas, ya que la mejora cognitiva descrita es más bien a nivel global. Es por este motivo que en este estudio nos planteamos la posibilidad de profundizar sobre los beneficios que puede tener este producto en las zonas de la corteza cerebral de las que dependen las diferentes capacidades agrupadas en las áreas de la orientación, memoria, calculo-concentración, lenguaje-construcción y fijación, desglosando para ello las puntuaciones del test para cada una de esas áreas. En este sentido, a los pacientes con deterioro cognitivo de diferente naturaleza, se les aplica el test MEC como una prueba de cribaje, y a continuación se les realizan otros test más exhaustivos, que sin embargo pueden resultar demasiado largos o complejos para éste tipo de enfermos, especialmente si la patología se encuentra en estadios avanzados. Por el contrario en nuestro estudio, de un modo muy sencillo, dada la brevedad del cuestionario, se obtiene unos valores que a continuación se desglosan para obtener una valoración inicial de las áreas que más mejoran.

Tras administrar el aceite durante 21 días se pudieron observar los buenos resultados obtenidos de los ítems del test utilizado comparados con los resultados registrados en los pacientes a los que no se les administraba el producto, corroborando los beneficios del aceite de coco a nivel cognitivo. Concretamente se puede ver una mejoría estadísticamente significativa en la puntuación sobre orientación y lenguaje-construcción, quizá por un aumento del metabolismo a partir de una mayor utilización de la energía obtenida de los cuerpos cetónicos en las diferentes zonas corticales de_las que dependen (27), o por una mejora en la resistencia a la insulina de las mismas (16). Sin embargo, las funciones de fijación, memoria y cálculo no han experimentado una mejora significativa, aunque sí hay un aumento de la puntuación, pudiendo hablar de una tendencia a la mejora; esto puede ser debido a que se consiga un aumento metabólico en las áreas cerebrales de las que dependen dichas funciones (lóbulos témporo-parietales) o una mejor utilización de la insulina, aunque por razones anatómicas no sean tan eficaces, lo que determine una mejora menos intensa.

En relación a esto, y observando la heterogeneidad de los resultados obtenidos en las diferentes funciones cognitivas analizadas, esta se podría relacionar con el propio proceso fisiopatológico de la EA y las regiones neuroanatómicas que más sufren las consecuencias de la enfermedad. En este sentido respecto al lenguaje, que se considera la función menos afectada por el envejecimiento normal, se consigue una gran mejoría con la intervención, mientras que las funciones de la memoria y la fijación, relacionadas con estructuras como la zona adyacente al tercer ventrículo que se ven prematuramente afectas por las placas amiloides y ovillos neurofibrilares, y la función del cálculo-concentración procesada en las cortezas de los lóbulos temporales y frontal (28), son las que menos mejoran. Esto podría indicarnos que quizás las zonas más dañadas directamente por la propia fisiopatología de la enfermedad, son también las más difíciles de recuperar con la terapia.

Sin embargo, completando este razonamiento que trata de explicar los resultados obtenidos, cabe destacar que ninguna parte del cerebro puede funcionar aislada del resto, pues todas contribuyen en diferente medida y con distintos procesos a que las demás trabajen correctamente. El nuevo paradigma del funcionamiento cerebral está basado en la existencia de las redes corticales que están distribuidas y dispersas por toda la corteza cerebral. Se desarrollan a través de módulos nucleares de funciones elementales, sensoriales y motoras. Una red puede servir a varias funciones cognitivas. Las funciones cognitivas consisten en interacciones entre estas redes. Es por ello que cuando mejora una función se puede observar una mejoría en otras muchas y, en definitiva, una mejoría cognitiva global (29,30).

Por estos motivos pensamos que hay que seguir profundizando en las variaciones que se producen a diferentes niveles cerebrales para conseguir entender a qué se deben por un lado las mejoras observadas en cada una de las funciones y, por otro, la diferencia entre estas mejorías. Además existen limitaciones en nuestro estudio, como son el tamaño muestral y el periodo de tratamiento, por lo que sería necesario profundizar sobre los resultados obtenidos a partir de una población mayor de modo que se mejore la potencia estadística de los resultados obtenidos, y a lo largo de un periodo superior al mes de intervención para valorar a largo plazo si el efecto obtenido se mantiene, aumenta o disminuye.

Para finalizar, es importante resaltar la seguridad de la toma de este nutriente, ya que a lo largo de todo el estudio, no se registró ningún acontecimiento adverso, siendo bien aceptado por todos los enfermos. Esto hace pensar que *a priori,* el tratamiento puede ser continuado en el tiempo, con periodos de intervención superiores, e incluso proponemos, viendo los prometedores resultados obtenidos, el diseño de alimentos funcionales basados en este extracto. Por otra parte, creemos que también se pueden abrir nuevas expectativas de mejora en otras demencias cuyo origen, al igual que en el caso de la EA, pueda estar vinculado a una alteración energética a nivel mitocondrial, como puede ser la enfermedad de Parkinson o esclerosis lateral amiotrófica (ELA).

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Nutrición Hospitalaria

Trabajo Original

Obesidad y síndrome metabólico

# Abdominal obesity is strongly associated to blood pressure in young Mexicans

## *La obesidad abdominal está fuertemente asociada a hipertensión arterial en jóvenes mexicanos*

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## Abstract

**Objective:** The objective of this study was to determine associations between abdominal obesity (AOb) and the other components of metabolic syndrome (MetS) in young Mexicans in a cross-sectional survey completed during a 4 year period.

**Methods:** This cross-sectional study reports on components and prevalence of MetS by using Alberti et al. (16) criteria, as well as association between AOb and elevated blood pressure (BP) of 2,993 Mexican university students, ages 17 to 25 years (66% women) from central and northern Mexico, over a 4-year survey (2010-2013).

**Results:** The most prevalent MetS components in the total sample were low HDL-C concentration (43.6%) and AOb (41.1%). MetS prevalence was 11.8%, more men than women were classified with MetS (14.3% *vs.* 10.5%, $p < 0.01$). BP was the MetS component with the lowest prevalence (8.6%). A strong association between AOb and altered BP with in both men and women was found (OR 4.3, IC95% 2.5-7.4).

**Conclusions:** Even BP was the component with the lowest prevalence, AOb was more strongly associated with it. This fact, could explain the prevalence of hypertension among young Mexican adults.

**Key words:**

Abdominal obesity.
Blood pressure.
Young adults.

## Resumen

**Objetivo:** el objetivo de este estudio fue determinar la asociación entre la obesidad abdominal (OAb) y los otros componentes del síndrome metabólico (SMet) en jóvenes mexicanos a través de una encuesta transversal completada durante un período de 4 años.

**Métodos:** este estudio transversal informa sobre los componentes y la prevalencia del SMet usando los criterios de Alberti y cols. (16), así como la asociación entre OAb y la presión arterial (PA) elevada de 2.993 estudiantes universitarios mexicanos, con edades de 17 a 25 años (66% mujeres), procedentes del centro y norte de México, a través de una encuesta de 4 años (2010-2013).

**Resultados:** los componentes del SMet de mayor prevalencia en la muestra total fueron baja concentración de HDL-C (43,6%) y OAb (41,1%). La prevalencia de SMet fue del 11,8%, mayor en hombres que en mujeres (14,3% *vs.* 10,5%; $p < 0,01$). La PA elevada fue el componente del SMet con la prevalencia más baja (8,6%). Se encontró una fuerte asociación entre OAb y PA elevada, tanto en hombres como en mujeres (OR 4,3; IC 95% 2,5 a 7,4).

**Conclusiones:** a pesar de que la PA elevada fue el componente con menor prevalencia, la OAb estuvo más fuertemente asociada con esta, hecho que podría explicar la prevalencia de hipertensión entre los adultos jóvenes mexicanos.

**Palabras clave:**

Obesidad abdominal.
Presión arterial.
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## INTRODUCTION

Metabolic syndrome (MetS) is a clustering of symptoms associated with obesity that include abdominal obesity (AOb), increased blood pressure (BP), altered glucose metabolism, and dyslipidaemia. This syndrome strongly predicts the future development of both cardiovascular disease (CVD) and diabetes (1,2).

The MetS and its individual components have been widely studied in adults (3-5), as well as in younger ages (6,7); however, association between AOb measured by waist circumference and elevated BP, has not been examined comprehensively in young university students of Mexico. Our group estimated a national wide prevalence of MetS of 15.8% in young people from Mexico (7). In this regard, young adults entering university are making their own lifestyle behaviors that could impact in their health, even in short-term (8,9). This conversion into adulthood is a good opportunity to adopt healthy lifestyle, since dietary intake and lack of physical activity can affect all MetS components. If poor lifestyle habits are adopted during this stage, young adults will likely carry them through adulthood and progress to negatively impact the individual's health status (9).

Screening young adults, especially first-year university students, regarding MetS components and related risk factors is vital to decrease the risk of future chronic diseases development. First-year university students experience faster weight gain than the average adult, up to 11 times faster (10,11).

In 2012 reports of the Mexican National Health and Nutrition Survey in young adults (20-29 y) found a prevalence of AOb of 53.3% (12), which could represent a high degree of physical inactivity. In relation to diet, a study in college students from northern Mexico reported only 13.2% of fruits and 15.6% of vegetables daily consumption (13). In addition, in 2008 the overall prevalence of risk factors for eating behaviour disorders in a Mexican university of the US-Mexico border was higher in women (8.5%) than men (3.3%) (14). Given these high rates of overweight/obesity and poor diet, young adult populations may be at risk, which is relevant to consider since an increase in body weight augments the probability of developing MetS, and consequently CVD and type 2 diabetes. Thus, risk identification early in life may support healthier and better choices, based upon personalized information during an age when lifestyle changes may be transformed into lifelong behaviours (15).

The present research includes a detailed investigation of first-year students from three universities located in central and northern Mexico.

As it is known that abdominal obesity prevalence in young Mexicans is high (53.3%) (12), and may indicate the beginning of metabolic alterations in young, the objective of this study was to determine the relative association between AOb and the other components of MetS, and the next most probable altered components given that AOb is one of the first metabolic alterations in young.

## METHODS

### DESIGN AND POPULATION

The study sample consisted of first-year Mexican university students, ages 17 to 25 years. Data were obtained by the Multidisciplinary Group to Investigate Health and Academic Performance (GMISARA), from Facultad de Estudios Superiores Iztacala, Universidad Nacional Autonoma de México (UNAM), Universidad Autonoma de la Ciudad de México (UACM), and Healthy University Program (Medical Services) from Universidad Autonoma de Ciudad Juárez (UACJ). This cross-sectional, observational study reports on MetS prevalence, and relative associations of AOb and the other MetS components of 2.993 (66% women) university students from central (n = 2,387, UNAM and n = 271, UACM from Mexico City) and northern (n = 335, UACJ from Ciudad Juárez, Chihuahua) México, over a 4-year survey (2010-2013). All first year students were invited to participate in the 'Healthy University' program, so that no inclusion neither exclusion criteria were adopted since before the study; participants were voluntary and none of the students reported any illness, and no metabolic disorders were diagnosed by a physician.

In the four surveys conducted at the 3 universities (2010, 2011, 2012 and 2013), trained personnel (physicians, biochemists and anthropometrists) conducted the interviews to assure reliable demographic, socioeconomic, and health related data. After explaining the nature, objectives and risks inherent to the study, all subjects signed an informed consent (when the student was 17 years old, authorization of his (her) parent was obtained). The protocol was approved by the Facultad de Estudios Superiores Iztacala UNAM, and UACJ ethics committees (5).

### BIOCHEMISTRY

Healthy University Medical Services (UACJ) and Grupo Diagnóstico Médico PROA, S.A. de C.V. (UNAM/UACM), internationally accredited laboratories, were responsible for sample collection, biochemical analysis and laboratory data handling. Students came to laboratory facilities, either to the UACJ, UNAM or UACM, between 7-10 AM after overnight fasting. Plasma glucose (GLU), triacylglycerol (TAG), and HDL-cholesterol (HDL-C) were assayed by automatized enzymatic-colorimetric methods.

### BLOOD PRESSURE AND ANTHROPOMETRICS

BP and anthropometric techniques have been described elsewhere (5). In brief, diastolic and systolic BP values were obtained twice, *i.e.,* after resting quietly in a sitting position for 5 min and determination of the maximum inflation level, then BP readings were obtained with a standard aneroid sphygmomanometer (Model DS44, Welch Allyn).

Anthropometric data were obtained following the Official Mexican Norm (NOM-008-SSA3-2010, Mexican Ministry of Health). All measurements were performed by trained study staff and were obtained using standard procedures: height and waist circumference (WC) were recorded to the nearest 0.1 cm using a wall stadiometer (Seca mod. 208, Mexico City), and a flexible anthropotape (Rosscraft, USA). Body weight was recorded to the nearest 0.1 kg using a digital scale (Seca 700). Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Subjects were classified as obese if BMI was ≥ 30 kg/m$^2$ and overweight if BMI was ≥ 25 and < 30 kg/m$^2$. Waist circumference was measured in supine position at the level of the umbilicus. Hip circumference was measured in standing position at the level of the greater trochanters.

## METABOLIC SYNDROME CLASSIFICATION

The updated Alberti et al. (16) criteria were used to determine MetS prevalence. The criteria included increased abdominal fat measured by WC (≥ 80 cm for women and ≥ 90 cm for men), elevated TAG (≥ 150 mg/dL), low HDL-C (< 40 mg/dL for men and < 50 mg/dL for women), elevated fasting glucose (≥ 100 mg/dL), and hypertension (≥ 130 mmHg systolic blood pressure [SBP] or ≥ 85 mmHg diastolic blood pressure [DBP]). Subjects bearing 3 or more of the components were classified with MetS (16).

## STATISTICAL ANALYSIS

Descriptive data are presented as mean ± SD and percentages. Differences in physical and biochemical characteristics between men and women students were tested by independent Student's *t* test. Fisher's exact Chi-square tests were used to analyse the prevalence of MetS in the total sample by gender and the number of MetS components present by gender. Univariate analysis by using logistic regression was employed to explain association between AOb and MetS components. Data were considered significant when $p < 0.05$. All analyses were performed using STATA software (version 11.0; Stata Corp, College Station, TX, USA).

## RESULTS

Table I shows total and gender differences in anthropometric, clinical and biochemical measures. Approximately 66% of the sample were women. The mean age and BMI of the study population were 19 years and 24.0 kg/m$^2$, respectively. Average BMI was in the normal range; however 1,059 subjects (35.6%) were either overweight or obese. Comparison by sex showed that men had a significantly greater mean BMI than women (24.3 *vs.* 23.9 kg/m$^2$, $p \leq 0.01$). Men also had a significantly greater mean elevated BP, elevated TAG, low HDL-C, and elevated GLU.

**Table I.** Anthropometric, clinical and biochemical characteristics of subjects by sex

| Variables | All | Women | Men |
|---|---|---|---|
| | 2,993 | 1,979 | 1,041 |
| Age (years old) | 19.0 ± 1.7 | 18.9 ± 1.7 | 19.1 ± 1.8 |
| Weight (kg) | 63.7 ± 14.5 | 59.8 ± 12.3 | 71.2 ± 15.3 |
| Height (cm) | 162.4 ± 8.5 | 158.1 ± 5.9 | 170.8 ± 6.4 |
| BMI (kg/m$^2$) | 24.0 ± 4.6 | 23.9 ± 4.5 | 24.3 ± 4.7 |
| Waist circumference (cm) | 81.3 ± 11.5 | 79.7 ± 10.8 | 84.5 ± 12.2 |
| Systolic blood pressure (mmHg) | 106.9 ± 12 | 103.4 ± 10.4 | 113.7 ± 12.1 |
| Diastolic blood pressure (mmHg) | 71.8 ± 8.9 | 69.8 ± 8.1 | 75.7 ± 9.1 |
| HDL-cholesterol (mg/dL) | 48.1 ± 10.1 | 49.8 ± 10.1 | 44.9 ± 9.3 |
| Triacylglycerol (mg/dL) | 107.6 ± 58.1 | 102.2 ± 50.2 | 118.2 ± 69.8 |
| Glucose (mg/dL) | 88.8 ± 9.1 | 88.2 ± 8.6 | 8.9 ± 9.8 |
| HOMA-IR | 2.3 ± 1.5 | 2.4 ± 1.6 | 2.1 ± 1.4 |
| Insulin (mg/dL) | 10.4 ± 6.7 | 10.9 ± 6.9 | 9.2 ± 6.2 |
| *BMI class (%)* | | | |
| Underweight or normal weight | 64.4% | 65.6% | 62.1% |
| Overweight | 24.9% | 25.3% | 24.1% |
| Obese | 10.7% | 9.1% | 13.8% |

*Differences between averages of women and men were statistically significant (p ≤ 0.01) for all variables.*

## METABOLIC SYNDROME PREVALENCE

The overall MetS prevalence was 11.8%. We observed more men than women classified with MetS (14.3% *vs.* 10.5%, respectively, $p < 0.01$). A total of 68.6% of the sample had at least one component for MetS. Although MetS prevalence is higher in men than in women, the percentage of healthy subjects (with none MetS component) is also higher in men than in women (40.7% *vs.* 26.7%, respectively, $p \leq 0.01$; Table II). The most prevalent MetS components in the total sample were low HDL-C concentration (43.6%) and AOb (41.1%). A greater proportion of women had low HDL-C concentration (51.5% *vs.* 28.1%, $p \leq 0.01$), and higher proportion of AOb (47.1% *vs.* 29.3%, $p \leq 0.01$).

Although the percentage of men with elevated TAG concentrations was significantly larger than in women ($p \leq 0.01$), the same was observed with elevated fasting glucose (13.8% *vs.* 8.3%, $p \leq 0.01$) and elevated BP (17.5% *vs.* 4.0%, $p \leq 0.01$).

**Table II.** Prevalence of individual components of MetS among subjects by sex

| MetS component | All | Women | Men |
|---|---|---|---|
| *Low HDL-cholesterol (%) | 43.6 | 51.5 | 28.1 |
| *Abdominal obesity (%) | 41.1 | 47.1 | 29.3 |
| *Elevated triacylglycerol (%) | 15.7 | 12.7 | 21.4 |
| *Elevated fasting glucose (%) | 10.2 | 8.3 | 13.8 |
| *Elevated blood pressure (%) | 8.6 | 4.0 | 17.5 |
| *Elevated systolic blood pressure (%) | 4.8 | 1.5 | 11.2 |
| *Elevated diastolic blood pressure (%) | 6.3 | 3.4 | 11.9 |
| *No. of MetS components* | | | |
| *None (%) | 31.4 | 26.7 | 40.7 |
| *1 (%) | 33.3 | 35.9 | 28.3 |
| *2 (%) | 23.4 | 26.9 | 16.7 |
| *3 or more (%) (MetS prevalence) | 11.8 | 10.5 | 14.3 |

*$p < 0.001$ when comparing women and men using $\chi^2$ test.*

## ABDOMINAL OBESITY ASSOCIATIONS WITH METS COMPONENTS

The magnitude of associations between AOb and the other MetS components in men and women was explored. In both, men and women AOb was significantly associated with all of the MetS components ($p \leq 0.01$); the observed association followed the magnitude order BP > TAG > HDL-C > GLU ($p \leq 0.01$) (Table III).

When examining MetS components by AOb in both men and women, we observed significant greater mean values in SBP and DBP in obese men than in non-obese (120.2 *vs.* 111.0 mm/Hg, $p \leq 0.01$ and 79.9 *vs.* 74.0 mm/Hg, $p \leq 0.01$, respectively). As expected, a lower mean value in HDL-C concentration was found in obese men when compared with non-obese (40.7 *vs.* 46.6 mg dL, $p \leq 0.01$). Mean values for glucose were grater in obese than in non-obese (92.2 *vs.* 89.0 mg/dL, $p \leq 0.01$), as well as TAG (158.7 *vs.* 101.4 mg/dL, $p \leq 0.01$) (Table IV).

The same was observed in women, SBP and DBP mean values were significantly greater in obese compared to those in non-obese (106.3 *vs.* 100.8 mm/Hg, $p \leq 0.01$ and 72.2 *vs.* 67.8 mm Hg, $p \leq 0.01$, respectively). With respect to HDL-C, lower value was observed in obese (47.4 mg/dL) than in non-obese (52.0 mg/dL, $p \leq 0.01$). Regarding glucose concentration we found significantly lower values in non-obese (87.5 mg/dL) than in obese (88.9 mg/dL, $p \leq 0.01$). Even TAG concentration was considered normal in both, obese and non-obese, these values were higher in obese.

## DISCUSSION

The main findings from this study is that a great number of Mexican university students presented unhealthy HDL-C levels and AOb, and a relatively high association of AOb with elevated BP, which could be at risk for developing chronic diseases, including type 2 diabetes and CVD (1,2,8,9). On the other hand, men have higher prevalence of MetS than women; however, the percentage of healthy men (with no MetS components) is also higher in men than in women.

According to the National Health and Nutrition Survey (ENSANUT 2012), the prevalence of overweight and obesity was 71.3%

**Table III.** Relative associations of AOb with MetS components in men and women

| MetS Component | Women | | | Men | | |
|---|---|---|---|---|---|---|
| | AOb (%) | No-AOb (%) | OR (IC 95%) | AOb (%) | No-AOb (%) | OR (IC 95%) |
| Elevated BP | 78.5 | 21.5 | 4.3 (2.5-7.4) | 62.2 | 37.9 | 5.7 (4.0-8.1) |
| Elevated TAG | 69.1 | 31.0 | 2.9 (2.1-3.8) | 57.1 | 42.9 | 4.8 (3.5-6.6) |
| Low HDL-C | 56.2 | 43.8 | 2.2 (1.8-2.6) | 47.4 | 52.6 | 3.2 (2.4-4.2) |
| Elevated GLU | 54.6 | 45.5 | 1.4 (1.0-1.9) | 43.6 | 56.4 | 2.1 (1.4-3.0) |

*AOb: abdominal obesity; BP: blood pressure; TAG: triacylglycerol; HDL-C: HDL-cholesterol; GLU: glucose. All odd ratios (OR) values were statistically significant ($p < 0.01$).*

**Table IV.** Averages of individual components of MetS by AOb in women and men

| | Women | | Men | |
|---|---|---|---|---|
| | **Obese** | **Non-obese** | **Obese** | **Non-obese** |
| n (subjects) | 932 | 1,047 | 297 | 717 |
| Systolic blood pressure (mmHg) | 106.3 ± 10.3 | 100.8 ± 9.7 | 120.2 ± 11.9 | 111.0 ± 11.1 |
| Diastolic blood pressure (mmHg) | 72.2 ± 8.1 | 67.8 ± 7.6 | 79.9 ± 9.5 | 74.0 ± 8.3 |
| Triacylglycerol (mg/dL) | 114.6 ± 59.4 | 91.2 ± 36.9 | 158.7 ± 84.9 | 101.4 ± 54.3 |
| HDL-cholesterol (mg/dL) | 47.4 ± 9.7 | 52.0 ± 10.0 | 40.7 ± 8.8 | 46.6 ± 8.9 |
| Glucose (mg/dL) | 88.9 ± 8.4 | 87.5 ± 8.8 | 92.2 ± 10.0 | 89.0 ± 9.5 |

*Data (mean ± SD) analyzed using independent samples t test to determine differences by sex. All parameters show differences ($p < 0.01$) between abdominal obese and non-obese, in women and men.*

(overweight 38.8% and obesity 32.4%) in Mexican adults, and the prevalence of abdominal adiposity was 74.0%, being higher in women (82.8%) than in men (64.5%) (12). In our study, the prevalence of overweight and obesity in young adults was 35.6%, being slightly higher in men. Total prevalence of AOb in this sample was lower compared with that found in a nationwide Mexican young adults 20-29 y (41.1% *vs.* 53.3%, respectively) (12), which is alarming since these elements are closely related to the MetS. Assuming the MetS as a multifactorial process, it is a progress between "healthy" and "not healthy" status, early events of that process might predict progression to future chronic disease (17). Screening and identifying young adults, especially men, with conditions such as AOb, dyslipidaemia and the MetS are crucial steps in establishing effective educational and intervention strategies to reduce the incidence and burden of chronic diseases.

MetS prevalence was higher in men than in women, but the percentage of healthy men (with no MetS components) is higher than healthy women, similar to what has been reported (18).

From the five MetS components, three of them, TAG, fasting GLU and BP, showed a higher prevalence in men than in women; while two, HDL-C and WC, showed higher prevalence in women when compared with men. Abdominal obesity and low HDL-C were 1.6 and 1.8 times higher, respectively, in females. Our results suggest that dyslipidemia presence in women is favored by the central body fat distribution.

In our study, MetS prevalence was 11.8% using criteria from Alberti et al. (16) (14.3% in men and 10.5% in women), these values are higher than those found in college students from Latin America countries, including Ecuador, Chile and Argentina where the reported prevalence was 7.5%, 4.9% and 4.1%, respectively (19-21). The prevalence of MetS in our study is higher, even compared with that found in college students from developed countries like United States where MetS was identified in 10% of men and 3% of women (22), and 4.7% (men) 1.6% (women) in first-year college students between 18 and 24 years (23).

It is worth to mention that the prevalence of abdominal obesity in young adults of Mexico was 53.3%, in Ecuador 43.2% and in Argentina 12%, using as reference the IDF criteria; while in Chile it was 6.0% using the ATPIII-2002 criteria. The difference in the prevalence of MetS between Mexico, Ecuador and Argentina, could be explained due to higher differences in the prevalence of abdominal obesity in the studied populations; whereas the differences with Chile are related to a lack of comparability because of the different diagnostic criteria used.

Mean values in all of the related components of the metabolic syndrome through AOb were significantly higher in obese young adults, compared to non-obese ($p \leq 0.01$). Among those students who are non-obese, only 1% has the MetS. A similar trend was observed by DuBose et al., in elementary school children, as well as other studies observed a higher prevalence for each component of the MetS (24,25).

It is important to notice that the chronological development of AOb increases the cardiovascular risk, which is at the core of metabolic syndrome. In young adults, moderate obesity generally is well tolerated; however, with advancing years, there is a common progressive weight gain, a gradual loss of muscle mass, stiffening of the arterial tree, decline in secretory capacity of pancreatic β-cells, mitochondrial dysfunction, and increased inflammatory changes in adipose tissue as well as other age-related alterations (22). The syndrome often culminates in type 2 diabetes in which risk for vascular disease is markedly raised (1).

With the purpose to establish future interventions aimed to reducing risk factors for MetS development, it is important to know the prevalence of its components. According to the results of this study, low HDL-C was the most frequent, followed by AOb. In 2012, our research group suggested that the binomium HDL/WC is the main prevalence factor and the main predictor of MetS occurrence, since low HDL-C is very frequent in this population (17). However, to increase the effectiveness of these interventions and as a goal of this report, we consider that is more important to know the degree of association of each of these elements on its development. In this study, AOb was selected as one of the most important components of the MetS due to its high prevalence, and other studies have shown that AOb is a factor of high importance for its development (19,26). The degree of association of AOb with the other components of MetS was established and we found that elevated BP was more strongly associated in both men and women. This finding is important because in our university population, high BP is the lowest frequent individual component of MetS, but the importance on its development could

be greater than biochemical components, including low HDL-C, despite being the most frequent component in this population.

Our results could be very important to public health authorities for the design and implementation of focused preventive policies to reduce MetS and CVD in college students.

As it is known, cross-sectional design limits causal inferences; however, this design allows researchers to obtain the current health status of the desired population at one point in time. Some studies define young adults as 18 to 24 (8,18), others from 20 to 39 (23), as in this study was from 17 to 25 years old, we think a single operational definition for young adults would be beneficial for future data comparisons. Our reported prevalence of MetS in students could not be generalized to all Mexican university students; even, our sample was derived from two universities from central (UNAM and UACM) and one from northern (UACJ) locations, more universities need to be sampled. Yet, to our knowledge no other study of this sample size has examined MetS in young Mexicans.

## CONCLUSIONS

Central obesity and low HDL-C are the most prevalent components of MetS, while elevated BP shows the lowest prevalence. Nevertheless, the degree of association between AOb and the other components of MetS was established, and we found that elevated BP is more strongly associated in both men and women. This finding is important because in our Mexican university population, elevated BP is the lowest frequent individual component of MetS, but the importance on its development could be greater than biochemical components, including low HDL-C, the most frequent component in this population.

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Nutrición Hospitalaria

Trabajo Original

Obesidad y síndrome metabólico

# Association of 4-hydroxynonenal with classical adipokines and insulin resistance in a Chinese non-diabetic obese population

## *Asociación del hydroxynonenal 4 con las adipoquinas clásicas y la resistencia a la insulina en una población china obesa no diabética*

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## Abstract

**Background:** The prevalence of obesity is increasing worldwide. Oxidative stress plays an etiological role in a variety of obesity-related metabolic disorders. 4-hydroxynonenal (4-HNE) is the most abundant and reactive aldehydic product derived from the peroxidation of n-6 polyunsaturated fatty acids with diverse biological effects that are not well detailed. Obesity is associated with decreased plasma adiponectin concentrations and increased production of lipid peroxidation products, including 4-HNE, in adipose tissue. There may be some association between the level of adipokines and 4-HNE.

**Material and methods:** To analyze the associations between 4-HNE and classical adipokines, namely, adiponectin and leptin in a Chinese population, the plasma 4-HNE, adiponectin and leptin levels of 160 non-diabetic obese (NDO) patients and 160 healthy subjects were determined by ELISA, and their associations with adiposity, glucose, lipid profiles, insulin secretion and insulin sensitivity were studied.

**Results:** Plasma 4-HNE levels were significantly increased in patients with NDO compared with healthy controls ($p < 0.01$). 4-HNE was negatively correlated with adiponectin and positively correlated with leptin. The plasma levels of 4-HNE were significantly correlated to several parameters involved in body mass index (BMI) and insulin resistance (IR). The 4-HNE levels were positively correlated with BMI and negatively correlated with insulin sensitivity.

**Conclusion:** We conclude that 4-HNE is associated with the secretion of adiponectin and leptin and is correlated with IR in NDO humans. These findings indicate a pro-inflammatory role of 4-HNE in NDO patients, which supports the potential role of 4-HNE in the development of obesity-related disorders.

**Key words:**

Obesity. Inflammation. Adipokine. Insulin resistance. Metabolism.

## Resumen

**Introducción:** la prevalencia de la obesidad está aumentando en todo el mundo. El estrés oxidativo desempeña un papel etiológico en una variedad de desórdenes metabólicos relacionados con la obesidad. El hydroxynonenal 4 (4-HNE) es el aldehido más abundante y más reactivo derivado de la peroxidación de los ácidos grasos poliinsaturados n-6, con efectos biológicos diversos que no son bien conocidos. La obesidad se asocia a concentraciones disminuidas de adiponectinas en el plasma y a un aumento en los productos de la peroxidación lipídica, incluyendo el 4-HNE, en tejido adiposo. Puede haber una cierta asociación entre el nivel de adipoquinas y el 4-HNE.

**Material y métodos:** para analizar las asociaciones entre 4-HNE y las adipoquinas clásicas, adiponectina y leptina se determinaron por ELISA los niveles de adiponectina y de leptina, así como de 4-HNE, en una población de 160 pacientes chinos obesos no diabéticos (NDO) y de 160 controles sanos, y se estudió su asociación con adiposidad, perfil glucémico y lipídico, secreción de la insulina y sensibilidad de la insulina.

**Resultados:** los niveles de 4-HNE aumentaron significativamente en los pacientes con NDO comparado con los controles sanos ($p < 0,01$). El nivel de 4-HNE se correlacionó negativamente con la adiponectina y positivamente con la leptina. Los niveles de 4-HNE se correlacionan positivamente con el IMC y negativamente con la sensibilidad a la insulina.

**Conclusión:** concluimos que el 4-HNE está asociado a la secreción de adiponectina y de leptina y correlacionado con la resistencia a la insulina en sujetos obesos no diabéticos. Estos resultados indican un papel proinflamatorio del 4-HNE en pacientes NDO, que apoya el papel potencial del 4-HNE en el desarrollo de alteraciones relacionadas con la obesidad.

**Palabras clave:**

Obesidad. Inflamación. Adipoquina. Resistencia de insulina. Metabolismo.

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## INTRODUCTION

Obesity is characterized by an excessive accumulation of adipose tissue, which is associated with an increase in the number and size of adipocytes. Adipocytes are not only involved in storing triglycerides (TGs) as key regulators in energy homeostasis but are also involved in secreting multiple biologically active molecules, so-called adipokines, which link obesity to its associated complications, especially insulin resistance (IR) and type 2 diabetes. Notable among these adipokines, plasma adiponectin is decreased in obesity and associated complications (1,2); however, leptin contributes to obesity-associated IR (3-5). Dysregulated production or secretion of these adipokines caused by excess or dysfunctional adipose tissue may contribute to the development of obesity-related metabolic diseases.

Based on the complex interplay between adipokines, obesity is also characterized by a chronic low-grade inflammation with increased oxidative stress state (6,7). Oxidative stress is caused by increased free radical production. Cells' ability to detoxify radicals and to repair damaged molecules is impaired. Increased oxidative stress in obesity is associated with metabolic disorders and is suggested to participate in the onset and progression of these disease processes (8-11). Free radical production in oxidative stress may covalently modify membrane-associated or intracellular proteins, inducing a variety of cellular damage directly or indirectly through the production of a variety of membrane lipid peroxidation products. Principal among these is 4-hydroxynonenal (4-HNE), which is derived from the peroxidation of n-6 polyunsaturated fatty acids, such as arachidonic and linoleic acids. 4-HNE reacts with amino acids, such as cysteine, lysine and histidine, and forms stable adducts with proteins, thereby modulating the activities and expression of various proteins. As we have previously reported, at high concentrations, 4-HNE is cytotoxic to several cell types, whereas micromolar and submicromolar concentrations of 4-HNE have been shown to induce various nontoxic, cell-specific effects (2). Oxidative stress in adipose tissue plays an etiological role in a variety of obesity-related metabolic disorders. Using a high-fat diet-induced obesity mouse model, we reported that obesity was associated with increased adipose tissue 4-HNE formation (2,12). In both 3T3-L1 and primary mouse adipocytes, 4-HNE treatment at nontoxic concentrations decreased adiponectin secretion via an ubiquitin-proteasome regulated mechanism (2).

Obesity is associated with decreased plasma adiponectin concentrations and increased production of lipid peroxidation products in adipose tissue, including 4-HNE (13,14). There may be a relationship between the level of adipokines and 4-HNE. This study aimed to investigate the effects of 4-HNE accumulation on plasma adiponectin and leptin secretion in the Chinese non-diabetic obese (NDO) population. Plasma 4-HNE, adiponectin and leptin levels of 160 non-diabetic obese (NDO) patients and 160 healthy subjects were determined by ELISA, and their associations with adiposity, glucose, lipid profiles, insulin secretion and insulin sensitivity were studied.

## MATERIALS AND METHODS

### STUDY POPULATION

The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association and was approved by the local and regional ethics committees. All investigated patients gave their written informed consent to participate in the study. We enrolled 320 people who participated in a health check-up at the Department of Medicine Examination Center, the Second Affiliated Hospital of Harbin Medical University, China. There were 160 NDO subjects, and the others were non-diabetic non-obese control participants matched by age and gender. People with active liver or endocrine disease (including any type of diabetes mellitus), cardiovascular disease, renal impairment, malignancy, and alcohol or drug dependence were excluded. The study population was also limited to non-smoker, non-pregnant individuals free of clinically significant infectious diseases. Neither obese patients nor non-obese controls were taking lipid lowering, hypoglycemic, anti-inflammatory or antithrombotic medications or dietary supplements.

### ANTHROPOMETRIC MEASUREMENTS

Anthropometric measurements of individuals wearing light clothing and without shoes were conducted by well-trained examiners. Height was measured to the nearest 0.1 cm with a portable stadiometer. Weight was measured in an upright position to the nearest 0.1 kg with a calibrated scale. BMI was calculated by dividing the weight (kg) by height squared ($m^2$). Obesity was defined as BMI $\geq$ 27.5 kg $m^{-2}$. Waist and hip circumferences (WC and HC) were measured at the level of the umbilicus and at the level of the maximum girth between the iliac crest and the crotch, respectively. Blood pressure (BP) was measured at the subjects' right hand with the subjects sitting after 5 min of rest using a calibrated sphygmomanometer (Hawksley, WA Baum Co, USA). All measurements of anthropometric indices and BP were performed by well-trained physicians, nurses or research staff. Each measurement was taken twice, and the average value was calculated. The homoeostasis model assessment for insulin resistance (HOMA-IR) was calculated using the following formula: HOMA-IR = Glucose-Oral glucose tolerance test (OGTT) 0 min (mmol/L) $\times$ fasting insulin (μ IU/mL) / 22.5 (15).

### BIOCHEMICAL MEASUREMENTS

After an overnight fast of 10 h, venous blood samples were collected to measure glucose-OGTT 0 min, fasting insulin, blood lipids including total cholesterol (TC), total triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) and liver function, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), hemoglobin A1C (HbA1C). Blood samples were also drawn 120 min after 75 g glucose load to measure glucose. Plasma glucose levels

were measured using a hexokinase enzymatic method. Insulin was measured by a radioimmunoassay with human insulin as a standard (Linco, St Charles, MO). TG, TC, LDL-C, HDL-C and tests were performed enzymatically (16).

### 4-HNE AND ADIPOKINES MEASUREMENTS

The plasma concentrations of 4-HNE, adiponectin and leptin were measured by commercially available ELISA kits (Cusabio Life Science Inc., Wuhan, China, for 4-HNE measurements; RayBiotech, Norcross, UK for adiponectin and leptin determinations). 4-HNE ELISA kits were used to test the total endogenous 4-HNE bound to protein. The intra- and inter-assay coefficients of variations were < 8% and < 10% (4-HNE), < 10% and < 12% (adiponectin) and < 10% and < 12% (leptin), respectively. Measurements of the 4-HNE and adipokine levels in plasma were performed according to the recommendations of the manufacturers.

### STATISTICAL ANALYSES

Data are expressed as the means ± SD for parameters with a normal distribution. Comparisons between groups (NDO *vs.* healthy controls) were analyzed by Student's unpaired t-tests for parameters with a normal distribution. Correlations between continuous variables were assessed by calculation of the linear regression using Pearson's test. $p < 0.05$ was considered statistically significant. We performed sample size estimation of the case-control study according to the formula 1 below.

$$N = \left[\frac{Z_\alpha\sqrt{\pi_c(1-\pi_c)(Q_1^{-1}+Q_2^{-1})}+Z_\beta\sqrt{\pi_1(1-\pi_1)/Q_1+\pi_2(1-\pi_2)/Q_2}}{\pi_2-\pi_1}\right]^2 \quad (1)$$

Based our preliminary experiment, some parameters were estimated as $\pi_1 = 0.3$, $\pi_2 = 0.6$, $\pi_c = 0.5$, $Q_1/Q_2 = 1$, $\alpha = 0.05$, $\beta = 0.10$, and we obtained $N \approx 90$. To better find some differences between groups, we increased the sample size to 160 for each group.

**Table I.** Anthropometric and selected laboratory parameters of the study population

| Variables | NDO (160) | Control (160) | p |
|---|---|---|---|
| Gender (female/male) | 84/76 | 92/68 | |
| Age (years) | 51.96 ± 9.22 | 51.05 ± 8.11 | ns |
| BMI (kg/m$^2$) | 34.11 ± 6.20 | 22.05 ± 1.78 | < 0.01 |
| Height (cm) | 158.98 ± 9.22 | 160.43 ± 6.85 | ns |
| Weight (kg) | 85.55 ± 12.93 | 56.84 ± 6.64 | < 0.01 |
| WC (cm) | 98.17 ± 15.00 | 77.07 ± 6.72 | < 0.01 |
| HC (cm) | 106.00 ± 6.30 | 92.91 ± 4.30 | < 0.01 |
| Glucose-OGTT 0 min | 5.69 ± 0.67 | 5.45 ± 0.25 | < 0.01 |
| Glucose-OGTT 120 min | 7.96 ± 0.67 | 7.15 ± 1.34 | < 0.01 |
| HbA1C (%) | 5.45 ± 0.83 | 5.26 ± 0.27 | < 0.01 |
| Insulin (mU/L) | 8.95 ± 1.47 | 6.00 ± 0.51 | < 0.01 |
| HOMA-IR | 2.67 ± 0.57 | 1.22 ± 0.21 | < 0.01 |
| SBP (mmHg) | 128.90 ± 12.13 | 125.49 ± 19.89 | ns |
| DBP (mmHg) | 78.18 ± 8.66 | 76.67 ± 10.76 | ns |
| HR (beat/min) | 73.79 ± 8.44 | 75.07 ± 8.38 | ns |
| HDL-C (mmol/L) | 1.22 ± 0.27 | 1.33± 0.23 | < 0.01 |
| LDL-C (mmol/L) | 2.73 ± 0.56 | 2.63 ± 0.43 | ns |
| TC (mmol/L) | 4.98 ± 0.74 | 4.97 ± 0.92 | ns |
| TG (mmol/L) | 2.23 ± 1.52 | 1.56 ± 0.73 | < 0.01 |
| *Variables* | *NDO (160)* | *Control (160)* | p |
| ALT (U/L) | 14.59 ± 7.81 | 11.51 ± 4.59 | < 0.01 |
| AST (U/L) | 19.09 ± 5.55 | 17.80 ± 3.48 | < 0.05 |
| 4-HNE (μM) | 0.10 ± 0.01 | 0.08 ± 0.01 | < 0.01 |
| Adiponectin (pg/mL) | 4.89 ± 3.40 | 17.18 ± 9.65 | < 0.01 |
| Leptin (ng/mL) | 268.43 ± 8.06 | 79.72 ± 23.44 | < 0.01 |

*Data are presented as means ± SD. p value: NDO patients* vs. *control individuals. ns: no significant differences. SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate.*

## RESULTS

### CHARACTERISTICS OF THE STUDY POPULATION

The characteristics of the study participants are shown in table I.

### PLASMA 4-HNE LEVELS WERE INCREASED IN THE NDO POPULATION

Fasting plasma 4-HNE levels ranged from 0.09 to 0.11 μM, and the median was 0.10 ± 0.01 μM in the NDO population. The plasma concentrations of 4-HNE were significantly higher in the NDO subjects than in the control subjects (0.10 ± 0.01 μM *vs.* 0.08 ± 0.01 μM, NDO *vs.* control, $p < 0.01$) (Table I).

### PLASMA ADIPONECTIN LEVELS WERE DECREASED WHEREAS PLASMA LEPTIN LEVELS WERE INCREASED IN THE NDO POPULATION

The fasting plasma adiponectin levels were more than 3 times lower in the NDO group compared with the healthy controls (4.89 ± 3.40 pg/mL *vs.* 17.18 ± 9.65 pg/mL, $p < 0.01$) (Table I).

However, fasting plasma leptin levels were lower in the NDO group compared with healthy controls (268.43 ± 8.06 ng/mL *vs.* 79.72 ± 23.44 ng/mL, $p < 0.01$) (Table I).

## CORRELATION BETWEEN PLASMA 4-HNE AND ADIPONECTIN/LEPTIN LEVELS

In all subjects, the levels of fasting plasma 4-HNE were positively correlated with leptin and were negatively correlated with adiponectin ($p < 0.01$) (Table I, Figs. 1 and 2).

## 4-HNE LEVELS ARE CLOSELY RELATED WITH GLUCOSE METABOLISM, INSULIN SECRETION AND SENSITIVITY

To further investigate the relationship between 4-HNE and other anthropometric parameters, multiple stepwise regression analysis involving all parameters, including fasting glucose, 2 h-glucose, fasting insulin, HbA1C, HOMA-IR, TC, TG, LDL-C and HDL-C, with significant correlations with plasma 4-HNE was performed. In all subjects, the levels of fasting plasma 4-HNE were positively correlated with BMI and HOMA-IR ($p < 0.05$) (Table II).

## DISCUSSION

Oxidative stress is associated with obesity and IR and is considered to contribute to the progression toward obesity-related metabolic disorders. Recent evidence demonstrates that the imbalance between oxidative stress and antioxidant defense also triggers insulin resistance (6,17). As reported in 3T3-L1 adipocytes, 4-HNE treatment at nontoxic concentrations increased 4-HNE-insulin receptor substrate (IRS) adducts levels, leading to adipocyte IR (18). 4-HNE may play an important role in the pathogenic cellular changes that cause IR and other abnormalities in obesity, and 4-HNE may also mediate disease processes promoted by obesity (19). We and others have found that the levels of 4-HNE are higher in the blood and/or muscle tissue of obese individuals

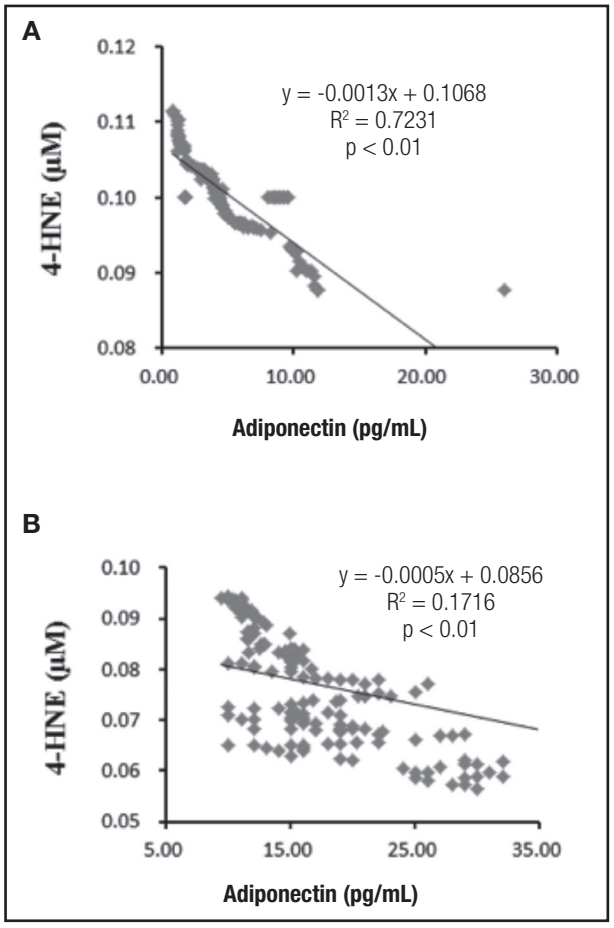


**Figure 1.**

Association of 4-HNE with adiponectin. In NDO individuals (A) and healthy controls (B). The levels of fasting plasma 4-HNE were negatively correlated with adiponectin.

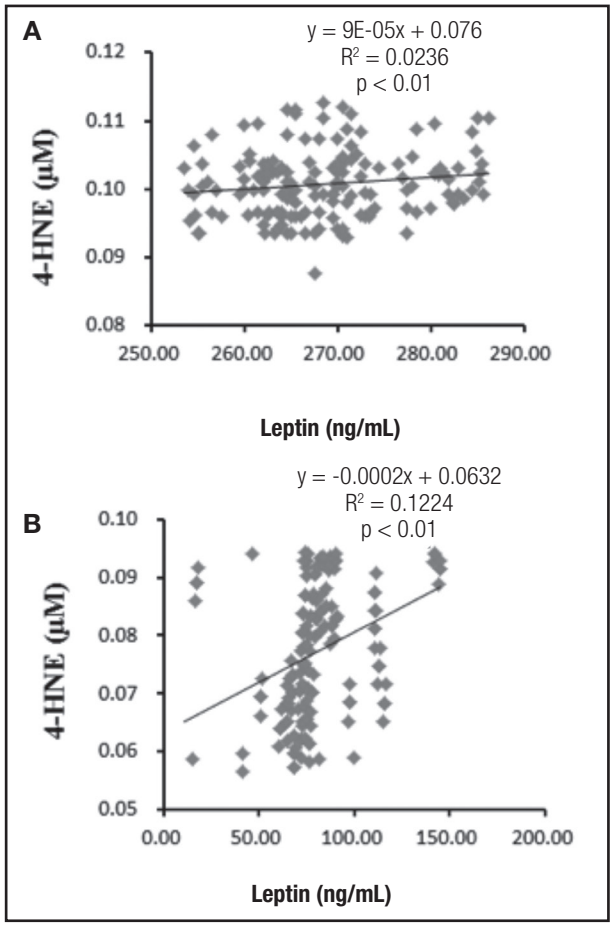


**Figure 2.**

Association of 4-HNE with leptin. In NDO individuals (A) and healthy controls (B). The levels of fasting plasma 4-HNE were positively correlated with leptin.

**Table II.** Association between 4-HNE selected laboratory parameters

| Variable | β | p |
|---|---|---|
| BMI | 0.124 | < 0.01 |
| HOMA-IR | 0.238 | < 0.01 |
| Adiponectin | -0.238 | < 0.01 |
| Leptin | 0.475 | < 0.01 |

*Statistical analyses was performed using multiple regression analysis for 4-HNE as a dependent variable.*

than in lean subjects (19). Previous studies indicated that 4-HNE inhibited adiponectin gene expression and secretion in 3T3-L1 adipocytes; however, the mechanisms were not investigated (20). Strong evidence supports that oxidative stress plays a pathologic role in obesity-related disorders; however, the underlying mechanisms of the effects of 4-HNE on adiponectin gene expression and secretion, as well as its involvement in obesity-related decline, remain elusive. As reported 4-HNE, the most abundant lipid peroxidation end product, differentially regulates adiponectin gene expression and secretion by activating PPARγ and accelerating ubiquitin-proteasome degradation (2). Although several animal experiments have suggested 4-HNE as an important regulator of glucose metabolism and insulin sensitivity, the clinical relevance of these findings in humans remains poorly characterized (18,20). The HNE-protein adduct ELISA is a method to detect HNE bound to proteins, which is considered as the most likely form of HNE in living systems (21). Although the detected absolute values of HNE-protein adducts were different, depending on the antibody used, both ELISA methods showed significantly higher values of HNE-protein adducts in the obese group (21). Intracellular HNE reacts rapidly with the thiol groups of glutathione and cysteine, with the ε-amino groups of lysine, and with the histidine residues of proteins (21). In this study, we used commercial ELISA kits to test the total endogenous 4-HNE bound to protein; our data showed that 4-HNE might be involved in the pathogenesis of non-diabetes obesity, as supported by two novel findings. First, the plasma 4-HNE concentrations were significantly increased in subjects with NDO compared with the age- and gender-matched healthy subjects, in contrast to the change pattern of circulating adiponectin levels. Second, the plasma 4-HNE levels were strongly associated with insulin sensitivity in both non-diabetes obese and healthy subjects.

Accumulated evidence suggests that adipose tissue oxidative stress plays a central and causal role in the pathogenesis of metabolic syndrome (8-11). Excessive fat accumulation increases the production of reactive oxygen species and lowers cellular antioxidant levels, leading to oxidative stress in adipose tissue. Various reactive oxygen species react with all cellular components; the hydroxyl radical-mediated peroxidation of polyunsaturated acyl chains of glycerophospholipids is particularly harmful because it results in the formation of lipid peroxidation production considered second messengers and the ultimate mediator of toxic effects elicited by oxidative stress. Of the lipid peroxidation products, 4-HNE is the most abundant and reactive aldehydic product derived from the peroxidation of n-6 polyunsaturated fatty acids (22-24). The results from our study are consistent with previous clinical observations and experimental investigations showing that obesity is associated with decreased plasma adiponectin concentrations and increased production of lipid peroxidation products in adipose tissue, including 4-HNE (13,14). A long-term high-fat diet led to obesity in mice, accompanied by decreasing the plasma adiponectin and increasing the adipose tissue 4-HNE content (2). Exposure of adipocytes to exogenous 4-HNE resulted in decreased adiponectin secretion in a dose-dependent manner, which was consistent with the significantly decreased intracellular adiponectin protein abundance (2). Polyunsaturated fatty acid (PUFA) in the membrane phospholipids or in circulating lipoproteins might be subjected to non-enzymatic, free radical-driven lipid peroxidation under certain pathological conditions, such as inflammation and obesity (25). Both types of lipid oxidation result in the formation of highly reactive lipid hydroperoxides, including proinflammatory leukotrienes. Small end-products of lipid peroxidation, such as 4-HNE and other aldehydes transported by activated granulocytes/monocytes, may facilitate and maintain generalized inflammation (25). The plasma adiponectin level is determined by complex intracellular regulatory mechanisms involved in gene expression, post-transcriptional/translational modification, and trafficking/secretion processes (26,27). Adiponectin is predominantly produced and secreted into circulation by adipocytes. Obesity-related plasma adiponectin decline is critically involved in the pathogenesis of obesity-related metabolic disorders. In contrast, 4-HNE exposure led to marked reductions in both intracellular adiponectin protein contents and secretion into media. The CHX-chase assay revealed that 4-HNE accelerated the intracellular adiponectin protein degradation rate by the ubiquitin-proteasome system. These data collectively suggest that 4-HNE can differentially regulate adiponectin gene expression and protein secretion in adipocytes, which may contribute to obesity-related plasma adiponectin decline (2).

Obesity represents a major health burden worldwide. White adipose tissue, especially in the visceral compartment, was recently discovered to be not just a simple energy depository tissue but also an active endocrine organ, releasing a variety of biologically active substances termed adipokines. Generally, adipokines play key roles in the regulation of glucose/lipid metabolism, insulin sensitivity and inflammation. Several adipokines are associated with obesity and have potential impact on obesity-related metabolic diseases. Multiple lines of evidence provide valuable insight into the roles of adipokines in the development of obesity and its metabolic complications.

BMI was correlated positively with leptin levels and negatively with adiponectin concentrations (6,28). By assessing the correlations between 4-HNE, as an oxidative stress product, and the formerly discovered classical adipokines, we found a significant negative correlation between the concentrations of adiponectin and 4-HNE. A significant positive correlation was also detected between leptin and the 4-HNE levels, which further supports the

potential role of 4-HNE in the development of obesity-related disorders. Because adiponectin and leptin are considered to have opposing effects on inflammation in obesity (6,29), these findings indicate a pro-inflammatory role of 4-HNE in NDO patients, giving support to our study hypothesis.

There are several limitations of this study. For example, the sample size was relatively small. The correlation between 4-HNE and adipokines did not guarantee the existence of a causal relationship. Further prospective studies are required to determine whether elevated plasma 4-HNE is the enabling step of obesity or simply an accompanying or secondary response to obesity.

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Trabajo Original

Obesidad y síndrome metabólico

# Micronutrient supplementation in gastric bypass surgery: prospective study on inflammation and iron metabolism in premenopausal women

## *Suplementación con micronutrientes en pacientes con cirugía de bypass gástrico: estudio prospectivo sobre la inflamación y el metabolismo del hierro en mujeres premenopáusicas*

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## Abstract

**Background:** Low-grade chronic inflammation in morbid obesity is associated with impaired iron metabolism. Bariatric surgery is effective in weight loss; however, it can induce specific nutritional deficiencies, such as iron, especially in premenopausal women. Alternatively, after surgery, there is an improvement in systemic inflammation, raising questions concerning the dosages of micronutrient supplementation.

**Objectives:** This study aimed to assess the effect of two micronutrient supplementation schemes before and 6 months after a Roux-en-Y gastric bypass (RYGB) surgery on inflammation and iron metabolism in premenopausal women.

**Methods:** This prospective study included 45 premenopausal women (aged 20-45 years; body mass index [BMI] ≥ 35 kg/m$^2$) divided into two supplementation schemes: group 1 (n = 34): daily supplemental dose of 1 RDA 30 days before surgery and 2 RDAs during the six months following surgery; and group 2 (n = 11): daily supplementation of 1 RDA during the 6 months postsurgery. Anthropometry, dietary intake, inflammation, and iron metabolism were monitored.

**Results:** Evident reductions in BMI, high-sensitivity C-reactive protein, and ferritin levels for both groups occurred 6 months after surgery. Additionally, anemia was 9% in both groups after surgery. However, group 1 exhibited an increased transferrin saturation index and reduced transferrin levels. Multivariate regression analysis suggested serum iron, hepcidin, and iron intake determined ferritin values before and after RYGB surgery.

**Conclusion:** Six months after RYGB, systemic inflammation was reduced in both supplementation schemes. However, supplementation of 1 RDA before and 2 RDAs after surgery resulted in better improvements on iron metabolism.

**Key words:**

Obesity. Inflammation. Iron. Bariatric surgery. Micronutrient supplementation.

## Resumen

**Introducción:** la inflamación crónica de bajo grado en la obesidad mórbida se asocia con una alteración del metabolismo del hierro. La cirugía bariátrica es eficaz en la pérdida de peso, sin embargo, puede inducir deficiencias específicas nutricionales, como es el caso del hierro, especialmente en las mujeres premenopáusicas. Por otra parte, después de la cirugía, hay una mejora en la inflamación sistémica, planteando el tema de las dosis de suplementos de micronutrientes.

**Objetivos:** este estudio tuvo como objetivo evaluar el efecto de dos esquemas de suplementación de micronutrientes antes y 6 meses después de una cirugía de *by-pass* gástrico con Y de Roux (RYGB) sobre la inflamación y el metabolismo del hierro en las mujeres premenopáusicas.

**Métodos:** estudio prospectivo que incluyó 45 mujeres premenopáusicas (edades 20-40 años, índice de masa corporal [IMC] ≥ 35 kg/m$^2$) divididos en dos esquemas de suplementación: grupo 1 (n = 34): dosis suplementaria diaria de 1 vez las RDA 30 días antes de la cirugía y 2 veces las RDA durante los seis meses posteriores a la cirugía; y el grupo 2 (n = 11): la suplementación diaria de 1RDA durante los 6 meses después de la cirugía. Se monitorizaron las medidas antropométricas, la ingesta alimentaria, la inflamación y el metabolismo del hierro.

**Resultados:** se observó una disminución en el IMC, la proteína C reactiva de alta sensibilidad y los niveles de ferritina en ambos grupos después de 6 meses tras la cirugía. Además, la anemia fue del 9% en ambos grupos tras de la cirugía. Sin embargo, el grupo 1 exhibió un incremento del índice de saturación de transferrina y una reducción en los niveles de transferrina. En el análisis multivariante se apreció que los niveles de hierro sérico, hepcidina y la ingesta de hierro determinaron los valores de ferritina antes y después de la cirugía.

**Conclusión:** seis meses después de RYGB, la inflamación sistémica se redujo en ambos esquemas de suplementación. Sin embargo, la suplementación de 1 vez las RDA antes y 2 veces las RDA después de la cirugía consiguió mejorar el metabolismo del hierro.

**Palabras clave:**

Obesidad. Inflamación. Hierro. Cirugía bariátrica. Suplementos de micronutrientes.

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## INTRODUCTION

Obesity is associated with systemic low-grade chronic inflammation, which has been related to changes in iron metabolism (1-5). The inflammation condition is supported by increases in pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-$\alpha$), interleukin-1 beta (IL-1$\beta$), interleukin-6 (IL-6), and from acute phase proteins, such as C-reactive protein (4,6).

The Roux-en-Y gastric bypass (RYGB) surgery employed in the treatment of morbid obesity affects iron supply to the organism through reduced food intake and/or through decreased intestinal absorption (7-11). Iron deficiency can also be aggravated by menstrual blood loss in reproductive-aged women (4,11-13).

Iron metabolism is affected by hepcidin, a hormone that promotes the inhibition of intestinal iron absorption, iron recycling by macrophages, and iron mobilization from the liver. In low-grade systemic inflammatory conditions, hepcidin is stimulated by inflammatory cytokine IL-6 (14-16) and synthesized by hepatocytes and adipocytes (17).

Increased hepcidin concentrations in obesity have been linked to low-grade chronic inflammation and seems to contribute to reduced iron availability and mineral deficiencies in this condition (2,18,19). In this context, Tussing-Humphreys et al. (18) observed that decreases of lowgrade inflammation and hepcidin levels improved iron metabolism 6 months after restrictive bariatric surgery in premenopausal women.

Some studies have also indicated that serum ferritin levels tends to rise in obesity in response to proinflammatory cytokines (20,21) and can be used as both an indicator of iron stores and as an indirect inflammatory marker. After bariatric surgery, pronounced weight loss is accompanied by a reduction of low-grade inflammation, but a decrease in ferritin levels and anemia can also occur, mainly in premenopausal women (13,22).

Iron deficiency is the main cause of anemia after bariatric surgery, however, other micronutrient deficiencies (e.g., vitamin B12 and folic acid) can also influence iron metabolism (2,11,12,23). Bariatric surgery, especially RYGB surgery, induces a process of nutritional deficiencies that affect food intake and micronutrient absorption (23,24). With these conditions, micronutrient supplementation is indicated to maintain normalized iron levels and prevent anemia (2,11).

Changes in iron metabolism associated with obesity and after bariatric surgery, as with the effect of micronutrient supplementation, need to be better elucidated (25). Therefore, this study aimed to assess the effect of two micronutrient supplementation schemes on inflammation and iron metabolism in premenopausal women who had undergone RYGB surgery.

## METHODS

### SUBJECTS

This study included 45 women (aged 20-45 years; body mass index $\geq$ 35 kg/m$^2$) in menacme and undergoing RYGB surgery. The exclusion criteria for participation in this study included: a) diabetes mellitus; b) anemia; c) hemoglobinopathies; d) thrombosis; e) infectious processes; f) hysterectomy; g) smoking; h) HIV positive; and i) the use of corticosteroids in the last six months. All participants signed an informed consent form after being informed about the research and procedures. This study was approved by the local Ethics Research Committee (protocol number: 3303-2009). The same medical staff performed the RYGB surgeries.

### EXPERIMENTAL DESIGN

A prospective interventional study was conducted to assess the effect of two micronutrient supplementation schemes on iron metabolism and systemic inflammation markers. Sixty women on the waiting list for bariatric surgery were eligible and randomly allocated into one of two groups. Group 1 (n = 45) received daily micronutrient supplementation 30 days before surgery at a dose of 1 Recommended Dietary Allowance (RDA) (26) and 2 RDAs during the 6-month period after RYGB surgery. Group 2 (n = 15) received daily supplementation of 1 RDA during the 6-month period after surgery, according to the most commonly-used clinical practices adopted in Brazil. Additionally, we chose micronutrient supplementation instated of specific iron supplementation, because it is recommended according to clinical practice guidelines after bariatric surgery and specific deficiencies of micronutrients can influence iron metabolism. Completing all study procedures 34 subjects from group 1 and 11 from group 2, for a total of 45 subjects (75% of the subjects recruited). Anthropometric assessments, dietary intake, and blood samples were collected during baseline, after 30 days of micronutrient supplementation during the preoperative period, and at 6 months after the RYGB surgery in group 1. In group 2, the same assessments were collected at baseline and 6 months after the RYGB surgery.

#### Blood biochemical analysis

Twelve-hour fasting blood samples were collected by standard venipuncture in tubes containing ethylenediaminetetraacetic acid (EDTA) and without an anticoagulant. Hematocrit and hemoglobin were determined by flow cytometry. Serum analyses were conducted in automated equipment to determine: a) serum iron and total iron binding capacity (TIBC) by the calorimetric method; b) transferrin and high-sensitive C-reactive protein (hs-CRP) by the immunoturbidimetric method; and c) ferritin by the chemiluminescence method. Hepcidin and soluble transferrin receptor (sTfR) were determined by enzyme-linked immunosorbent assays (ELISA) using commercial kits (Human Hepcidin; USCN Life Science Inc., TX, USA) and Human sTfR (BioVendor, Candler, NC, USA). The TNF-$\alpha$, IL-10, and IL-6 were analyzed by chemiluminescence methods (Milliplex® MAP Human Cytokine; Millipore, Billerica, MA, USA). The reference values used were: hsCRP = 0.0-0.3 mg/dL; iron = 50.0-170.0 mg/dL; and hepcidin = 0.06-4.00 ng/mL (as suggested by the manufacturer [USCN Life Science Inc., TX, USA]).

Iron deficiency was identified when transferrin saturation index (TSI) values were less than 20%, calculated as: TSI = (serum iron/TIBC) x 100 (19,27). Anemia was defined as hemoglobin values < 12 g/dL, criteria established by the World Health Organization according to sex and age (29).

## ANTHROPOMETRIC ASSESSMENT

Weight and height were assessed using a digital balance (Welmy, SP, Brazil) precise to within 100 g, and a stadiometer (Seca) precise to within 0.1 cm. Body mass index (BMI) was calculated as: body weight (kg) ÷ height squared ($m^2$). The assessment procedures were conducted in accordance with Gibson (30).

## MICRONUTRIENT INTAKE

A quantitative assessment was performed on nutritional intake from food records from three nonconsecutive days. The subjects were instructed to record all food and drink intake throughout the day. All subjects were trained by a dietitian, and the records were conferred to clarify any questions and to discuss the use of the micronutrient supplementation prescribed.

Food intake was recorded as household measures and converted into grams with the aid of a table of food intake in household measures (31). All data were tabulated in MS Excel software and quantitative data of nutrient intake were derived from the calculation based on information of food intake table (100 g) for the Brazilian population (32). The amount of micronutrient supplementation intake was added to the food intake. To remove personal variations, it was necessary to obtain intrapersonal (Sw 2) and interpersonal variances (Sb 2) using an analysis of variance (ANOVA), and the calculated adjusted average. In this study, vitamin intake was calculated for vitamins B6, B12, A, C, and folic acid, and mineral intake for iron, zinc, and copper.

### Micronutrient supplementation

The supplementation was manipulated in capsules before, and in powder after, RYGB surgery. The minerals presented in the formula were chelated into an amino acid (glycine). The micronutrient supplementation of 2 RDAs (26) was suggested to be given daily for RYGB surgery in two doses (11,22-35). Adequate Intake (AI) (26) was used when the RDA was not established for the micronutrient (except for calcium).

The amounts of vitamins and minerals provided in the 2 RDAs were: vitamin A (1,400 µg); vitamin D3 (cholecalciferol, 400 IU); vitamin E ($\alpha$-tocopherol; 30 mg); vitamin K (180 µg); vitamin C (150 mg); thiamine (2.2 mg); riboflavin (2.2 mg); nicotinamide (28 mg); pantothenic acid (10 mg); pyridoxine (2.6 mg); folic acid (800 µg); biotin (60 µg); cyanocobalamin (4.8 µg); magnesium (350 mg); calcium (500 mg); zinc (16 mg); copper (1,800 µg); chromium (50 µg); iron (36 mg); selenium (110 µg); manganese (3.6 mg); iodine (300 µg); silicon (10 µg); and vanadium (10 µg). A adequate intake (AI) (26) were used when RDA was not established for the micronutrient (except for calcium). The amounts of vitamins and minerals provided in 1 RDA were half the values described for 2 RDAs.

## STATISTICAL ANALYSIS

Continuous variables were expressed as mean ± standard deviation, median, and minimum and maximum (min-max). Prior to statistical analyses, data normality were tested. For parametric data, comparisons were assessed by paired *t*-tests (two moments –pre to post), unpaired *t*-tests (between groups), and ANOVA (three moments) followed by Tukey's *post hoc* test. For non-parametric data, comparisons were assessed by the Wilcoxon test (two moments), the Mann-Whitney U test (between groups), and the Kruskal-Wallis test (three moments), followed by Dunn's post hoc test. The associations of continuous variables were analyzed using chi-square tests ($\chi^2$). The interaction between study variables, using the ferritin concentration as the dependent variable, was assessed by multivariate linear regression tests. The level of significance adopted was $p < 0.05$. Statistical analyses were performed using STATISTICA software 10 (StatSoft, Inc., Tulsa, OK, USA).

## RESULTS

The groups investigated (group 1 [1 RDA pre and 2 RDA after] *vs.* group 2 [1 RDA after]) did not differ with regard to age ($p = 0.874$) and presence of comorbidities on admission into this study ($p = 0.324$). Among the investigated comorbidities, the frequencies identified were: hypertension (29%); dyslipidemia (31%); sleep apnea (11%); osteoarthritis (4.5%); and infertility (2.2%). The absence of comorbidities was 65% and the use of contraceptives was 29%.

At baseline assessments (for all subjects, n = 45), 95.5% and 91.0% had hepcidin and hs-CRP levels above reference values, respectively. Hypoferremia was identified in 2 subjects (4.5%), serum ferritin between 30-100 ng/dL in 27 subjects, and less than 30 ng/dL in 4 subjects (9.0%), however all hemoglobin values were ≥ 12 g/dL. Regarding iron deficiency (as determined by TSI values below 20%), it was observed in 10 subjects (22.2%) at baseline, 20.6% for group 1, and 27.3% for group 2 (Chi-square test, $p = 0.643$). The micronutrient supplementation schemes of 1 RDA before RYGB surgery resulted in reduction in iron deficiency for group 1 (5.9%). The supplementation schemes of 2 RDAs after RYGB surgery were associated with a reduction in iron deficiency for group 1 (2.9%, $p = 0.032$), but not for group 2 (27.3%, $p = 0.100$), who received micronutrient supplementation of only 1 RDA after RYGB surgery.

The results obtained before micronutrient supplementation (baseline), after preoperative supplementation (group 1), and after 6 months following the RYGB surgery, with regard to BMI and biochemical variables are show in table I. Group 1 had lower

**Table I.** Biochemical variables for groups 1 and 2 before and 6 months after RYGB surgery

| Variables | Group 1 (n = 34) | | | p-value* | Group 2 (n = 11) | | p-value** |
|---|---|---|---|---|---|---|---|
| | Baseline Median (Min-Max) | Before RYGB surgery and post supplementation Median (Min-Max) | 6-months after RYGB surgery Median (Min-Max) | | Baseline Median (Min-Max) | 6-months after RYGB surgery Median (Min-Max) | |
| BMI (kg/m$^2$) | 47.8 (39.2-62.0) [a] | 44.5 (36.0-59.4) [b] | 34.3 (26.8-46.1) [c] | < 0.001 | 41.5 (40.1-66.4) | 30.6 (27.6-50.9) | 0.003 |
| Hb (g/dL) | 13.8 (12.3-15.2) [a] | 13.5 (12.1-14.8) [a] | 13.1 (11.5-14.8) [b] | < 0.001 | 13.5 (12.2-14.7) | 13.0 (11.8-14.7) | 0.799 |
| Ht (%) | 41.8 (35.0-46.5) [a] | 41.2 (37.0-45.2) [a] | 40.3 (31.3-44.8) [b] | 0.002 | 41.0 (37.4-45.4) | 39.2 (37.6-44.0) | 0.045 |
| Iron (µg/dL) | 83.5 (48.0-151.0) | 84.5 (50.0-135.0) | 95.5 (31.0-159.0) | 0.337 | 67.0 (49.0-119.0) | 91.0 (56.0-161.0) | 0.017 |
| TIBC (µg/dL) | 279.0 (202.0-462.0) [a] | 234.5 (94.0-286.0) [b] | 133.0 (62.0-280.0) [b] | < 0.001 | 269.0 (269.0-396.0) | 294.0 [†] (255.0-412.0) | 0.026 |
| TSI (%) | 32.6 (12.2-65.4) [b] | 36.1 (17.5-129.4) [b] | 67.0 (11.1-204.7) [a] | < 0.001 | 28.1 (15.0-39.2) | 34.0 [†] (17.2-57.5) | 0.182 |
| Tf (mg/dL) | 311.0 (227.0-436.0) [a] | 309.0 (186.0-418.0) [a] | 281.5 (176.0-403.0) [b] | 0.004 | 323.0 (269.0-396.0) | 302.0 (255.0-412.0) | 0.424 |
| sTfR (nmol/mL) | 10.2 (5.4-26.7) | 10.1 (5.1-23.3) | 9.1 (5.3-25.3) | 0.360 | 12.0 (4.7-18.0) | 9.3 (7.3-14.0) | 0.100 |
| Ferritin (ng/mL) | 64.5 (15.0-400.0) [a] | 64.0 (11.9-304.1) [ab] | 59.7 (5.5-238.5) [b] | 0.020 | 61.9 (29.5-190.6) | 52.4 (10.6-132.5) | 0.004 |
| Hep (ng/mL) | 16.0 (2.9-129.0) | 15.7 (4.5-108.9) | 15.5 (0.7-52.3) | 0.282 | 17.2 (1.3-45.9) | 12.4 (2.5-30.4) | 0.091 |
| hs-CRP (mg/dL) | 1.3 (0.1-6.5) [a] | 1.1 (0.1-4.9) [a] | 0.3 (0.0-2.8) [b] | < 0.001 | 1.4 (0.3-3.5) | 0.2 (0.01-0.74) | 0.003 |
| TNF-$\alpha$ (pg/mL) | 13.9 (0.6-26.0) | 12.8 (1.4-56.8) | 13.5 (0.6-50.1) | 0.585 | 13.7 (9.0-70.3) | 13.4 (8.0-69.6) | 0.570 |
| IL-6 (pg/mL) | 0.1 (0.0-131.0) [a] | 0.1 (0.0-115.0) [ab] | 0.1 (0.0-67.6) [b] | 0.042 | 0.1 (0.0-80.5) | 0.1 (0.0-54.1) | 0.230 |
| IL-10 (pg/mL) | 1.3 (0.0-11.6) | 1.3 (0.0-88.4) | 1.3 (0.0-59.7) | 0.452 | 0.9 (0.0-22.5) | 1.0 (0.0-38.9) | 0.360 |

*BMI: body mass index; Hb: hemoglobin; Ht: hematocrit; TIBC: total iron-binding capacity; TSI: transferrin saturation index; Tf: transferrin; sTfR: soluble transferrin receptor; Hep: hepcidin; hs-CRP: ultra-sensitive C-reactive protein; TNF-$\alpha$: tumor necrosis factor alpha; IL-6: interleukin-6; and IL-10: interleukin-10. *Friedman test for intra-group 1 comparisons, considering that variables marked with different letters on the same line were statistically different ($p < 0.05$). **Wilcoxon test for intra-group 2 comparisons. [†]Variables presenting statistical differences by the Mann-Whitney U test ($p < 0.05$) in the comparison between groups. Different letters on the same line are significantly different ($p < 0.05$).*

TIBC and higher TSI values compared to group 2, 6 months after the RYGB surgery. In the intragroup comparisons, both groups had decreased BMI and CRP-us 6 months after the RYGB surgery, and IL-6 interleukin decreases were evident only for group 1.

For the variables related to iron metabolism, group 1 had reductions in TIBC, transferrin, and ferritin levels, and an increase in TSI values. For group 2, there were increases in TIBC and serum iron values, and a reduction of ferritin levels. Group 1 had a reduction in hemoglobin values, and both groups showed decreases in hematocrit levels 6 months after RYGB surgery (Table I). Six months after surgery, anemia was diagnosed in three subjects in group 1 and one subject in group 2, representing about 9% in both groups. It should be highlighted that there were four women who already had serum ferritin levels below 50 ng/dL prior to RYGB surgery (at baseline).

In the comparisons between groups, after micronutrient supplementation in the preoperative period, group 1 showed a significant difference compared with group 2 (preoperative period without supplementation) for TIBC (234.5 *vs.* 269.0 µg/dL for groups 1 and 2, respectively, $p = 0.003$) and TSI values (36.1 *vs.* 28.1% for groups 1 and 2, respectively, $p = 0.036$).

Regarding micronutrients, there was an increased intake after 6 months following RYGB surgery in both groups (except for vitamin B12, zinc and cooper for group 2). However, group 1 obtained higher values compared to group 2 due to the supplementation of 2 RDAs following surgery (Table II).

**Table II.** Micronutrient intake for both groups before and 6 months after RYGB surgery

| Variables | Group 1 (n = 34) | | | p-value* | Group 2 (n = 11) | | p-value** |
|---|---|---|---|---|---|---|---|
| | Baseline | Before RYGB surgery and post supplementation | 6-months after RYGB surgery | | Baseline | 6-months after RYGB surgery | |
| Iron (mg/dL) | 12.0 ± 4.3 [a] | 25.7 ± 1.4 [b] | 42.4 ± 2.1 [c] | < 0.001 | 13.3 ± 3.2 | 24.7 ± 1.1 † | < 0.001 |
| Vitamin B12 (µg/dL) | 5.3 ± 3.3 [a] | 6.1 ± 1.1 [a] | 8.7 ± 2.6 [b] | < 0.001 | 5.1 ± 2.1 | 5.7 ± 0.9† | 0.485 |
| Folic acid (µg/dL) | 309.6 ± 105.2 [a] | 611.1 ± 59.9 [b] | 962.9 ± 52.7 [c] | < 0.001 | 329.9 ± 130.5 | 575.9 ± 37.2 † | < 0.001 |
| Vitamin C (mg/dL) | 107.6 ± 111.1 [a] | 138.4 ± 18.9 [a] | 202.8 ± 30.1 [b] | < 0.001 | 89.9 ± 56.5 † | 142.8 ± 36.7 † | 0.034 |
| Vitamin B6 (mg/dL) | 1.6 ± 0.5 [a] | 2.4 ± 0.3 [b] | 3.6 ± 0.3 [c] | < 0.001 | 1.3 ± 0.2 | 2.3 ± 0.2 † | < 0.001 |
| Vitamin A (µg/dL) | 666.3 ± 297.6 [a] | 1169.0 ± 158.9 [b] | 1765.5 ± 138.2 [c] | < 0.001 | 627.6 ± 217.6 | 1058.9 ± 117.1 † | < 0.001 |
| Zinc (mg/dL) | 13.8 ± 7.2 [a] | 17.1 ± 2.5 [b] | 23.5 ± 2.2 [c] | < 0.001 | 15.1 ± 5.5 | 15.7 ± 2.4 † | 0.725 |
| Copper (µg/dL) | 1.0 ± 0.4 [a] | 1.6 ± 0.2 [b] | 2.4 ± 0.2 [c] | < 0.001 | 1.2 ± 0.6 | 1.5 ± 0.2 † | 0.070 |

**Analysis of variance (ANOVA), followed by Tukey's* post hoc *test to compare intra-group 1 of the adjusted mean (± standard deviation), considering that the same variables marked with different letters on the same line presented statistical differences (p < 0.05). **Student´s t-tests to compare intra-group 2 of the adjusted mean (± standard deviation). †Variables that showed statistical differences by unpaired Student´s t-test (p < 0.05) in comparisons between groups. Different letters on the same line are significantly different (p < 0.05).*

Multivariate linear regression analysis, using ferritin as a dependent variable, indicated that before and after RYGB surgery, the variable that best explained ferritin levels was hepcidin, followed by serum iron values and iron intake. Additionally, there was a significant influence of hs-CRP for determining ferritin levels during the perioperative period, and TSI in influencing ferritin levels 6 months after RYGB surgery (Table III).

**Table III.** Multivariate linear regression of iron metabolism and inflammation variables at baseline and 6 months after RYGB surgery, using ferritin as a dependent variable

| Variables* | B | **p-value |
|---|---|---|
| *Baseline: without micronutrient supplementation* | | |
| High-sensitivity C-reactive protein | 3.4 | 0.001 |
| Serum Iron | 0.3 | 0.004 |
| Iron Intake | 0.9 | 0.043 |
| Hepcidin | 3.9 | < 0.001 |
| *6 months after RYGB surgery* | | |
| Transferrin saturation index | 0.2 | 0.017 |
| Serum iron | 0.4 | 0.009 |
| Iron intake | 1.4 | 0.041 |
| Hepcidin | 2.8 | < 0.001 |

*B: partial regression coefficient. *Groups 1 and 2: n = 45. **p < 0.05.*

## DISCUSSION

This study investigated the influence of two micronutrient supplementation schemes of 1 RDA prior (for 1 month) and 2 RDAs after RYGB surgery (for 6 months) *versus* 1 RDA only after surgery (for 6 months). Both groups had significant reductions in body mass index (IMC), hs-CRP, IL-6, and ferritin levels after RYGB surgery. However, our data indicated that 1 RDA pre-surgery and 2 RDAs of micronutrient supplementation post-surgery was more efficient in controlling iron metabolism (increased TSI and reduced transferrin levels).

In general, the baseline analysis in our study revealed that subjects had alterations in iron metabolism (increased hepcidin levels and iron deficiency) and systemic inflammatory markers (hsCRP and IL-6). This data was consistent with morbid obesity as described in others studies (2,18,19,36). A previous study has shown a correlation between hepcidin and ferritin values prior to surgery and a reduction of inflammation 6 months after surgery was associated with hepcidin and sTfR reductions (18). In the current study, hepcidin determined ferritin values pre- and 6 months post-RYGB surgery, and with hs-CRP at baseline, showed a relationship between hepcidin and systemic low-grade inflammation in morbid obesity.

Hepcidin plays a key role in the regulation of iron metabolism, acting as a negative regulator of iron absorption in the intestine and stimulating iron retention in macrophages when higher systemic concentrations occur (37). The increase of serum iron values, as observed with group 2 after surgery (1 RDA micronutrient supplementation), indicates the effect of weight loss on improvements in iron status, and the role of hepcidin in this process. Group 2 had higher iron deficiency rates 6 months after RYGB surgery, probably due to a lower supplementation dosage, as indicated by lower TSI and higher TIBC values compared to

group 1. Additionally, group 2 had a clear trend reduction in hepcidin values (28% *vs.* 2.5% for groups 2 and 1, respectively) during the same period (Table II). The reduction in hepcidin values occurs with iron deficiency to stimulate physiological pathways to elevate iron concentrations, thus, improving availability. Therefore, hepcidin probably had a lower percentage of reduction for group 1 due to the higher availability of iron via micronutrient supplementation (2 RDAs).

Ferritin is an important iron stores marker, but it also serves as an acute phase protein indicating systemic inflammation (8), and our multivariate regression analysis suggests this may be an accurate statement. Before surgery (at baseline), systemic low-grade inflammation influenced the increase of ferritin levels; however, before and after surgery, ferritin values were determined by serum iron levels, iron intake, and hepcidin. In obesity, increased ferritin levels are associated with low transferrin saturation and hypoferremia, but those with obesity do not seem to be more prone to anemia, compared to eutrophic subjects (25,38). Most of these changes are related to the anemia of inflammation, in which mechanisms are stimulated by proinflammatory cytokines and hepcidin (16).

In this study, at baseline assessments, only 2 subjects had low iron values, however, a low TSI was identified in 10 subjects (22.2%) and the majority (95.5%) of subjects had elevated hepcidin concentrations. Anemia caused by low-grade systemic inflammation or iron deficiency, occurs decrease of transferrin saturation (21), indicating that a functional iron deficiency may be associated with inflammation or a real mineral deficiency.

The effect of 1 RDA before and a 2 RDA micronutrient supplementation after RYGB surgery was effective in reducing iron deficiency (Table I). The number of subjects with iron deficiency was reduced (20.6% to 5.9% for baseline and pre-surgery, respectively) in accordance with TSI, after micronutrient supplementation during preoperative period of 1 RDA (group 1), indicating a real iron deficiency before surgery, since lowgrade systemic inflammation conditions persisted post initial supplementation.

Micronutrient supplementation of 2 RDAs after RYGB surgery was effective in maintaining TIBC, decreasing transferrin, and increasing TSI values. It is important to note that iron intake and TSI determined the increase of ferritin values 6 months after RYGB surgery when the analysis of both groups confirmed the influence of iron intake as the main marker of iron stores post-surgery in premenopausal women. The reduction of ferritin during the postoperative period increased the risk of anemia (13,23).

The current study indicated that low-grade inflammation with obesity contributed to changes in iron metabolism, however, this emphasizes the preoperative actual iron deficiency, as analyzed by the markers of TSI and ferritin levels. Of all subjects that completed the study (n = 45), 27 had ferritin levels between 30-100 ng/mL, suggesting an association of a functional and real iron deficiency, and 6 subjects had ferritin levels less than 30 ng/dL at baseline assessments, suggesting a real iron deficiency (21). Anemia was diagnosed in four subjects (~ 9%) within 6 months after RYGB surgery, with no difference between groups. However, all subjects had ferritin levels below 50 ng/dL, a value considered low for premenopausal women, and suggestive of the need for supplementation in the absence of anemia and presence of fatigue (28).

In an attempt to prevent decreases in hemoglobin and ferritin levels, and the development of anemia, which is a common outcome after RYGB surgery, specific recommendations are described in the literature (39). Aills et al. (33) recommend micronutrient supplementation at a dosage of 2 RDAs after malabsorptive surgery procedures, and in the specific case of iron, 36 mg per day. Recently, higher doses of iron (45-60 mg/day) have been suggested to prevent anemia in premenopausal women (40).

In our study, although there was a significant improvement in iron metabolism for group 1, the amount of iron supplementation before (1 RDA) and after (2 RDAs) RYGB surgery was insufficient to maintain postoperative erythropoiesis and a high number of subjects (premenopausal women) developed anemia. The decrease of ferritin levels occurred in both groups, showing a decrease of systemic inflammation levels, but also the beginning of an iron depletion process after RYGB surgery.

In the pre-surgical assessment, there are established serum iron levels, but no specification on minimum values for serum ferritin levels for submission to bariatric surgery (35,40). This may contribute to having patients with low iron stores, which may be more aggravating for premenopausal women and malabsorptive surgeries. Therefore, it is necessary to carefully assess iron metabolism and systemic inflammatory markers before RYGB surgery, and to establish a cut-off point for ferritin levels in premenopausal women since the depletion of iron stores associated with low nutritional demands after RYGB surgery culminate with premature anemia. It has been suggested that with a depletion of iron stores, as seen with ferritin levels of less than 50 ng/dL, the preoperative micronutrient supplementation and increase of iron intake after surgery is fundamental for premenopausal women. This was a prospective study that elucidated a small part of the metabolic and inflammatory events involved in morbid obesity, and in the context of RYGB surgery and iron metabolism. Other prospective and controlled studies with different micronutrient supplementation schemes will complement our findings. The limitation of the current study was the number of subjects, mainly for group 2, who were a sample of convenience patients cared for by the public health system.

## CONCLUSION

Six months after RYGB surgery systemic inflammation was reduced in both supplementation schemes tested. However, micronutrient supplementation of 1 RDA before and 2 RDAs after surgery resulted in better improvements in iron metabolism.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Obesidad y síndrome metabólico

# Effects of a high-fat meal on postprandial incretin responses, appetite scores and *ad libitum* energy intake in women with obesity

## *Efectos de una comida rica en grasas en la respuesta posprandial de las incretinas, del apetito y en la ingestión de energía* ad libitum *en mujeres con obesidad*

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## Abstract

**Background:** Considering the possible role of triglycerides (TG), glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) in the regulation of appetite, this study aimed to compare high fat meal-induced response of GIP and GLP-1, appetite scores and ad libitum energy intake in women with obesity, according to postprandial increment in triglyceridemia (ΔTG).

**Methods:** Thirty-three no-diabetic women (BMI = 35.0 ± 3.2 kg.m$^{-2}$) were divided into two groups: Group with ΔTG ≤ median were called "Low TG change -LTG" and ΔTG > median, "High TG change - HTG". Plasma concentrations of GIP, GLP-1 and appetite sensations were measured prior to, and every 30 min for 180 min after ingestion of a high-fat breakfast. An ad libitum lunch was served 3 h after the test meal.

**Results:** The AUC incrementalGIP were significant lower in HTG *vs.* LTG group (p = 0.03). The same was observed for GIP levels at 150 min (p = 0.03) and at 180 min (p < 0.01). Satiety was lower in HTG at 120 min (p = 0.03) and 150 min (p < 0.01). The AUC totalGLP1 were similar between groups and there were no between-group differences for the GLP-1 at each time point. *Ad libitum* food intake were also similar between groups.

**Conclusions:** The HTG group exhibited differences in satiety scores and lower postprandial secretion of GIP, however with no impact on ad libitum food intake in short term.

**Key words:**

Incretins. Glucagon-like peptide 1. Glucose-dependent insulinotropic polypeptide. Hunger. Appetite. Food intake.

## Resumen

**Introducción:** teniendo en cuenta las posibles acciones de los triglicéridos (TG), del *glucose-dependent insulinotropic polypeptide* (GIP) y del *glucagon-like peptide-1* (GLP-1), en la regulación del apetito (hambre y saciedad), este estudio tuvo como objetivo comparar la respuesta posprandial inducida por una comida rica en grasas en los niveles del GIP y GLP-1, en el apetito y en la ingestión de energía *ad libitum* en mujeres con obesidad, clasificadas de acuerdo con el aumento de la trigliceridemia postprandial (ΔTG).

**Métodos:** treinta y tres mujeres sin diabetes (IMC = 35,0 ± 3,2 kg.m$^{-2}$) fueron clasificadas en dos grupos: grupo con ΔTG ≤ mediana ("bajo cambio en los TG - LTG") y grupo ΔTG > mediana ("alto cambio en los TG-HTG"). Los niveles plasmáticos del GIP, GLP-1 y del apetito fueron evaluados antes y cada 30 minutos durante 180 minutos después de la ingestión de un desayuno rico en grasas. Un almuerzo *ad libitum* fue servido 3 h después del desayuno.

**Resultados:** el área bajo la curva (AUC) del aumento del GIP (AUC aumentoGLP1) fue significativamente menor en el grupo HTG *vs.* LTG (p = 0,03). Lo mismo se observó para los niveles del GIP en los 150 minutos (p = 0,03) y en los 180 minutos (p < 0,01). La saciedad fue menor en el grupo HTG en los 120 minutos (p = 0,03) y en los 150 minutos (p < 0,01). La AUC totalGLP1 fue similar entre los grupos y no hubo diferencias entre ellos para los niveles del GLP-1 en los tiempos evaluados. La ingesta alimentaria *ad libitum* también fue similar entre los grupos.

**Conclusiones:** el grupo HTG presentó diferencias en la saciedad y menor secreción posprandial del GIP, sin embargo, sin impacto en la ingesta de alimentos *ad libitum* en el corto plazo.

**Palabras clave:**

Incretinas. Péptido análogo al glucagón tipo 1. Polipéptido insulinotrópico dependiente de glucosa. Hambre. Apetito. Ingesta alimentaria.

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## INTRODUCTION

The homeostatic mechanisms regulating food intake rely on a neuroendocrine system that involves peripheral and central signaling. The peripheral gastrointestinal signs consist of a series of peptides that are produced in response to food intake and modulate hunger and satiety (1). There is growing evidence to suggest that glucagon-like peptide-1 (GLP-1) is one of the mediators of the post-meal satiety response. The main mechanism of satiety exerted by GLP-1 is related to the "ileal brake", which slows down gastric emptying (2-4). Previous studies have shown that peripheral GLP-1 infusion increases satiety and reduces hunger in a dose-dependent way (3). The underlying mechanisms of action combine slow gastric emptying with direct effects on central nervous system (2). However, these effects are impaired in the obesity and individuals with obesity exhibit attenuated postprandial GLP-1 secretion in comparison to normal-weight controls, which may harms food intake regulation (5-7).

Importantly, most studies evaluating the role of GLP-1 in hunger and satiety have employed peripheral infusion of this hormone, which elevates the serum GLP-1 levels to supraphysiological values, and in these conditions it increases satiety and reduces hunger and energy intake in the short term (8-10). However, gaps in the knowledge of the role of this hormone in appetite modulation in a physiological way, that is, secondary to food intake, still exist, especially in obesity.

In contrast, whether glucose-dependent insulinotropic polypeptide (GIP) has a role in appetite modulation remains unclear. Raben et al. (1994) (11) showed that a higher postprandial GIP response to a high-fat meal were seen in women after weight loss compared to normal-weight controls, and the authors suggest that GIP may promote hunger and excessive food intake. Other studies have founded that postprandial GIP response was inversely related to the subsequent feeling of satiety (5,12,13). On the other hand, positive (14) or neutral (9,10,15) correlation between postprandial GIP and satiety were also observed.

Added to this, evidences in animal studies suggests the involvement of the TG, which are markedly elevated after a high-fat meal, in stimulate hypothalamic peptides known to increase feeding (16-19), and the hyperphagia after a high-fat meal is preceded by a marked increase in circulating TG levels (19).

In this context, the primary aim of the present study was to compare the response of GLP-1 and GIP and the *ad libitum* energy intake to a standardized high-fat test meal in women with obesity classified according to the change in plasma TG after this meal. We also wanted to examine the relationship between postprandial GLP-1, GIP and TG responses with subjective appetite regulation (hunger and satiety) and *ad libitum* energy intake.

## MATERIALS AND METHODS

### STUDY DESIGN AND SUBJECTS

This is a transversal clinical study. Thirty three women with obesity (BMI 30.0-39.9 $kg.m^{-2}$) between the ages of 20 and 45 years were recruited by posters in public places, e-mail and radio programs. None of the subjects used oral hypoglycemic agents, contraceptives and/or hormones, or anti-psychotic with drugs (washout of 3 months); had been diagnosed with diabetes mellitus, hypertriglyceridemia, thyroid dysfunction, hormone disorders; infections diseases or eating disorders; did not like the foods used in the study (bread, margarine, cheese, whole milk, pasta, tomato sauce and ground meat); had undergone nutritional monitoring during the previous 3 months; were pregnant or nursing or were in a menopausal period.

To compare the role of change in circulating TG after a high-fat meal in the postprandial response of GLP-1 and GIP and the *ad libitum* energy intake, women were classified in two groups according to their TG response after this meal. The median was used as a cutoff point of the postprandial change in TG levels: $\Delta TG$ in % = (TG at 180 min-TG at 0 min) x 100 / TG at 0 min. Group $\Delta TG \leq$ median were called "Low TG change - LTG" and $\Delta TG >$ median, "High TG change -HTG".

The study was approved by the Research Ethics Committee of University of São Paulo, Ribeirão Preto Medical School (process number 4618/2009). The patients received 2 consent forms for signature, one before and the other after the study. Only after the study the women were informed that *ad libitum* food intake would be quantified, thus preventing them from being influenced by this information regarding the amount of food to be consumed.

### HIGH-FAT MEAL

On each test day, patients arrived in the research unit in the morning after a 12 h overnight fast. A standardized, fixed energy high-fat breakfast (50 g of french bread with 15 g of margarine and 20 g of cheese and 150 ml whole milk; energy 414 kcal with 50% calories from fat, 35% from carbohydrates and 15% from protein) was then served, and they were instructed to eat all the food offered. Previous studies with high-fat meals also used this same percentage of energy from fat (20,21). Our aim with the high-fat meal was to elicit a sharp rise in the TG levels and stimulate physiological GIP and GLP-1 secretion (22,23).

### *AD LIBITUM* ENERGY INTAKE

The *ad libitum* meal (lunch) were offered three hours after breakfast and consisted of pasta bolognese. The preparation of the pasta and sauce was standardized and rigorously applied on each day of administration. Each *ad libitum* meal consisted of 1,900 g (energy density 1.22 $kcal.g^{-1}$) in order to make participants eat to their satisfaction, without being concerned about food availability and also to avoid variations in the quantity of food offered to each individual, which could interfere in the food intake. Each individual ate alone with no time restriction. The quantity of pasta consumed was evaluated by the difference between the starting amount and the leftovers on the pan and the plate.

## BIOCHEMICAL ANALYSES

Venous blood was drawn through an indwelling antecubital cannula into syringes. Blood was collected into tubes containing sodium fluoride and EDTA for the analysis of plasma glucose concentrations, in tubes containing clot activator and gel separator for insulin and TG, and in tubes containing EDTA and anti-DPP-IV protease inhibitor (10 μL.mL$^{-1}$ of blood) for the GIP and GLP-1. All blood samples were kept in ice until centrifugation at 3500rpm for 15 minutes at 4 °C, and serum and plasma samples were stored at -70 °C until analysis.

The analyses were performed at 0 (fasting), 30, 60, 90, 120, 150, and 180 min (this latter period was considered as preprandial, because it occurred before the *ad libitum* meal). The times selected for analysis of the postprandial curve of GIP and GLP-1 were adapted from the methodology proposed by Verdich et al. (2001) (5), which were also similar to the times used in other studies that described/evaluated postprandial curves of these hormones (24,25).

Total GIP and GLP-1 were determined by the Luminex™ xMAP methodology, by means of the kit GIP and GLP-1-HGT-68k (Millipore®); sensitivities were 0.2 and 5.2 pg.mL$^{-1}$, respectively, and the CV values were 3.7 and 8.7%, respectively. TG was quantified by the endpoint enzymatic method, by employing the kit Triglycerides Liquiform (Labtest®); sensitivity and CV were 0.99 mg.dL$^{-1}$and ≤ 5%, respectively.

Glucose was analyzed by the endpoint photometric method (Glucose PAP Liquiform), with the aid of the kit Glucose PAP Liquiform (Labtest®); the sensitivity and the coefficient of variation (CV) were 0.32 mg.dL$^{-1}$ and 3.0%, respectively. Insulin was determined by the Luminex™ xMAP methodology, using the kit insulin-HGT-68K (Millipore®); sensitivity and CV were 1.1 μU.mL$^{-1}$ and 7.3%, respectively. TG was quantified by the endpoint enzymatic method, by employing the kit Triglycerides Liquiform (Labtest®); sensitivity and CV were 0.99 mg.dL$^{-1}$ and ≤ 5%, respectively.

## ASSESSMENT OF HUNGER, SATIETY, PREFERENCE AND PALATABILITY

Previously validated 100-mm visual analogue scales (VAS) were used to assess hunger ("How hungry do you feel now?") and satiety ("How full/satisfied do you feel now?") (26). The participants were asked to fill in VAS before breakfast (0 min) and 30, 60, 90, 120, 150 and 180 min after the end of this meal (the same times when biochemical analyses were accomplished).

Moreover, after meal, the participants were asked to fill in 100-mm VAS to evaluate preference ("How much do you like pasta bolognese?") and meal palatability ("How tasty are this pasta?").

## SAMPLE CHARACTERIZATION

### Anthropometric and body composition analysis

Body weight (kg) and height (m) were measured to calculate the body mass index (BMI, in kg.m$^{-2}$). Body composition (fat mass and fat free mass) was evaluated by bioelectric impedance analysis (Biodynamics 450 Bioimpedance Analyzer). These measures were taken at the beginning of the study, in a fasting state.

## STATISTICAL ANALYSIS

The linear regression model with mixed effects (random and fixed effects) was employed to evaluate the differences in biochemical parameters and appetite between the groups at each time, as well as the difference between times within the same group. This methodology assumes that the residues have normal distribution, with mean 0 and constant variance $\sigma^2$. When this assumption was not verified, the response variable was transformed with the aid of the software SAS®9.0 and PROC MIXED. The orthogonal contrasts post-test aided the comparisons. The comparisons for orthogonal contrasts do not include adjustments for multiple testing. To study the variation between the groups of variables measured along time, the trapezium rule was employed to estimate the area under the curve ($AUC_{total}$ and $AUC_{incremental}$) for each participant. To compare the variables of quantitative characterization (anthropometric and body composition data, *ad libitum* energy intake and biochemical and appetite variables in fasting) between the groups, non-parametric Mann-Whitney test was applied for independent samples. The correlations were determined by Spearman correlation coefficient. The level of significance was set at 5% ($p < 0.05$).

## RESULTS

### SUBJECT CHARACTERISTICS

There were no significant differences between the groups HTG and LTG for any anthropometric variables or fasting levels of biochemical parameters and appetite scores (Table I).

### TRIGLYCERIDES (TG) AND POSTPRANDIAL INCRETIN RESPONSES (GIP AND GLP-1)

In HTG group (n = 16), the TG levels significant change from baseline at 60 min ($p < 0.01$) and remained at this level up to 180min. In contrast, for LTG group (n = 17), TG levels did not increase significantly as compared with basal levels at any of the evaluated times. The ΔTG (%) was higher in the HTG group compared to LTG group (78.8 ± 44.4% *vs.* 16.7 ± 18.4%, $p < 0.01$).

In the HTG group, the $AUC_{incrementalGIP}$ was significant lower when compared with LTG group (2423 ± 1979 pmol.L.min$^{-1}$ *vs.* 2809 ± 1042 pmol.L.min$^{-1}$, respectively, $p = 0.03$) and $AUC_{totalGIP}$ also presented trend to be lower in this group ($p = 0.08$) (Table II). GIP was also significantly lower in HTG group at 150 min (16.4 ± 6.4 pmol.L$^{-1}$ x 12.1 ± 7.3 pmol.L$^{-1}$, $p = 0.03$) and at 180 min (13.8 ± 4.7 pmol.L$^{-1}$ *vs.* 9.2 ± 6.3 pmol.L$^{-1}$, $p < 0.01$) (Fig. 1).

**Table I.** Basal characteristics of the participants

| | | LTG group (n = 17) | HTG group (n = 16) | p-value |
|---|---|---|---|---|
| Anthropometric parameters and body composition | Age (years) | 35.1 ± 5.6 | 35.6 ± 6.6 | 0.79 |
| | Body weight (kg) | 90.1 ± 12.9 | 91.0 ± 11.3 | 0.73 |
| | BMI ($kg.m^{-2}$) | 35.0 ± 3.0 | 35.0 ± 3.5 | 0.87 |
| | Fat mass (%) | 39.4 ± 3.0 | 39.9 ± 2.1 | 0.54 |
| Biochemical evaluation at fasting | Triglycerides ($mg.dL^{-1}$) | 104.4 ± 27.7 | 97.4 ± 40.5 | 0.19 |
| | Glucose ($mg.dL^{-1}$) | 82.1 ± 9.4 | 87.5 ± 12.4 | 0.13 |
| | Insulin ($\mu U.mL^{-1}$) | 14.5 ± 8.3 | 16.7 ± 10.9 | 0.56 |
| | GLP-1 ($pmol.L^{-1}$) | 4.7 ± 5.3 | 4.1 ± 6.3 | 0.63 |
| | GIP ($pmol.L^{-1}$) | 3.6 ± 2.2 | 4.5 ± 3.8 | 0.29 |
| Appetite scores at fasting | Hunger (mm) | 41.7 ± 35.4 | 39.6 ± 33.0 | 0.81 |
| | Satiety (mm) | 23.5 ± 25.8 | 35.2 ± 35.0 | 0.27 |
| *Ad libitum* food intake | *Ad libitum* food intake (kcal) | 483 ± 211 | 580 ± 249 | 0.33 |
| | Palatability (mm) | 85.1 ± 24.4 | 85.4 ± 24.0 | 0.44 |
| | Preference (mm) | 82.3 ± 23.4 | 82.1 ± 25.2 | 0.90 |

*Data are expressed as mean ± DP. LTG: low TG change group; HTG: high TG change group.*

**Table II.** Postprandial responses of hormones and appetite scores in LTG and HTG groups

| | | LTG group (n = 17) | HTG group (n = 16) |
|---|---|---|---|
| *GIP* | AUC (180 min.pmol.L-1) | 3775.6 (3229.5-4321.6) | 3539.4 (2313.8-4764.9)* |
| | Incremental AUC (180 min.pmol.L-1) | 2809.0 (2273.0-3345.1) | 2423.1 (1368.9-3477.2)# |
| *GLP-1* | AUC (180 min.pmol.L-1) | 1251.0 (675.5-1826.6) | 1030.8 (315.6-1746.0) |
| *Hunger* | AUC (180 min.mm-1) | 4849.4 (2798.5-6900.3) | 5727.2 (3492.2-7962.2) |
| | Incremental AUC (180 min.mm-1) | -1846.8 (-3879.1-185.6) | -1362.2 (-4460.0-1735.6) |
| *Satiety* | AUC (180 min.mm-1) | 11815.0 (9623.4-14006.0) | 9745.3 (7898.7-11592.0) |
| | Incremental AUC (180 min.mm-1) | 4816.8 (2770.4-6863.2) | 4630.0 (2305.0-6955.6) |

*Data are expressed as mean and 95% CI. LTG: low TG change group; HTG: high TG change group. *p = 0.08; #p = 0.02.*
*Because of the presence of some undetectable and negative values in the postprandial period, it was not possible to calculate the* $AUC_{incrementalGLP-1}$.

The $AUC_{totalGLP-1}$ were similar between groups (Table II). There were no between-group differences for the GLP-1 at each time point (Fig. 1).

## HUNGER, SATIETY, AND *AD LIBITUM* FOOD INTAKE

Satiety was significantly lower in HTG group at 120 min (46.4 ± 32.3 mm *vs.* 67.0 ± 25.2 mm in LTG group, p = 0.03) and at 150 min (30.2 ± 24.4 mm *vs.* 62.3 ± 26.0 mm in LTG group, p < 0.01). This same trend was noted at 180 min (27.6 ± 29.9 mm *vs.* 44.5 ± 27.6mm in LTG group, p = 0.08). There were no between-group differences for hunger at each time point (Fig. 2).

The HTG group showed a higher preprandial hunger (at 180 min) compared to hunger in fasting (64.2 ± 29.4 mm *vs.* 41.7 ± 35.4 mm, respectively, p < 0.01), which did not occur in LTG group (50.8 ± 31.7 mm *vs.* 39.6 ± 33.0 mm, respectively, p = 0.22) (Fig. 2).

Despite these findings, *ad libitum* energy intake, palatability, and preference were similar in both groups (Table I). However, it is noteworthy that HTG group presented 20% higher energy intake compared to LTG group, which corresponded to +97 kcal during this meal.

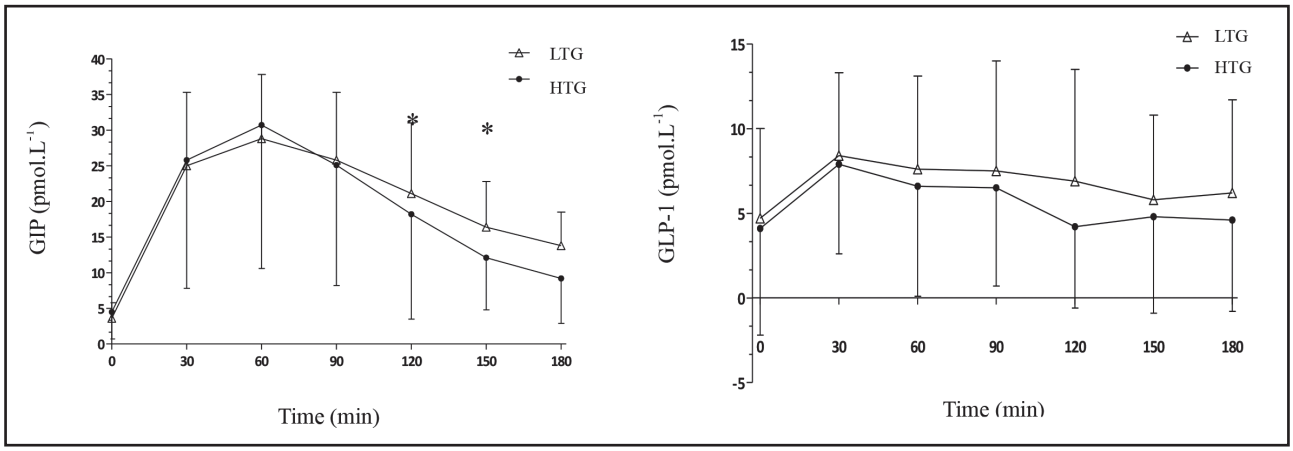


**Figure 1.**

Postprandial GIP and GLP-1 response along time in LTH and HTG groups (*significant difference between the groups).

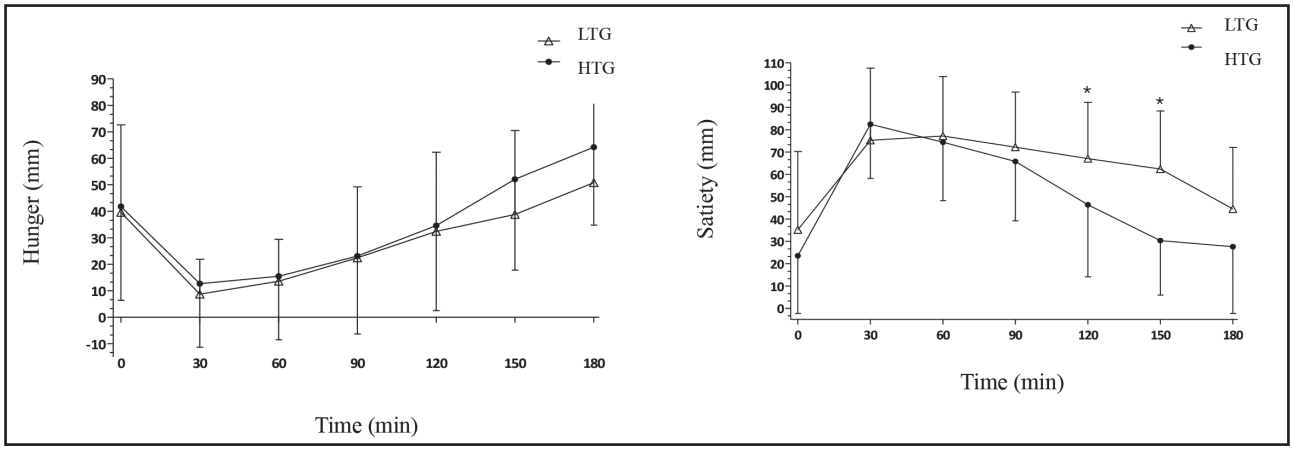


**Figure 2.**

Postprandial hunger and satiety response along time in LTG and HTG groups (*significant difference between the groups).

## TRIGLYCERIDES, INCRETIN RESPONSES AND APPETITE REGULATION

A positive correlation between preprandial TG levels and AUCTG with *ad libitum* food intake was found in the total sample ($r = 0,40$, $p = 0,03$ and $r = 0,38$, $p = 0,03$, respectively). Also for the total sample, an inverse correlation between preprandial TG levels and satiety (in the same period) was found ($r = -0,37$, $p = 0,04$). Only in LTG group, a positive correlation between GIP and GLP-1 (in fasting) with satiety ($r = 0.47$, $p = 0.05$ and $r = 0.70$, $p = 0.01$, respectively); and an inverse correlation between *ad libitum* food intake and $AUC_{totalGLP-1}$ ($r = -0.69$, $p = 0.01$) were observed.

## DISCUSSION

The findings of this study pointed out that women with larger increase in circulating TG levels after a high-fat meal intake exhibited some differences in incretin and appetite profile, that suggests attenuated postprandial GIP and satiety responses. We also found that preprandial TG levels and AUCTG levels correlated positively with *ad libitum* food intake, which indicates that TG somehow participated in appetite regulation.

Karatayev et al. (2009) (27) confirm the importance of post-prandial TG levels as a predictor of meal size in animals. However, the possibility that TG levels after a high-fat meal are causally related to subsequent hyperphagia still require further elucidation. Evidences suggests that circulating TG act physiologically on brain mechanisms, through orexigenic peptides, to stimulate feeding and, in particular, to mediate high-fat-induced hyperphagia (17,27,28). In fact, a lower secretion of GIP, which is a hormone with possible actions in the food intake regulation, were observed in the HTG group. Moreover, higher TG levels after a meal could be related to limited TG metabolization by the organism, which would stimulate food intake (29). This might point to difficult energy storage in the adipocytes, which could trigger

food intake as an attempt to revert the situation, since the human homeostatic system aims to maintain body storage (1,30).

However, despite these differences for the incretin between HTG and LTG groups, there was no impact on *ad libitum* energy intake. Some studies that aimed to assess GIP function in appetite and food intake using exogenous infusion of different rates (from 0.8 to 5.0 pmol.kg.min$^{-1}$) and distinct evaluation times did not find that GIP levels affected hunger, satiety, or prospective food intake (9,10). In contrast, Verdich et al. (2001) (5) showed an inverse correlation between the $AUC_{incrementalGIP}$ and *ad libitum* food intake, and our study also found a positive correlation between GIP and satiety (in fasting) in LTG group. Methodological differences, especially those related to the type of meal (quantity and quality) used to stimulate GIP secretion, and concomitant exogenous GIP infusion, may have been the reason for the diverse results. This is because several factors, such as chewing (31) and meal size and composition (25,32), can affect GIP levels, which are sensitive to abrupt and chronic alterations in the diet, especially those regarding the fat content (33).

Previous studies have demonstrated that exogenous infusion of GLP-1, in supraphysiological rates, reduces hunger and food intake (8-10). It is also known that GLP-1 reduces food intake in a dose-dependent way and the infusion rate was the only independent predictor of this reduction (3). In our work, it was observed that *ad libitum* food intake correlated negatively with $AUC_{totalGLP-1}$ in at least one group (LTG group). However, most consistent relationship between GLP-1with hunger and satiety upon physiologically stimulated secretion (secondary to food intake) were not find. Authors who used a methodological design similar to ours; i.e., GLP-1 secretion stimulated by food intake, did not find any GLP-1 effect on appetite or *ad libitum* food intake in eutrophic and men with obesity (5). Other studies that used infusions of exogenous GLP-1 at low rates (to reflect physiological postprandial concentrations) did also not detect any influence of GLP-1 on food intake (2,34). All these results suggest that, in physiological conditions, changes in GLP-1 along and after a meal do not significantly impact appetite regulation and subsequent energy intake in the short term, especially in individuals with obesity who seem to have an attenuated GLP-1 response during meals (5-7).

This lack of influence of GLP-1 in physiological conditions can be related to its short half-life, as well as GIP, which hinders the action of these hormones in appetite regulation. Both are, after its secretion, rapidly metabolized in their inactive forms by the enzyme DPP-IV, produced in high quantities by intestinal epithelial cells (33,35). Although providing an increased secretion in the postprandial period of around 5-10 times its baseline value, the biologically active quantity of these hormones in the blood stream is significantly smaller than the amount produced (36). Only about 10-15% of GLP-1 secreted reaches peripheral tissues and pancreatic β cells (35). It is important to consider the larger activity of DPP-IV verified in obesity; this degrades GLP-1 more precociously, thereby limiting its appetite-regulating actions in this condition (6,7).

Moreover, high-fat diets modify the intestine-brain axis communication, reduce the basal levels of GLP-1 and also reduce the activation of the GLP-1 receptor, attenuating its posterior satiety signaling (37-39). Besides that, lipotoxicity (which is associated with high-fat diets intake) affects GLP-1 receptors expression and signaling (40,41). Therefore, individuals with obesity, who are chronically exposed to high-fat diets, undergo rapid GLP-1 inactivation and require larger GLP-1 receptor stimulus to produce its anorexigenic effects.

The sample size can be considered a limitation in this study since some analysis showed no conclusive results but rather borderline p-values. Due to the pulsatile incretin secretion, the AUC's analysis also can be a limitation to find more conclusive results. Furthermore, it is important to consider that other variables related to emotional and environmental factors that influence food intake are difficult to control. The simple fact of participating in a survey can interfere with food intake.

In conclusion, our findings showed that women with larger increments in TG levels after a high-fat meal presented differences in satiety scores and lower postprandial secretion of GIP. This indicated an impaired incretin and appetite profile in women with this metabolic profile, however with no impact on *ad libitum* food intake in short term.

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Nutrición Hospitalaria

Trabajo Original

Obesidad y síndrome metabólico

# Relation of Trp64Arg polymorphism of beta 3 adrenoreceptor gene with metabolic syndrome and insulin resistance in obese women

*Relación del polimorfismo Trp64Arg del gen del receptor beta 3 con el síndrome metabólico y la resistencia a la insulina en mujeres obesas*

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## Abstract

**Background and aim:** Trp64Arg variant in beta 3 adrenoreceptor has been reported to be associated with increased body weight and insulin resistance. These risk factors are the ones that make up the so-called metabolic syndrome. The aim of our study was to investigate the relationship between metabolic syndrome and Trp64Arg polymorphism in the beta3 adrenoreceptor gene in obese women.

**Methods:** A population of 531 obese women was analyzed in cross-sectional survey. A bioimpedance, blood pressure, a serial assessment of nutritional intake with 3 days written food records and biochemical analysis were performed. Genotype of beta 3 adrenoreceptor gene polymorphism (Trp64Arg) was studied.

**Results:** Prevalence of metabolic syndrome (MS) with ATP III definition was 47.1% (250 patients) and 52.9% patients without MS (n = 281 patients). Prevalence of beta 3 genotypes was similar in patients with metabolic syndrome (87.6% wild genotype and 12.4% mutant genotype) and without metabolic syndrome (87.9% wild genotype and 12.1% mutant genotype). Insulin and HOMA levels were higher in patients with mutant genotype than wild type, in patients with and without metabolic syndrome.

**Conclusion:** In mutant group of beta3 adrenoreceptor gene patients have higher insulin and HOMA levels than wild type group, without relation with metabolic syndrome.

**Key words:**

Adipocytokines. Females. Insulin resistance. Metabolic síndrome. Trp64Arg beta 3 adrenoreceptor. Obesity.

## Resumen

**Antecedentes y objetivo:** la variante Trp64Arg en el receptor beta 3 adrenérgico se ha relacionado con un aumento de peso corporal y la resistencia a la insulina. Estos factores de riesgo son los que conforman el denominado síndrome metabólico. El objetivo de nuestro estudio fue investigar la relación entre el síndrome metabólico y el polimorfismo en el gen Trp64Arg adrenérgicos beta 3 en mujeres obesas.

**Métodos:** se evaluó una población de 531 mujeres obesas en un estudio transversal. A todos los pacientes se les realizó una bioimpedancia, determiancion de presión arterial, evaluación seriada de la ingesta nutricional de 3 días y análisis bioquímicos. Se evaluó el genotipo de beta 3 polimorfismo del gen del receptor adrenérgico (Trp64Arg).

**Resultados:** la prevalencia de síndrome metabólico (SM) con la definición de ATP III fue de 47,1% (250 pacientes) y un 52,9% de los pacientes sin SM (n = 281 pacientes). La prevalencia de los genotipos del receptor beta 3 fue similar en los pacientes con síndrome metabólico (genotipo salvaje 87,6% y el 12,4% genotipo mutante) y sin síndrome metabólico (genotipo salvaje 87,9% y el 12,1% genotipo mutante). Los niveles de insulina y HOMA-IR fueron mayores en los pacientes con genotipo mutante que salvaje, en pacientes con y sin síndrome metabólico.

**Conclusión:** el grupo de pacientes con genotipo mutante presentaban niveles más altos de insulina y HOMA-IR que el grupo con genotipo salvaje, sin tener una relación con el síndrome metabólico.

**Palabras clave:**

Adipocitoquinas. Mujeres. Resistencia a la insulina. Síndrome metabólico. Trp64Arg beta 3 adrenorreceptor. Obesidad.

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## INTRODUCTION

Obesity has multiple causes, and it´s determined by the interaction between genetic factors and environmental (1). Especially, gene defects showing no or only minor effect when expressed alone might influence on the phenotype. A variant is the tryptophan-to-arginine (Trp64Arg) missense mutation in the beta 3 adrenoreceptor (Beta3-AR). Beta3-AR is the principle mediator of cathecolamine-stimulated thermogenesis and lipolysis, which mainly occur at subcutaneous and visceral sites (2). Trp64Arg variant in this receptor has been reported to be associated with increased body weight and insulin resistance (3).

The factors associated with cardiovascular disease (CVD) (4) include high blood pressure, high triglyceride levels, hyperglycaemia, low high-density lipoprotein (HDL), and obesity. Many of these risk factors are the ones that make up the so-called syndrome X or metabolic syndrome (MS) (5,6). One of the most accepted classifications for defining the metabolic syndrome is the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III) (7).

Moreover, adipose tissue is considered an active secretory organ, sending out and responding to signals that modulate appetite, insulin sensitivity, energy expenditure, and inflammation. Adipocytokines are proteins produced mainly by adipocytes (8). These molecules have been shown to be involved in the pathogenesis of the metabolic syndrome and cardiovascular disease.

The aim of our study was to investigate the relationship between metabolic syndrome and Trp64Arg polymorphism in the beta 3 adrenoreceptor gene in obese women.

## SUBJECTS AND METHODS

### SUBJECTS

A population of 531 (body mass index > 30) obese females patients was analyzed in cross-sectional survey. The recruitment of subjects was a non probabilistic method of sampling among patients send from Primary Care Physicians with obesity from Valladolid (norwest of Spain). Exclusion criteria included history of cardiovascular disease or stroke during the previous 36 months, malignant tumour or major surgery during the previous 6 months as well as the use of glucocorticoids, antineoplastic agents, and drinking and/or smoking habit. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving patients were approved by the HURH ethics committee. Written informed consent was obtained from all patients and signed.

### PROCEDURES

Weight, blood pressure, basal glucose, insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides blood and citokines (leptin, adiponectin, resistin) levels were measured at basal time. Genotype of beta 3 adrenoreceptor gene polymorphism was studied. To estimate the prevalence of Metabolic Syndrome, the definitions of the ATPIII was considered (7). The cutoff points for the criteria used are three or more of the following; central obesity (waist circumference > 88 cm), hypertriglyceridemia (triglycerides > 150 mg/dl or specific treatment), hypertension (systolic BP > 130 mmHg or diastolic BP > 85 mmHg or specific treatment) or fasting plasma glucose > 110 mg/dl or drug treatment for elevated blood glucose

### GENOTYPING OF BETA 3 ADRENORECEPTOR GENE POLYMORPHISM

Oligonucleotide primers and probes were designed with the Beacon Designer 4.0 (Premier Biosoft International®, LA, CA). The polymerase chain reaction (PCR) was carried out with 250 ng of genomic DNA, 0.5 uL of each oligonucleotide primer (primer forward: 5'-CAA CCT GCT GGT CAT CGT-3'; primer reverse: 5'-AGG TCG GCT GCG GC-3'), and 0.25 uL of each probes (wild probe: 5'-Fam-CCA TCG CCT GGA CTC CG-BHQ-1-3') and (mutant probe: 5'-Hex-CAT CGC CCG GAC TCC G- BHQ-1-3') in a 25 uL final volume (Termociclador iCycler IQ (Bio-Rad®), Hercules, CA). DNA was denaturated at 95 °C for 3 min; this was followed by 50 cycles of denaturation at 95 °C for 15 s, and annealing at 59.3 °C for 45 s). The PCR were run in a 25 uL final volume containing 12.5 uL of IQTM Supermix (Bio-Rad®, Hercules, CA) with hot start Taq DNA polymerase.

### ASSAYS

Serum total cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay (Technicon Instruments, Ltd., New York, N.Y., USA), while HDL cholesterol was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulfate-magnesium. LDL cholesterol was calculated using Friedewald formula.

Plasma glucose levels were determined by using an automated glucose oxidase method (Glucose analyser 2, Beckman Instruments, Fullerton, California). Insulin was measured by enzymatic colorimetry (Insulin, WAKO Pure-Chemical Industries, Osaka, Japan) and the homeostasis model assessment for insulin sensitivity (HOMA) was calculated using these values (9).

Adiponectin was measured by ELISA (R&D systems, Inc., Mineapolis, USA) with a sensitivity of 0.24 ng/ml and a normal range of 8.65-21.43 ng/ml, interassay coefficients of variation were less than 10%. Resistin was measured by ELISA (Biovendor Laboratory, Inc., Brno, Czech Republic) with a sensitivity of 0.20 ng/ml with a normal range of 4-12 ng/ml, interassay coefficients of variation were less than 10%. Leptin was measured by ELISA (Diagnostic Systems Laboratories, Inc., Texas, USA) with a sensitivity of 0.05 ng/ml and a normal range of 10-100 ng/ml, interassay coefficients of variation were less than 15%.

## ANTHROPOMETRIC MEASUREMENTS AND DIETARY INTAKE

Body weight was measured to an accuracy of 0.1 kg and body mass index computed as body weight/(height$^2$). Waist (narrowest diameter between xiphoid process and iliac crest) and hip (widest diameter over greater trochanters) circumferences to derive waist-to hip ratio (WHR) were measured, too. Tetrapolar body electrical bioimpedance was used to determine body composition (Biodynamics Model 310e, Seattle, WA, USA) (10). Blood pressure was measured twice after a 10 minutes rest with a random zero mercury sphygmomanometer, and averaged. Patients received prospective serial assessment of nutritional intake with 3 days written food records. All enrolled subjects received instruction to record their daily dietary intake for three days including a weekend day. Food scales and models to enhance portion size accuracy were used. National composition food tables were used as reference (11). Aerobic exercise was recorded in the same questionnaire.

## STATISTICAL ANALYSIS

All the data were analysed using SPSS for Windows, verson 15.0 software package (SPSS Inc. Chicago, IL). Sample size was calculated to detect differences over 40% of prevalence of metabolic syndrome with 90% power and 5% significance. The results were expressed as average ± standard deviation. The statistical differences in genotype distribution and allele frequencies between groups and analysis of deviation from the Hardy Weinberg equilibrium were assesses usin chi-square or fisher exact test. Other variables were analyzed with ANOVA test (for normally-distribited variable) or Kruskal-Wallis test (for non-normally-distribited variable). The statistical analysis was performed for a dominant model. Logistic regression analyses were used to calculated odds ratio (OR) and 95% confidence interval (CI) to estimate the association of the rd161547 SNP with the risk of metabolic syndrome. A p-value under 0.05 was considered statistically significant.

## RESULTS

Five hundred and thirty one patients gave informed consent and were enrolled in the study. The mean age was 45.9 ± 12.8 years and the mean BMI 36.5 ± 6.2.

Four hundred and sixty six patients (87.8%) had the genotype *Trp64/Trp64* (wild group), whereas 65 (12.2%) had genotype *Trp64/Arg64* (mutant group). Age was similar in both groups (wild type: 45.8 ± 12.3 years *vs.* mutant group: 46.1 ± 11.2 years:ns).

Prevalence of metabolic syndrome (MS) with ATP III definition was 47.1% (250 patients) and 52.9% patients without MS (n = 281 patients). Prevalence of beta 3 genotypes was similar in patients with metabolic syndrome (87.6% wild genotype and 12.4% mutant genotype) and without metabolic syndrome (87.9% wild genotype and 12.1% mutant genotype). Prevalence of each criteria of metabolic syndrome was calculated in wild and mutant type genotypes, without statistical differences. Elevated waist circumference was detected in 92.0% patients with wild type genotype and 94.8% patients with mutant type genotype. Elevated levels of triglycerides or specific treatment were detected in 20.4% patients with wild type genotype and 14.5% patients with mutant type genotype. Elevated levels of blood pressure or specific treatment were detected in 54.7% patients with wild type genotype and 54.7% patients with mutant type genotype. Elevated levels of glucose or specific treatment were detected in 33.6% patients with wild type genotype and 33.9% patients with mutant type genotype.

Table I shows the subjects´differences in anthropometric and cardiovascular variables with and without metabolic syndrome (MS). Females with MS had higher weight, BMI, waist circumference, waist to hip ratio, systolic and diastolic blood pressure, glucose, HOMA, insulin, total cholesterol, LDL cholesterol and triglycerides than patients without MS. Table II shows the subjects´levels of adipokines. Females with MS had lower adiponectin levels than patients without MS.

Subject´s nutritional intake was similar in both groups (MS *vs.* no MS); calory (1757 ± 68 cal/day *vs.* 1689 ± 567 cal/day), carbohydrate (187.8 ± 68 g/day *vs.* 171.5 ± 73 g/day), fat (80.8 ± 35 g/day *vs.* 73.3 ± 29.3 g/day), protein (87.7 ± 24 g/day *vs.* 84.8 ± 25 g/day) and fiber intakes (14.9 ± 6.1 g/day *vs.* 14.1 ± 6.2 g/day). Hours of exercise per week were similar (1.54 ± 2.6 h/week *vs.* 1.37 ± 2.9 h/week), too. No differences in dietary intakes or physical activity were detected in both genotypes (wild *vs.* mutant type) in metabolic and no metabolic syndrome groups.

Table III shows the subjects´differences in anthropometric and cardiovascular variables secondary to genotype in metabolic and no metabolic syndrome. Patients with MS, in both genotypes, had higher weight, BMI, waist circumference, blood pressure, glucose, HOMA, insulin, and triglycerides than patients without MS. Significant differences in insulin and HOMA levels were detected between genotypes in the same group of metabolic syndrome. Insulin and HOMA levels were higher in patients with mutant genotype than wild type.

Table IV shows the subjects' levels of adipokines in both genotypes in metabolic and no metabolic syndrome. Patients with MS, in both genotypes had lower adiponectin levels than patients without MS. No differences in adipocytokines levels were detected between genotypes in the same group of metabolic syndrome.

## DISCUSSION

The main finding of this study is the lack of association of the *Trp64/Trp64* and *Trp64/Arg64* genotypes with metabolic syndrome. Women of mutant genotype group of beta3 adrenoreceptor gene (*Trp64/Arg64*) have higher insulin and HOMA levels than wild type group, with and without metabolic syndrome.

Our present finding that the frequency of the Arg64 allele was 12.2% in obese female's patients agrees with previous

**Table I.** Anthropometric and biochemical variables, metabolic syndrome *vs.* no metabolic syndrome

| Characteristics | Metabolic syndrome (n = 250) | No metabolic syndrome (n = 281) |
|---|---|---|
| BMI | 37.2 ± 6.6 | 35.2 ± 5.8* |
| Weight (kg) | 92.7 ± 17.3 | 90.4 ± 15.9 |
| Fat mass (kg) | 47.8 ± 14.5 | 41.8 ± 12.3* |
| WC (cm) | 110.9 ± 14.6 | 105.4 ± 13.3* |
| Waist to hip ratio | 0.91 ± 0.07 | 0.88 ± 0.07* |
| Systolic BP (mmHg) | 136.5 ± 15.7 | 122.5 ± 13.5* |
| Diastolic BP (mmHg) | 87.1 ± 9.9 | 78.2 ± 9.3 * |
| Glucose (mg/dl) | 109.9 ± 28.7 | 91.2 ± 11.4* |
| Total ch. (mg/dl) | 209.4 ± 37.4 | 195.7 ± 41.2* |
| LDL-ch. (mg/dl) | 127.1 ± 36.5 | 116.4 ± 40.2* |
| HDL-ch. (mg/dl) | 56.9 ± 24.1 | 57.5 ± 16.3 |
| TG (mg/dl) | 134.5 ± 60.6 | 95.6 ± 39.1* |
| Insulin (mUI/L) | 16.9 ± 10.1 | 13.2 ± 6.3* |
| HOMA | 4.70 ± 2.9 | 2.95 ± 1.5* |

*BMI: body mas index; Ch: cholesterol; TG: triglycerides; hOMA: homeostasis model assessment; WC: waist circumference. (*) p < 0.05, between groups.*

**Table II.** Circulating adypocitokines, metabolic syndrome *vs.* no metabolic syndrome

| Characteristics | Metabolic syndrome (n = 250) | No metabolic syndrome (n = 281) |
|---|---|---|
| Adiponectin (ng/ml) | 32.1 ± 31.1 | 40.4 ± 36.8* |
| Resistin (ng/ml) | 3.85 ± 1.83 | 4.03 ± 1.73 |
| Leptin (ng/ml) | 90.8 ± 54.1 | 95.8 ± 51.1 |

*IL-6: interleukin 6. *p < 0.05, between groups.*

**Table III.** Anthropometric and biochemical variables

| Characteristics | Metabolic syndrome (n = 250) | | No metabolic syndrome (n = 281) | |
|---|---|---|---|---|
| | WT | MT | WT | MT |
| BMI | 37.2 ± 6.5 | 37.1 ± 7.2 | 35.2 ± 5.5$^{+}$ | 35.8 ± 7.3$^{+}$ |
| Weight (kg) | 92.7 ± 16.7 | 92.6 ± 22.6 | 90.1 ± 15.1$^{+}$ | 92.3 ± 21.2$^{+}$ |
| Fat mass (kg) | 43.7 ± 8.1 | 44.8 ± 15.2 | 41.7 ± 11.7$^{+}$ | 42.9 ± 14.3$^{+}$ |
| Waist c. | 110.9 ± 14.4 | 110.8 ± 15.9 | 105.4 ± 12$^{+}$ | 106.7 ± 16.4$^{+}$ |
| Waist to hip | 0.91 ± 0.07 | 0.91 ± 0.07 | 0.90 ± 0.1 | 0.89 ± 0.09 |
| SBP (mmHg) | 136.8 ± 14 | 140.8 ± 21.2 | 122.4 ± 13$^{+}$ | 122.8 ± 15.3$^{+}$ |
| DBP (mmHg) | 87.1 ± 9.8 | 87.3 ± 11.4 | 78.1 ± 9.1$^{+}$ | 78.5 ± 11.1$^{+}$ |
| Glucose (mg/dl) | 110.1 ± 27 | 109.4 ± 36.1 | 91.1 ± 11.1$^{+}$ | 91.8 ± 13.8$^{+}$ |
| Total ch. (mg/dl) | 209.2 ± 37 | 206.8 ± 36 | 194.8 ± 40 | 203.0 ± 41 |
| LDL-ch. (mg/dl) | 128.1 ± 37 | 120.9 ± 35 | 121.8 ± 34 | 122.8 ± 41 |
| HDL-ch. (mg/dl) | 55.7 ± 26.9 | 66.8 ± 49.9 | 58.1 ± 16.4 | 54.1 ± 13.6 |
| TG (mg/dl) | 136.4 ± 61 | 123.2 ± 47.3 | 93.6 ± 34.1$^{+}$ | 110.3 ± 62$^{+}$ |
| Insulin (mUI/L) | 16.4 ± 9.4 | 19.6 ± 12.7* | 13.1 ± 6.4$^{+}$ | 14.6 ± 9.1$^{+*}$ |
| HOMA-IR | 4.5 ± 2.9 | 5.4 ± 3.3* | 2.9 ± 1.3$^{+}$ | 3.3 ± 2.2$^{+*}$ |

*MS: metabolic syndrome; BMI: body mas index; Ch: cholesterol; HOMA-IR: homeostasis model assessment; TG: triglycerides; WC: waist circumference; WT (wild type genotype* Trp64Trp*) MT (mutant type genotype* Trp64Arg*). $^{+}$p < 0.05, statistical differences between MS and no MS groups in different allele groups* (Trp64Trp *vs.* Trp64Arg). **Statistical differences between WT and MT in each allele group.*

**Table IV.** Circulating adypocitokines

| Characteristics | Metabolic syndrome | | No metabolic syndrome | |
|---|---|---|---|---|
| | WT | MT | WT | MT |
| Adiponectin (ng/ml) | 31.5 ± 42.2 | 35.9 ± 48.6 | 41.3 ± 34$^{+}$ | 40.1 ± 38$^{+}$ |
| Resistin (ng/ml) | 3.88 ± 1.8 | 3.61 ± 1.9 | 4.05 ± 1.9 | 3.86 ± 1.0 |
| Leptin (ng/ml) | 89.7 ± 46 | 98.4 ± 46 | 97.2 ± 56 | 86.7 ± 65 |

*MS: metabolic syndrome; WC: waist circumference; WT (wild type genotype* Trp64Trp*) MT (mutant type genotype* Trp64Arg*)(*). $^{+}p < 0.05$, statistical differences between MS and no MS groups in different allele groups* (Trp64Trp vs. Trp64Arg). *No statistical differences between WT and MT in each allele group.*

reports (12,13). Secondly, a meta-analysis assessing quantitative phenotypes in relation to Trp64Arg polymorphism with BMI across diverse populations did not find evidence of this association (14), as our study shows.

Thirdly with respect to insulin resistance, omental adipocyte beta 3 adrenoreceptor sensitivity was related to waist hip ratio and insulin resistance in subjects with Arg allele of this polymorphism (15). Perhaps, defects in beta 3 adrenoreceptor signal transduction, binding, or regulatory mechanism may result in a disminished lipolytic response in visceral adipose tissue, aggravating insulin resistance. Our data showed metabolic differences between wild and mutant type patients, with increased levels of insulin and HOMA in females with and without metabolic syndrome. The mechanism through which the Arg64 variant alters insulin sensitivity could be explained by adipocytokine actions, too. Resistin and adiponectin appear to be important in regulating insulin sensitivity (16). Leptin is another adipocytokine that has been implicated in glucose homeostasis. It is thought to have some role in regulating insulin sensitivity (17), too. The mechanism through which adipocytokines alters sensitivity cannot be explained from our data, because we did not observe differences among adipocytokines in wild and mutant type groups. The decreased levels of adiponectin in our patients with metabolic syndrome are expected. Adiponectin decreases lipid synthesis and glucose production in the liver and causes decreases in glucose and free fatty acid concentrations in the blood. In offspring of diabetes mellitus type 2 patients (18).

Other previous study has demonstrated that obese postmenopausal women who are heterocygous for this beta 3 adrenoreceptor variant had greater insulin resistance than women homozygous for the normal gene (19). Kurabayashi et al. (20) showed that females heterozygous for this variant, but not men, have clinical manifestations of obesity and insulin resistance syndrome. Our results have been confirmed by Gjesing et al. (21), too. In this study, the Trp64 polymorphism was not associated with obesity, but, the Arg allele was associated with increased insulin resistance and insulin levels. Therefore, the lack of association with BMI and waist circumference as a measure of obesity may reflect that these measures do no adequately represent the biological body fat related variable influenced by the Trp64Arg variant.

Perhaps, these unclear results in the literature (22-24) may partially explain by differences in ethnic background, baseline BMI, gender distribution, previous weight loss, experimental design (early stage or late stage type 2 diabetes mellitus), accuracy of measures of insulin, and basal adypocitokines levels of participants. Therefore, interaction between gene and ambient could explain these differences with bias in previous studies.

Nevertheless, the cross sectional design of our study showed the lack of association of this polymorphism with metabolic syndrome. Therefore, interaction between gene and environmental factors, such as dietary treatments (25,26), could influence in development metabolic syndrome in the following years of these patients

In conclusion, in mutant group of beta3 adrenoreceptor gene (*Trp64/Arg64*) patients have higher insulin and HOMA levels than wild type group, without relation with metabolic syndrome. Further studies are needed to explore this unclear topic area (27).

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Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

# BMI, BMIfat, BAI or BAIFels – Which is the best adiposity index for the detection of excess weight?

## *Índice de masa corporal (IMC), IMC ajustado a la grasa, índice de adiposidad (IA) e IA ajustado (BaIFels). ¿Cuál es el mejor índice de adiposidad para detectar el exceso de peso?*

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## Abstract

**Objective:** To compare the diagnostic performance of adiposity indeces body mass index (BMI), body mass index adjusted for fat mass (BMIfat), body adiposity index (BAI) and body adiposity index for the Fels Longitudinal Study sample (BAIFels) and the overweight detection in a sample of the Brazilian population.

**Methods:** Cross-sectional study with 501 individuals (female/male = 387/114), which underwent anthropometric measurements and body composition for subsequent calculation of adiposity indices. Statistical analyzes considered $p < 0.05$ as statistically significant.

**Results:** The averages were: age of 46.94 ± 14.22 years and 48.05 ± 14.40 years, weight 79.5 ± 16, 14 kg and 70.42 ± 16,62 kg, height 172.86 ± 7.6 cm and 159.0 ± 7,35 cm, for men and women, respectively. According to the eutrophic ratings and overweight, the BMIfat ranked 40.3% and 34.0% for men and 21.7% and 65.0% for females, respectively. While the BAI held 47.7% and 62.3% for men and 65.6% and 34.4% for women, respectively. The receiver operating characteristic (ROC) curve of BMIfat was clearly superior to all other indexes for both men (93.1%) and women (97.8%), respectively.

**Conclusion:** Findings suggest that BMIfat is the index that has better relationship with the prediction of body fat, BAI did not exceed the limitations of BMI. Future studies should seek to expand this study by adopting the gold standard methods such as DXA and it is necessary to extend the investigation of the validity of adiposity indices to different ethnic groups.

**Key words:**

Body mass index. Adiposity index. Fat mass.

## Resumen

**Objetivo:** comparar el rendimiento diagnóstico de índices de adiposidad: índice de masa corporal (IMC), índice de masa corporal ajustado para la masa grasa (BMIfat), índice de adiposidad corporal (BAI) y el índice de adiposidad corporal para la muestra Fels Longitudinal Study (BAIFels) para detectar en una muestra de la población brasileña.

**Métodos:** estudio transversal con 501 individuos (mujeres/hombres = 387/114), que se sometieron a mediciones antropométricas y de composición corporal para el posterior cálculo de los índices de adiposidad. Se consideró $p < 0,05$ como estadísticamente significativo.

**Resultados:** los promedios fueron para hombres y mujeres, respectivamente: edad de 46,94 ± 14,22 años y 48,05 ± 14,40 años, peso 79,5 ± 16, 14 kg y 70,42 ± 16,62 kg, altura de 172,86 ± 7,6 cm y 159,0 ± 7,35 cm. De acuerdo con las clasificaciones eutróficos y con sobrepeso, el BMIfat varió entre el 40,3% y el 34,0% en varones y el 21,7% y el 65,0% para las mujeres, respectivamente. Mientras que el BAI estuvo entre el 47,7% y el 62,3% para los hombres y 65,6% y 34,4% para las mujeres, respectivamente. La curva de características operativas del receptor (ROC) de BMIfat fue claramente superior a todos los demás índices, tanto para los hombres (93,1%) como para las mujeres (97,8%).

**Conclusión:** los resultados sugieren que BMIfat es el índice que tiene mejor relación con la predicción de la grasa corporal. El BAI no superó las limitaciones del índice de masa corporal. Los estudios futuros deben tratar de desarrollar este estudio mediante la adopción de los métodos estándar de oro como DXA; es necesario ampliar la investigación de la validez de los índices de adiposidad en diferentes grupos étnicos.

**Palabras clave:**

Índice de masa corporal. Índice de adiposidad. Masa grasa.

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## INTRODUCTION

The global prevalence of obesity has increased to the point of representing a worldwide epidemic such that in 2015, approximately 2.3 billion people are considered overweight and 700 million are considered obese (1,2), corresponding to a 75% increase over ten years. In Europe (3), the prevalence of obesity has increased three-fold over the last two decades, and excess weight and obesity have also increased significantly in Brazil with 50.8% of all Brazilians considered overweight and 17.5% as obese (4). In the United States, more than 97 million people in the United States are overweight or obese (approximately 50% of the population) and this number continues to increase (5). Yet, it is still unclear how to best detect excess body fat and classify people as overweight or obese in terms of body composition. Such indices are essential for the assessment of nutritional status in a population since an early diagnosis of obesity would permit the adoption of some measures for the prevention of comorbidities associated with obesity such as type 2 diabetes mellitus and cardiovascular diseases. Therefore, the focus of this study was to compare various indices of body mass and body composition in a sample of adults in Brazil.

The body mass index (BMI), proposed by Quetelet in 1835, has been adopted worldwide as a tool for the classification of obesity by the World Health Organization since 1997. However, today we know that the BMI has important limitations, being a relatively weak indicator of body fat which does not discriminate the location of adiposity (6). In order to overcome the limitations of the BMI, other indices have been currently proposed such as the BAI (body adiposity index), BAIFels (Body Adiposity Index for the Fels Longitudinal Study sample) and BMIfat (BMI corrected for fat mass). In 2011, Mialich et al. formulated the BMIfat, which proved to be able to overcome the limitations of the BMI by including weight, height and percent fat mass in its calculation (7). The index, which expanded the diagnostic capacity of the classical BMI, was later tested in a sample to 500 Brazilian individuals (8).

The body adiposity index (BAI) was created by Bergman et al. (2011) for Mexican-American individuals and its variables are hip circumference and height (9). However, some authors who tested the use of the BAI suggested that it overestimates body fat in men and underestimates it in women. Thus, Johnson et al. in 2012 adjusted the BAI in a study of 626 European-American adults and created the BAIFels (10). Since these new indices have only recently appeared in the literature, further comparative studies are needed to determine which one best reflects and diagnoses adiposity in a given population. Thus, the objective of the present study was to compare these indices in the Brazilian population, an original and fundamental proposal in order to assess the behavior, diagnostic acuity, possible limitations and refinement of each method.

## MATERIALS AND METHODS

### SUBJECTS

Participants in this study included 501 adults of both genders (female/male = 387/114), consisting of patients and their accompanying persons, employees of the University Hospital, Ribeirao Preto Medical School, University of São Paulo (USP), and university students enrolled in the undergraduate courses of USP on the Ribeirao Preto campus. Exclusion criteria were age of less than 17 years, subjects with amputated or immobilized limbs, unable to walk, bedridden, having edema and/or ascites and receiving intravenous hydration, procedures that would impair the measurements. Also excluded were individuals wearing a heart pacemaker, an aneurysm clip, metal implants of any type (metal wire, plate or screw), and patients isolated from contact. Participation was on a volunteer basis and each individual was evaluated only once during the study by a group of trained examiners. The study was approved by the Research Ethics Committee and all subjects gave written informed consent to participate (Protocol nº 1955/2010).

### ANTHROPOMETRIC ASSESSMENT

Each subject underwent standard anthropometric measurements such as weight, height and arm, waist and hip circumference and tested for body composition by biolelectrical impedance (BAI) in triplicate by the same examiner. Weight was measured with a BC-558 Ironman Segmental Body Composition Monitor electronic scale (Tanita Corp., Tokyo, Japan), with maximum capacity of 150 kg and precision of 0.01 kg, with the subjects barefoot, wearing light clothing and no accessories. Height was measured with a 2 meter anthropometer, with the subject standing erect and barefoot, with his neck and head aligned with the trunk (11). The circumferences were measured with an inextensible metric tape with 0.1 cm divisions according to the anatomic points standardized by Lohman et al. (1988) (12).

### ASSESSMENT OF BODY COMPOSITION

The BC-558 Ironman Segmental Body Composition Monitor (Tanita Corp., Tokyo, Japan) was used to assess body composition (fat mass, fat-free mass and body water). For the exam the subjects were barefoot and wore light clothing and care was taken to certify that their heels were correctly aligned with the electrodes of the measuring platform. The subjects were required to have fasted for at least 5 hours, not to have practiced vigorous physical activity during the last 12 hours, to have urinated 30 minutes before the beginning of the exam and to have abstained from alcoholic or caffeine-containing drinks for 24 hours before the exam. During the exam, the subjects held with their hands retractable levers that acted together with the foot electrodes forming a 90 ºC angle between the base of the electrode and the rod connecting it to the equipment. After this measurement, which lasted approximately 30 seconds, the display automatically showed the final result of the assessment of body composition.

### ADIPOSITY INDICES

The body mass index (BMI) was determined as the ratio between current weight in kg and height in meters squared, i.e., BMI =

weight/height$^2$ (6). Nutritional status was classified according to the cut-off points and the classification proposed by the WHO (WHO, 1998) as follows: BMI of less than 18.49 kg/m$^2$, undernutrition; BMI between 18.5 and 24.9 kg/m$^2$, normal weight; BMI between 25.0 and 29.9 kg/m$^2$, overweight, BMI between 30.0 and 34.9 kg/m$^2$, grade I obesity, BMI between 35.0 and 39.9 kg/m$^2$, grade II obesity, and BMI above 40.0 kg/m$^2$, grade III obesity. BMIfat (BMI adjusted for fat mass) proposed by Mialich et al. (2011) was calculated by the following equation: [(3 weight + 4 fat mass)/height], with weight as kg, fat mass as percentage (%), and height as meters (m). The ranges proposed by Mialich et al. (2014) were considered for the classification of nutritional status based on this adiposity index, as follows: 1.35 to 1.65, nutritional risk for undernutrition; > 1.65 to ≤ 2.0, normal weight, and > 2.0 obesity. The BAI, proposed by Bergman et al. (2011), was obtained from the ratio of hip circumference in cm to height in meters elevated to 1.5 minus 18: BAI = [(hip circumference)/((height)$^{1.5}$) - 18]. The BAIFels (Body Adiposity Index for the Fels Longitudinal Study sample) developed by Johnson et al. (2012) was obtained using the BAI formula although with height elevated to 1.4 and the ratio product multiplied by 1.26, minus 32.85: [1.26 × (hip circumference)/height$^{1.4}$) - 32.85]. The values proposed by the WHO were considered for both the BAI and BAIFels for the classification of obesity, i.e., 25% for men and 35% for women (13).

## STATISTICAL ANALYSIS

Data are reported as mean and standard deviation and were compared by the Student t-test. Sensitivity, specificity, and predictive values with their respective 95%CI were calculated for the analysis of the diagnostic performance of the adiposity indices (BMI, BMIfat, BAI and BAIFels), and receiver operating characteristic (ROC) curves were constructed for the detection of the areas under the curve. The analyses were carried out using the SAS software version 9, with the level of significance set at $p < 0.05$.

## RESULTS

The study was conducted on 501 volunteers, 114 (23%) males and 387 (77%) females. Mean age was 46.94 ± 14.22 years for men and 48.05 ± 14.40 years for women. Both weight and height values were significantly higher in men, i.e. 79.5 ± 16.14 kg and 172.86 ± 7.6 cm *vs.* 70.42 ± 16.62 kg and 159.0 ± 7.35 cm in women. As expected, mean fat-free mass (FFM) and total body water (TBW) were higher in men, with FFM values of 58.35 ± 9.45 kg for men and 42.34 ± 6.21 kg for women ($p < 0.0001$) and TBW values of 56.35 ± 6.15% for men and 47.56 ± 5.9 for women ($p < 0.0001$). In contrast, fat mass (FM) was higher in women, i.e., 35.14 ± 8.27% *vs.* 21.57 ± 7.3% for men. Except for age, BMI, arm circumference and waist circumference, all other variables differed significantly between men and women ($p < 0.05$). All of these data are presented in table I.

Regarding BMI, most individuals (about 33.33%) were classified as being of normal weight, approximately 3% as undernourished, 32.5% as overweight, 18.3% as grade I obese, and 12.4% as grade II obese. Data analysis according to gender revealed that males predominated in the overweight range, whereas females predominated in the more severe cases of obesity, as shown in figure 1.

The mean values for the adiposity indices were 27.47 ± 5.92 kg/m$^2$ for BMI, 2.13 ± 0.49 for BMIfat, 31.60 ± 6.5% for BAI, and 32.74 ± 8.27% for BAIFels. When stratified according to gender, the mean values for men and women were 26.5 ± 4.5 kg/m$^2$ and 27.76 ± 6.25 kg/m$^2$ for BMI, 1.87 ± 0.38 and 2.21 ± 0.49 for

**Table I.** Anthropometric and body composition characterization of the sample studied

| Variable | All subjects | Males | Females | p value |
|---|---|---|---|---|
| n | 501 | 114 | 387 | - |
| Age (years) | 47.8 ± 14.36 | 46.94 ± 14.22 | 48.05 ± 14.40 | 0.4684 |
| Weight (kg) | 73.49 ± 16.93 | 79.5 ± 16.14 | 70.42 ± 16.62 | < 0.0001 |
| Height (cm) | 162.7 ± 9.24 | 172.86 ± 7.6 | 159.0 ± 7.35 | < 0.0001 |
| BMI (kg/m²) | 27.47 ± 5.92 | 26.5 ± 4.5 | 27.76 ± 6.25 | 0.456 |
| Total FFM (kg) | 45.99 ± 9.75 | 58.35 ± 9.45 | 42.34 ± 6.21 | < 0.0001 |
| Total FM (%) | 32 ± 9.87 | 21.57 ± 7.3 | 35.14 ± 8.27 | < 0.0001 |
| TBW (%) | 49.56 ± 7.0 | 56.35 ± 6.15 | 47.56 ± 5.9 | < 0.0001 |
| AC (cm) | 30.08 ± 5.12 | 30.54 ± 3.9 | 31.05 ± 6.27 | 0.4488 |
| WC (cm) | 94.71 ± 14.46 | 96.0 ± 12.89 | 94.31 ± 14.89 | 0.2733 |
| HC (cm) | 102.42 ± 11.35 | 99.74 ± 10.35 | 103.21 ± 11.42 | 0.0037 |

*BMI: body mass index; FFM: fat-free mass, FM: fat mass, TBW: total body water, AC: arm circumference, WC: waist circumference, HC: hip circumference.*
**Data are reported as mean ± standard deviation and the p value was calculated by the Student t-test, with $p < 0.05$ indicating a significant difference between genders.*

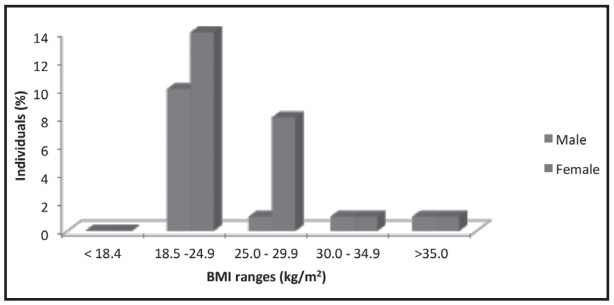


**Figure 1.**

Classification of the individuals according to body mass index values and gender.

BMIfat, 25.93 ± 4.4% and 33.27 ± 6.09% for BAI, and 25.62 ± 5.80% and 34.83 ± 7.9% for BAIFels, respectively.

Analysis of the mean values obtained after the calculation of the adiposity indices and considering their respective classification of nutritional status showed that both genders were classified as overweight by the BMI, men were classified as obese and women as normal weight by the BAI and BAIFels, and men were classified as normal weight and women as obese by the BMIfat, as shown in table II.

Comparison of the capacity for inclusion of the individuals of the present sample according to the cut-off points stipulated for each adiposity index for the classification of nutritional status, i.e., normal weight and excess weight, showed that normal weight of $< 24.9$ kg/m$^2$ and excess weight above 25.0 kg/m$^2$ were used for the BMI, while the values for BMIfat were $> 1.65$ and $\leq 2.0$ for normal weight and more than 2.0 for excess weight. Finally, for BAI, BAIFels and FM determined by BIA we adopted the criterion proposed by the WHO ($\geq$ 25% for men and $\geq$ 35% for women). The results showed that, according to the BMI, 29.0% of the males studied were of normal weight and 22.0% showed excess weight, while 33.3% of the women were of normal weight and 30.0% showed excess weight. The BMIfat classified 40.3% of the men as being of normal weight and 34.0% as having excess weight and 21.7% of the women as being of normal weight and 65.0% as having excess weight. The BAI classified 47.7% of the men as being of normal weight and 62.3% as having excess weight, and 65.6% of the women as being of normal weight and 34.4% as having excess weight. The BAIFels classified 44.7% of the men as being of normal weight and 55.3% as having excess weight and 56.0% of the women as being of normal weight and 44.0% as having excess weight. Finally, the BIA classified 64.0% of the men as being of normal weight and 36.0% as having excess weight and 53.0% of the women as being of normal weight and 47.0% as having excess weight. Table III lists these data in absolute values and as percentage of individuals classified as being of normal weight or as having excess weight for each adiposity index assessed.

Correlations between the adiposity indices and some of the anthropometric variables studied, including FFM and FM obtained by BIA and presented in table IV. BMI and BMIfat had a high correlation with weight ($r = 0.86$, $p < 0.001$ for BMI; $r = 0.78$, $p < 0.001$ for BMIfat), with waist circumference ($r = 0.87$, $p < 0.001$ for BMI; $r = 0.84$, $p < 0.001$ for BMIfat) and FM ($r = 0.71$, $p < 0.001$ for BMI; $r = 0.89$, $p < 0.001$ for BMIfat). All indices showed a low and inverse correlation with stature, while BAI ($r = 0.98$, $p < 0.001$) and BAIFels ($r = 0.98$, $p < 0.001$), as expected, showed high correlation coefficients with hip circumference and low coefficients with FM ($r = 0.24$, $p < 0.001$ for both indices).

Analysis of the ROC curves provides a description of discriminatory capacity of each index regarding the classification of obesity based on body fat (%) obtained by BIA. The area under the curve (AUC) for BMIfat was greater than that of all other indices for both men (93.1%) and women (97.8%) (Table V). The sequence of the more satisfactory AUC values was for BMI, BAIFels and BAI and was maintained for both genders. The ROC curves demonstrated that the cut-off point for BMI was 27.5 for men (BMI95% 76.3-91.1%), with 68.3% sensitivity and 86.3% specificity. Among women, the cut-off point for BMI was 27.0 (BMI95% 91.1-95.7%), with 83.3% sensitivity and 87.5% specificity. The

**Table II.** Comparison of the values obtained by calculating the adiposity indices and their respective classifications of nutritional status according to gender

| Indices | All subjects | Males (M) | Females (F) | p value | Classification |
|---|---|---|---|---|---|
| BMI (kg/m$^2$) | 27.47 ± 5.92 | 26.5 ± 4.5 | 27.76 ± 6.25 | 0.456 | M: overweight<br>F: overweight |
| BMIfat | 2.13 ± 0.49 | 1.87 ± 0.38 | 2.21 ± 0.49 | < 0.0001 | M: normal weight<br>F: obesity |
| BAI (%) | 31.60 ± 6.5 | 25.93 ± 4.4 | 33.27 ± 6.09 | < 0.0001 | M: obesity<br>F: normal weight |
| BAIFels (%) | 32.74 ± 8.27 | 25.62 ± 5.80 | 34.83 ± 7.9 | < 0.0001 | M: obesity<br>F: normal weight |

*BMI: body mass index, BMIfat: body mass index adjusted for fat mass; BAI: body adiposity index; BMIfat: body mass index adjusted for fat mass; BAIFels: adiposity Index for the Fels Longitudinal Study sample; M: males, F: females.*

**Data are reported as mean ± standard deviation and the p value was calculated by the Student t-test, with $p < 0.05$ indicating a significant difference between genders.*

**Table III.** Classification of nutritional status according to adiposity indices and fat mass obtained by bioelectrical impedance

| Indices | Normal weight | | Obesity | |
|---|---|---|---|---|
| | M | F | M | F |
| BMI | 34 (29%) | 129 (33.3%) | 25 (22%) | 116 (30%) |
| BMI fat | 45 (40.3%) | 84 (21.7%) | 39 (34%) | 252 (65%) |
| BAI | 42 (47.7%) | 254 (65.6%) | 72 (62.3%) | 133 (34.4%) |
| BAIfels | 51 (44.7%) | 217 (56%) | 63 (55.3%) | 170 (44%) |
| BIA (FM%) | 73 (64%) | 205 (53%) | 41 (36%) | 182 (47%) |

*BMI: body mass index; BMIfat: body mass index adjusted for fat mass; BAI: body adiposity index; BAIFels: adiposity Index for the Fels Longitudinal Study sample; BIA: bioelectrical impedance; FM: fat mass; M: male; F: female.*

**Table IV.** Pearson correlations of the adiposity indices (BMI, BMIfat, BAI, BAIFels) with the variables weight (kg), height (cm), waist circumference (cm), hip circumference (cm), fat-free mass (kg), and fat mass (%)

| | Weight (kg) | Height (cm) | WC (cm) | HC (cm) | FFM (kg) | FM(%) |
|---|---|---|---|---|---|---|
| BMI | 0.868 | -0.106 | 0.870 | 0.242 | 0.422 | 0.719 |
| BMIfat | 0.782 | -0.184 | 0.840 | 0.242 | 0.218 | 0.895 |
| BAI | 0.122 | -0.196 | 0.180 | 0.984 | -0.043 | 0.247 |
| BAIFels | 0.127 | -0.185 | 0.182 | 0.986 | -0.035 | 0.245 |

*BMI: body mass index; BMIfat: body mass index adjusted for fat mass; BAI: body adiposity index; BAIFels: adiposity Index for the Fels Longitudinal Study sample; WC: waist circumference; HC: hip circumference; FFM: fat-free mass; FM: fat mass.*

**Table V.** ROC curve analysis for the adiposity indices (BMI, BMIfat, BAI and BAIFels), area under the curve (AUC), standard error, sensitivity, specificity, confidence interval (95% CI), and cut-off point for each index for males and females, respectively

| | AUC (%) | Standard error (%) | p value | Cut-off point | Sensitivity (%) | Specificity (%) | 95% CI |
|---|---|---|---|---|---|---|---|
| *Males* | | | | | | | |
| BMI | 83.7 | 3.8 | < 0.001 | 27.5 | 68.3 | 86.3 | 76.3-91.1 |
| BMIfat | 93.1 | 2.2 | < 0.001 | 1.83 | 90.2 | 84.9 | 88.7-97.5 |
| BAI | 78.7 | 4.6 | < 0.001 | 27.3 | 68.3 | 84.9 | 69.7-87.6 |
| BAIFels | 79.5 | 4.5 | < 0.001 | 27.7 | 68.3 | 84.9 | 70.7-88.2 |
| *Females* | | | | | | | |
| BMI | 93.4 | 1.2 | < 0.001 | 27.08 | 83.3 | 87.5 | 91.1-95.7 |
| BMIfat | 97.8 | 0.5 | < 0.001 | 2.18 | 90.6 | 94.0 | 96.7-98.9 |
| BAI | 87.9 | 1.7 | < 0.001 | 32.89 | 75.4 | 84.8 | 84.6-91.2 |
| BAIFels | 88.6 | 1.6 | < 0.001 | 34.4 | 74.9 | 86.4 | 85.4-91.7 |

*BMI: body mass index; BMIfat: body mass index adjusted for fat mass; BAI: body adiposity index; BAIFels: adiposity Index for the Fels Longitudinal Study sample.*

cut-off point for BMIfat was 1.83 for men (BMI95% 88.7-97.5%), with 90.2% sensitivity and 84.9% specificity. Among women, the cut-off point for BMIfat was 2.18 (BMI95% 96.7-98.9%), with 90.6% sensitivity and 94.0% specificity. For the BAI, the cut-off point for men was 27.3 (BMI95% 69.7-87.6%), with 68.3% sensitivity and 84.9% specificity. Among women, the cut-off point for BAI was 32.89 (BMI95% 84.6-91.2%), with 75.4% sensitivity and 84.8% specificity. Finally, the cut-off point for BAIFels was

27.7 for men (BMI95% 70.7-88.2%), with 68.3% sensitivity and 84.9% specificity. Among women, the cut-off point for BAIFels was 34.4 (BMI95% 85.4-91.7%), with 74.9% sensitivity and 86.4% specificity.

## DISCUSSION

In view of the global panorama marked by high rates of overweight/obesity in the population, it is essential the use of indices that measure and classify individuals in relation to their body composition for the early diagnosis of this overweight. Thus, this study proposes a comparison between the use of adiposity indices for the diagnosis of overweight, and the BMIfat highlighted with better correlation with the prediction of body fat, while BAI could not overcome the limitations of BMI this sample.

Our results for the distribution of individuals according to BMI ranges are compatible with data reported in the 2008-2009 Family Budget Survey (POF in the Portuguese acronym) which showed that overweight is greater among men and obesity among women, especially in cases of marked excess weight (14). When we compared the BMI to the remaining indices we observed that this was the tool that least included obese individuals in both genders, with a greater inclusion of females. These results confirm and reinforce the fact that the BMI has limitations due to its low diagnostic power for obesity. In this respect, some authors are already trying to refine this index by questioning the cut-off points used to classify obesity, even showing a tendency to reduce these points in different ethnic groups (15,16), including the Brazilian population (7,8).

López et al. (2012) detected similar strong correlation coefficients between BMI and body fat ($r = 0.74$; $p < 0.001$), weight (0.85; $p < 0.001$) and waist circumference ($r = 0.85$; $p < 0.001$) in a study conducted on 3200 Spanish individuals. In the same study, López et al. (2012) reported the correlations between BAI and height ($r = -0.58$; $p < 0.001$), weight ($r = 0.22$; $p < 0.001$) and waist circumference. The same tendency to a low and inverse correlation between BAI and height ($r = -0.19$; $p < 0.001$) and low correlation coefficients between BAI and weight ($r = 0.12$; $p = 0.006$) and waist circumference ($r = 0.18$; $p < 0.001$) were observed in the present study (17).

The results of the relationship between the adiposity indices (BMI, BMIfat, BAI and BAIFels) and body fat (%) determined by BIA and the ability to discriminate individuals with a high or low fat percentage of this study agree with data reported by others (17-19). López et al. (2012) reported AUC values of 0.920 and 0.877 for BMI and BAI, respectively, in Spanish women (17). In a study conducted on 302 Chinese men and women, Zhao et al. (2013) reported AUC values of 0.900 and 0.893 for BMI and BAI in women. In a study conducted on 2950 Korean women (18), Sung et al. (2014) detected AUC values of 0.908 and 0.868 for BMI and BAI, respectively (19). Considering male subjects, these studies also reported similar AUC values, i.e., 0.837 and 0.787 in the present study, 0.894 and 0.823 in the study by López et al. (2012), and 0.920 and 0.899 in the study by Zhao et al. (2013) for BMI and BAI, respectively (17,18).

The ROC curves also provide suggestions of cut-off points for these adiposity indices showing a tendency to reduce these values and other studies also reported similar results, Zhao et al. (2013) suggested similar values for IMC, i.e. 26.89 (89.7% sensitivity and 80.7% specificity) and 27.67 (77.6% sensitivity and 89.7% specificity) for men and women, respectively (18). López et al. (2012) reporting cut-off points of 27.0 for the BAI (69% sensitivity and 79% specificity) and of 32.0 (79% sensitivity and 86% specificity), and Zhao et al. (2013) reporting 27.8 (87.2% sensitivity and 81.7% specificity) and 36.0 (76.1% sensitivity and 90.8% specificity), both for men and women, respectively (17,18).

The BMIfat and BAIFels indices were included in the present study, with BMIfat showing the highest AUC values, 0.931 and 0.978, while BAIFels values were 0.795 and 0.886 for men and women, respectively. Previous studies were strictly limited to evaluation of the relationship between BMI and BAI only (10,17,20). The main findings of the present study are:

- Analysis by Pearson correlation showed that the correlation coefficients of BMIfat and BMI with total body fat were higher than those of BAI and BAIFels with body fat.
- ROC curve analysis showed that the AUC for BMIfat was greater than that of the remaining indices, suggesting that the discriminatory capacity of BMIfat is superior to that of the other indices studied.

When BMI and BAI are considered exclusively, it can be seen that the BMI yielded more satisfactory results for the prediction of body fat. Some investigators have observed that the BMI had a similar or better diagnostic capacity than the BAI for the estimate of adiposity (17,20-24), while others have reported controversial findings (10,25-27). The present study does not support the findings of Bergman et al. (2011) who stated that the BAI is superior to the BMI for the estimate of body fat. In addition to the possible effect of the different samples sizes of the various studies, the discrepancy among results may be due to two major differences: first, differences between the methods adopted for the assessment of body composition may influence the BMI/BAI ratio and its corresponding body weight value. Bergman et al. (2011) used DXA, while López et al. (2012) and the present study adopted the BIA method, Geliebter et al. (2013) used plethysmography, and Zhao et al. (2013) used anthropometry (skin folds). Second, different ethnic groups were evaluated in these validation studies and it has been reported that obesity and body composition differ between these groups (28).

Among the limitations of the present study, we point out that caution is recommended in extrapolating these results to different ethnic groups since the sample of the Brazilian population studied here is not representative of the general population despite the significant miscegenation of the Brazilian population, characterized by wide ethnic and racial diversity.

Also, the use of biolelectrical impedance for the assessment of body fat has been considered a valid alternative such as easy application, absence of radiation and a relatively low cost and this method has been validated against reference methods (29). Previous studies have shown that impedance bioelectrical can be used as a reference measure of adiposity and results obtained

are similar to the ones obtained using DXA as standard measure (17,30,31). In addition to the technical ones, biolelectrical impedance and DXA show other important differences: bioelectrical impedance is absolutely harmless and is much cheaper than DXA and it can be a viable alternative for the measurement of fat mass, especially in large populations.

In conclusion, the present findings suggest that BMIfat is the index best related to the prediction of body fat, whereas the BAI, despite its great repercussions in the scientific literature, did not overcome the limitations of the BMI. The different behavior of the indices between men and women may suggest a different capacity to discriminate individuals with greater or lower percentages of body fat. Future studies by our group will seek to expand this work by adopting gold standard methods such as the DXA. Finally, it is necessary to extend the investigation of the validity of adiposity indices to various ethnic groups in order to facilitate the introduction of still poorly explored indices such as the BMIfat, BAI and BAIFels in clinical practice and in research as predictors of morbidity and mortality.

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Trabajo Original

Valoración nutricional

# Effect of satiety on body composition and anxiety in university athletes: cohort study

## *Efecto de la saciedad en la composición corporal y en la ansiedad en atletas universitarios: un estudio de cohortes*

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## Abstract

**Background:** Satiety is a determining parameter in nutrient intake control, which in the long run impacts on body weight. Many athletes need strict control on their weight to achieve their aims of the season.

**Aim:** The aim of this study is to analyse the influence of satiety on body weight control and competitive anxiety in a university athletes population when they ingest *ad libitum* foods (SATIETY), or follow a nutritional dietary programme (DIET).

**Methods:** The present study was a cohort study, in which 40 male university athletes participated. The assessment of body weight was done using the ISAK recommendations in its limited profile. The study of competitive anxiety was evaluated using the CSAI-2 questionnaire.

**Results:** Results showed that the DIET group decreased significantly their body weight compared to the SATIETY group, they also obtained a significant improvement in their body composition, reducing fat mass. The SATIETY group didn't show significant reductions in fat mass. This group showed higher competitive anxiety values than the DIET group.

**Conclusions:** The university athletes that follow an adapted and individualized diet seem to show improvements in their body composition and anxiety compared to those with *ad libitum* food.

**Key words:**

Dietary intake. Sport nutrition. Psychology. Fat mass. Muscle mass. Exercise.

## Resumen

**Introducción:** la saciedad en un parámetro determinante en el control de la ingesta y que afecta, por tanto, al peso corporal. Muchos atletas necesitan un control estricto del peso para alcanzar sus objetivos deportivos de la temporada.

**Objetivo:** analizar la influencia de la saciedad en el control del peso y en la ansiedad competitiva en atletas universitarios cuando siguen una dieta libre (SATIETY) o un programa de seguimiento nutricional (DIET).

**Métodos:** se trató de una cohorte de 40 atletas universitarios varones. La valoración del peso se realizó de acuerdo a las recomendaciones ISAK, mientras que la ansiedad se evaluó con el cuestionario CSAI-2.

**Resultados:** los resultaron mostraron que el grupo DIET disminuyó significativamente en el peso, comparado con el grupo SATIETY. También se obtuvo una disminución en la masa grasa en el grupo DIET, que no se obtuvo en el SATIETY. Este último grupo obtuvo puntuaciones de ansiedad competitiva superiores.

**Conclusiones:** los atletas universitarios que siguen una dieta adaptada individualizada parecen mejorar su composición corporal y sus niveles de ansiedad cuando se comparan con los que siguen una dieta libre.

**Palabras clave:**

Ingesta dietética. Nutrición deportiva. Psicología. Masa grasa. Masa muscular. Ejercicio.

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## INTRODUCTION

Satiety is a determining parameter in nutrient intake control, which in the long run impacts on body weight (1). Many athletes need strict control on their weight to achieve their aims of the season. Intense physical exercise temporarily causes ingestion reduction that is accompanied characteristically by physical exercise with the aim of defending the organism against metabolic stress caused by an increase in nutrient demands (2,3).

Appetite is only a part of ingestion behaviour that has many aspects. A sociocultural dimension exists given that people normally eat in groups and all the process is subjected to a circadian rhythm. In this way, although daily energy use isn't measured consciously and varies in function of physical activity, climate and other factors, appetite adjusts to necessities, maintaining stable body weight (4).

The need and wish to fill oneself that is complemented with the added value of pleasure as a consequence of an act of consuming, is produced in neuronal networks that extensively overlap. The pleasure system is associated to cerebral structures that generate consumerist acts. The bases of all of these are the survival mechanisms, where decisions are taken to cover vital needs. Eating is one of these needs. However, since some decades ago, in developed countries, humans maintain a normal weight within strict limits, this is because of a homeostatic process that the organism has (5). When eating starts, the balance between hunger and satiety depends on numerous factors, such as emotional, the time of the day, the hedonic value of foods, social uses, etc. All of this, mostly, escapes homeostatic energy control, allowing us to eat even in absence of the sensation of appetite. However, the instant when ingestion finishes seems to be biologically more controlled, thanks to the mediation of nerve and hormonal signals called by satiety (6). As a result, the nervous system intervenes in the emergence of satiety, advancing or retroceding it and can affect the magnitude of meals and in this way, the quantity of energy consumed. In this manner, the regulation of food intake in the long term is assured by the adjustment of control in short term. For this reason, hunger and appetite and the sensations that they transmit are the episodes in which the organism searches, chooses and ingests food and the phenomenon's that provisionally finalize with ingestion and procure the sensation of satiety (7).

At an intracellular level, the metabolic pathways benefit from the nutrients provided as a result of ingestion that trigger satiety signals. In the homeostasis of the metabolic pathways, the role of certain enzymes is highlighted so that when resting they stimulate the thermogenesis process or use nutrients in a more efficient way when doing an activity (6). Here the involved signals play a leading role in the homeostasis of fatty tissue, like leptin, that is a small circulating peptide secreted by the white adipose tissue, whose synthesis increases when fat mass increases in the organism (8).

Altered psychological states like depression or anxiety are related with abnormal food behaviours, affecting appetite in a great manner and the choice of food. In this way, according to pretensions at psychological or negative emotional levels or anguish, an increment or decrement of ingestion of food or control of satiety can be activated (9).

In this way, in athletes, the event of a sporting challenge influences in the psycho-physiological state of the athlete (10). Intrinsically, it can mean threatening aspects that can convert into a challenge for athletes (11) and the levels of anxiety can increase before sporting events. Anxiety has been considered a negative emotional state (12) as a discouraging emotional reaction that accompanies the arousal of the autonomous nervous system and considered thereby as a dis-adaptive emotional condition. This is a multidimensional construct that is constituted of different components, making a difference between intensity and directionality of anxiety (13), and somatic and cognitive anxiety.

A nutritionally inadequate diet or an adequate control in the diet intake of athletes can also affect processes related with the ingestion of foods and thus, satiety (14). Recent studies show a relation between alterations in food behaviour and the presence of anxiety (15,16). In this regard, an increase in ingestion of ad libitum foods, in absence of hunger, is related with an increment of body weight (17). In terms of sport contexts, an increment of weight at the cost of fat mass, will impact negatively in the performance of athletes during sport practice (18).

Overall, the aim of this study is to determine the influence of satiety on anxiety and body weight control in a university athlete population comparing them in two groups, those that followed a free diet ad libitum and those that followed a supervised nutritional program in order to reach the correct weight. The hypothesis of this study is that satiety plays a determining role in the control of body weight in sport, for this reason, it will be adequate establish dietetic strategies to permit the subjects manage this sensation without generating anxiety states, allowing better control of body weight long term.

## METHODS

### PARTICIPANTS

This cohort study was in accordance with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statements. Forty male volunteers were selected from students of Sport Science and Physical Activity at the Univesidad Miguel Hernández, who practice running in different clubs of Alicante (Spain). Selection criteria included, beginning of the season, to have performed regular aerobic training in the previous season and have a minimal mark of 4 min in 1,000 m, and have a regular running trainings at least 2 days at week from the last 2 years. Study size was arrived at 40 male volunteers that were informed of the objective and demands of the study and gave their written consent to participate. The protocol was in accordance with local legal requirements and the Helsinki Declaration for research on human beings, and approved by the Ethical Committee of Universidad Miguel Hernández.

### PROCEDURE

The study performed with athletes consisted in comparing 2 randomized groups (20 athletes each one) following an isocaloric diet

under supervision by our laboratory, but: a group with the possibility of incrementing the intake of foods freely (SATIETY), and the other strictly following our isocaloric diet (DIET). Participants were randomized by a computer-generated number, which was concealed in sequentially numbered, sealed, and opaque envelopes, and kept by a trained nutritionist who delivered the intervention.

All subjects performed a supervised aerobic routine (determined by calibrated pedometers), during 4 weeks and under the supervision of the corresponding coaches and pedometer. No other physical activity was performed during the study.

## INSTRUMENTS/MEASURES

Caloric expenditure was theoretically estimated and designed diets were adapted accordingly for each particular subject, divided into 3 components: resting metabolic rate, thermic effect of feeding and physical activity expenditure. Resting metabolism was calculated according to Harris-Benedict equation that takes into account for each gender, the weight in kg, height in cm and the age in years (19). The physical activity expenditure was estimated from published tables (20). Dietetic program for DIET was designed using Dietsource software (Novartis, Barcelona, Spain) and adapted to aerobic training (60% carbohydrates, 25-30% lipids and 10-15% proteins). The free diets followed by the SATIETY group were analysed from daily records provided by participants. The record included the type of food, quantity and moment of the day for consumption.

Anthropometry was performed according to International Society for Advancement of Kinanthropometry recommendations (21). Body fat mass was calculated using Siri's equation (22) from the body density values obtained according to Withers. Bone mass was calculated from Rocha's equation (23,24) and muscle mass from Lee's equation (25).

The percentage or kg of body fat mass, muscle mass and weight at the beginning of the study (PRE) was compared with the percentage or kg of body fat mass at the end of the study (POST). The difference between both values ($\Delta$ = POST - PRE) indicated the variation in fat component, muscle component or weight of each volunteer during the study.

CSAI-2 questionnaire (Competitive State Anxiety Inventory-2) (26) was used to determine cognitive anxiety (CA), anguish and loss of concentration related to sport performance; somatic anxiety (SA) refers at activation of the autonomous nervous system that provokes physiological responses and self-confidence (SC), taking into account confidence in skill performance and possibilities for winning (27). In this questionnaire we can obtain intensity and directionality, intensity considers the dimension of CA, SA and SC parameters (values between 1-4; corresponding to none, low, medium, and high, respectively); and directionality refers to the personal appretiation of the athlete and the possible influence in performance (values regarding if the state is harmful (0 to -3) or beneficial (0 to +3) for the athlete). The analysis of internal validity and consistency of the questionnaire (Cronbach's alpha) for the 3 factors that measure intensity was: SA (0.78), CA (0.82) and SC (0.83). In this respect, the Cronbach's alpha of directionality for SA obtained a value of 0.74, 0.80 for CA and 0.73 for SC.

Values of CSAI-2 at the beginning of the study (SA PRE - CA PRE - SC PRE) were compared with the percentage of values of CSAI-2 at the end of the study (SA POST - CA POST - SC POST). The difference between both values ($\Delta$CSAI-2 = %CSAI-2 POST - CSAI-2 PRE) indicated the variation in competitive anxiety component or subscale of each volunteer during the study.

Quantitative variables handled in the analyses were: total body weight, fat mass, muscle mass, CA intensity, CA directionality, SA intensity, SA directionality, SC intensity and SC directionality.

## STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, v. 20.0 for Windows). The results were expressed as means ± standard error of the mean (mean ± sem). One-sample K-S test (Kolmogorov-Smirnov test) was performed in order to assess if each variable fits a normal distribution. T-test for independent samples was used to compare means between different groups. Test for related samples was used to compare means in the same group. Same non-parametric test was used to compare means if variables don't have a normal distribution. Pearson correlation test was computed for correlations between anxiety and body composition variables. Statistical significance was set at $p < 0.05$. The effect size were calculated using Cohen's d. ESs were considered negligible (< 0.2), small (0.2-0.50), moderate (0.50-0.80), and large (> 0.80).

## RESULTS

All participants included in study, followed the intervention protocol, assessments and concluded each stage of our study. When comparing both groups of athletes, significant differences were observed between both in the variation of weight ($p = 0.004$), where the SATIETY group incremented their weight whilst the DIET group decreased. Although no significant differences were found, the DIET group showed an increase in muscle mass accompanied by a decrease in fat mass, in absolute values (kg) and in relative values (%), contrary to the SATIETY group (Fig. 1). The anxiety results (Fig. 2), found significant differences between both DIET and SATIETY groups in the POST CS intensity values ($p = 0.040$), where the DIET group has higher SC values. Regarding significant differences ($p = 0.043$) between the SA intensity between the two groups, the DIET group showed a fall in the SA levels whilst the SATIETY group increased these levels at the end of the study.

On one hand, when comparing the subjects within each of the groups, the DIET group before and after the intervention, have shown a significant decrease in both total body weight ($p = 0.016$) and fat mass in absolute (kg) ($p = 0.045$) and relative (%) ($p = 0.044$) values (Fig. 1) with moderate ES. However, in the rest of the studies variables there were no significant differences.

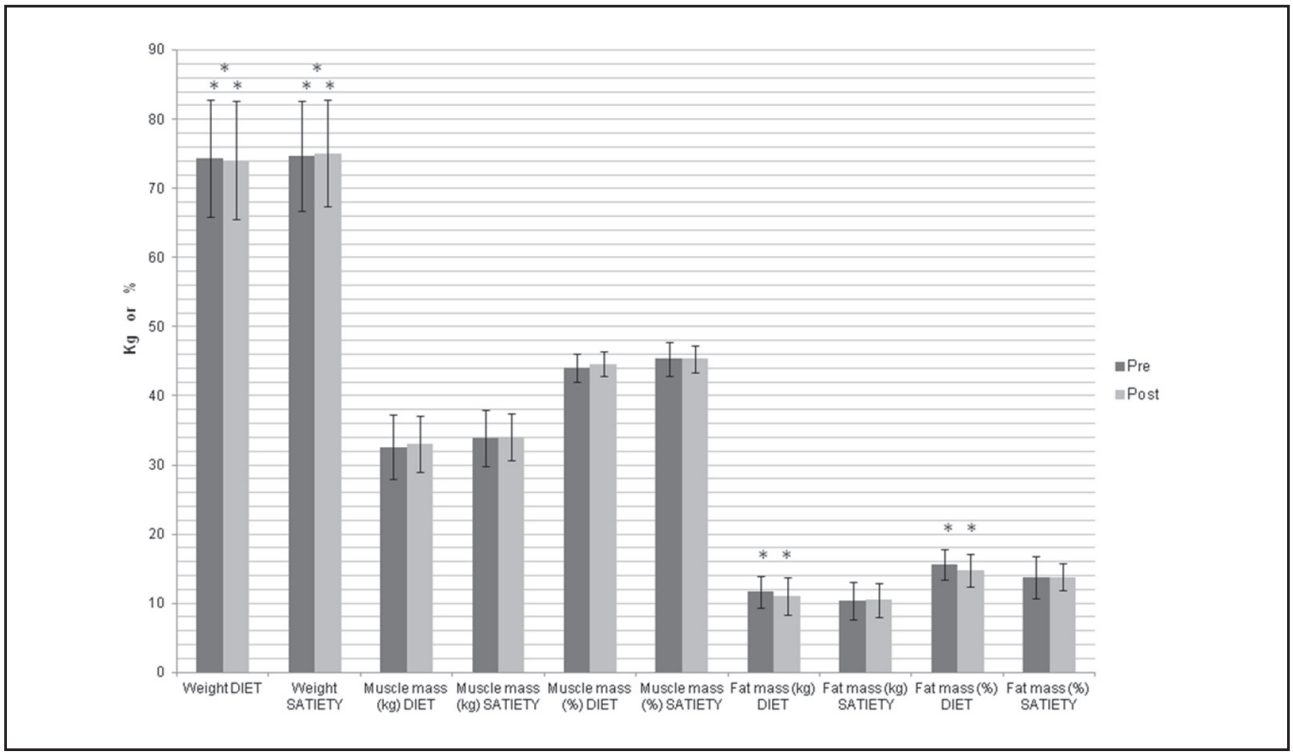
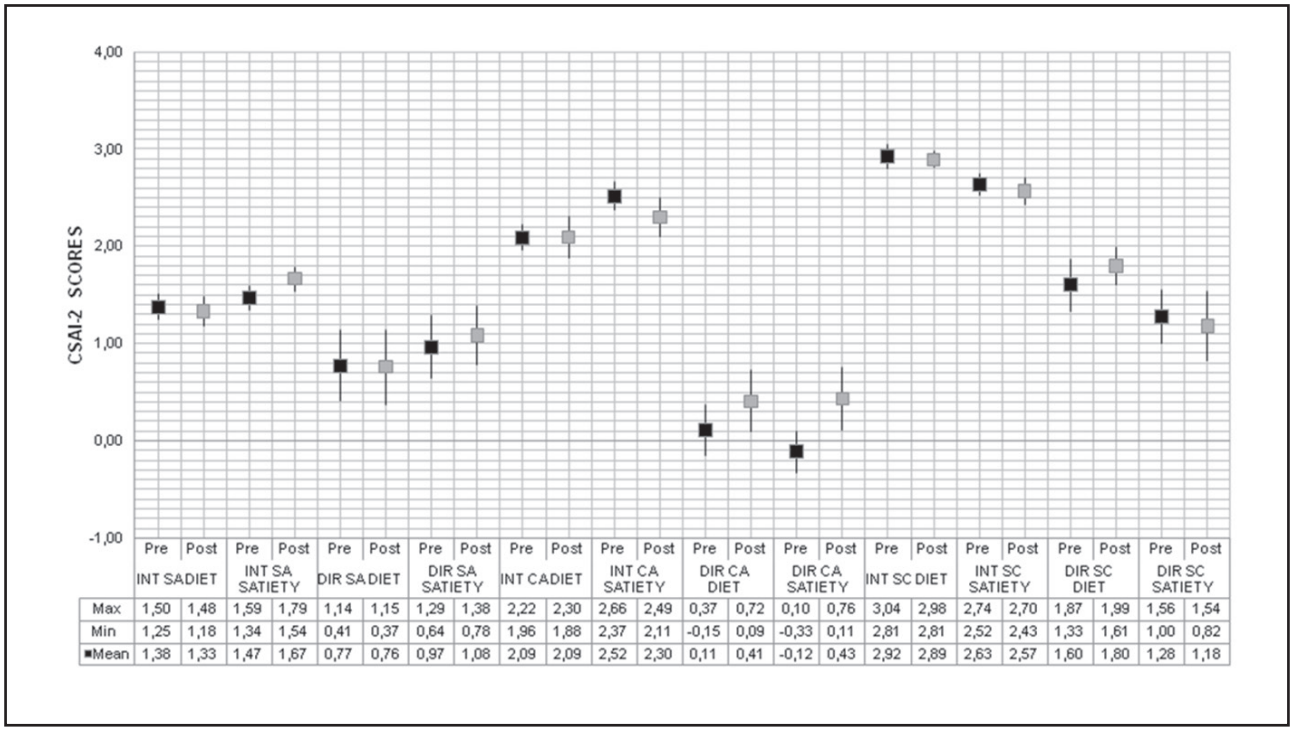



**Figure 1.**

Body composition assessment PRE and POST intervention on DIET and SATIETY groups (*pvalor < 0.05; differences between DIET and SATIETY groups; **pvalor < 0.05; differences between PRE and POST evaluation into the same group).




| | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | INT SA DIET | | INT SA SATIETY | | DIR SA DIET | | DIR SA SATIETY | | INT CA DIET | | INT CA SATIETY | | DIR CA DIET | | DIR CA SATIETY | | INT SC DIET | | INT SC SATIETY | | DIR SC DIET | | DIR SC SATIETY | |
| Max | 1,50 | 1,48 | 1,59 | 1,79 | 1,14 | 1,15 | 1,29 | 1,38 | 2,22 | 2,30 | 2,66 | 2,49 | 0,37 | 0,72 | 0,10 | 0,76 | 3,04 | 2,98 | 2,74 | 2,70 | 1,87 | 1,99 | 1,56 | 1,54 |
| Min | 1,25 | 1,18 | 1,34 | 1,54 | 0,41 | 0,37 | 0,64 | 0,78 | 1,96 | 1,88 | 2,37 | 2,11 | -0,15 | 0,09 | -0,33 | 0,11 | 2,81 | 2,81 | 2,52 | 2,43 | 1,33 | 1,61 | 1,00 | 0,82 |
| Mean | 1,38 | 1,33 | 1,47 | 1,67 | 0,77 | 0,76 | 0,97 | 1,08 | 2,09 | 2,09 | 2,52 | 2,30 | 0,11 | 0,41 | -0,12 | 0,43 | 2,92 | 2,89 | 2,63 | 2,57 | 1,60 | 1,80 | 1,28 | 1,18 |

**Figure 2.**

Competitive anxiety assessment: Competitive State Anxiety Inventory-2 (CA: cognitive anxiety; SA: somatic anxiety; SC: self-confidence; DIR: directionality; INT: intensity).

On the other hand, the SATIETY group also presented significant differences in the total body weight (p = 0.046), having incremented after the intervention (Fig. 1). Also, significant differences were found in the SA intensity (p = 0.031) and the CA directionality (p = 0.033), producing in both a significant post intervention increase, both with moderate ES (Table I).

After making correlations between the different variables in both groups, the DIET group showed a significant correlation between the increment of fat mass percentage and CA intensity (R = -0.612; p = 0.046), the lower the muscle mass increment, the higher the CA intensity in the DIET group. In the rest of the variables, no significant differences were found. Furthermore, in the SATIETY group, significant correlations were observed between the increment of muscle mass and the CA directionality (R = -0.715; p = 0.020), in percentage (R = -0-72; p = 0.017) and also the CA directionality, in this case in a negative form.

## DISCUSSION

Body weight is a determining parameter in sport performance. Achieving an optimal weight for a better adaptation to sport isn't an easy task. Diets don't seem to achieve the desired results, although they seem to be well designed, they generate anxiety states in the subjects, especially if they have to lose weight. Moreover, many sport groups lack professional services to plan correct diets.

Even though, in the present study no significant differences have been highlighted, it seems that the DIET group has an increased predisposition in exhibiting modification in body composition that favours sport performance. The obtained results show that following an adequate, individualized nutritional dietary programme that is adapted to each athlete, helps them to decrease their weight in a significant form compared to those who ingest food freely. This fact coincides with the importance of satiety control to control body weight (1). Also, this weight reduction influences on fat mass in a significant form without muscle mass being affected in the DIET group.

**Table I.** Difference between both values (Δ = POST - PRE) indicated the variation in body composition assessment or competitive anxiety of each group during the study

| | DIET | | | SATIETY | | |
|---|---|---|---|---|---|---|
| | **Mean** | | **SD** | **Mean** | | **SD** |
| Δ Weight | -0,27 | ± | 0,31 | 0,36 | ± | 0,51 |
| Δ Muscle mass (kg) | 0,46 | ± | 0,90 | 0,18 | ± | 1,83 |
| Δ Muscle mass (%) | 0,65 | ± | 1,42 | -0,02 | ± | 2,56 |
| Δ Fat mass (kg) | -0,60 | ± | 0,86 | 0,11 | ± | 1,77 |
| Δ Fat mass (%) | -0,85 | ± | 1,28 | 0,09 | ± | 2,58 |
| Δ SA Intensity | -0,05 | ± | 0,28 | 0,20 | ± | 0,24 |
| Δ SA Directionality | -0,01 | ± | 0,41 | 0,12 | ± | 0,32 |
| Δ CA Intensity | 0,02 | ± | 0,49 | -0,22 | ± | 0,44 |
| Δ CA Directionality | 0,30 | ± | 0,48 | 0,55 | ± | 0,69 |
| Δ SC Intensity | -0,03 | ± | 0,33 | -0,07 | ± | 0,20 |
| Δ SC Directionality | 0,20 | ± | 0,75 | -0,10 | ± | 0,64 |

In the SATIETY group, the results obtained from an increment in the SA intensity could be due to the fact that the subjects are conscious that they probably haven't used the most adequate nutritional dietary strategies to achieve an improvement in their body composition and sport performance, as they have had no limits when ingesting food along the day. For this reason, it is necessary that athletes follow an adapted diet to their particular energetic needs, so that they can replace lost energy through exercise, however, without exceeding the replenishment as this increments total body weight, as seen in the results of this present study; as an increment of weight that isn't exclusively of muscle mass will negatively impact on sports performance.

In this way, it seems that in the sample of studied athletes, appetite can be altered by energetic needs and body weight isn't always maintained, in opposition to other studies (4,5). Likewise, it is necessary to highlight the influence of psychological aspects as a conditioning factor of satiety mechanisms (9).

The results obtained in the correlations of the DIET group, reveal the importance of body composition values regarding the CA intensity level. Furthermore, regarding the correlations of the SATIETY group, it seems that as the body composition improves in relation to muscle mass and fat mass parameters, the CA directionality increments favourably which benefits sport performance (28). In this regard, the athletes show at cognitive level that a favourable body composition is favourable when doing sporting events.

It seems evident that anxiety is a factor that influences on sport performance (29). However, there are many theories that associate different parameters of anxiety with opposite effects on performance. The first tendencies focused on decreasing anxiety and increasing SC to achieve higher sporting success (30). In our study, after the intervention, the DIET group achieved higher SC intensity levels than the SATIETY group, which could be because the nutritional dietary strategies help athletes to cope with ease the sporting challenge in question, also having a higher control at cognitive level of their own possibilities and confidence in their abilities. The differences between the DIET and SATIETY groups in relation to the increment of the SA intensity, highlights that those athletes that don't control their diet show a series of impacts at a psychological level, that can influence at a physiological level like tension increments at muscle level, stomach upsets and increases in sweating and heartbeats (31).

It has been proven that stressful situations or anxiety states can affect our food behaviours, influencing in the choice and ingestion of food, like in satiety mechanisms. Moreover, it seems that elevated anxiety levels, seen in the SATIETY group in the current study, also corresponds with an excess of food intake, equally seen in other scientific studies (9).

The fact that no significant differences were found in the different fat and muscular compartments of the body composition between the studied groups could be due to the reduced number of the sample and differences between athletes in metabolism and exercise adaptations. Because of these limitations, the need to do an intervention incrementing the number of athletes and the control of metabolic parameters in both DIET and SATIETY group is highlighted. In this way, other limitation of this study was the absence of gas analyzer to measure oxygen uptake to assess the energy cost (METs), and data could be converted to units of energy expenditure (METs). Furthermore the control of body composition by DXA and blood biomarkers could also provide complementary information. Also, it could have been interesting to do specific tasks that assess physical performance, like exercise tests that are useful for objectively evaluating body composition changes with the intention of correlating them with better performance. However, these tests were not done in the present study.

In conclusion, athletes that followed a specific nutritional dietary programme show favourable modifications in body composition without showing higher levels of competitive anxiety. A diet without controlling satiety mechanisms could produce an increment in competitive anxiety.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

# Malnutrition in hospitalized patients: results from La Rioja

*Desnutrición en pacientes hospitalizados: resultados en La Rioja*

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## Abstract

**Background:** There is a high malnutrition prevalence in hospitalized patients.

**Aim:** To determine the malnutrition prevalence in hospitalized patients of La Rioja Community (Spain) when evaluated with different screening/evaluation tools and its relationship with hospital stay and mortality.

**Methods:** Cross sectional observational study of hospitalized adult patients (age > 18 years old) from medical and surgical departments that underwent within 72 h of their admission a nutritional screening with Malnutrition Universal Screening Tool (MUST), Nutritional Risk Screening (NRS) 2002, Controlling Nutritional Status (CONUT) y Subjective Global Assessment (SGA).

**Results:** 384 patients (273 medical and 111 surgical) were evaluated. Almost fifty percent of them were considered malnourished independently of the screening/assessment tool used. High concordance was found between SGA and NRS-2002 (k = 0.758). Malnourished patients had a longer hospital stay than those well-nourished (9.29 *vs.* 7.10 days; p = 0.002), used a greater number of medicines (9.2 *vs.* 7.4; p = 0.001) and underwent a higher number of diagnostic tests (16.4 *vs.* 12.5; p = 0,002).

**Conclusions:** Half of the hospitalized patients in the medical and surgical department of La Rioja are malnourished. This is associated with a longer hospital stay, higher use of medicines, diagnostics tests and greater mortality. Malnutrition could be detected with easy screening tools to treat it appropriately.

**Key words:**

Hospital malnutrition. Nutritional status. Nutritional screening. Nutritional assessment.

## Resumen

**Antecedentes:** existe una alta prevalencia de malnutrición en los pacientes hospitalizados.

**Objetivo:** conocer la prevalencia de la desnutrición en la comunidad de La Rioja con distintos métodos de cribado/valoración nutricional y su relación con la estancia media y mortalidad.

**Métodos:** estudio transversal de 384 pacientes mayores de 18 años (273 pacientes en servicios médicos y 111 en servicios quirúrgicos), a los que se les realizó en las primeras 72 horas del ingreso un cribado/valoración nutricional con MUST *(Malnutrition Universal Screening Tool),* NRS-2002 *(Nutritional Risk Screening),* CONUT *(Controlling Nutritional Status)* y VGS *(Subjective Global Assessment).*

**Resultados:** la desnutrición fue observada en más del 50% de los pacientes independientemente del método de cribado/valoración nutricional utilizado. Existe una fuerte concordancia entre la VGS y el NRS-2002. La desnutrición se relaciona con aumento de la estancia hospitalaria (9,29 *vs.* 7,10 días; p = 0,002), mayor consumo de fármacos (9,2 *vs.* 7,4; p = 0,001) y mayor consumo de pruebas diagnósticas durante la estancia hospitalaria (16,4 *vs.* 12,5; p = 0,002).

**Conclusiones:** uno de cada dos pacientes hospitalizados en la comunidad de La Rioja está desnutrido. La desnutrición se relaciona con aumento de la estancia hospitalaria, aumento de la utilización de pruebas diagnósticas, mayor consumo de medicamentos y aumento de la mortalidad. La desnutrición puede ser detectada con medidas de cribado nutricional sencillas que permitirían tratarla adecuadamente.

**Palabras clave:**

Desnutrición hospitalaria. Estado nutricional. Cribado nutricional. Valoración nutricional.

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## INTRODUCTION

Malnutrition is highly prevalent in hospitalized patients. Butterworth et al. in 1974, were the first in talking about malnutrition in these patients (1). In the same year, Bistrian et al. reported in two different studies that half of the hospitalized patients (44% medical, 50% surgical) have certain degree of malnutrition (2,3).

Surprisingly, since then the malnutrition percentages reported in last four decades in hospitalized patients has been the roughly the same. Percentages go from 30 to 60%, in studies performed in Spain (4-8) or other parts of the world (9-15).

Malnourished hospitalized patients are at high risk of infections (16), falls (17) and pressure ulcers (18). Malnutrition is also associated with a higher mortality (19,20), higher hospital costs caused by a longer stay higher readmission rates and greater health care services utilization (21).

Consistent data have demonstrated that nutritional treatment with diet modification including oral nutritional supplements (ONS), enteral or parenteral nutrition has consistently demonstrated a beneficial effect on clinical and economical outcomes. These include improvement of the nutritional status (22), muscular mass, strength and performance, morbitity (23) quality of life (24) and mortality. Health care costs decrease is a consequence of a shorter in hospital stay (25), decrease readmission rate (26) and use of health care services in general (27).

Despite this high prevalence, malnutrition in hospitalized patients is a under-diagnosed and undertreated problem (28). Even more, 60% of them worsen their nutritional status during their admission (29).

In the PREDYCES study (30), a multicentric Spanish study, 1 out of 4 inpatients were malnourished, a condition that is associated with a longer hospital stay and with an increased health care costs especially in those that developed malnutrition during their admission.

European authorities have recognized that disease associated malnutrition is a European health problem (Praha Declaration June 11th 2009), recommending specific directives to prevent this problem and avoid the morbi-mortality associated to it (31). This directives have been integrated in the European Strategic Health Program UE 2008-2013 (32).

A systematic malnutrition screening on admission and during hospital stay would be desirable aiming at improving clinical and economical outcomes.

The present study was planned to explore the nutritional status of medical and surgical patients admitted to a tertiary university hospital in La Rioja, Spain.

## METHODS

This is a cross sectional study of a prospectively recruited population of a randomly sample of adult inpatients (age > 18 years old) admitted to medical and surgical wards of the Hospital Universitario de San Pedro in Logroño (La Rioja, Spain), from February to June 2011. Sample size was estimated in 384 patients considering 30-60% malnutrition prevalence with a 95% confidence interval and a precision of 5%.

Nutritional evaluation was performed within the first 72 hours of patient's admission by qualified personnel (certified dietitian). Every day patients were randomly selected using a table of aleatory numbers from the admission list.

Exclusion criteria were patients with an expected hospital stay of less than 72 hours, those with a severe disease with an imminent expected death, patients admitted to Psychiatry, Obstetrics, Ophthalmology, Intensive Care Unit, Pediatrics or those that refused to participate in the study.

Social and demographic data was registered in each patient including diagnosis and number of admissions in the previous year and laboratory lab results. Three different nutritional screening tools were used: Malnutrition Universal Screening Tool (MUST), Nutritional Risk Screening (NRS-2002) and Nutritional Control (CONUT for its spelling in Spanish), using another nutritional evaluation tool: Subjective Global Assessment (SGA). On discharge, number of diagnostic tests performed, days of hospital stay, place of discharge and mortality were registered in all patients.

## STATISTICAL ANALYSIS

Results are presented as mean and standard deviation for quantitative variables and percentages for qualitative variables. Normality was tested in quantitative variables with the Kolmogorov-Smirnov test.

Difference between quantitative variables with normal distribution was evaluated with Student t test or Mann-Whitney U test for those with non-parametric distribution. Difference between quantitative variables was evaluated with $\chi^2$. Comparison between different nutritional screening tools was explored with $\chi^2$ and ANOVA. Concordance between nutritional screening tools was evaluated with kappa index. A statistical significance level of $p < 0.05$ was determined. The statistical package IBM SPSS Statistics 21 was used for the statistical analysis.

The study was approved by the Clinical Research Ethical Committee of La Rioja and all the participants signed the informed consent.

## RESULTS

Three hundred and eighty four inpatients were evaluated, 71.7% admitted to medical wards and 28.9% to surgical wards. Fifty percent of them were men and their mean age was 64.6 ± 16.5. Eighteen percent of patients had a previous diagnosis of diabetes mellitus, 42% of high blood pressure, 21% of dyslipemia and 16% had obesity.

Table I shows the cause of admission being neoplastic the most frequent one in 16.7%.

Mean body mass index (BMI) was 25.7 kg/m$^2$, 6.2% of patients had a BMI < 18.5; 33.7% have overweight and 15.7% obesity. Mean percentage of weight loss from regular weight was

**Table I.** Diagnosis on admission

| Diagnosis on admission (n = 384) | (%) |
|---|---|
| Neoplastic | 16.7 |
| Acute GI pathology | 15.1 |
| Respiratory failure/infection | 12.8 |
| Others | 12 |
| Scheduled mayor surgery | 8.1 |
| Cardiovascular disease | 7 |
| Urinary pathology/infection | 6 |
| Cerebrovascular disease | 4,9 |
| Scheduled major abdominal surgery | 3.6 |
| Scheduled other major surgery | 3.4 |
| CNS/Cognitive impairment | 2.3 |
| Weight loss | 2.1 |
| Metabolic decompensation | 1.8 |
| Nonscheduled other major surgery | 1.8 |
| Nonscheduled major abdominal surgery | 1.6 |
| Peripheral vascular disease | 0.8 |

*CNS: central nervous system; GI: gastrointestinal.*

4.8 ± 5.8. The mean hospital-stay was 8.7 ± 6.8 days and 51% of patients had an admission in the previous 12 months.

Results of the nutritional screening using 3 different nutritional screening tools are shown in figure 1.

All patients underwent a SGA showing that 44% of them were well nourished, 38% mildly malnourish and 18% severely malnourished.

Concordance between SGA and the other screening tools was explored showing a good kappa index with NRS-2002 (k = 0.758), moderate with MUST (k = 0.422) and weak with CONUT (k = 0.340).

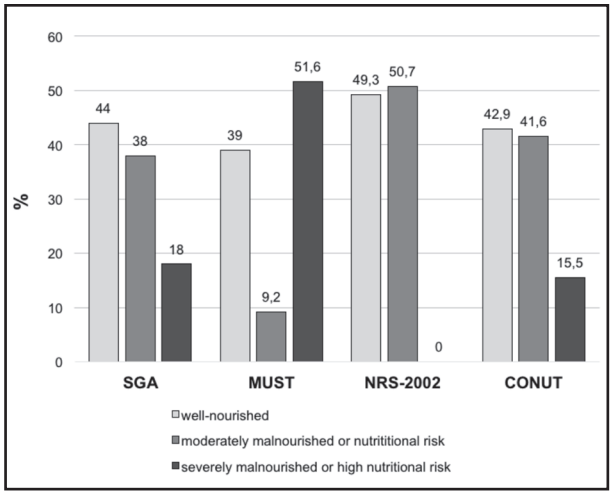


**Figure 1.**

Malnutrition prevalence according to the different nutritional screening tools.

Malnutrition according to the cause of admission was 23.4% in neoplastic patients, 18.2% in those with acute GI pathology and 15.4% in those with acute respiratory infection/failure.

No statistical significant gender differences were found in malnutrition. A higher percentage of patients older than 70 years old was malnourish (70.4 *vs.* 45.7%, $p < 0.05$) and higher in medical than in surgical services (63.1 *vs.* 38.7%, $p < 0.05$).

Malnourished patients had a mean age 10 years higher than those well-nourished, weighted 11 kg lower and have a BMI 4 points lower. Mean weight loss of malnourished patients were 4.9 kg *vs.* 0.7 kg of those well-nourished. Statistical significant differences were found also in other anthropometric measurements: tricipital skinfold (TSF), arm circumference (AC) and calf circumference (CC) (Table II).

Malnourished patients also had lower values of albumin, prealbumin, transferrin, cholesterol and CRP (Table III).

Sixty two percent of the malnourished patients had an admission in the previous year compared with only 45.5% of well-nourished ones. Mean hospital stay was 2 days higher in those malnourished (9.29 *vs.* 7.10, $p < 0.05$). During their hospital stay the number of diagnostic procedures in malnourished patients was higher compared with well-nourished ones (16.4 ± 12.6 *vs.* 12.5 ± 10.6, $p < 0.005$) and they used a greater number of medicines (9.2 *vs.* 7.4; $p = 0.001$) (Table IV).

Being malnourished increased the hospital length of stay by 1.8 days (IC ± 95%: 0.3-3.2; $p < 0.05$) in a regression model adjusted by age, gender, weight on admission, BMI, weight loss and diagnosis on admission.

Ninety two percent of the well-nourished patients went home at the time of discharge compared with 77% of those malnourished. A higher percentage of malnourished patients were discharged to a chronic health facility compared with those well-nourished (7 *vs.* 0.6%, $p < 0.05$). Three percent of the malnourished patients died during their hospital stay compared with only 0.6% of those well-nourished ($p = 0,06$).

Only 17.7% of the malnourished patients received nutritional support during their hospital stay.

**Table II.** Anthropometric parameters according to their nutritional state (SGA)

| | Malnourished n = 215 | Well-nourished n = 169 | |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | p |
| Weight (kg) | 64.61 ± 14.55 | 75.71 ± 15.55 | < 0.001 |
| BMI (kg/m$^2$) | 23.99 ± 5.11 | 27.82 ± 5.73 | < 0.001 |
| Weight loss (kg) | 4.9 ± 5.5 | 0.7 ± 2.7 | < 0.001 |
| TSF (mm) | 13.24 ± 6.15 | 16.43 ± 6.033 | < 0.001 |
| AC (cm) | 28.49 ± 4.53 | 31.44 ± 4.04 | < 0.001 |
| CC* (cm) | 33.11 ± 4.05 | 36.47 ± 3.60 | < 0.001 |

**In > 65-years-old. SGA: subjective global assessment; BMI: body mass index; TSF: triceps skinfold; AC: arm circumference; CC: calf circumference.*

**Table III.** Laboratory parameters according to their nutritional state (SGA)

| | Malnourished n = 215 | Well-nourished n = 169 | |
|---|---|---|---|
| | **Mean ± SD** | **Mean ± SD** | **p** |
| Albumin (g/dl) | 3.5 ± 0.63 | 3.97 ± 0.58 | < 0.001 |
| Prealbumin (g/dl) | 14.38 ± 6.78 | 19.6 ± 7.28 | < 0.01 |
| Transferrin (mg/dl) | 186,1 ± 62 | 220.8 ± 56 | < 0.01 |
| Cholesterol (mg/dl) | 152.79 ± 42.151 | 175 ± 44 | < 0.01 |
| Lymphocites (cell/ml) | 1408 ± 1532 | 1595 ± 757 | NS |
| CRP (mg/L) | 71.79 ± 85.80 | 45.1 ± 66.1 | 0.001 |

*SGA: subjective global assessment (SGA); CRP: C-reactive protein.*

**Table IV.** Main outcomes

| | Malnourished n = 215 | Well-nourished n = 169 | |
|---|---|---|---|
| | **Mean ± SD** | **Mean ± SD** | **p** |
| Length of stay (day) | 9.2 ± 6.8 | 7.1 ± 4.5 | < 0.001 |
| Number of diagnostic tests | 16.4 ± 13.5 | 12.5 ± 9.4 | < 0.001 |
| Medication number | 9.2 ± 4.5 | 7.4 ± 3.7 | < 0.001 |

## DISCUSSION

Malnutrition is frequent in hospitalized patients causing a negative impact on mobility and mortality with the expected increase in health care associated costs.

Disease and malnutrition have a two way relationship. While disease could cause malnutrition, malnutrition negatively affects the main outcomes of the disease closing a vicious cycle (33).

La Rioja is an autonomous community with centralized sanitary system with only one tertiary university hospital where the present surveillance was performed.

The study sample of 384 hospitalized patients is representative of the acute hospitalized patients of this autonomous community.

Using the SGA evaluation, malnutrition was found in 56% of the hospitalized patients (38% with moderate and 18% with severe) while using any of the other screening tools (MUST, NRS-2002 y CONUT) malnutrition prevalence was always above 50%. If we compared the malnutrition prevalence found in the present work with the one found in the PREDYCES study (30) including a large Spanish sample of hospitalized patients, the figures found in La Rioja are two times higher indicating that one out of two patients are malnourished in La Rioja while one out of four in the rest of Spain. The present study confirms previous findings from a study performed in 2001 that found only 12.5% of hospitalized patients in La Rioja have a normal nutritional state on discharge, with 55% of them with mild malnutrition and 28.3% severe malnutrition (34). The prevalence of disease-associated malnutrition in other Spanish areas ranges from 24 to 66% (4,5,7). If we compared the present study findings with the ones from Latin American countries, the figures are quite similar, again with a prevalence of disease associate malnutrition of approximately 50% in the latter (10). The British Association for Parenteral and Enteral Nutrition (BAPEN) estimate that around 34% of the patients admitted to a hospital have some degree of disease associated malnutrition (35). These percentages are similar to those found in other European countries (36,37). The differences found between these studies could be related to study populations and methodology to define malnutrition in each cohort.

The present study also confirmed other studies findings indicating that a higher percentage of malnutrition is found in those patients older than 70 years old (8,30).

We also confirmed that those patients classified as malnourished have a 2.19 days longer hospital stay than those classified as well nourished (4,5,8,27,29) supporting the importance of detecting this problem on admission to avoid important health care associated costs. Then, the detection of malnutrition on admission with easy screening tools could contribute indirectly to save health care associated costs (38).

Our study also confirmed that disease associated malnutrition is also associated with higher medication consumption and performing a higher number of diagnostics tests, findings previously described in other studies performed in Spanish populations (7,29). This confirmed the external validity of our findings and again supporting the critical role of the malnutrition screening tools to detect this important issue.

The percentage of malnourished patients that were discharged home was significantly higher in those well-nourished

while a higher percentage of those malnourished needed to be transferred to a chronic health facility. But most importantly, the mortality rate was also significantly higher in the malnourished patients. These findings are all in line with the findings reported in other Spanish as well as North and Latin American studies (4,5,10,27,28,30).

Finally, the present study also showed that SGA evaluation has a good concordance with NRS-2002 and weaker with the CONUT, confirming previous reports that those screening tools including biochemical parameters are not probably the adequate tools to be used in nutritional screening (39).

There are some limitations in the present study. Firstly, this is a single center study, therefore the present findings could not be translated to other populations. Secondly, we only evaluated three screening tools. We did not included Mini Nutritional Assessment (MNA) that is the recommended screening tools for patients older than 65 years old. Thirdly, the present study only included a limited number of surgical patients, but this is a representative sample of the type of patients seen in our hospital.

The most important findings from the present work are:

- Malnutrition is highly prevalent (almost 50% on admission) in La Rioja.
- Of them only 7% received nutritional support.
- We also confirmed that malnourished patients are associated with worse clinical outcomes, higher health care resource utilization, longer hospital stay and higher mortality.

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ARÁN

Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

# Assessment of individual carotenoid and vitamin A dietary intake in overweight and obese Dominican subjects

## *Valoración de la ingesta individualizada de carotenoides y de vitamina A en sujetos dominicanos con sobrepeso y obesidad*

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## Abstract

**Introduction:** Carotenoids are plant pigment with important biological activities in humans, such as provitamin-A among others. At present, there are no individual carotenoid intake data in the Dominican population, which is at risk of vitamin A deficiency and has an important percentage of overweight and obese individuals.

**Objective:** To assess the individual components of vitamin A intake (retinol, α-carotene, β-carotene and β-cryptoxanthin) and that of other relevant dietary carotenoids like lutein, zeaxanthin and lycopene of Dominican daily food intake.

**Methods:** Fifty overweigth and obese subjects (22-69 y). Individual carotenoid intake, from whole diet and from the ingestion of fruits and vegetables, was determined using three 24 h diet recalls and a specific carotenoid database. Retinol, macronutrient and energy intake were calculated using DIAL® software.

**Results:** The total carotenoid intake was 6363.2 µg/day, 56.1% corresponding to provitamin A carotenoids (74.3% β-carotene). Vitamin A intake was supplied by retinol (40%) and by provitamin A carotenoids (60%); vegetables contributed more than fruits (39.2% and 19.2%, respectively). Non-provitamin A carotenoid intake represents 43.9% of the total intake and is supplied by lycopene and lutein plus zeaxanthin in similar percentages (52.3% and 47.7%, respectively).

**Conclusions:** The diet of these Dominican subjets met the recommended vitamin A intake, when expressed as retinol equivalents, 59% of which was supplied by provitamin-A carotenoids from plant sources, mainly by red/orange and white/yellow foods. Individual carotenoid intake is an aspect of great interest for issuing dietary recommendations in the public health setting.

**Key words:**

Carotenoids. Dominican Republic. Dominicans. Dietary intake. Vitamin A. Fruit and vegetables.

## Resumen

**Introducción:** los carotenoides son pigmentos con importantes actividades biológicas en los seres humanos, entre las que detaca la actividad provitamínica A. No hay datos de ingesta de carotenoides en la población dominicana, en la que hay un elevado porcentaje de individuos con sobrepreso y obesidad, así como riesgo de deficiencia en vitamina A.

**Objetivo:** valorar la ingesta de los componentes individuales de vitamina A (retinol, β-caroteno, α-caroteno, β-criptoxantina) y de otros carotenoides relevantes (licopeno, luteína, zeaxantina) en sujetos dominicanos.

**Métodos:** cincuenta sujetos con sobrepeso y obesidad (22-69 años). Tres recuerdos de dieta de 24 h y una aplicación específica para carotenoides, para valorar ingesta de carotenoides a partir de la dieta total y de la ingesta de frutas y hortalizas. La ingesta de retinol, macronutrientes y energía se calcula utilizando la aplicación DIAL®.

**Resultados:** la ingesta total de carotenoides fue 6363,2 µg/día, correspondiendo el 56,1% a carotenoides provitamina-A (74,3% β-caroteno). La ingesta de vitamina A procede del retinol (40%) y de los carotenoides provitamínicos (60%); las hortalizas contribuyeron más que las frutas (39,2% y 19,2%, respectivamente). Los carotenoides no-provitamínicos representaron el 43,9% de la ingesta total, con un aporte de licopeno y de luteína más zeaxantina en proporciones similares (52,3% y 47,7%, respectivamente).

**Conclusiones:** la dieta de estos sujetos dominicanos cubre las recomendaciones de ingesta de vitamina A, expresada en equivalentes de retinol, siendo aportada por fuentes vegetales en un 59%, principalmente a partir de alimentos de colores rojo/anaranjado y blanco/amarillento. La ingesta individual de carotenoides es un aspecto de gran interés para emitir recomendaciones dietéticas en el ámbito de la salud pública.

**Palabras clave:**

Carotenoides. República Dominicana. Dominicanos. Ingesta dietética. Vitamina A. Frutas y hortalizas.

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## INTRODUCTION

Carotenoids are natural pigments widely distributed in nature, and esential to the human body, which depends on diet to obtain them. They exert a variety of functions and physiological actions, the most widely known of which is the provitamin A activity of some of them (mostly β-carotene, α-carotene and β-cryptoxanthin) (1,2). Moreover, carotenoids posess other important activities relevant for human health as antioxidants, enhancing the immune system, and photoprotection of structures such as epitelial and ocular tissues (3). The non-provitamin A carotenoids most frequently studied in terms of the relationship between diet and health are lutein, zeaxanthin and lycopene. Together with the provitamin A carotenoids and other bioactive compounds, they are partly responsible for the protective role in human health that is associated with the consumption of fruits and vegetables (3,4). Lutein and zeaxanthin are concentrated in retina and protect the photoreceptor cell layer from light damage by filtering blue light and acting as scavengers of radical oxygen species (5). High levels of carotenoids in the intake or in tissues are generally associated with a reduction in the risk of several chronic diseases such as cardiovascular, age-related macular degeneration, among others (3,6). Some carotenoids accumulate in certain tissues, such as lutein and zeaxanthin in retina (6) or lycopene in prostate (7), where they can carry out specific actions (8,9). The increase in the number of human studies involving these compounds in recent decades (3,10) highlights the importance of the knowledge of the contents of individual carotenoids in foods and in human tissues.

Vitamin A is also obtained through the diet, either as preformed vitamin A (retinol) in animal products or as provitamin A carotenoids (2). Vitamin A is involved in the visual system, maintenance of epitelial integrity and immunitiy, among other roles and its deficienty is the leading cause of preventable blindness in children and increases the risk of disease and death from severe infections. Vitamin A deficiency has been identified by means of biochemical and dietary markers as a public health problem especially in lower income countries (11). In Dominican Republic, it is identified as one of the micronutrient deficiences (12) mainly from data surveys on vitamin A status and intake in children and in pregnant women and nursing mothers (12,13). However, there is limited information on vitamin status or intake in the Dominican population and, to our knowledge, the most recent study is that resulting from a household budget survey (2006-2007) that showed a moderate consumption of vitamin A, which is more concerning in poorer populations (14). That report supplied information on vitamin A intake as a whole, but not about its individual components (retinol and individual provitamin A carotenoids), an aspect that is of great interest for issuing dietary recommendations in the public health area to avoid their deficiency.

On the other hand, an important percentage of the adult population in the Dominican Republic is overweight (55%) or obese (22%) (15). Adipose tissue is an important site of retinol (16) and carotenoid (17) storage, and obesity can modify the status of these compounds (e.g. of lutein and zeaxanthin) (18). On the other hand, there is evidence suggesting that deficiences of some micronutrients are related to obesity and fat deposition (19) and some of them may increase the risk of the latter and thus, of obesity and related diseases (20). In particular, in the Caribbean region, a high body mass index and low fruit and vegetable intake are important risk factors for the global burden of disease (21).

The aim of this study was to assess the individual components of vitamin A intake (retinol, α-carotene, β-carotene and β-cryptoxanthin) and that of other relevant dietary carotenoids, such as lutein, zeaxanthin and lycopene, in overweight and obese inhabitants of the Dominican Republic, from the diet as a whole, from the intake of fruits and vegetables, as the major contributors to their dietary intake, and from foods plants grouped according to color.

## SUBJECTS AND METHODS

### SUBJECTS

Fifty subjects (23 men and 27 women), ranging in age between 22-69 years old were selected from upper middle class patients who asked for dietary assessment to reduce body weight. Their overall body mass index (BMI) was 31.2 ± 5.3 kg/m$^2$. There were 25 overweight individual (BMI: 25-29.9 kg/m$^2$) and 25 obese patients (BMI: > 30 kg/m$^2$; four of the latter had a BMI between 40-42 kg/m$^2$). Some patients required medication for hypertension (n = 13) and hyperlipemia (n = 6). The characteristics of the subjects are shown in table I. The physical activity of most of the patients was of light or moderate intensity (12 men, 17 women and 8 men, 9 women, respectively); it was vigorous in only four patients (3 men). Ethics approval was considered no required as the dietary intake assessment is widely used in the clinical practice. All 50 gave their written informed consent after receiving oral information about the study.

### DIETARY INTAKE ASSESSMENT

Recent dietary intake was evaluated using three 24 h diet recalls, one of which coincided with a weekend or holiday, carried out within a period of 7 to 10 days. Although dietary assessment was focused on individual carotenoid intake, general information about the frequency of intake of fruits (raw, cooked, in syrup), vegetables (raw, garnish, main course), legumes, fish, eggs and oils, was obtained by means of a food frequency questionnaire. For the first recall, the participants underwent a face-to-face encounter with a specialized interviewer, the same person who, subsequently, performed the other two recalls by telephone or chat (to supply images). The amounts consumed were estimated from the weights of the portions described by the patients (in most cases by means of images), of the raw or cooked food depending on how it was to be consumed. The amounts of cooked pasta, rice and legumes were transformed into raw weight utilizing established conversion factors, dividing by 4 the amounts of legumes and rice and by 5 that of pasta (22). On the basis of this information, we calculated

**Table I.** Characteristis of study subjects (mean ± standard deviation)

| | Men (n = 23) | Women (n = 27) | Total sample |
|---|---|---|---|
| Age (years) | 46.8 ± 12.8 | 49.3 ± 11.4 | 48.1 ± 12.0 |
| BMI (kg/m$^2$) | 32.3 ± 5.4 | 30.3 ± 5.1 | 31.2 ± 5.3 |
| Cholesterol (mg/dl) | 189.2 ± 32.8 | 166.3 ± 56.1 | 176.9 ± 47.0 |
| HDL-cholesterol (mg/dl) | 53.6 ± 24.1 | 45.9 ± 18.4 | 49.4 ± 21.3 |
| LDL-cholesterol (mg/dl) | 114.8 ± 30.7 | 106.2 ± 40.2 | 110.2 ± 36.0 |
| Coffee | Yes: 18<br>No: 5 | Yes: 23<br>No: 4 | Yes: 41<br>No: 9 |
| Smoking habit | Smokers: 2<br>Non-smokers: 21 | Smokers: 2<br>Non-smokers: 25 | Smokers: 4<br>Non-smokers: 46 |
| Alcohol consumption[a] | Yes: 17<br>No: 6 | Yes: 19<br>No: 8 | Yes: 36<br>No: 14 |

*[a]Alcohol consumption: social drinkers. BMI: body mass index; HDL: high-density lipoproteins; LDL: low-density lipoproteins.*

food intake in grams/day, which served as the basis for the determination of nutrients intake. The data on the foods and amounts consumed were introduced into two different software applications, one to calculate preformed retinol, macronutrients (carbohydrates, proteins, lipids), cholesterol, saturated fatty acids (SFA), monounsaturated and poliinsaturated fatty acids (MUFA, PUFA) and energy intake (DIAL®) (23), with data from a food composition table widely used in Spain (22) and, the other, a specific software application for the assessment of carotenoid intakes (24) that includes a carotenoid database developed by our group (25), that enables us to assess the carotenoid intake from foods grouped according to their color (white/yellow, green and red/ orange). The carotenoid database used comprises information on the major dietary carotenoids present in foods, with data generated entirely by high-performance liquid chromatography (HPLC) (25-27) using an analytical procedure that is considered to be highly acceptable (28). The food groups included in the software are: fruit and vegetables, oils and fats, snacks, nonalcoholic beverages, milk and dairy products, eggs and egg products, sauces, herbs and spices. However, some of the foods consumed during the study by Dominican participants were similar but not equal to those included in the carotenoid database used. In those cases, the carotenoid composition was considered to be that of similar foods included in the carotenoid database. The assumptions made for carotenoid intake calculations were as follows (the name in the carotenoid database in brackets): tomato *bugalú o barcelo* (Canary island and salad tomato -mean value), *ají cubanela* (green pepper), *lechosa* (papaya), *guandul or arvejas* (peas), *vainitas* (green beans), sweet lemon (lemon), *chinola* (passion fruit), *toronja* (rose grapefruit), *auyama* (round and oblong shape pumpkin), *guineo or guineíto* (Canary Island banana) and *plátano* (plantain or cooking plantain; carotenoid data from Enrique Murillo, University of Panamá, unpublished data: 884 µg β-carotene/100 g, 626 µg α-carotene/100 g and 95 µg lutein/100 g), lettuce *repollada* (lettuce type iceberg), lettuce *romana* and *sweet* lettuce (romaine /leaf type lettuce).

The food contribution to the vitamin A intake (µg/day) is expressed as retinol equivalents (RE) = retinol + (β-carotene/6) + (α-carotene/12) + (β-cryptoxanthin/12) (22,29) and as retinol activity equivalents (RAE) = retinol + (β-carotene/12) + (α-carotene/24) + (β-cryptoxanthin/24) (2).

## STATISTICAL ANALYSIS

Data are expressed as the mean and standard deviation (for characteristics of subjects and macronutrients and energy intake) or standard error (for carotenoids and vitamin A intake), median and 95% confidence interval. The normal distribution of the data from the whole diet was assessed (Kolmogorov-Smirnov test) and individual carotenoid intake did not follow a normal distribution (except for α-carotene), nor did retinol intake in men. To compare results according sex, Student's t-test was used to compare macronutrients and energy intake and the Willcoxon test was used for carotenoid and cholesterol dietary intakes. SPSS v.22 (SPSS Inc., Chicago, IL, USA) software package was used for all statistical calculations.

## RESULTS

The subjects included in this study showed no significant sex-related differences in their age, blood lipids, smoking habit, alcohol and coffee consumption or level of physical activity (Table I). Table II shows the concentrations of protein, carbohydrates and fiber, fat and saturated fatty acids (SFA), monounsaturated fatty and polyunsaturated fatty acids (MUFA, PUFA) and dietary cholesterol and energy intake of the sample as a whole and grouped according to sex, expressed as the mean and standard deviation. The energy, protein, fat and cholesterol intake were higher in men than in women. The contribution of carbohydrates, proteins

**Table II.** Dietary intake of macronutrients and energy expressed as mean ± standard deviation

| | Men (n = 23) | Women (n = 27) | p value | Total sample |
|---|---|---|---|---|
| Protein (g/d) | 114.0 ± 33.1 | 85.7 ± 24.9 | 0.004 | 98.7 ± 32.0 |
| Carbohydrates (total) (g/d) | 200.3 ± 89.0 | 158.2 ± 57.3 | n.s. | 177.6 ± 75.6 |
| Fiber (g/d) | 22.3 ± 10.1 | 17.1 ± 6.0 | | 19.5 ± 8.5 |
| Fat (g/d) | 96.7 ± 34.3 | 75.0 ± 27.0 | 0.025 | 85.0 ± 32.2 |
| SFA (g/d) | 35.1 ± 15.2 | 27.5 ± 11.6 | n.s. | 31.0 ± 13.8 |
| MUFA (g/d) | 36.1 ± 12.6 | 28.2 ± 10.8 | 0.021 | 31.9 ± 12.2 |
| PUFA (g/d) | 14.4 ± 6.6 | 11.3 ± 5.3 | n.s. | 12.7 ± 6.1 |
| Cholesterol (mg/d) | 410.3 ± 152.7 | 294.0 ± 148.1 | 0.004 | 347.5 ± 159.8 |
| Energy (kcal/d) | 2,265.9 ± 764.3 | 1,752.1 ± 503.3 | 0.018 | 1,988.5 ± 680.9 |

*MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; SFA: saturated fatty acids. n.s: no significant difference.*

and fat to the energy intake was 35.7%, 19.9% and 38.5%, respectively (the contribution of energy and alcoholic drinks and infusions were not assessed). The PUFA intake was lower than that of MUFA and SFA, in both sexes, and represented 5.75% of the fat intake, and those of MUFA and SFA represented 14.4% and 14%, respectively.

The fruits most frequently consumed were *lechosa* (papaya), *guineo* (banana), pineapple and apple (red and green). The highest rate of consumption was between two and five times per week (24 out of 50 subjects). Ten subjects had a fruit consumption of 1 per week or less, and two subjects did not eat fruit. Among the vegetables: lettuce, tomato, onion and rocket were those most widely-consumed as raw items, with a maximun consumption of 1-2 times/day (24 out of 50 subjects; two participants ate no cooked vegetables); 20 subjects ate raw vegetables 2-5 times/week and 6 subjects had them once a week or less. Those consumed after cooking processes included broccoli, eggplant, carrot, green pepper, cauliflower and *vainitas* (green beans), with a consumption of 1-2 times/day (11 subjects), 2-4 times/week (28 subjects) and once a week or lower (11 subjects; and 4 participants ate no cooked vegetables). Egg consumption was of interest because of its contribution to lutein and zeaxanthin intake and eggs were eaten 2-6 times/week (29 out of 50 subjects) and once a week or less (16 subjects). Olive oil was the most frequently used oil for salads and, for cooking, the variety of oils employed was greater (olive, soya, canola and corn).

Regarding other foods in the diet of these subjects, there was a low consumption of fish (the highest consumption being once a week or less) (32 subjects, 13 of them never eat fish), and only 17 subjects preferred it 2-3 times/week. Salmon, gilthead bream, grouper, *chillo* (sea bream) and tuna were the most widely-consumed. Instead, legumes, mainly ckickpeas, *guandules* (peas), beans (red, white, black) and lentils were those most frequently eaten, with a consumption between 2-6 times/week in 32 subjects and only 11 subjects consumed them less than once per week.

The intake of the carotenoids: α-carotene, β-carotene , β-cryptoxanthin, lycopene, lutein and zeaxanthin and, that of preformed retinol and the vitamin A intake, expressed as retinol equivalents (RE) and retinol activity equivalents (RAE), are shown in table III. In this table, the lutein and zexanthin rows provide intake data of these two carotenids when they were determined separately (97 out of 124 foods included in the database used), and the lutein-zeaxanthin row shows their joint value as obtained from the literature (see database in reference 25); consequently, in some cases, the value for lutein plus zeaxanthin did not coincide with the sum of the concentration of each. The row for total lutein and zeaxanthin reports the total lutein and zeaxanthin intake. There were no significant differences in the intake of provitamin A carotenoids (α-carotene, β-carotene, β-cryptoxanthin) or non-provitamin A carotenoids (lycopene, lutein and zeaxanthin) between sexes, from total diet. Retinol intake was higher in men than in women but it did not reach statistical significance ($p = 0.064$).

The dietary vitamin A intake in this group of subjects was supplied by preformed retinol in 40% and by provitamin A carotenoids in 60%. Fruits contributed less to the vitamin A intake than vegetables (19.2% and 39.2%, respectively). The total carotenoid intake in this subjects was 6,363.2 µg/day (mean), with something more than half being provitamin A carotenoids (3,570.4 µg/day, 56.1% of the total carotenoid intake). Of the provitamin A carotenoids, that consumed most widely was β-carotene (74.3%); the contribution of α-carotene and β-cryptoxanthin was quite lower (19.6% and 6%, respectively). The mean dietary intake of non-provitamin A carotenoids was 2,792.9 µg/day, which represented almost half of the total carotenoid intake (43.9%) and was supplied by lycopene and lutein plus zeaxanthin in similar percentages (52.3% and 47.7%, respectively).

Table IV shows the dietary intake of the individual carotenoids provided by fruits and vegetables, as major contributors to that ingestion, as well as that supplied from foods of plant origin grouped according their color (white-yellow, red-orange, green). Lutein, zeaxanthin, β-carotene and lycopene were mainly sup-

**Table III.** Dietary intake of carotenoids, retinol and vitamin A (μg/day) from total diet expressed as mean ± standard error, (median) and [95% confidence interval]

| | Men | Women | Total sample |
|---|---|---|---|
| *No provitamin A carotenoids* | | | |
| Lutein | 719.8 ± 120.8<br>(398.0)<br>[515.8-1436.0] | 1,194.0 ± 410.4<br>(338.8)<br>[350.4-2,037.7] | 975.9 ± 229.0<br>(391.3)<br>[515.8-1,436.0] |
| Zeaxanthin | 61.3 ± 14.1<br>(28.7)<br>[28.8-107.9] | 74.4 ± 34.7<br>(25.0)<br>[3.1-145.7] | 68.4 ± 19.7<br>(26.8)<br>[28.8-107.9] |
| Lutein + zeaxanthin | 395.3 ± 73.1<br>(239.1)<br>[243.6-547.0] | 373.5 ± 76.8<br>(249.7)<br>[215.5-531.4] | 383.5 ± 52.9<br>(244.4)<br>[277.2-489.8] |
| Total lutein and zeaxanthin | 1,103.4 ± 148.6<br>(893.1)<br>[846.1-1,816.4] | 1,525.4 ± 429.3<br>(492.6)<br>[643.0-2,407.9] | 1,331.3 ± 241.4<br>(720.3)<br>[846.1-1,816.4] |
| Lycopene | 1,523.4 ± 222.3<br>(1,219.0)<br>[1,077.6-1,845.6] | 1,409.0 ± 302.7<br>(947.3)<br>[786.9-2,031.1] | 1,461.6 ± 191.1<br>(1093.5)<br>[1,077.6-1,845.6] |
| *Provitamin A carotenoids* | | | |
| β-carotene | 2,728.2 ± 556.1<br>(1,677.7)<br>[1574.9-3881.6] | 2,590.0 ± 581.9<br>(1,571.0)<br>[1,394.0-3,786.4] | 2,653.7 ± 401.3<br>(1,624.3)<br>[1,847.3-3,460.0] |
| α-carotene | 811.2 ± 149.0<br>(760.2)<br>[502.2-1,120.1] | 607.6 ± 103.0<br>(542.4)<br>[395.8-819.3] | 701.2 ± 88.5<br>(607.3)<br>[523.4-879.1] |
| β-cryptoxanthin | 255.2 ± 71.6<br>(129.8)<br>[106.8-403.6] | 181.0 ± 45.3<br>(56.0)<br>[88.5-274.6] | 215.4 ± 40.9<br>(75.7)<br>[133.2-297.6] |
| *Retinol and vitamin A (RE, RAE)* | | | |
| Retinol | 420.0 ± 54.8<br>(381.0)<br>[306.3-533.7] | 283.8 ± 28.7<br>(274.0)<br>[224.9-342.7] | 346.5 ± 30.8<br>(303.0)<br>[284.5-408.4] |
| Retinol equivalents (RE) | 963.6 ± 116.0<br>(770.8)<br>[772.9-1204.2] | 781.3± 102.1<br>(627.3)<br>[571.5-991.0] | 865.1 ± 77.0<br>(714.0)<br>[710.3-1019.9] |
| Retinol activity equivalents (RAE) | 691.8 ± 75.9<br>(613.2)<br>[534.4-849.2] | 532.5 ± 54.7<br>(476.7)<br>[420.0-645.1] | 605.8 ± 46.7<br>(538.2)<br>[512.0-699.6] |

plied by vegetables, and α-carotene and β-cryptoxanthin by fruits. Vegetables suppled 83.9% of lutein and 72.5% of zeaxanthin, and fruit provided 9.9% of lutein and 3.9% of zeaxanthin consumed in the total diet. Vegetables supplied 79.2% and 68.2% of total dietary lycopene and β-carotene intake. Fruits were greater contributors than vegetables to the dietary intake of α-carotene (60.2%) and β-cryptoxanthin (18.4%). Orange juice (natural and commercial) was the major contributor to the dietary β-criptoxanthin intake (72.2%).

Carotenoid intakes from food of plan origin, including fruits and vegetables, as well as others supplied by oils and fats, non-alcoholic beverages, milk and dairy products, eggs and sauces among others, are shown in table IV, grouped according to their color. Lutein intake was supplied mainly by foods of green color and, to a lesser extent, by those of white/yellow and red/orange color. Zeaxanthin was supplied in greater amounts by red/orange foods than by green or white/yellow. Red/orange foods were the only contributors to lycopene intake (some fruits like watermelon

**Table IV.** Dietary intake of carotenoids from fruits and vegetables, and including other foods of plant origin grouped according to their color, expressed in µg/day. Data reported as mean ± standard error, (median), [95% CI]

| | Fruits and vegetables group | | Food of plant origin grouped according to their color | | |
|---|---|---|---|---|---|
| | **Fruits** | **Vegetables** | **White/yellow** | **Red/ orange** | **Green** |
| Lutein | 96.9 ± 11.8[a] (80.8) [73.2-120.6] | 819.0 ± 230.0[b] (228.3) [356.7-1,281.2] | 158.1 ± 13.2[b] (141.0) [131.5-184.6] | 110.2 ± 25.6[a] (41.8) [58.7-161.7] | 707.6 ± 224.4[c] (157.3) [256.7-1,158.5] |
| Zeaxanthin | 2.7 ± 1.7[a] (0.0) [-0.7-6.1] | 49.6 ± 8.3[b] (26.8) [32.8-66.4] | 12.9 ± 3.3[a] (1.2) [6.2-19.5] | 25.5 ± 6.2[ab] (0.0) [13.2-37.9] | 13.9 ± 5.2[b] (0.0) [3.4-24.4] |
| Lutein + zeaxanthin | 4.8 ± 2.0[a] (0.0) [0.7-8.9] | 152.9 ± 41.8[b] (0.7) [68.9-237.0] | 88.8 ± 29.9[b] (0.0) [28.6-148.9] | 33.7 ± 11.0[a] (5.8) [11.6-55.7] | 99.6 ± 34.1[a] (0.0) [31.2-168.1] |
| Total lutein and zeaxanthin | 45.1 ± 7.7[a] (33.4) [29.7-60.5] | 1,021.5 ± 235.4[b] (333.0) [548.5-1,494.5] | 200.5 ± 35.5[a] (102.4) [129.1-271.9] | 169.4 ± 32.0[a] (73.3) [105.1-233.7] | 821.1 ± 227.5[b] (189.5) [363.9-1,278.3] |
| Lycopene | 261.8 ± 135.9[a] (0.0) [-11.3-534.9] | 1,157.2 ± 143.9[b] (943.5) [868.0-1,446.3] | 0 | 1461.8 ± 191.1 (1093.5) [1,077.8-1,845.8] | 0 |
| α-carotene | 422.3 ± 67.7[a] (255.5) [286.3-558.4] | 277.4 ± 73.9[b] (6.9) [128.8-426.0] | 420.2 ± 67.8[c] (253.7) [284.1-556.4] | 278.3 ± 74.0[b] (5.7) [129.5-427.1] | 2.7 ± 0.5[a] (0.0) [1.6-3.8] |
| β-carotene | 729.3 ± 97.0[a] (544.6) [534.4-924.2] | 1809.5 ± 398.4[a] (636.7) [1,008.9-2,610.1] | 636.2 ± 94.9[b] (419.1) [445.6-826.9] | 1588.2 ± 373.7[b] (1149.0) [837.2-2,339.2] | 390.5 ± 112.7[a] (79.1) [164.1-616.9] |
| β-cryptoxanthin | 39.7 ± 13.6[a] (10.6) [2.7-76.6] | 20.1 ± 4.7[a] (0.0) [10.7-29.5] | 2.7 ± 0.7[a] (0.5) [1.3-4.1] | 209.2 ± 40.8[b] (73.3) [127.3-291.2] | 3.5 ± 0.6[a] (0.3) [2.1-4.8] |

*Different superscript letters within rows means significant differences (p = 0,000 for all except p = 0,019 for α-carotene) in the fruits and vegetables group and in the foods of plants origin grouped according to their colors (p < 0.05, most of them p = 0.000).*

and rose grapefruit, vegetables like raw tomato, tomate sauces and juices). α-carotene intake came mainly from white/yellow foods and red/orange, with green foods being minor contributors. Greater contributors to β-carotene and β-criptoxhantin were red/orange foods, as compated to those white/yellow or green.

## DISCUSSION

To our knowledge, the data on individual carotenoid intake presented in this study in overweight/obese subjects are the first data on carotenoid intake in the Dominican Republic. Although the contribution of provitamin A carotenoids is taken into account in studies assessing vitamin A intake in several population groups, mainly children and pregnant /nursing women, but with no information on the individual components (30,31).

The dietary intake of proteins and carbohydrates in the overweight and obese subjects included in this study widely exceeds the dietary reference intakes, mainly for proteins (96%, on average, for men and women) and, to a lesser extent for carbohydrates (37%, on average, for men and women) (32). When these patients went to consult their physician, they had limited their carbohydrate consumption to reduce weight, since that is the popular bilief to achieve this objective. They were also far from the acceptable macronutrient distribution range for fat intake, with a SFA contribution to the dietary energy intake higher than the 10% recommendation (32). In contrast, they met the dietary reference intakes for PUFA and nearly for fiber (32). A high percentage of energy from total dietary fat was also described by Saito et al. (33) in Dominican hospital workers of characteristics similar to those of the present study. The vitamin A intake in our subjects did not meet the recommended intake expressed in RAE (900 and 700 µg/d for men and women, respectively) (RDA in reference 2) and is in agreement with a recent analysis of dietary sufficiency in the Dominican Republic, based on the Survey of household income and expenses, that concluded it to be moderately inadequate for vitamin A, in all socioeconomic groups (14), although it is important to point out that, in this report, the contribution of

provitamin A carotenoids to vitamin A intake was calculated in a manner not utilized by the World Health Organization (WHO)/ Food and Agriculture Organization of the United nations (FAO) or the Institute of Medicine (USA) (2,29), since they do not consider carotenoid contribution in the bases of their chemical structure and/or bioavailability, but depending on the type of food; thus provitamin A carotenoids supplied by fruits and plant roots are divided by 12, and those provided by leafy green vegetables by 24. Therefore, that supplied by β-carotene is underestimated. β-carotene and lutein are widely distributed in foods, from leafy green vegetables (e.g. cabbage, spinach and different varieties of lettuce), and whose importance will depend on the amount of these foods present in the diet.

In this study, vitamin A is supplied in a higher percentage by foods from plant sources (59%) than from animal sources (41%). These percentages are quite different from those obtained in the previously mentioned national survey, in which, more than 80% of vitamin A intake came from foods of plant origin (mainly fruits from the *Musaceae* family, due to their higher consumption and also, to the high content of α- and β-carotene content of plantain) and, the rest is supplied by foods from animal origin (mainly eggs and milk) and ready-to-eat foods (14). This difference can be attributed to the socioeconomic level of the participants, since those in the present study were from upper middle class and those in the national survey were representative of the population and, as the socioeconomic level increases, the availability of total vitamin A is greater, and the larger the proportion of vitamin A from animal sources, something that occurs in all developed countries (e.g. in Spain, 58% of animal origen) (34).

Fruits and vegetables, major sources of carotenoids and of provitamin A intake among populations (3), and in this study, vegetables make a higher contribution to vitamin A intake than fruits (37.7% *vs.* 18.5%), as is also observed in the Spanish (32.9% and 4.4% from vegetables and fruits, respectively) (34) and Brazilian populations (70.3% and 21.5% from vegetables and fruits, respectively) (35). *Guineos* (bananas) (*Cavendish a*nd *Gross Michell)* and plantain (*Musa paradisiaca*) were widely consumed, the first is mainly consumed raw and the second cooked. According to a report by Menchú et al. (14), bananas and plantain represent approximately 35% of the vitamin A intake, provided by fruits, regardless of the socioeconomic status. On the other hand, subjects included in the present study did not meet the Dietary Guidelines for Dominican Republic (36) for fruits (2-3 portions of fruits/day) and less than half of the sample met the recommended intake for vegetables (2 portions of vegetables/day), the maximm consumption for fruits was 2-5 times fruits/week and for vegetables, 1-2 times/day.

Of the provitamin A carotenoids, that for which the diet included most was β-carotene, with a consumption that is nearly four times higher than that of α-carotene; the latter is consumed in amounts that triplicate that of β-cryptoxanthin. The mean intake of α-carotene and β-carotene in this group of Dominican patients was much greater than that of the Spanish population (269.2 and 1458.9 µg/day, respectively) (34), and that observed in the United States (USA) (451 and 2,500 µg/d, respectively) (37). However, the consumption of β-cryptoxhantin in those subjects (215 µg/d), is lower than that of the Spanish population (322.4 µg/d) (34), but greater than that of the USA (82 µg/d) (37). β-cryptoxhantin intake from fruit and vegetables in these subjects is lower than that in the Brazilian population (59,8 *vs.* 126,2 µg/d), and that of α-carotene and β-carotene in this study (699,7 and 2538,8 µg/d, respectively), is much higher than that in the Brazilian population (162.6 and 917.5 µg/d, respectively) (35). The amount of β-carotene present in the total diet of these subjects represents more than 2.5 times the amount consumed of the other two provitamin-A carotenoids, as occurred in the Spanish (34). In this study, β-carotene is provided mainly by vegetables (68.1%); however, α-carotene and β-cryptoxanthin are mainly supplied by fruits (60.2% and 72%, respectively), orange juice being the major contributor to the β-cryptoxanthin intake. The greater contribution of α-carotene from fruits is due to the frequent consumption of foods with a high content, like the banana (*guineo*) and the avocado. However, in other populations with differerent dietary patterns, for example, the Spanish, α-carotene is mainly provided by vegetables (e.g. in Spain, 94.8%), although vegetables are also the major providers of β-carotene (84.5%) (34).

Concerning, non-provitamin A carotenoids, vegetables are the major contributors to the intake of lutein (83.9%), zeaxanthin (72.5%) and lycopene (79.2%). The dietary intake of lycopene in this study is quite lower than that reported in the populations from Spain (1,462 *vs.* 3,056 µg/d) (38) and from the USA (1,462 *vs.* 5,279 µg/d) (37). The total dietary intake of lutein and zeaxanthin is similar to that found in the Spanish population (1,331 *vs.* 1,235 µg/d) (38) and somewhat less than that reported in the USA (1,331 *vs.* 1,734 µg/d) (37). The intake of these carotenoids from the consumption of fruit and vegetables, with that in Brazilian population differs regarding lutein and lycopene, and are higher in this study than in the Brazilians (915.9 *vs.* 776 µg lutein/d and 1,419 *vs.* 656 µg lycopene/d), and is similar to that of zeaxanthin (52.3 *vs.* 56.9 µg/d, this study *vs.* the Brazilians, respectively) (35). There are no dietary reference intakes for any of the non-provitamin A carotenoids, but there are some suggestions of intake based on the decreased risk of some chronic diseases (i.e. age-related macular degeneration), mainly observed in epidemiological studies, as is, for instance, the recommendation of 6 mg lutein/day (8). This level is much higher than the lutein intake observed in this study.

Finally, as fruit and vegetables show a broad range of color (lycopene associated with red-colored foods, provitamin carotenoids with orange-colored foods and lutein and zeaxanthin with dark-green-colored foods), each of which is associated with different phytochemical profile and, thus, with different biological activities (39). Moreover, as the classification of fruit and vegetables according to the color of their edible portion is becoming increasingly common in recent years, especially for the establishment of public health dietary recommendations (40), we grouped the foods according to their color (white/yellow, green and red/ orange). The red /orange and white/ yellow fruit and vegetables were the major contributors to the provitamin A intake from fruit and vegetables in these subjects, and were much higher than

that supplied by green-colored foods. In the Spanish population, provitamin A carotenoids are also supplied by red/orange fruit and vegetables, followed by green produce, with white/yellow foods being those that contributed the least to dietary intake (34), a difference that is due to the greater contribution of *guineo* (or banana) and plantain in the Dominican subjects. This also occurs in the Spanish population, in whom green fruit and vegetables are the main source of lutein plus zeaxanthin and, zeaxanthin is supplied mainly by red/orange fruit and vegetables (38).

Although, to determine the contribution of fruits and vegetables to the intake of each of the provitamin A carotenoids in the Dominican diet, it would be necessary to increase the sample size, because the subjects included in this study do not constitute a representative sample and because the dietary carotenoid intake did not show a homogeneus distribution. However, the data presented here is of great interest, since they are the first individualized data on carotenoid intake in Dominican subjects, and they contribute to improving the understanding of the relationship between diet and health. In short, the diet of these overweight/obese Dominican subjects, from the upper middle class, complied with the recommended vitamin A intake (2) when expressed as RE, but would be somewhat low when expressed as RAE, and were supplied in larger amounts by foods from plant rather than animal sources (59% *vs.* 41%, respectively), and mostly by red/orange and white/yellow foods. Vegetables were the major contributors to the non-provitamin A carotenoids and to the β-carotene intake, and fruits the major contributors to the intake of α-carotene and β-cryptoxanthin.

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Nutrición Hospitalaria

Trabajo Original

Epidemiología y dietética

# Antihypertensive effect of fermented skim camel *(Camelus dromedarius)* milk on spontaneously hypertensive rats

## *Efecto antihipertensivo de la leche de camello fermentada* (Camelus dromedarius) *en ratas hipertensas*

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## Abstract

**Background:** Hypertension is one of the most common diseases in worldwide, thus prevention of hypertension is important in reducing the risks of cardiovascular disease. Milk contains bioactive peptides released during milk fermentation which lead to exhibit angiotensin I converting enzyme (ACE) inhibitory.

**Objective:** The aim of this study was to investigate the antihypertensive effect of fermented skim camel milk on rats and compared with unfermented skim camel milk as control.

**Methods:** The antihypertensive effect of fermented skim camel milk on thirty six male spontaneously hypertensive rats (SHR) was carried out for (short-term) and (long-term) using different doses (80, 240 and 1200 mg/kg body weight). Angiotensin converting enzyme (ACE) activity was also measured using ACE Kit.

**Results:** The blood pressure (systolic and diastolic) of spontaneously hypertensive rats (SHR) in short term administration (24 hours) of 1200 mg/kg body weight fermented skim camel milk decreased significantly ($p < 0.05$) from 22 to 36 mmHg and 28 to 32 mmHg, respectively, at four and eight hour of post administration. On the other hand, the blood pressure of fermented skim camel milk for long-term (20 days) decreased and affected the heart rate (beats/min). The lowest record of systolic (41 mmHg) and diastolic blood pressure (19 mmHg) were at dose of 1200 mg/kg body weight of fermented skim camel milk at 15 days of administration. Likewise, ACE activity in plasma of SHR administered fermented skim camel milk decreased significantly ($p < 0.05$) compared with the control group.

**Conclusion:** The hypotensive effect of fermented skim camel milk by *L. helveticus* and *S. thermophillus* in SHR rats depends on the high dose of fermented skim camel milk in short and long-term. The ACE activity inhibitory was clear with fermented skim camel milk.

**Key words:**

Hypertension. Skim camel milk. Blood pressure. Angiotensin I converting enzyme activity.

## Resumen

**Introducción:** la hipertensión es una de las enfermedades más frecuentes en el mundo, por lo que su prevención es importante en el objetivo de disminuir el riesgo de enfermedad cardiovascular. La leche contiene péptidos bioactivos que se liberan durante su fermentación con un efecto inhibitorio sobre el enzima convertidor de la angiotensina (ECA).

**Objetivo:** el objeto de este estudio fue investigar el efecto antihipertensivo de la leche de camello fermentada en un modelo experimental de ratas con hipertensión comparándolas con un grupo control alimentado con la misma leche sin fermentar.

**Métodos:** se valoró el efecto antihipertensivo de la leche de camello fermentada en 36 ratas macho hipertensas de forma espontánea a corto y a largo plazo usando diferentes dosis (80, 240 y 1.200 mg/kg de peso). También se midió la actividad del ECA.

**Resultados:** la presión arterial (sistólica y diastólica) disminuyó a corto plazo (24 horas) con la dosis de 1.200 mg/kg ($p < 0,05$), pasando de 36 a 22 mmHg y de 32 a 28 mmHg, respectivamente a las 4 y 8 horas postadministración. Por otra parte, la tensión arterial a largo plazo en el grupo que consumió la leche de camello fermentada afectó disminuyendo la frecuencia cardiaca. Las medidas inferiores de presión sistólica (41 mmHg) y distólica (19 mmHg) aparecieron en el grupo que recibía 1.200 mg/kg a los 15 días del inicio de la administración de leche de camello fermentada. Por otra parte, la actividad del ECA disminuyó significativamente en el grupo con leche fermentada ($p < 0,05$).

**Conclusiones:** el efecto antihipertensivo de la leche de camello fermentada con *L. helveticus* y *S. Thermophillus* en ratas con hipertensión depende la cantidad administrada, tanto a corto como a largo plazo. El efecto inhibitorio sobre el ECA fue manifiesto en el grupo que recibió leche de camello fermentada.

**Palabras clave:**

Hipertensión. Leche de camello desnatada. Presión arterial. Enzima convertidor de la angiotensina.

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## INTRODUCTION

Hypertension disease is an important public health problem around the world. Unprocessed hypertension leads to cardiovascular and renal diseases such as coronary heart disease, stroke and kidney dysfunction (WHO, 2015). Dietary factors influence the development of hypertension (McCarron et al., 1984), on the other hand, the use of dietary approaches to stop hypertension using a diet rich in vegetables, fruits and low fat dairy products, was associated with useful decrease in blood pressure (Harsha et al., 1999). Food protein is now being consumed as a source of biologically active components that might have health benefits when ingested (Roberts et al., 1999). Milk is a rich source of dietary proteins and could play an important role in promotion of health and prevention of diseases (Meisel, 2005). Camel milk contains all essential nutrients found in bovine milk (El-Agamy et al., 1998) and is consumed in Saudi Arabia as fresh or sour (Abu-Taraboush et al., 1998). Milk protein derived biologically active peptides prevented the rise of blood pressure in SHR (Sipola et al., 2001) and decreased blood pressure (BP) in mildly hypertensive subjects (Sipola et al., 2002). Moreover, many studies have reported the ACE inhibitor activity of various bioactive peptides isolated by milk proteins fermentation (Gobbetti et al., 2000; FitzGerald & Murray (2006). Milk protein contain bioactive peptides could be angiotensin I converting enzyme (ACE) inhibitors, this peptides can be release during milk fermentation with *Lactobacillus helveticus* strains (Yamamoto et al., 1999; Sipola et al., 2002) or combined with *Streptococcus thermophilus* (Donkor et al., 2007). It has been reported that milk fermentation by two or more different types of strain might contain wide variety of functional substances than milk cultured with a single strain (Kuwabara et al., 1995). Few studies reported the ACE inhibitor activity of fermented camel milk proteins. The elevated ACE-inhibitory activity was observed in cultured camel milk peptide fractions compared to bovine milk. This is due to the presence of higher proline content in the primary structure of camel milk caseins than in bovine milk (Moslehishada et al., 2013). Moreover, whole casein and β-CN of camel milk found to have significant ACE-inhibitory activity after hydrolysis with pepsin alone or after pepsinolysis followed by trypsinolysis and chymotrypsinolysis (Salami et al., 2011). Therefore, the aim of this study was to investigate the antihypertensive effect of fermented and unfermented skim camel milk using rats.

## MATERIALS AND METHODS

### MATERIALS

*Lactobacillus helveticus* (LMG11445) strain was from Belgian coordinated collection of microorganisms (BCCM-LMG) and *Streptococcus thermophilus* (ATCC 19258) was from American type culture collection (ATCC) in freeze dried form. Lactase enzyme (*Aspergillus oryzae* 9000 FCC lactase units) supplied by Webber Naturals Co. Canada. Captopril was from Sigma, St. Louis, MO, USA) ACE Kit was from Buhlmann Laboratories AG, Switzerland.

### PREPARATION OF FERMENTED AND UNFERMENTED SKIM CAMEL MILK

Camel milk was obtained from private farm located in central region of Saudi Arabia. Fat was removed using centrifugal separation at temperature of 45 °C and lactose was hydrolyzed using lactase enzyme. Skimmed milk was pasteurized at 85 °C for 30 minutes. Then, skimmed camel milk (lactose hydrolyzed) was divided into two parts (unfermented and fermented skim camel milk). Then, one part of the milk was inoculated with 3% of active cultures (*L. helveticus* + *S. thermophilus*) and incubated at 40 °C until reaching pH reached 4.3. Later, fermented skim milk samples were frozen at -80 °C, and then freeze-dried and kept in the refrigerator until used as a diet for rats to determine the antihypertensive effect of fermented skim camel milk on rats. In this study, captopril (a proven hypotensive drug, 50 mg/kg of body weight) was used to make sure that rat's response to ACE- inhibitors.

### ANIMALS GROUPING AND FEEDING

Thirty six male spontaneously hypertensive rats (SHR) were supplied from Harlan Laboratory co, USA, at age of 11 week-old and weighting 272 ± 3 g. Rats were housed in stainless steel cages at 22 ± 2 °C with 12 h light/dark cycles and 50 ± 5% relative humidity. The rats were given free access to water during the experimental period. Animals handling, treatment, euthanasia and other experimental procedures were in agreement with the National Institute of Health Guide for the care and use of Laboratory Animals, Institute for Laboratory Animal Research (NIH Publications No. 80-23; 1996) as well as the obtained approval (108-EACC-2015) from the Ethical committee of Experimental Animal Care Center, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia. Rats were divided into six groups after a 1-week period of adaptation after arrival, each consisting of six rats: a negative control group were only fed distilled water orally, a positive control group were orally fed captopril (50 mg/kg b.w./day), one group of rats fed unfermented skim camel milk (UFCM) 1200 mg/kg b.w./day orally and three groups of rats were orally fed with different doses of fermented skim camel milk (FCM) at 80, 240 or 1200 mg/kg b.w./day, respectively (Wang et al., 2012). Diet for maintenance of rats was prepared according to the American Institute of Nutrition (AIN). Rats were orally fed between 10-11 a.m. for 20 d (long-term).

### ANTIHYPERTENSIVE EFFECT MEASUREMENTS

Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate value (HR) were measured by tail-cuff instrument noninvasive blood pressure method using CODA 20830 (Kent Scientific, USA). The measurements were taken before administration and continued for every five day in long-term study (21 days) and 0, 2, 4, 8 and 24 hours after single oral administration

(short-term study). Rats were kept at 38 °C for 10 min before taking the measurements to calm down and make the pulsations of the tail artery readable. To avoid the influence of the circadian, blood pressure measurements were conducted during day at time between 10 a.m. and 14 p.m. and the SBP and DBP values were obtained by calculating the average reading of 15 measurements.

## DETERMINATION OF ACE ACTIVITY

Rats were allowed to fast for 12 h before anesthetization with diethyl ether and sacrificed at the end of experiment period. The blood samples were collected in EDTA tubes by orbital venipuncture and centrifuged for 10 min at 4000 × g at 4 °C to obtain blood plasma (Tuck et al., 2009). The plasma samples were immediately stored at -80 °C until day of analysis. Angiotensin Converting Enzyme activity was measured using ACE Kit (Buhlmann Laboratories AG, Switzerland).

## STATISTICAL ANALYSIS

Data were expressed as means ± standard deviation (SD). Group's differences were analyzed using one-way ANOVA, followed by Duncan's Multiple Range (DMR) test using SPSS 21 software (SPSS Inc., Chicago, IL, USA). Difference was considered statistically significant when P value is less than 0.05 ($p < 0.05$).

## RESULTS

### THE EFFECT OF SHORT-TERM ADMINISTRATION OF FERMENTED SKIM CAMEL MILK ON BLOOD PRESSURE OF SHR

Figure 1 shows the effect of the different treatments (PC, UFCM1200, FCM80, FCM240 and FCM1200) on SBP of SHR. All treatments except unfermented skim camel milk and the low dose (80 mg) of fermented skim camel milk decreased significantly ($p < 0.05$) the SBP of SHR in four and eight hours of the administration compared with NC group. The high dose (1200 mg) of fermented skim camel milk significantly ($p < 0.05$) reduced the SBP by 22 and 36 mmHg at four and eight hours, respectively, followed by (240 mg) of fermented skim camel milk which significantly ($p < 0.05$) decreased the SBP by 16 and 21 at four and eight hours, respectively. The effect of high dose (1200 mg) of fermented skim camel milk in SBP was similar to the captopril at these two time intervals. Furthermore, figure 2 shows that fermented skim camel milk (1200 mg and 240 mg) significantly ($p < 0.05$) reduced the DBP by 28 and 12 mmHg at four hours and 32 and 22 mmHg at eight hours, respectively compared with negative control (NC). Generally, this effect decreased the SBP and DBP after eight hours of the administration and the milk had no effect after this time (24 h).

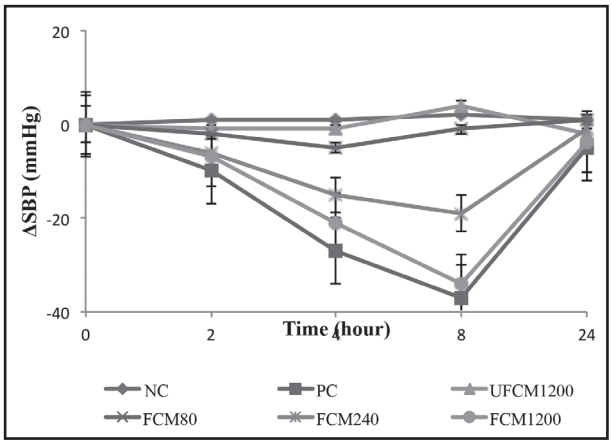


**Figure 1.**

The effect of fermented skim camel milk on systolic blood pressure (SBP) of spontaneously hypertensive rats (SHR), distilled water (♦), captopril (■), 1200 mg unfermented camel milk/kg b.w. (▲), 80 mg fermented camel milk/kg b.w. (×), 240 mg fermented camel milk/kg b.w. (*), 1200 mg fermented camel milk/kg b.w. (●). Data are expressed as mean ± SD (n = 6).

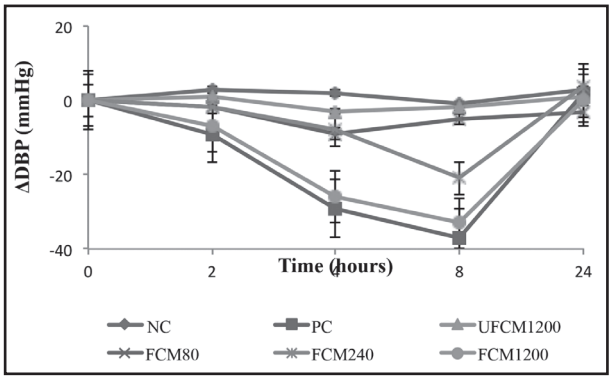


**Figure 2.**

The effect of fermented skim camel milk on diastolic blood pressure (DBP) of spontaneously hypertensive rats (SHR), distilled water (♦), captopril (■), 1200 mg unfermented camel milk/kg b.w. (▲), 80 mg fermented camel milk/kg b.w. (×), 240 mg fermented camel milk/kg b.w. (*), 1200 mg fermented camel milk/kg b.w. (●). Data are expressed as mean ± SD (n = 6).

### THE EFFECT OF LONG-TERM ADMINISTRATION OF FERMENTED SKIM CAMEL MILK ON BODY WEIGHT, HEART RATE AND BLOOD PRESSURE OF SHR

#### Body weight of SHR

The body weight increased throughout the experimental period in all groups: NC, PC, UFCM1200, FCM80, FCM240 and FCM1200 from 273 ± 2 to 326 ± 2, 271 ± 4 to 293 ± 4, 275 ± 2 to 321 ± 2, 269 ± 2 to 308 ± 3, 273 ± 4 to 320 ± 3 and 271 ± 2 to 302 ± 3, respectively. The PC group had significantly ($p < 0.05$) less body weight than that of other groups at the end of the experiment (20 d).

### The heart rate value of SHR

Generally, the heart rates of rats fed fermented skim camel milk treated groups 1200, 240 mg and captopril group (PC) were significantly ($p < 0.05$) lower than that of the negative control group (NC) throughout the experimental period as shown in figure 3. Moreover, the heart rate of rats fed 1200 and 240 mg fermented skim camel milk generally significantly lower than captopril group (PC).

### The systolic and diastolic blood pressure

Figure 4 shows the effect of the different treatments on the blood pressure of SHR. All treatments except unfermented skim camel milk and the low dose (80 mg) of fermented skim camel milk reduced significantly ($p < 0.05$) the SBP in the fifth day of the experiment compared to the control group. SHR received the high dose (1200 mg) of fermented skim camel milk had significantly ($p < 0.05$) lower SBP than those received the low dose (240 mg). However, the effect of fermented skim camel milk on SBP was generally lower than that exerted by captopril. The significant lowering effect of the two doses (240 and 1200 mg) of fermented skim camel milk in the SBP of SHR generally continued until the end of the experiment. On the other hand, the high dose (1200 mg) only significantly ($p < 0.05$) decreased the DBP compared with the control group and the reduction of DBP in SHR rats continued to the last day of the treatment (Fig. 5). Moreover, the effect of the high dose (1200 mg) of fermented skim camel milk in DBP of SHR was generally not significantly ($p > 0.05$) different from the captopril.

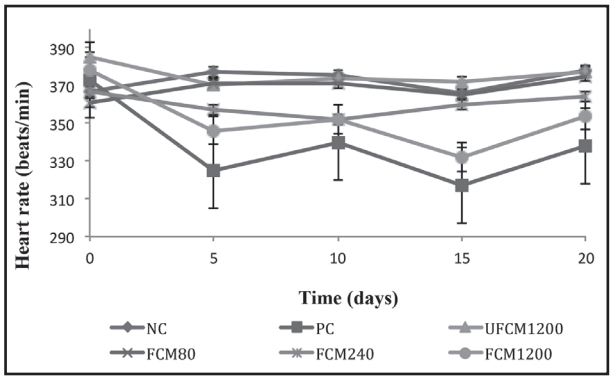


**Figure 3.**

The effect of fermented skim camel milk on heart rate of spontaneously hypertensive rats (SHR), distilled water (♦), captopril (■), 1200 mg unfermented camel milk/kg b.w. (▲), 80 mg fermented camel milk/kg b.w. (×), 240 mg fermented camel milk/kg b.w. (*), 1200 mg fermented camel milk/kg b.w. (●). Data are expressed as mean ± SD (n = 6).

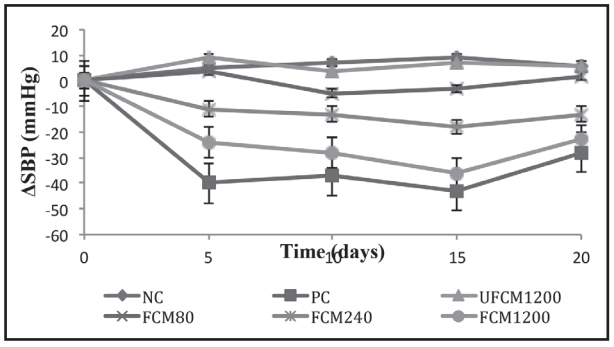


**Figure 4.**

The effect of fermented skim camel milk on systolic blood pressure (SBP) of spontaneously hypertensive rats (SHR), distilled water (♦), captopril (■), 1200 mg unfermented camel milk/kg b.w. (▲), 80 mg fermented camel milk/kg b.w. (×), 240 mg fermented camel milk/kg b.w. (*), 1200 mg fermented camel milk/kg b.w. (●). Data are expressed as mean ± SD (n = 6).

### ACE ACTIVITY IN PLASMA OF SHR

The effect of fermented skim camel milk (after oral administration) on ACE activity in plasma of SHR is shown in figure 6. Fermented skim camel milk (240 and 1200 mg) and captopril (PC) groups had significantly ($p < 0.05$) lower ACE activity in plasma of rats than negative control group.

## DISCUSSION

In short-term study, the antihypertensive effect of fermented skim camel milk on SBP and DBP depended on dose of fermented milk (Figs. 1 and 2). The lowest reading of SBP and DBP was noticed with the highest concentration (1200 mg) of fermented skim camel milk, this reading was close to that recorded by captopril. the results are in agreement with Nakamura, et al. (1995) who

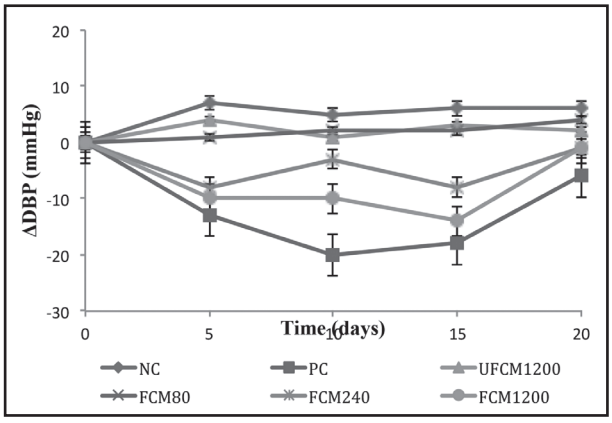


**Figure 5.**

The effect of fermented skim camel milk on diastolic blood pressure (DBP) of spontaneously hypertensive rats (SHR), distilled water (♦), captopril (■), 1200 mg unfermented camel milk/kg b.w. (▲), 80 mg fermented camel milk/kg b.w. (×), 240 mg fermented camel milk/kg b.w. (*), 1200 mg fermented camel milk/kg b.w. (●). Data are expressed as mean ± SD (n = 6).

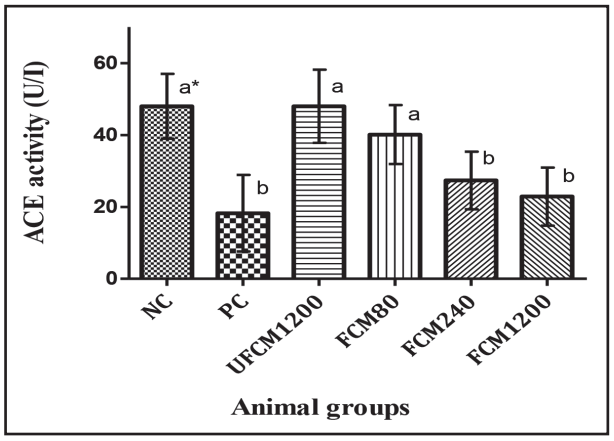


**Figure 6.**

The effect of fermented skim camel milk on ACE activity in plasma of SHR (NC: negative control; PC: captopril; UFCM1200: unfermented skim camel milk; FCM80: fermented skim camel milk; FCM240: fermented skim camel milk; FCM1200: fermented skim camel milk). *Mean ± SD (n = 5). Bars with unlike letters differ significantly ($p < 0.05$).

noticed that SBP significantly reduced ($p < 0.05$) after four, six and eight hours of administration of bovine sour milk by 20.0 ± 5.2, 21.8 ± 4.2 and 17.7 ± 3.5, respectively. The effect of fermented milk administration to SHR was also observed by Muguerza, et al. (2006) who reported that the decrease in SBP was at maximum after four hours of oral feeding (34.81 ± 4.48 milk fermented with *E. faecalis* CECT 5727 and CECT 5728), the reading was returned to the baseline after 24 hour.

Generally, fermented skim camel milk by *L. helveticus* and *S. thermophilus* had reducing effect on SBP and DBP in the long-term administration (Figs. 4 and 5). The high doses of 1200 and 240 mg of fermented skim camel milk decreased SBP throughout the treatment period, but high dose (1200 mg) only reduced the DBP and its effect was similar to that exerted by captopril. No effect was noticed on SBP and DBP of SHR rats by the use of low dose of 80 mg of fermented skim camel milk. These results are agreement with Sipola et al. (2002) who found that milk fermented by *L. helveticus* LBK16H was able to decrease SBP by 21 mmHg in hypertensive rats. In addition, Rodriguez-Figueroa et al. (2013) stated that the SBP and DBP of SHR decreased significantly ($p < 0.05$) in the second and third week when these rats received milk fermented with *L. Lactis* NRRL B-50571. This study suggests that antihypertensive effect of fermented skim camel milk (1200 and 240 mg) could be due to presence of bioactive peptides in the protein of the camel milk generated by the active bacterial cultures. The trend of heart rate decrease in FCM1200 and PC groups was also reported by Wang et al. (2012), who noticed that heart rate was decreased after oral feeding of captopril and two different doses of whey protein hydrolysate (1200 mg/kg b.w. and 240 mg/kg b.w.). Bioactive peptides derived from fermented skim camel milk may improve the oxygen consumption of myocardial which reduces the cardiac stress; this was obvious after orally taking of fermented skim camel milk and drug (captopril). Fluctuations in heart rate could be due to the unrest of rats which not given relaxed period during blood pressure measurement by CODA tail-cuff method system. In current study, all groups except PC group showed increase in body weight of SHR rats. This result suggest that the slight increase in body weight of PC group compared to the other groups could be attributed to the side effects of captopril drug which cause weight loss according to the leaflet of the drug.

The rennin angiotensin system is a key factor in the protection of blood pressure. ACE (EC 3.4.15.1) prevents formation of angiotensin II. In the current study, the high ACE-inhibitory activity was noticed with the high doses (1200 and 240 mg) of fermented skim camel milk. This effect was similar to that noticed by captopril (PC group) which is proven as hypotensive drug. No effect was noticed with unfermented skim camel milk and the low dose (80 mg) of fermented skim camel milk. Thus, ACE-inhibitory activity in the current study could be attributed to the ACE-inhibitory peptides derived from fermented skim camel milk by *L. helveticus* and *S. thermophilus*. These result are in agreement with Wang et al. (2012) who showed decrease in ACE activity in plasma of SHR fed whey protein hydrolysate and captopril drug. Fermented milk containing IPP and VPP reduced ACE activity in the aorta and elevated plasma rennin activity in a long-term treatment (14 weeks) of SHR (Nakamura et al., 1996). Sipola et al. (2002) stated that lack of negative feedback for angiotensin II, lead to ACE inhibition.

## CONCLUSION

Antihypertensive effect of fermented skim camel milk by *L. helveticus* and *S. thermophillus* in SHR rats depends on the fermentation and dose. In short-term, hypotensive effect on SBP and DBP was clear with high concentration of fermented skim camel milk but it did not continue until the end of the experimental period (24 h). The same effect was noticed in the long-term administration; however, the cessation of effect was not evaluated in this study. The decrease in ACE activity was noticed using fermented skim camel milk.

## ACKNOWLEDGEMENT

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Trabajo Original

Epidemiología y dietética

# Prevalencia y factores asociados al consumo de bebidas azucaradas en escolares de 9 a 17 años de Bogotá, Colombia: Estudio FUPRECOL

*Prevalence and associated factors of sugar-sweetened beverages intake among schoolchildren aged 9 to 17 years from Bogotá, Colombia: the FUPRECOL Study*

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## Resumen

**Objetivo:** determinar la prevalencia y los factores asociados al consumo de bebidas azucaradas en una población escolar de Bogotá, Colombia, pertenecientes al Estudio FUPRECOL.

**Métodos:** estudio descriptivo y transversal, realizado en 8.136 niños y adolescentes en edad escolar entre 9 y 17 años de Bogotá, Colombia. El peso, la estatura, el índice de masa corporal (IMC), la circunferencia de cintura y el porcentaje de grasa se recogieron como marcadores antropométricos y de composición corporal. El consumo de bebidas azucaradas (bebidas carbonatadas, jugos ultra-procesados y/o té), y los factores asociados (sexo, edad, obesidad abdominal, clasificación del IMC, grado de estudios de la madre/padre, y nivel nutricional por cuestionario "Krece plus" indicador de adherencia a la dieta mediterránea), se recogieron por encuesta estructurada. Se establecieron asociaciones mediante la construcción de modelos de regresión logística simple.

**Resultados:** de la población general, el 58,4% eran mujeres. En función al sexo, los varones acusaron la mayor ingesta de "bebidas carbonatadas" con una frecuencia semanal y diaria de 70,9% y 21,0%, respectivamente, seguido de "jugos ultra-procesados" (64,4% semanal *vs.* 11,3% diario). En ambos sexos, la prevalencia de obesidad abdominal fue mayor en los escolares que respondieron consumir diariamente "bebidas carbonatadas" (23,3%), "jugos ultra-procesados" (13,2%) y "bebidas té" (9,7%). La edad [OR 1,15 (IC 95% 1,03-1,28)], el menor grado de educación del padre [OR 1,34 (IC 95% 1,01-1,79), o de la madre OR 1,30 (IC 95% 1,03-1,65)], y la baja adherencia a la dieta mediterránea [OR 2,60 (IC95% 2,09-3,25)], se asociaron como factores predisponentes al consumo diario de "bebidas carbonatadas".

**Conclusión:** variables como la edad, la educación de los padres y los patrones dietarios se asociaron con el consumo de bebidas azucaradas en escolares de Bogotá, Colombia. Se recomiendan intervenciones integrales en las que estén involucrados los componentes nutricional y educativo entre los niños y adolescentes de Bogotá, Colombia.

**Palabras clave:**

Bebidas gaseosas. Nutrición en salud pública. Factores de riesgo. Obesidad. Estudiantes.

## Abstract

**Objective:** The aim of the present study was to describe the intake of sugar-sweetened beverages and to examine of associated factors among schoolchildren from Bogotá, Colombia.

**Methods:** From a total of 8,136 schoolchildren and adolescents (age 9-17.9 years) taking part in the FUPRECOL Study. Sugar-sweetened beverages intake was based on intake from "regular soda", "drink tea" and/or "concentrated juices". Body weigth, heigth, body mass index (BMI), waist circumference, and percentage body fat by electrical bioimpedance analysis were measured such as adiposity markers. Associated factors (sex, age, abdominal obesity, BMI classification, mothers' and fathers' educational level and nutritional status by "Krece plus" questionnaire), were collected by structured questionnaire. Associations were established through a binary logistic regression.

**Results:** Of the subjects, 58.4% were women. According to sex, boys response highest intake of "regular soda" daily/weekly frequency of the 70.9% and 21.0%, respectively, followed by "concentrated juices" (64.4% weekly *vs.* 11.3% daily). In both gender, the prevalence of abdominal obesity was higher in schoolchildren that responded to intake "regular soda" (23.3%), "concentrated juices" (13.2%) and "drink tea" daily (9.7%). Age [OR 1.15 (95%CI 1.03 to 1.28)], mothers' [OR 1.30 (95%CI 1.03 to 1.65)], and fathers' [OR 1.34 (95%CI 1.01 to 1.79) low educational level and nutritional status [OR 2.60 (95%CI 2.09 to 3.25)], were associated with daily intake of "regular soda".

**Conclusion:** Age, parental education level and dietary patterns were associated with sugar-sweetened beverages in schoolchildren in Bogotá, Colombia. We recommended comprehensive interventions which are involved nutritional and educational component among children and adolescents from Bogotá, Colombia.

**Key words:**

Sugar beverages. Public health nutrition. Risk factors. Obesity. Students.

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## INTRODUCCIÓN

El sobrepeso y la obesidad en niños y adolescentes se consideran como uno de los principales problemas de Salud Pública alrededor del mundo, debido al incremento en su prevalencia y al impacto que tiene sobre la salud de quienes la padecen (1). Según Dietz (2), cerca del 10% de los niños en edad escolar, presentan sobrepeso y un cuarto de ellos son obesos. En América latina, Rivera y cols. (3), analizando los datos obtenidos a través de estudios poblacionales realizados en países como Brasil, México, Argentina, Perú, Colombia y Chile entre el 2008 y el 2013, muestran que uno de cada cinco niños y adolescentes presentan exceso de peso (tomando como criterio diagnóstico al índice de masa corporal [IMC] superior al percentil $P_{85}$ del patrón de referencia obtenido en la Encuesta Nacional de Salud y Nutrición). En Colombia, datos de la última Encuesta de la Situación Nutricional en Colombia (ENSIN-2010) (4), y el *Colombian Report Card* publicado por González y cols. (5) estiman que el 13,4% de los niños en edad escolar presentan exceso de peso y el 4,1% de los adolescentes son obesos.

Se ha descrito que el exceso de peso y la adiposidad que caracteriza a niños y adolescentes con obesidad, se debe en parte a la presencia combinada de factores genéticos y ambientales, que aunado a la ingestión de energía que excede el gasto y los requerimientos para el crecimiento durante un periodo prolongado de tiempo, hace perentorio profundizar dicha problemática desde diversos enfoques (1,6). En adición a lo anterior, cambios en los patrones dietarios (ingesta de comidas con alto contenido energético, ricos en grasa saturadas y azúcares refinados), como alimentos ultra-procesados y bebidas azucaradas, contribuyen también, al aumento en la prevalencia del exceso de peso en etapas tempranas de la vida (7,8).

En lo que respecta al consumo de bebidas azucaradas y alimentos ultra-procesados, existe fuerte evidencia que asocia su ingesta, con la presencia de factores de riesgo cardiovascular desde la infancia (9,10). Conceptualmente, las bebidas azucaradas se describen como concentrados de frutas y bebidas carbonatadas, con alto contenido energético, alto índice glucémico y bajo índice de saciedad, que induce a mayor consumo de alimentos después de su ingesta (11). Recientemente, Pérez-Morales y cols. (12) observaron una asociación entre la ingesta de bebidas azucaradas antes de los 6 años de edad con el aumento del tejido adiposo en periodos posteriores de la vida, relación que fue constatada también por Gómez-Miranda y cols. (13) en población adolescente. En Colombia, Ramírez-Vélez y cols. (14), en un trabajo que incluyó 10.373 niños y adolescentes entre 5 y 17 años, se demostró que cerca de 23% de los evaluados acusaron un consumo de al menos una vez a la semana, de bebidas azucaradas y que factores demográficos como la etnia, la edad y la procedencia se asociaron como factores predisponentes al consumo de estos alimentos. Otros factores que determinan la elección de los alimentos, varían en función de la fase de la vida, del individuo o de los grupos de individuos (15). Por ejemplo, los ingresos económicos del hogar, la seguridad alimentaria, la influencia cultural, el contexto social y el nivel de educación, se han identificado también como factores predisponentes al consumo de dietas con alto contenido energético (16).

Aunque la obesidad infantil es un problema de salud, aún falta mucho por conocer sobre su origen y sus efectos en la salud. Colombia, un país de mediano ingreso, se ubica entre los mayores consumidores mundiales de bebidas azucaradas; específicamente en el consumo de bebidas carbonatadas, ocupa el décimo lugar mundialmente, con un consumo *per cápita*, en 2013, de 66,5 litros (266 botellas individuales de 250 cc). Además, datos de la última ENSIN-2010 muestran que estos productos son consumidos por el 81,2% de los colombianos; donde el 22,1% lo incluye dentro de su alimentación diaria, y casi el 50% lo consume con una frecuencia semanal (4). En comparación con otros países (9,10,13,15,16), pocos estudios en Colombia han identificado los factores asociados al consumo de bebidas con alto valor energético, por ello resulta urgente estudiar dicho problema desde diversos enfoques (14). Este estudio tiene como objetivo determinar la prevalencia y los factores asociados al consumo de bebidas azucaradas en una población escolar de Bogotá, Colombia, pertenecientes al Estudio FUPRECOL.

## MÉTODOS

### DISEÑO Y MUESTRA DEL ESTUDIO

El presente trabajo forma parte del Estudio FUPRECOL, cuya metodología completa ha sido publicada con anterioridad (17,18). Se trata de un estudio de corte transversal en 10.000 niños y adolescentes en edad escolar de 9 a 17 años de edad, residentes en Bogotá y pertenecientes a 28 instituciones educativas de zonas urbanas. La distribución geográfica no se realizó de forma aleatoria y la muestra fue por conveniencia. Todos los alumnos pertenecían al estatus social o posición socioeconómica 1-3 (nivel bajo), según el Sistema de Identificación de Potenciales Beneficiarios de Programas Sociales SISBEN definido por el gobierno Colombiano) (4). Se excluyeron escolares con discapacidad física, sensorial e intelectual permanente, enfermedades no transmisibles como diabetes tipo 1 o 2, enfermedad cardiovascular, autoinmune o cáncer diagnosticado, estado de gestación, abuso en el consumo de alcohol o drogas y, en general, en patologías que no estuvieran relacionadas directamente con la nutrición como errores congénitos del metabolismo, síndrome metabólico, obesidad mórbida, trastornos psiquiátricos (anorexia, bulimia), etc. Para el cálculo del tamaño muestral se tomó como referencia poblacional los 546.000 registros de matrícula del 2013, suministrado por la Secretaria de Educación Distrital. Para este cálculo se utilizó la ecuación de Schlesselmann (19) en muestras conocidas, teniendo un $\alpha = 0,05$ (fiabilidad del 95%). La varianza estimada para los sujetos con exceso de peso (obesidad/sobrepeso) usada para esta población fue del 20% de acuerdo con la última Encuesta de la Situación Nutricional (ENSIN-2010) (4).

## CONSUMO DE BEBIDAS AZUCARADAS Y NIVEL NUTRICIONAL

Se indagó por el tipo de bebidas azucaradas que consumen con mayor frecuencia en los últimos 7 días con el "Cuestionario breve para evaluar la ingesta habitual de bebidas" BEVQ-15 (en inglés "Brief Questionnaire to Assess Habitual Beverage Intake") (20) en las dimensiones: a) bebidas carbonatadas regulares tipo cola; b) concentrados de jugo ultraprocesados/envasados; y c) bebidas té envasados. Las respuestas fueron recodificadas con opción múltiple y 3 posibles: "diariamente", "semanalmente", y/o "nunca, no consume". El análisis de fiabilidad mostró resultados de consistencia interna ($\alpha$ *Cronbach*) de (0,61) para la dimensión "bebidas carbonatadas"; (0,64) en "jugos ultra-procesados"; y (0,65) en "refrescos tipo té". El $\alpha$ *Cronbach* para el cuestionario total del BEVQ-15 se encontró en (0,65). Adicionalmente, en una sub-muestra de 229 escolares (media de edad 12,8 ± 2,4 años, 46,2 ± 12,4 kg, 1,50 ± 0,1 m y 19,9 ± 3,1 kg/m$^2$) y un tiempo entre cada prueba de 7 días, se obtuvieron valores de reproducibilidad *test-retest* (Kappa index) de (0,78) para "bebidas carbonatadas"; (0,68) en "jugos ultra-procesados"; y (0,60) en "refrescos tipo té". Adicionalmente, se identificó la calidad de la dieta (tomando como patrón de oro la dieta mediterránea), con el cuestionario rápido "Krece Plus" validado en el estudio "enKid" por Serra-Majem y cols. (21) el cual indaga el riesgo nutricional con puntuaciones (+1 o -1) para los 16 ítems incluidos. La puntuación máxima posible es +11 y mínima -5. Con los resultados del "Krece Plus" se clasificó el nivel nutricional de los participantes en alto (test ≥ 9), medio (test 6-8) y bajo (test ≤ 5). En nuestra población, este cuestionario mostró moderada fiabilidad ($\alpha$ *Cronbach* 0,64) y adecuada reproducibilidad (*Kappa index* 0,76).

## ANTROPOMETRÍA Y COMPOSICIÓN CORPORAL

Se midió el peso con balanza de piso TANITA® modelo BF-689 (Arlington Heights, IL 60005, USA), con resolución 0,100 kg. La estatura se midió con un estadiómetro portátil SECA 206® (Hamburgo, Alemania), rango 0-220 cm de 1 mm de precisión. Con estas variables se calculó el índice de masa corporal (IMC) en kg/m$^2$ y su puntaje z del IMC o desviación estándar (DE). Se clasificó en sobrepeso si escolar estaba entre los percentiles 85 y 95, y obesos cuando era superior al percentil 95. La circunferencia de cintura (CC) se tomó con los referentes anatómicos y puntos de corte los descritos por la OMS (22), con una cinta métrica inextensible a la mitad de la distancia entre el reborde costal y la cresta iliaca (espina iliaca anterosuperior) en bipedestación y espiración. Se consideró obesidad abdominal por CC (no saludable o riesgo) cuando esta medida superaba el percentil 75 de los referentes sugeridos por de Ferranti y cols. (23) en función al sexo y edad, para criterio diagnóstico de síndrome metabólico en menores de 17 años. El porcentaje de grasa se determinó utilizando bioimpedancia eléctica (BIA) bipolar pie-pie con equipo TANITA® modelo BF-689 (Arlington Heights, IL 60005, USA). Los estudios de validación y ecuaciones pueden ser consultados directamente en la página del fabricante (http://www.tanita.com/en/bf-689/) o en el estudio de Kasvis y cols. (24). La frecuencia de inducción se valoró a una intensidad de 50 kHz, con una sensibilidad de estimación de la masa de grasa de 0,1 kg (0,1%). La medición se realizó luego de 10-12 h de ayuno, con la vejiga vacía y sobre una superficie no conductora. El error técnico de la medida (TEM) fue 0,639 y el coeficiente de reproducibilidad de 0,985% (25). Se consideró exceso de adiposidad, cuando esta medida superaba el percentil 90 (≥ 23,4% en varones y ≥ 31,0 en mujeres) a partir del trabajo de Escobar-Cardozo y cols. (25).

## FACTORES ASOCIADOS AL CONSUMO DE BEBIDAS AZUCARADAS

Las variables: a) sexo (hombre/mujer); b) grupo etario (niñez [9 a 12 años]/adolescencia [13 a 17 años]); c) obesidad abdominal (saludable/riesgo); iv) porcentaje de grasa corporal (saludable/exceso de adiposidad); d) clasificación del IMC (bajo peso/normal o saludable/sobrepeso + obesidad); e) grado máximo de estudios alcanzados por la madre/padre (no reporta, primaria o secundaria/técnico o tecnólogo/universitario o postgrado); y f) nivel nutricional y calidad de la dieta (baja/media/alta), se consideraron como factores asociados al consumo de bebidas azucaradas "diariamente" y "semanalmente" para este trabajo.

## ASPECTOS ÉTICOS

El Estudio FUPRECOL se llevó a cabo siguiendo las normas deontológicas reconocidas por la Declaración de Helsinki y la Resolución 008439 de 1993 del Ministerio de Salud de Colombia que regula la investigación clínica en humanos y ha obtenido la aprobación del Comité de Investigación en Seres Humanos del centro coordinador (UR Nº CEI-ABN026-000262). Antes de la medición, cada niño y/o adolescente asintió participar y el padre/madre o tutor/a responsable firmó por escrito el consentimiento informado del menor.

## ANÁLISIS ESTADÍSTICO

Los valores continuos se expresaron como media y DE y frecuencias en las variables ordinales. Se aplicaron pruebas de homogeneidad de varianzas (Prueba t de Student) para estudiar las diferencias entre las variables continuas por sexo y edad y la prueba chi cuadrado ($\chi^2$) en las variables categóricas. Posteriormente, se realizó un análisis exploratorio para determinar la distribución porcentual por cada uno de los factores asociados y tipo de bebida azucarada. Por último, una regresión logística binaria simple fue aplicada para determinar la asociación entre los factores estudiados y el consumo "diario/semanal" como evento de interés. Los análisis fueron realizados en el programa Statistical Package for Social Science® software, versión 20 (SPSS;

Chicago, IL, Estados Unidos), y se consideró como significativo un valor $p < 0,05$.

## RESULTADOS

Constituyeron la muestra 8.136 escolares pertenecientes a 28 instituciones educativas oficiales de la ciudad de Bogotá, Colombia (tasa de respuesta 81%). De la población general, el 58,4% eran mujeres, con edad media de 12,8 ± 2,4 años, peso corporal 44,8 ± 11,4 kg, estatura 148,7 ± 10,2 cm e IMC 20,0 ± 3,5 kg/m$^2$. En función al sexo, el análisis ANOVA mostró que los varones tenían mayores valores de edad, peso y estatura que las mujeres ($p < 0,001$), mientras que estas presentaron mayores valores en los marcadores de composición corporal (circunferencia de cintura, IMC, porcentaje de grasa, $p < 0,001$). Aproximadamente uno de cada cinco, y siete de cada diez niños y adolescentes, acusaron un patrón de consumo diario y semanal de bebidas "gaseosas carbonatadas", respectivamente. En ambos grupos, el 10% de los evaluados mostraron alta adherencia a la dieta mediterránea en función al cuestionario "Krece Plus, (test ≥ 9 puntos)" (Tabla I).

En población general, el mayor consumo de bebidas azucaradas se observó en "bebidas carbonatadas" con una frecuencia semanal y diaria de 68,8% y 21,4%, respectivamente, seguido de "jugos ultra-procesados" (64,9% semanal *vs.* 12,0% diario). Independiente de la elección de la bebida, los varones en edad adolescente (12 a 17 años) acusaron mayor consumo semanal que las mujeres de esta misma edad. La prevalencia de obesidad abdominal fue mayor en los escolares que respondieron consumir diariamente "bebidas carbonatadas" (23,3%), "jugos ultra-procesados" (13,2%) o "té" (9,7%). En lo que respecta al nivel nutricional, una importante proporción de baja calidad en la dieta -entendida como menor adherencia a la dieta mediterránea, por cuestionario Krece plus-, fue observada en los escolares que acusaron consumir diariamente cualquiera de las tres bebidas azucaradas indagadas en este trabajo. No se observaron diferencias en las variables IMC, exceso de adiposidad por BIA o grado de estudios en los padres (Tabla II).

En la figura 1 se presentan los resultados entre los factores asociados y la frecuencia de consumo "diariamente/semanalmente" en función al tipo de bebida reportada. La regresión logística simple muestra que los escolares entre 13 y 17 años [OR 1,15 (IC 95% 1,03-1,28)], cuyos padres/madres acusaron menor grado académico "primaria/secundaria" [OR 1,30 (IC 95% 1,02-1,65)], "técnico/tecnológico" [padre OR 1,34 (IC 95% 1,01-1,79); madre OR 1,30 (IC 95% 1,03-1,65)], y que presentaron menor adherencia a la dieta mediterránea [baja adherencia OR 2,60 (IC95% 2,09-3,25 *vs.* moderada adherencia OR 1,66 (IC95% 1,33-2,07)]; tenían mayor probabilidad de ingerir "bebidas carbonatadas" (Fig. 1A). En complemento a lo anterior, el consumo de "jugos ultra-procesados" se asoció con menor adherencia a la dieta mediterránea según la clasificación del "Krece Plus" [baja adherencia OR 1,75 (IC95% 1,33-3,28 *vs.* moderada adherencia OR 1,40 (IC95% 1,08-1,83)] (Fig. 1B). No se observaron asociaciones entre el consumo de bebidas "tipo té" con las variables estudiadas (Fig. 1C).

## DISCUSIÓN

El principal hallazgo de este trabajo es que aproximadamente uno de cada cinco, y siete de cada diez niños y adolescentes pertenecientes al Estudio FUPRECOL, acusan un patrón de consumo diario (21,4%) y semanal (68,8%) de "bebidas carbonatadas", respectivamente. La ingesta diaria de este reporte, es menor al encontrado en Norteamérica por Rader y cols. (62%) (26), similar al reportado en adolescentes de Colombia por Ramírez-Vélez y cols. (23%) (14), y menor al reportado por Ribeiro y cols. (87%) (27) en Belo Horizonte, Brasil (2006). En adición a lo anterior y sin importar la elección de la bebida, los varones en edad adolescente (13 a 17 años) acusaron mayor consumo semanal que las mujeres (69,1% *vs.* 68,6% en "bebidas carbonatadas"; 64,6% *vs.* 60,9% en "jugos ultra-procesados"; y 46,9% *vs.* 45,4% en bebidas "tipo té"). Tres cuartas partes de la población estudiada prefirió los refrescos de cola, lo cual podría significar una adicción a este tipo de bebidas, o bien, a una gran capacidad mercadotécnica de penetración de las empresas productoras (1). Este hallazgo coincide con el reciente informe de Ramírez-Vélez y cols. (14), en un estudio que incluyó 10.373 niños y adolescentes entre 5 y 17 años. Sin importar el sexo, estos autores encontraron que pertenecer al grupo de 14 y 17 años de edad, incrementaba en OR = 1,65 (IC95% 1,32 a 2,06) la predisposición de consumir "bebidas carbonatadas". Sobre este hallazgo, Andreyeva y cols. (28) demostraron que existe una clara orientación del mercadeo de bebidas carbonatadas y alimentos ultra-procesados hacia los jóvenes, especialmente hacia la población afrodescendiente e hispana. En el trabajo de Reedy y cols. (29) se pudo determinar que las bebidas azucaradas son la mayor fuente de azúcares añadidos en la dieta estadounidense y la principal fuente de calorías en la dieta de los jóvenes y se ha descrito que la elevada prevalencia en el consumo regular de bebidas carbonatadas y alimentos ultra-procesados, puede estar relacionado con la publicidad que se emite en la franja infantil de la televisión, la cual presenta un mayor porcentaje de alimentos y bebidas no alcohólicas, clasificados como "altos" en valor energético, aditivos y conservantes (30).

En el presente trabajo se encontró que la prevalencia de obesidad abdominal fue mayor en los escolares que respondieron consumir diariamente "bebidas carbonatadas" (23,3%), "jugos ultra-procesados" (13,2%) o "té" (9,7%). Sin embargo, la regresión logística no muestra asociación con los marcadores de adiposidad y composición corporal estudiados en este trabajo, resultado similar al encontrado por O'Connor y cols. (31) (15,4 *vs.* 17,5 p = 0,45 en el IMC y consumo diario de soda), y Newby y cols. (32) ($\beta$ = 0,01 IC95% -0,11 a 0,13, p = 0,82 Lb/año de peso ganado en consumo de bebidas azucaradas), y difiere del estudio ISCOLE en inglés "International Study of Childhood Obesity, Lifestyle and the Environment" (OR = 2,5 IC95% 1,99 a 3,89 en niñas y OR = 1,57 IC95% 1,33 a 2,29 en niños, el incremento en el z-score del IMC) (33) o del estudio "Cardiovascular Risk in Young Finns Study" de Finlandia (34) (OR = 1,90 IC95% 1,38 a 2,61 la probabilidad de tener sobrepeso). Como se ha sugerido en otros estudios, el hecho de no encontrar asociaciones en el consumo de bebidas azucaradas entre escolares obesos y no-obesos puede deberse al

**Tabla I.** Características generales de los escolares evaluados (n = 8.136)

| Característica | Mujeres n = 4.750 | Varones n = 3.386 | p |
|---|---|---|---|
| *Antropometría y composición corporal (media ± DE)*[a] | | | |
| Edad (años) | 12,8 ± 2,4 | 13,0 ± 2,4 | < 0,001 |
| Peso (kg) | 44,8 ± 11,4 | 45,8 ± 13,0 | < 0,001 |
| Estatura (cm) | 148,7 ± 10,2 | 152,4 ± 14,2 | < 0,001 |
| IMC (kg/m$^2$) | 20,0 ± 3,5 | 19,3 ± 3,3 | < 0,001 |
| *Clasificación nutricional por IMC (%)*[b] | | | |
| Bajo peso | 808 (17) | 508 (15) | 0,662 |
| Normopeso o saludable | 2.423 (51) | 2.167 (64) | 0,008 |
| Sobrepeso/obesidad | 1.520 (32) | 711 (21) | 0,501 |
| Circunferencia de cintura (cm) | 64,7 ± 8,0 | 66,0 ± 8,0 | < 0,001 |
| Obesidad abdominal (%)[b] | 257 (5,4) | 200 (5,9) | 0,789 |
| Porcentaje de grasa corporal | 24,1 ± 6,5 | 16,5 ± 6,7 | < 0,001 |
| Exceso de adiposidad (%)[b] | 1.853 (39) | 1.185 (35) | 0,460 |
| *Grado de estudio de la madre n, (%)*[b] | | | |
| Primaria/Secundaria | 3.753 (79) | 2.753 (81) | 0,055 |
| Técnico o tecnólogo | 570 (12) | 327 (11) | 0,645 |
| Universitario o postgrado | 428 (9) | 271 (8) | 0,739 |
| *Grado de estudio del padre n,(%)*[b] | | | |
| Primaria/Secundaria | 3.895 (82) | 2.810 (83) | 0,061 |
| Técnico o tecnólogo | 428 (9) | 339 (10) | 0,409 |
| Universitario o postgrado | 428 (9) | 237 (7) | 0,739 |
| *Consumo de bebidas gaseosas carbonatadas n, (%)*[b] | | | |
| Nunca | 523 (11) | 271 (8) | 0,936 |
| Diariamente | 1.045 (22) | 711 (21) | 0,447 |
| Semanalmente | 3.183 (67) | 2.404 (71) | 0,049 |
| *Consumo de jugos ultra-procesados n,(%)*[b] | | | |
| Nunca | 1.235 (26) | 847 (25) | 0,393 |
| Diariamente | 618 (13) | 372 (11) | 0,781 |
| Semanalmente | 2.898 (61) | 21.672.233 (64) | 0,069 |
| *Consumo de bebidas tipo té n, (%)*[b] | | | |
| Nunca | 2233 (47) | 1.456 (43) | 0,365 |
| Diariamente | 380 (8) | 271 (8) | 0,579 |
| Semanalmente | 2138 (45) | 1.569 (49) | 0,080 |
| *Nivel nutricional por Krece Plus n,(%)*[b] | | | |
| Bajo (test ≤ 5) | 1.710 (36) | 1.185 (35) | 0,291 |
| Medio (test 6-8) | 2.518 (53) | 1.862 (55) | 0,101 |
| Alto (test ≥ 9) | 475 (10) | 339 (10) | 0,535 |

*[a]Diferencias con prueba ANOVA de una vía; [b]Diferencias con prueba ($\chi^2$); IMC: índice de masa corporal.*

sub-reporte de la ingestión de alimentos por niños y adolescentes con esta condición (35,36), motivo por el que se decidió usar el "Cuestionario Krece Plus" como complemento de valoración del nivel nutricional de los participantes. A pesar de este resultado, la prevalencia de obesidad abdominal fue mayor en los escolares que acusaron consumir diariamente "bebidas carbonatadas". Este hallazgo cobra relevancia, pues los niños no compensan las calorías líquidas adicionales con la ingesta de sólidos, sugiriendo

[Nutr Hosp 2017;34(2):422-430]

**Tabla II.** Distribución de frecuencias en función al tipo de bebida azucarada y variables estudiadas

| | Bebidas carbonatadas, n (%) | | | Jugos ultra-procesados, n (%) | | | Té, n (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Diariamente** | **Semanalmente** | **No consume** | **Diariamente** | **Semanalmente** | **No consume** | **Diariamente** | **Semanalmente** | **No consume** |
| Total | 1.742 (21,4) | 5.598 (68,8) | 796 (9,8) | 975 (12,0) | 5.119 (62,9) | 2.042 (25,1) | 663 (8,1) | 3.808 (46,8) | 3.665 (45,0) |
| *Sexo* | | | | | | | | | |
| Mujer | 1.031 (21,7) | 3.197 (67,3) | 522 (11,0) | 593 (12,5) | 2.938 (61,9) | 1.219 (25,7) | 383 (8,1) | 2.131 (44,9) | 2.236 (47,1) |
| Varones | 711 (21,0) | 2.401 (70,9)[a] | 274 (8,1) | 382 (11,3) | 2.181 (64,4)[a] | 823 (24,3) | 280 (8,3) | 1.677 (49,5)[a] | 1.429 (42,2) |
| *Grupo de edad* | | | | | | | | | |
| Niñez (9 a 12 años) | 741 (20,2) | 2.539 (68,6) | 396 (10,8) | 441 (12,0) | 2.240 (60,9) | 995 (27,1) | 308 (8,4) | 1.695 (46,1) | 1.673 (45,5) |
| Adolescencia (13 a 17 años) | 1.001 (22,4) | 3.059 (69,1) | 400 (9,0) | 534 (12,0) | 2.879 (64,6) | 1.047 (23,5) | 355 (8,0) | 2.113 (47,4) | 1.992 (44,7) |
| *Cintura de cintura* | | | | | | | | | |
| Obesidad abdominal | 108 (23,3) | 295 (63,7) | 60 (13,0) | 61 (13,2) | 272 (58,7) | 130 (28,1) | 45 (9,7) | 210 (45,4) | 208 (44,9) |
| Saludable | 1.634 (21,3) | 5.303 (69,1)[a] | 736 (9,6) | 914 (11,9) | 4.847 (63,2)[a] | 1.912 (24,9) | 618 (8,1) | 3.598 (46,9)[a] | 3.457 (45,1) |
| *Porcentaje de grasa corporal* | | | | | | | | | |
| Exceso de adiposidad | 1.091 (21,1) | 3.550 (68,7) | 528 (10,2) | 608 (11,8) | 3.240 (62,7) | 1.321 (25,6) | 403 (7,8) | 2.418 (46,8) | 2.348 (45,4) |
| Saludable | 651 (21,9) | 2.048 (69,0) | 268 (9,0) | 367 (12,4) | 1.879 (63,3) | 721 (24,3) | 260 (8,8) | 1.390 (46,8) | 1.317 (44,4) |
| *Clasificación por IMC* | | | | | | | | | |
| Bajo peso | 310 (22,5) | 947 (68,9) | 118 (8,6) | 154 (11.2) | 884 (64,3) | 337 (24,5) | 108 (7,9) | 631 (45.9) | 636 (46,3) |
| Normal o saludable | 983 (21,6) | 3.144 (69,2) | 414 (9,1) | 554 (12,2) | 2.877 (63,4) | 1.110 (24,4) | 373 (8,2) | 2.161 (47,6) | 2.007 (44.2) |
| Sobrepeso y obesidad | 449 (20.2) | 1.507 (67,9) | 264 (11,9) | 267 (12.0) | 1.358 (61,2) | 595 (26,8) | 182 (8,2) | 1.016 (45,8) | 1.022 (46,0) |
| *Grado de estudio de la madre* | | | | | | | | | |
| No reporta | 157 (21,0) | 508 (67,8) | 84 (11,2) | 108 (14,4) | 438 (58,5) | 203 (27,1) | 75 (10,0) | 318 (42,5) | 356 (47,5) |
| Secundaria | 1.282 (21,5) | 4.127 (69,2) | 558 (9,4) | 697 (11,7) | 3.758 (63,0) | 1.512 (25,3) | 462 (7,7) | 2.751 (46,1) | 2.754 (46,2) |
| Técnico o tecnólogo | 202 (22,6) | 606 (67,9) | 84 (9,4) | 108 (12,1) | 580 (65,0) | 204 (22,9) | 73 (8,2) | 467 (52,4) | 352 (39,5) |
| Universitario o postgrado | 101 (19,1) | 357 (67,6) | 70 (13,3) | 62 (11,7) | 343 (65,0) | 123 (23,3) | 53 (10,0) | 272 (51,5) | 203 (38,4) |
| *Grado de estudio del padre* | | | | | | | | | |
| No reporta | 208 (19,9) | 715 (68,6) | 120 (11,5) | 135 (12,9) | 601 (57,6) | 307 (29,4) | 92 (8,8) | 438 (42,0) | 513 (49,2) |
| Secundaria | 1.289 (21,9) | 4.063 (68,9) | 544 (9,2) | 693 (11,8) | 3.737 (63,4) | 1.466 (24,9) | 461 (7,8) | 2.752 (46,7) | 2.683 (45,5) |
| Técnico o tecnólogo | 158 (22,4) | 486 (68,8) | 62 (8,8) | 86 (12,2) | 463 (65,6) | 157 (22,2) | 59 (8,4) | 361 (51,1) | 286 (40,5) |
| Universitario o postgrado | 87 (17,7) | 334 (68,0) | 70 (14,3) | 61 (12,4) | 318 (64,8) | 112 (22,8) | 51 (10,4) | 257 (52,3) | 183 (37,3) |
| *Nivel nutricional por Krece Plus* | | | | | | | | | |
| Bajo (test ≤ 5) | 784 (27,3) | 1.871 (65,0) | 222 (7,7) | 398 (13,8) | 1.761 (61,2) | 718 (25,0) | 238 (8,3) | 1.294 (45,0) | 1.345 (46,8) |
| Medio (test 6-8) | 855 (19,3) | 3.135 (70,6) | 450 (10,1) | 508 (11,4) | 2.852 (64,2) | 1.080 (24,3) | 363 (8,2) | 2.096 (47,2) | 1.981 (44,6) |
| Alto (test ≥ 9) | 103 (12,6)[b] | 592 (72,3)[b] | 124 (15,1) | 69 (8,4)[b] | 506 (61,8)[b] | 244 (29,8) | 62 (7,6)[b] | 418 (51,0)[b] | 339 (41,4) |

*[a]Diferencias en el mismo grupo, con prueba ($\chi^2$), $p < 0.05$; [b]Diferencias bajo* vs. *alto, $p < 0,05$; IMC: índice de masa corporal.*

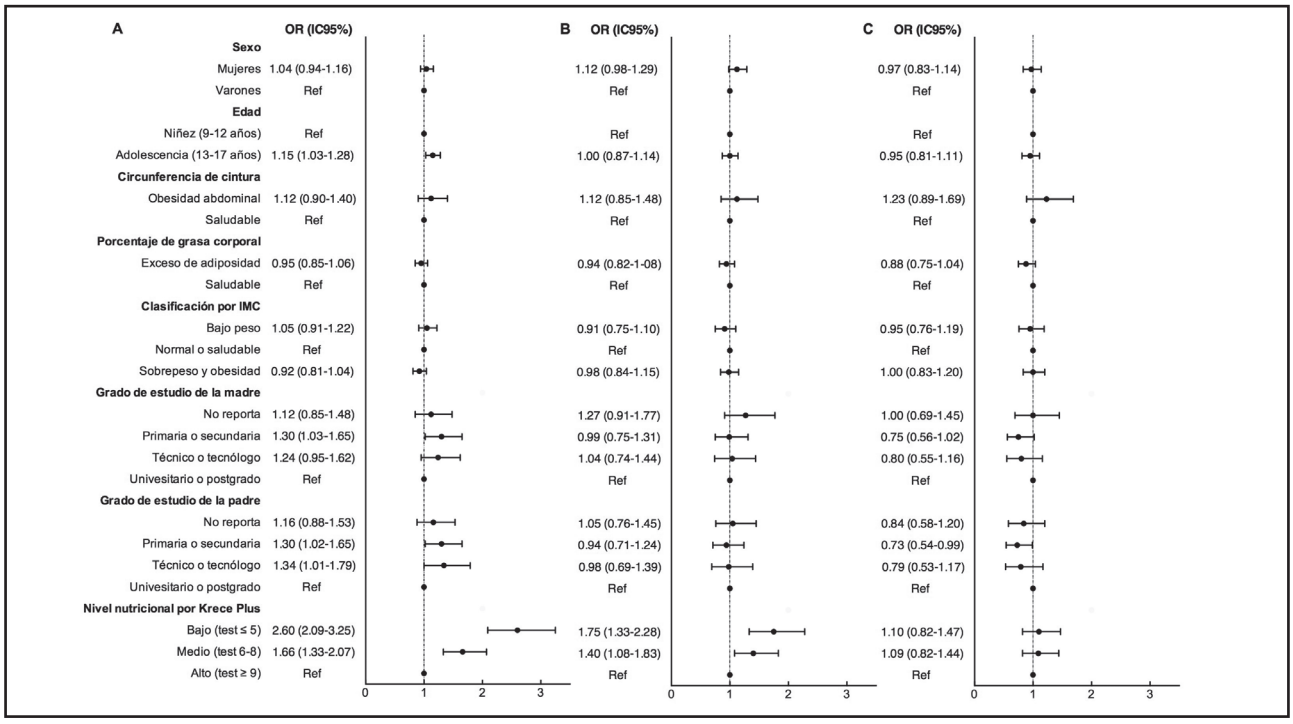


**Figura 1.**

Factores asociados a la frecuencia de consumo "diariamente/semanalmente" en función al tipo de bebida azucarada.

que el consumo excesivo de este tipo de alimentos aumentaría el riesgo de obesidad (14,37). En jóvenes americanos se reportó que el consumo semanal de bebidas azucaradas se asociaba a sobrepeso, y que cada ración adicional (360 mL) incrementaba en un 60% el riesgo de obesidad (38). En niños de 2 a 9 años de edad se encontró que un incremento de 200 mL/día de bebidas con alto contenido energético incrementaba el riesgo de obesidad abdominal en OR = 1,29 (IC95% 1,03 a 2,28) (39), hallazgo encontrado también en un reciente metaanálisis que incluyó 32 estudios observacionales en niños y adolescentes (40). Así, este tipo de estudios pueden sugerir al consumo excesivo de energía como una posible causa de la persistencia de obesidad en niños y adolescentes y permiten identificar los hábitos alimentarios que constituyen un probable factor de riesgo, a pesar que no hubo asociación estadística.

En la actualidad se plantea el carácter protector que la dieta mediterránea ejercería con relación al desarrollo de la obesidad, y varios estudios así lo han confirmado (41,42). En este sentido, podemos considerar que nuestra población presenta una aceptable adecuación a la mencionada dieta, a pesar que solo el 10% alcanzó un nivel nutricional alto. Estos resultados sugieren que la mayoría de los escolares presentan hábitos nutricionales inadecuados, lo que sugiere la puesta en marcha de programas para estimular unos hábitos alimentarios saludables, promoviendo el consumo de frutas y verduras diario y el consumo de bebidas como el agua o los jugos 100% naturales.

Por otro lado, se han descrito qué factores sociales y ambientales se relacionan con la compra y el consumo de bebidas azucaradas (14,30,34). En el ámbito escolar, el entorno familiar, las tendencias sociales, los medios de comunicación, el ingreso económico familiar, y la inseguridad alimentaria son los más reportados (43). En este estudio, participantes entre los 13 y 17 años, que tenían padres con menor grado académico y acusaban menor adherencia a la dieta mediterránea, se asociaron como factores de mayor probabilidad de consumo de bebidas gaseosas carbonatadas. Estos resultados coinciden con los reportes de otros autores (44), pues individuos con elevado consumo de refrescos carbonatados, presentan dietas nutricionalmente deficientes, debido a que el consumo de refrescos muestra una menor capacidad de inducir compensación dietética, lo que sugiere que la ingestión de energía a partir de las bebidas azucaradas no son rápidamente "registradas" en los sistemas de regulación del apetito. De la misma manera, el patrón de consumo de bebidas carbonatadas está determinado por la educación de los padres, hallazgo similar a lo encontrado en niños chilenos (45). Se ha descrito que la calidad de la dieta en la etapa escolar depende de la clase social, la educación y la situación laboral de la madre y la composición del hogar (43,44).

Una de las principales limitaciones del estudio fue la manera como fue reportado el consumo habitual de bebidas azucaradas en los niños y adolescentes encuestados en el Estudio FUPRECOL. A pesar que el "Cuestionario breve para evaluar la ingesta habitual de bebidas, BEVQ-15" no cuenta con estudios de validación en latinos, este estudio reporta una fiabilidad de 0,65 y valores de reproducibilidad *test-retest* de 0,68 *–ambos parámetros considerados como aceptables en encuestas poblacionales–*. Teniendo en

cuenta el carácter descriptivo transversal de este estudio, las conclusiones respecto al modelo de asociación no permiten establecer una relación de causalidad, sino únicamente una relación de asociación. Esto puede haber llevado a sobrestimar la prevalencia general de consumo de BA en este estudio, aspecto reportado en países europeos (39) y latinos (1,41). No obstante, eso no les resta validez a los hallazgos encontrados ya que ellos reflejan la realidad social del país y se basan en el análisis estratificado por el contexto demográfico y socioeconómico, todos factores que deben tomarse en cuenta para dar explicaciones y soluciones ante la actual presencia de la obesidad y el sobrepeso de niños y adolescentes de Colombia. Resaltamos la importancia de profundizar sobre otros aspectos relacionados con el consumo de los alimentos, como el poder adquisitivo familiar, el estrato social y la seguridad alimentaria, los cuales determinan la disponibilidad, el acceso, el consumo y el aprovechamiento biológico de los alimentos. En adición a lo anterior, se debe profundizar en la promoción de alimentación y nutrición saludable en los escolares, a partir del afianzamiento de la independencia, la búsqueda de nuevos patrones de socialización y la preocupación por la figura corporal etc., pues son elementos que condicionan la adquisición de nuevos estilos de vida y patrones de alimentación en este grupo etario.

Entre las fortalezas se encuentran que se trabajó con una muestra poblacional numerosa de ambos sexos, lo que ofrece nuevas perspectivas acerca del estado de salud y la nutrición de los escolares de Bogotá, Colombia, que deberán ser tenidas en cuenta por los actores involucrados en los ámbitos de planificación, decisión y ejecución de las políticas de salud. Sobre este aspecto, la Organización Mundial de la Salud (46) recomendaron varias estrategias para restringir el acceso y consumo de bebidas con alto valor energético, y alentar a los escolares a que opten por el agua, la leche baja en grasa o sin grasa o jugos con frutas 100% naturales. Esta directriz fue adoptada en el Distrito Bogotá, en el Proyecto de Acuerdo No. 112 de 2014 (47), por el cual se promueven hábitos de alimentación saludables en atención a las consecuencias nocivas para la salud del consumo en exceso de bebidas azucaradas. Este proyecto de ley prohíbe la venta de estos alimentos en las escuelas y fomenta la promoción del consumo de agua y bebidas con frutas 100% naturales.

En conclusión, los resultados de este estudio muestran una importante prevalencia en el consumo de bebidas azucaradas y factores como la edad, la educación de los padres y el nivel nutricional se asocian como elementos asociados. En opinión de los autores, se recomiendan intervenciones integrales en las que estén involucrados los componentes nutricional y educativo. Debido a que es un estudio transversal estos resultados podrían servir como línea de base para investigaciones cualitativas, longitudinales o mixtas que favorezcan el proceso de estudio y la construcción de nuevas estrategias de abordaje en el ámbito escolar.

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Nutrición Hospitalaria

Trabajo Original

Epidemiología y dietética

# Actitudes de escolares chilenos de distinto nivel socioeconómico al inicio de la implementación de la ley que regula la venta y publicidad de alimentos altos en nutrientes críticos

*Attitudes of Chilean students from different socioeconomic levels at the beginning of the implementation of the law governing the sale and advertising of foods high in critical nutrients*

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## Resumen

**Introducción:** el 27 de junio de 2016 se implementó en Chile la Ley sobre Composición Nutricional de los Alimentos y su Publicidad, que implica rotular el envase de los alimentos procesados, altos en calorías, grasas saturadas, azúcares y sodio.

**Objetivo:** determinar las actitudes de escolares de 8 a 12 años, de distinto nivel socioeconómico (NSE) y estado nutricional, ante el nuevo etiquetado de los alimentos.

**Métodos:** se aplicó una encuesta validada previamente, agregando preguntas sobre los nuevos sellos en los envases de alimentos y bebidas. Se realizó un análisis descriptivo de las variables estudiadas y se determinaron diferencias según NSE y estado nutricional con la prueba de $Chi^2$.

**Resultados:** no se observaron diferencias por género o ciudad. Al consultar sobre los nuevos sellos, el 87,3% de los niños de NSE medio-alto y 78,5% de NSE bajo señaló que les gustaba ser informados del contenido de los alimentos ($p < 0,01$). Dejarían de comprar los alimentos con sello el 53% de NSE medio-alto y 48% de NSE bajo. Del 14% al 22% seguirían comiendo galletas dulces, bebidas azucaradas, chocolates y papas fritas, sin diferencias por NSE. Los niños de estado nutricional normal y NSE medio-alto dieron mayor importancia a los sellos altos en calorías, grasas saturadas y sodio, y los de NSE bajo al contenido alto en azúcar. Entre los niños con sobrepeso y obesidad, los de NSE medio-alto consideraron más importantes los 4 sellos que los de NSE bajo.

**Discusión:** estos resultados facilitarán el apoyo educativo y publicitario para favorecer la comprensión y cumplimiento de la Ley.

**Palabras clave:**

Legislación alimentaria. Etiquetado. Nutrientes críticos. Actitudes escolares.

## Abstract

**Background:** On June 27th 2016 the law that regulates sale and advertising of foods high in critical nutrients was implemented in Chile. This law regulates the processed food packaging labelling of foods high in calories, saturated fats, sugars and sodium.

**Objective:** To determine 8-12 year old school children attitudes, from different socioeconomic levels (SEL) and nutritional status, toward the new food labelling law.

**Methods:** A previously validated survey was applied, adding questions regarding the new logos to be added on the packaging of foods and beverages. A descriptive analysis of the variables being studied was conducted and differences in relation to the SEL and nutritional status were determined using the $Chi^2$ test.

**Results:** Statistically significant differences were not observed for gender or city. Regarding the new logos, 87.3% of the children from a medium to high SEL and 78.5% from low SEL indicated that they liked to be informed about the contents of food ($p < 0.01$). Fifty-three per cent from medium to high SEL and 48% from low SEL would stop buying the foods with logos. Fourteen per cent to 22% will continue to consume sweet biscuits, sugary drinks, chocolates and chips, without a difference in SEL. Children with a normal nutritional status and medium to high SEL placed more importance on logos high in calories, saturated fats and sodium, and children of low SEL on logos high in sugar. Overweight or obese children from medium to high SEL considered all four logos more important than children of low SEL.

**Discussion:** These results will facilitate educational and social marketing support to improve the understanding, compliance and fulfillment of the law.

**Key words:**

Food law. Food labelling. Critical nutrients. Children attitudes.

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## INTRODUCCIÓN

La evidencia sobre la relación entre la publicidad de alimentos y el aumento en la prevalencia de obesidad infantil ha sido ampliamente documentada. Revisiones sistemáticas han mostrado que la promoción de alimentos y bebidas dirigida a los niños tiene un efecto directo sobre sus hábitos de consumo de alimentos y bebidas (1-3). Ya en el año 2004, la Organización Mundial de la Salud (OMS), identificó a la falta de actividad física, la publicidad de alimentos de alta densidad energética y bajo contenido de nutrientes, y el aumento en el tamaño de las porciones, como responsables del aumento en la prevalencia del sobrepeso y obesidad a nivel mundial, y solicitó a los gobiernos colaborar con los consumidores y el sector privado con el fin de establecer criterios apropiados para la comercialización de alimentos dirigida a los niños (4).

La prevalencia de obesidad en la población chilena se encuentra, junto a la de México y los Estados Unidos, entre las más altas de las Américas (5). Un estudio reciente ha señalado además que la población chilena ingiere la mayor cantidad mundial de calorías diarias *per cápita* proveniente de bebidas azucaradas, seguida por la población mexicana y estadounidense (6).

En los niños chilenos, los censos anuales de la Junta Nacional de Auxilio Escolar y Becas, dependiente del Ministerio de Educación, informan de una continua tendencia al aumento en la prevalencia de obesidad en los que ingresan a primer año básico en las escuelas públicas, la que ha aumentado de un 8,7% el año 1987 al 25,3% el año 2013 (7). En los adultos, la prevalencia de sobrepeso y obesidad alcanzó al 67% en la Encuesta Nacional de Salud del año 2009-2010 (8).

El efecto de la publicidad de alimentos sobre las preferencias alimentarias de escolares chilenos de distinto nivel socioeconómico (NSE) ha sido estudiado en distintas ciudades del país desde finales de la década del noventa. Los estudios han concluido que dicha publicidad, en especial la realizada a través de la televisión, ha tenido una gran influencia sobre los alimentos que los niños prefieren, consumen y compran con su dinero (9-11).

En respuesta a la evidencia sobre el efecto de la publicidad sobre las conductas alimentarias de los niños, y ante la presión del público para protegerlos, los gobiernos de varios países han logrado obtener promesas de autorregulación por parte de la industria, que se ha comprometido a restringirla. Sin embargo, revisiones científicas han observado que no existe evidencia sobre la efectividad de esa autorregulación en la reducción de la exposición de los niños a la publicidad en diversos países del mundo (12-14). Adicionalmente, se ha discutido sobre la dificultad para medir su impacto, debido a los distintos criterios utilizados por los gobiernos y la industria para definir qué es un alimento no saludable (15).

El 6 de julio del año 2012 fue publicada en el Diario Oficial de la República de Chile la Ley 20606, sobre "Composición Nutricional de los Alimentos y su Publicidad", convirtiendo al país en el primero en establecer la obligación de rotular los alimentos procesados con alto contenido de *calorías, grasas saturadas, azúcares y sodio*, según los niveles establecidos por el Ministerio de Salud (16). Para la implementación de la Ley fue necesario modificar el Reglamento Sanitario de los Alimentos (RSA), por lo que el 16 de junio del año 2015 fue publicado en el Diario Oficial de Chile el Decreto 13, que modificó el Decreto Supremo Nº 977, del año 1966, referido al citado Reglamento, para adecuarlo a la nueva Ley, la que inició su implementación el 27 de junio de 2016 (17).

Los cambios en el RSA establecieron los límites que serían considerados para el contenido de calorías y nutrientes críticos por cada 100 g en los alimentos sólidos o 100 ml en los alimentos líquidos procesados y que se venden envasados, así como la obligación de colocar en la cara frontal del envase de los alimentos procesados un sello con la frase "Alto en Calorías; Alto en Grasas Saturadas; Alto en Azúcares y/o Alto en Sodio", en aquellos que superen los límites establecidos en el RSA (Fig. 1). Adicionalmente, la Ley prohíbe la venta de los alimentos con uno o más de estos sellos en las escuelas y su publicidad a través de los medios de comunicación. En artículos transitorios del Decreto 13 se estableció que la implementación se haría en forma gradual, considerando un periodo de dos años para la primera etapa (junio 2016 a junio 2018); un año para la segunda (junio 2018 a junio 2019) y un año más para la fijación de límites definitiva (17) (Tabla I A y B).

Por otra parte, en forma previa al inicio de la implementación de la Ley 20606, el 13 de junio del año 2015 fue publicada en el Diario Oficial la Ley 20869, sobre "Publicidad de los Alimentos" que establece los horarios y lugares en los que se prohibirá la publicidad de alimentos para los menores de 14 años, así como las normas bajo las cuales se permitirá a las empresas de alimentos colocar su nombre cuando auspicien eventos deportivos o culturales (18).


**Figura 1.**

Sello frontal de advertencia en etiquetas de los alimentos envasados. Diario Oficial de la República de Chile. 26 de junio de 2015. Modifica Decreto Supremo Nº 977. Reglamento Sanitario de los Alimentos. Decreto 13.

**Tabla I.** Diario Oficial de la República de Chile. 26 de junio de 2015. Modifica Decreto Supremo Nº 977. Reglamento Sanitario de los Alimentos. Decreto 13

| **A. Límites de contenido de energía, sodio, azúcares totales y grasas saturadas en alimentos sólidos** | | | |
|---|---|---|---|
| **Nutriente o energía** | **Fecha de entrada en vigencia 27.06.2016** | **24 meses después de entrada en vigencia** | **36 meses después de entrada en vigencia** |
| Energía kcal/100 g | 350 | 300 | 275 |
| Sodio mg/100 g | 800 | 500 | 400 |
| Azúcares totales g/100 g | 22,5 | 15 | 10 |
| Grasas saturadas g/100 g | 8 | 5 | 4 |
| **B. Límites de contenido de energía, sodio, azúcares totales y grasas saturadas en alimentos líquidos** | | | |
| **Nutriente o energía** | **Fecha de entrada en vigencia 27.06.2016** | **24 meses después de entrada en vigencia** | **36 meses después de entrada en vigencia** |
| Energía kcal/100 ml | 100 | 80 | 70 |
| Sodio mg/100 ml | 100 | 100 | 100 |
| Azúcares totales g/100 ml | 6 | 5 | 5 |
| Grasas saturadas g/100 ml | 3 | 3 | 3 |

El objetivo de este estudio fue contar con un diagnóstico, en su primera etapa de implementación, de las actitudes y percepciones de escolares chilenos de 8 a 12 años, de distinto estado nutricional y nivel socioeconómico, ante la nueva rotulación, publicidad y prohibición de venta de alimentos en las escuelas, como base para el diseño e implementación de programas educativos o de marketing social que aumenten su comprensión y autoeficacia para el mejor el cumplimiento de la Ley.

## MATERIAL Y MÉTODO

Se realizó un estudio descriptivo, de corte transversal. La población objeto de estudio estuvo constituida por 812 escolares de 8 a 12 años (3º a 7º grados de enseñanza básica), de las ciudades de Santiago, Chillán y Temuco, ubicadas en el centro y sur del país.

En cada ciudad, se determinó una muestra de 150 escolares de NSE medio-alto y 150 escolares de NSE bajo, que fue calculada con un nivel de significación del 5% y una potencia del 80%. Para incluir escolares de distinto NSE, se seleccionaron aleatoriamente 3 colegios particulares pagados en sectores de altos ingresos (NSE medio-alto) y 3 escuelas públicas ubicadas en sectores de menores ingresos (NSE bajo). En los colegios con varios cursos del mismo nivel, se seleccionaron al azar cursos completos de los grados correspondientes al rango de edad y en los colegios pequeños se incluyó a todos los niños que se encontraban en el rango de edad.

Se consideraron los siguientes criterios de inclusión: niños y niñas de 8 a 12 años de las escuelas seleccionadas, por su capacidad para comprender las preguntas y contestar este tipo de encuestas, según lo observado en estudios previos (9-11). Los criterios de exclusión fueron: escuelas que se encontraran participando en intervenciones educativas en alimentación y nutrición y escolares con enfermedades genéticas o metabólicas.

## ESTADO NUTRICIONAL

Para evaluar el estado nutricional se comparó el índice de masa corporal (IMC) de cada niño o niña según edad (en meses) con las tablas de la OMS, utilizando los puntos de corte actualmente aceptados por el Ministerio de Salud para evaluar el estado nutricional del menor de 18 años: bajo peso ZIMC $<$ -1; peso normal ZIMC $\geq$ -1 y $<$ 1; sobrepeso ZIMC $\geq$ 1 y $<$ 2; obeso ZIMC $\geq$ 2 (19). El peso y la estatura de los niños y niñas fueron determinados por nutricionistas entrenadas, que utilizaron una balanza Seca con altímetro modelo 713, cuya escala presentaba una sensibilidad de 0,2 kg para el peso y 1 mm para la estatura.

Para determinar la actitud de los escolares ante la publicidad de alimentos y bebidas y sus preferencias alimentarias, se utilizó una encuesta validada en estudios previos (9-11). Seis nutricionistas entrenadas hicieron las preguntas a cada niño por separado. Las variables a considerar fueron: género, NSE, estado nutricional, actitud ante la promoción de alimentos y bebidas a través de la televisión y otros medios, alimentos que llevan desde su hogar para consumir en el colegio y alimentos que compran con su dinero. Al cuestionario se agregaron preguntas para determinar la actitud de los niños ante la Ley 20606, que establece la prohibición de realizar publicidad a los alimentos y bebidas altos en calorías y nutrientes críticos a los menores de 14 años.

La comprensión de las preguntas para determinar las actitudes de los niños ante la nueva rotulación de los alimentos fue evaluada con 20 escolares de distinto NSE en Santiago, con las encuestas aplicadas por especialistas en comunicaciones y por las investigadoras del proyecto. En esta etapa de verificación de la comprensión de las preguntas, los niños solicitaron que se les explicara el significado de cada descriptor, porque lo desconocían. Esta información fue incorporada en el instructivo que manejaban las encuestadoras, para que todos los niños entendieran el significado de los conceptos incluidos en los sellos.

Los padres que aceptaron que sus hijos contestaran la encuesta firmaron el consentimiento informado aprobado por el Comité de Ética del INTA. De acuerdo a las normas establecidas en los colegios del país, la dirección de cada establecimiento envió la Carta de Consentimiento a los padres, y se esperó su autorización antes de que los niños contestaran la encuesta. A los niños autorizados por sus padres, se les explicó que su participación era voluntaria y se les pidió firmar la Carta de Asentimiento.

## ANÁLISIS ESTADÍSTICO

Se realizó un análisis descriptivo de las variables en el total de la muestra según género y NSE; se estimaron prevalencias e intervalos de confianza del 95% (IC 95%). Para analizar la asociación entre las variables se utilizó el test de Chi-cuadrado. Todos los análisis estadísticos fueron desarrollados con el paquete STATA 14.1 (20).

## RESULTADOS

En la tabla II se muestran los principales resultados relacionados al efecto de la publicidad de alimentos en los niños según NSE, debido a que no se encontraron diferencias significativas según estado nutricional, sexo y ciudad de residencia.

Entre el 40% y 46% de los niños veía televisión todos los días, sin diferencias según NSE. En cambio, el porcentaje de niños que tenía un televisor en su dormitorio fue superior en los de NSE bajo ($p < 0,001$). También fue mayor el porcentaje de niños de NSE bajo a quienes le gustaban los comerciales de alimentos o bebidas que veían en la televisión ($p < 0,01$). Un porcentaje similar, cercano al 60%, recordaba algún comercial de alimentos o bebidas que le había gustado y también les gustaba probar los nuevos alimentos ofrecidos en los comerciales de la televisión.

Los comerciales favoritos de los niños eran los de bebidas azucaradas, *yogurt (*que no lleva sello), cereales de desayuno, papas fritas y galletas dulces. Una mayor proporción de niños de NSE bajo señaló que compraban los alimentos que ofrecían premios y regalos, lo que se redujo considerablemente en los de NSE medio-alto ($p < 0,001$).

La mayoría de los niños declaró llevar colación al colegio. Las colaciones más frecuentes en los de NSE bajo eran galletas dulces, bebidas o jugos azucarados, en tanto en los de NSE medio-alto eran más frecuentes las frutas, pan, *yogurt* y *leche* ($p < 0,001$).

Ante la pregunta sobre si llevaban dinero para comprar lo que querían comer o beber en el colegio, la mayoría contestó *"algu-*

**Tabla II.** Características relacionadas con la publicidad de alimentos en los escolares según NSE

| Variable | NSE medio-alto n = 400 % (IC 95%) | NSE bajo n = 412 % (IC 95%) | p |
|---|---|---|---|
| Ve televisión todos los días | 40,0 (35,4-45,0) | 46,0 (41,1-50,7) | NS |
| Tiene un televisor en su dormitorio | 48,1 (43,7-53,3) | 63,3 (58,3-67,6) | < 0,001 |
| Le gustan los comerciales de alimentos y bebidas | 40,1 (35,5-45,1) | 50,6 (46,0-55,7) | < 0,01 |
| Recuerda los comerciales de alimentos y bebidas | 59,8 (55,0-65,0) | 61,6 (56,8-66,3) | NS |
| Le gusta probar nuevos alimentos y bebidas que aparecen en comerciales | 60,4 (55,4-65,1) | 59,4 (54,5-64,0) | NS |
| Compra los alimentos que ofrecen premios y regalos | 39,1 (34,4-44,0) | 60,3 (55,4-64,9) | < 0,001 |
| Lleva colación desde su hogar al colegio | 90,7 (87,4-93,2) | 78,4 (74,1-82,1) | < 0,001 |
| Lleva dinero para comprar alimentos en el colegio | 68,6 (63,9-73,0) | 65,7 (60,8-70,0) | NS |

*Test de Chi².*

*nas veces* (68,6% de NSE medio-alto y 65,7% de NSE bajo), sin diferencia significativa. Los alimentos y bebidas que los niños compraban con su dinero eran los que aparecían en la publicidad.

Al consultar a los niños su opinión sobre el sello semejante a un disco Pare que aparece en la cara frontal del envase de los alimentos altos en calorías y nutrientes críticos (Fig. 1), el 87,3% de los de NSE medio-alto y 78,5% de los de NSE bajo señaló que les gustaba ser informados de lo que contenían los alimentos ($p < 0,01$). Sin embargo, solo el 53,4% de los niños de NSE medio-alto y el 48,0% de NSE bajo señaló que dejarían de comprar los alimentos que les gustaban si tenían uno o más de estos sellos. En la tabla III se observa que la proporción de niños de distinto NSE que declararon dejarían de comprar o comer algunos alimentos variaba según sus preferencias, apareciendo en primer lugar las papas fritas, bebidas o jugos azucarados, galletas dulces, caramelos, chocolates y helados. Un caso especial fue el *yogurt*, nombrado espontáneamente por los niños, que dejarían de comprar el 12% de los de NSE medio-alto y el 9% de los de NSE bajo.

En la tabla IV se muestran los diferentes alimentos que los niños declararon seguirían comprando o comiendo aunque tuvieran uno o más sellos de advertencia. No se encontraron diferencias significativas según NSE. Los más nombrados fueron galletas dulces, helados, bebidas o jugos azucarados, chocolates y papas fritas. Un importante porcentaje de niños de ambos NSE mencionó en forma espontánea al *yogurt* y la leche, que no llevan sello, probablemente debido a que estos alimentos tienen una importante presencia en la publicidad a través de la televisión y otros medios.

Se preguntó a los niños si ellos darían mayor importancia a la presencia en el envase del sello: "Alto en Calorías, Alto en Grasas Saturadas, Alto en Azúcares o Alto en Sodio", al momento de elegir los alimentos que dejarían de comprar. Las respuestas se analizaron según estado nutricional y NSE, con el fin de determinar si presentaban diferencias que podrían orientar la planificación de intervenciones educativas o de marketing social sobre el tema. En la tabla V se observa que al comparar los resultados en los

**Tabla III.** Alimentos que los niños declararon dejarían de comprar o comer si llevan uno o más sellos de advertencia

| | NSE alto n = 400 % (IC 95%) | NSE bajo n = 412 % (IC 95%) |
|---|---|---|
| Papas fritas | 31,7 (27,1-36,4) | 29,5 (25,4-34,3) |
| Bebidas o jugos azucarados | 28,5 (24,3-33,5) | 22,1 (18,4-26,5)* |
| Galletas dulces | 27,8 (23,6-32,6) | 15,4 (12,3-19,4)** |
| Caramelos | 20,7 (16,8-24,9) | 17,9 (14,5-22,0) |
| Chocolates | 16,8 (13,4-21,0) | 17,9 (14,5-22,0) |
| Helados | 8,9 (6,5-12,3) | 8,7 (6,3-11,9) |
| Yogurt (no lleva sello) | 11,8 (8,7-15,2) | 8,9 (6,3-11,9) |

*Test Chi². *p < 0,01; **p < 0,001. IC 95%: intervalos de confianza al 95%.*

**Tabla IV.** Alimentos que los niños afirman seguirían comprando o comiendo aunque tengan uno o más sellos de advertencia

| | NSE alto n = 400 % (IC 95%) | NSE bajo n = 412 % (IC 95%) |
|---|---|---|
| Galletas dulces | 22,2 (18,1-26,5) | 21,3 (17,4-25,4) |
| Helados | 22,2 (18,1-26,5) | 20,8 (17,0-25,0) |
| Bebidas o jugos azucarados | 17,7 (14,2-22,0) | 18,8 (15,1-22,8) |
| Chocolates | 20,3 (16,4-24,5) | 16,8 (13,1-20,4) |
| Papas fritas | 13,7 (10,4-17,4) | 14,9 (11,8-18,8) |
| Yogurt (no lleva sello) | 33,3 (28,8-38,4) | 31,7 (27,5-36,6) |
| Leche (no lleva sello) | 22,7 (18,8-27,3) | 21,5 (17,9-25,9) |

*Test Chi². p > 0,05. IC 95%: intervalos de confianza al 95%.*

**Tabla V.** Niños con estado nutricional normal que consideran importante dejar de comer un alimento según el sello de advertencia

| | NSE alto n % (IC 95%) | NSE bajo n % (IC 95%) |
|---|---|---|
| Alto en calorías | 35,0 (29,2-41,3) | 14,4 (10,0-20,4)** |
| Alto en grasas saturadas | 47,9 (41,6-54,3) | 32,2 (25,8-39,4)** |
| Alto en azúcares | 38,8 (32,8-45,1) | 50,0 (42,7-57,3)* |
| Alto en sodio | 32,5 (26,8-38,7) | 18,3 (13,3-24,7)** |

*Test Chi²: * p < 0,01; **p < 0,001; IC 95%: intervalos de confianza al 95%,*

**Tabla VI.** Niños con sobrepeso y obesidad que consideran importante dejar de comer un alimento según el sello de advertencia

| | NSE alto n = 400 % (IC 95%) | NSE bajo n = 412 % (IC 95%) |
|---|---|---|
| Alto en calorías | 44,7 (37,1-52,5) | 30,7 (25,1-37,0)** |
| Alto en grasas saturadas | 45,3 (37,7-53,1) | 38,1 (32,0-44,6) |
| Alto en azúcares | 47,2 (39,5-55,0) | 41,1 (34,9-47,6) |
| Alto en sodio | 39,0 (31,7-46,8) | 17,8 (13,3-23,3)** |

*Test Chi²: **p < 0,001; IC 95%: intervalos de confianza al 95%.*

niños con estado nutricional normal, la proporción que consideró más importantes los sellos "Alto en Calorías, Grasas Saturadas y Sodio" fue significativamente mayor en los de NSE medio-alto ($p < 0,001$), en tanto la proporción de niños que eligió el sello "Alto en Azúcares" como el más importante, fue mayor en los de NSE bajo ($p < 0,01$).

En la tabla VI se observa que una mayoría significativa de los niños de NSE medio-alto con sobrepeso y obesidad, consideró más importantes los alimentos con los sellos "Alto en Calorías y Alto en Sodio" ($p < 0,001$), en tanto la proporción fue similar en ambos NSE para los sellos "Alto en Grasas Saturadas y Alto en Azúcares".

## DISCUSIÓN

Hawkes y cols., en su publicación *Políticas de alimentación inteligentes para la prevención de la obesidad* (21), destacan cuatro mecanismos clave a través de los cuales las políticas pueden funcionar:

1. Proporcionar un ambiente que facilite el aprendizaje de preferencias saludables.
2. Superar las barreras para facilitar la expresión de las preferencias saludables.
3. Estimular a la población a reevaluar sus actuales preferencias poco saludables en el momento de la compra.
4. Estimular la respuesta positiva de los sistemas de alimentación.

Los autores destacan que para lograr un efecto sostenido en el tiempo, las políticas de alimentación deben crear un ambiente que apoye a los niños a hacer que la elección saludable no solo sea la más fácil, sino también la favorita. La nueva Ley de etiquetado en Chile aportaría parcialmente a los puntos 1 y 3, proporcionando información sobre el contenido de nutrientes críticos de los alimentos envasados y llamando la atención a través de un logo sobre aquellos alimentos menos saludables. Sin embargo, este aporte es insuficiente para cubrir las políticas "inteligentes" propuestas.

Asimismo, aunque la educación en nutrición en las escuelas ha sido identificada como un importante factor que ayudaría a superar las barreras a la alimentación saludable causada por la falta de información y habilidades, en los intentos para incorporarla con la intención de mejorar la alimentación de los niños, investigaciones tanto experimentales como descriptivas (22,23) han señalado que los conocimientos en forma aislada no son suficientes y que los profesionales de salud, los encargados de programas de *marketing* social y los padres necesitan considerar múltiples factores para abordar el problema de la obesidad infantil, colocando el énfasis en una educación persuasiva que considere las normas sociales de los pares, la autoeficacia y una estricta regulación de la publicidad dirigida a los niños.

Utilizando una encuesta aplicada a niños de 7 a 13 años y sus padres ($n = 354$) en el Sur de Australia, se realizó una regresión para examinar si las evaluaciones de productos se asociaban con el consumo de alimentos menos saludables y si los conocimientos alimentarios y nutricionales reducían la fuerza de esta asociación en las diferentes edades (7-8; 9-10 y 11-13 años). Se observó que los niños no consideraron a las comidas rápidas divertidas o saludables, pero sí se encontró una asociación positiva entre el atractivo del sabor, la aceptabilidad social percibida y el consumo de alimentos poco saludables (23). Los resultados de este estudio reflejan una conducta similar al mantenerse un porcentaje importante de niños (47% de NSE alto y 52% de NSE bajo), que seguirían comprando los alimentos con logo de advertencia de acuerdo a sus preferencias.

A pesar de que la mayoría de los escolares de ambos NSE participantes en este estudio señaló que le gustaba ser informado del contenido de los alimentos con las nuevas etiquetas impuestas por la Ley 20606, solo el 53,4% de los niños de NSE medio-alto y el 48,1% de los de NSE bajo señaló que dejaría de comprar los alimentos con mensajes de advertencia, mientras que entre el 14% y 22%, sin diferencias según NSE, declaró que seguiría comprando galletas dulces, bebidas o jugos azucarados, chocolates y papas fritas, todos muy publicitados a través de los distintos medios de comunicación y diversos sitios donde los niños encuentran avisos publicitarios (11).

El Decreto 13 establece que todos los productos alimenticios que lleven el descriptor "Alto en…", incluirán un mensaje saludable del Ministerio de Salud. En el artículo transitorio 3 del Decreto 13 se indica que las microempresas y pequeñas empresas dispondrán de un plazo de 36 meses contado desde la fecha de entrada en vigencia del Decreto, para cumplir con la obligación de rotular el descriptor "Alto en…", establecido en el artículo 120 bis (17). Para evitar la confusión de la población con esta medida, es indispensable realizar una campaña de difusión para ayudar, tanto a los padres y niños menores de 14 años, como a la población general, a comprender los objetivos del etiquetado y las razones de las excepciones transitorias por las que alimentos cuyo contenido en nutrientes críticos es semejante, no llevarán sello durante los primeros 3 años.

La nueva Ley y sus excepciones refuerzan la necesidad de desarrollar intervenciones educativas y de *marketing* social (24,25) que ayuden a su compresión e implementación. En el país han existido diversos intentos para incorporar la educación en nutrición en la enseñanza básica, algunos de los cuales han incluido también el aumento de la actividad física. Varios de estos esfuerzos han logrado un aumento significativo en los conocimientos alimentarios de los niños intervenidos y, en algunas ocasiones, han logrado detener el aumento en la prevalencia de obesidad, efecto que solo se ha mantenido mientras duró la intervención. Diversos autores han señalado que estas actividades deben formar parte del currículum escolar e incorporar a los padres en las acciones educativas (26-28).

Debido a la reciente implementación de la Ley, se desconoce el impacto que tendrá sobre los hábitos de consumo de la población infantil. Entre las motivaciones y barreras expresadas por niños de 9 a 13 años para cumplir con las indicaciones de las Guías Alimentarias vigentes en Chile (29,30), ellos destacaron que los mensajes referidos a frutas, verduras y lácteos, fueron los que más les gustaron "porque se parecían a los comerciales de la televisión". Ante los mensajes referidos a nutrientes críticos, los

niños manifestaron "que los adultos eran los responsables de haberlos acostumbrado a comer con muchas grasas, azúcar y sal desde pequeños". En este estudio, se observó un mayor conocimiento y sensibilidad sobre el sodio y azúcar en prácticamente todos los grupos, probablemente asociado a la alta frecuencia de parientes cercanos con hipertensión o diabetes, concordante con los resultados de la Encuesta Nacional de Salud 2009-2010 (8).

Si bien la Ley prohíbe la venta de alimentos "Altos en Calorías, Grasas Saturadas, Azúcares y Sodio" en el interior de los establecimientos educacionales, la gran cantidad de niños que lleva colación al colegio requerirá de estrategias educativas especiales para sensibilizar a los padres y profesores, ya que no habrá restricciones a los alimentos que los padres envíen como colación y los alimentos con sello seguirán presentes en el comercio establecido e informal.

La lealtad de los niños chilenos a ciertas marcas de bebidas azucaradas, galletas dulces y otros productos ha sido demostrada en diversos estudios (9-11). La primera etapa de la implementación de la Ley, que permite 350 calorías, 22,5 g de azúcares, 8 g de grasas saturadas y 800 mg de sodio por 100 g (17), ha facilitado la aparición de productos que han realizado cambios para ajustarse a las cantidades permitidas en esta fase y eliminar los sellos. Incluso, ha aparecido publicidad de productos "sin sello". También se ha observado un aumento en la variedad de bebidas y productos con endulzantes artificiales, que el Ministerio de Salud debería vigilar no superen la ingesta diaria admisible (IDA) establecida por el *Codex Alimentarius*, en especial en los niños (31).

En este contexto, la creación de la Red Internacional INFORMAS (International Network for Food and Obesity/non communicable diseases Research, Monitoring and Action Support), formada por alianzas de importantes organizaciones de interés público y destacados investigadores de distintos países, incluido Chile, cuyo objetivo es identificar indicadores que permitan monitorear el rendimiento de las políticas públicas y apoyar a los sectores público y privado a crear ambientes alimentarios saludables con el fin de reducir la obesidad, las enfermedades no transmisibles y las inequidades con las que se relacionan -incluyendo el análisis del etiquetado de los alimentos- representa una contribución que puede llegar a ser muy efectiva, con propuestas de acciones que aseguren la oportunidad de utilizar sus resultados para mejorar los ambientes alimentarios y estimular a la acción (32-34).

## CONCLUSIÓN

Los resultados confirman la favorable percepción de los niños ante la publicidad de alimentos de alta densidad energética, que consumen en forma habitual. Se estima que conocer sus actitudes ante la nueva Ley de Composición Nutricional de los Alimentos y su publicidad contribuirá al diseño de programas educativos, de *marketing* social y de promoción, a través de los medios de comunicación, que traten de mejorar la comprensión del significado de la presencia de estos sellos en los alimentos procesados y así contribuir a lograr el impacto buscado con esta medida legal.

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Nutrición Hospitalaria

Trabajo Original

Otros

# Capital psicológico y su relación con el estilo de vida de universitarios mexicanos

*Psychological capital and its relationship with lifestyle of Mexican university students*

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## Resumen

**Introducción:** en algunos estudios se ha reportado que los universitarios no tienen un estilo de vida saludable (EVS) por lo que es necesario identificar no solo las variables psicosociales negativas, sino también las variables de Psicología Positiva que pueden favorecerlo.

**Objetivo:** Determinar la relación entre el capital psicológico (CapPsi) y el estilo de vida (EV) de estudiantes universitarios mexicanos.

**Método:** se realizó un estudio transversal y correlacional con 320 estudiantes de una universidad pública. La muestra fue no probabilística por cuotas. Para evaluar los factores del CapPsi se utilizaron los instrumentos Escala General de Autoeficacia, Escala de Esperanza para Adultos, Cuestionario de Resiliencia y Test de Orientación en la Vida (optimismo); para evaluar el EV se usó el Cuestionario Fantástico.

**Resultados:** las variables del CapPsi mostraron una correlación estadísticamente significativa con el EV; resiliencia ($r = 0,505$, $p < 0,01$); esperanza ($r = 0,432$, $p < 0,01$); optimismo ($r = 0,412$, $p < 0,01$); autoeficacia ($r = 0,400$, $p < 0,01$). El 33,3 de la varianza total del EV es explicado por el CapPsi ($R^2 = 0,333$).

**Conclusiones:** con base en los resultados, se asume que el CapPsi favorece el EVS; no obstante, es necesario que futuras investigaciones detallen si la influencia es en la adopción y/o mantenimiento del EVS, así como identificar cómo influye particularmente en cada factor del EV. El CapPsi tiene un porcentaje representativo de predicción del EV saludable. Es necesario que los programas de promoción y prevención en salud incorporen el abordaje del CapPsi para lograr un EV saludable en los universitarios.

**Palabras clave:**

Capital psicológico.
Estilo de vida.
Estudiantes universitarios.

## Abstract

**Background:** University students don't have a healthy lifestyle so it is necessary to identify psychosocial variables that can increase it.

**Objective:** To determine the relationship between the psychological capital (CapPsi) and lifestyle (EV) of Mexican university students.

**Method:** A cross-sectional and correlational study was carried out among 320 students of a public university. The sample was non probabilistic by quotas. To assess the factors of CapPsi were used the General Scale of Self-efficacy, the Scale of Hope for Adults, Questionnaire of Resilience, the Life Orientation Test and; to assess the lifestyle was used the Fantastic questionnaire.

**Results:** The variables of the CapPsi correlated with the healthy lifestyle; resilience ($r = 0.505$, $p < 0.01$); hope ($r = 0.432$, $p < 0.01$); optimism ($r = 0.412$, $p < 0.01$); and self-efficacy ($r = 0.400$, $p < 0.01$). The 33.3 of the total variance of the lifestyle was explained by the CapPsi ($R^2 = 0.333$).

**Conclusions:** Based on the results, it is assumed that the CapPsi improve lifestyle; however, further research is necessary to determine if the influence of CapPsi is in the adoption and / or maintenance of healthy lifestyle and identify how each one of its factors influences it particularly. The CapPsi has a representative percentage of prediction of healthy lifestyle. It is necessary that health promotion and prevention programs incorporate the approach of CapPsi to achieve a healthy lifestyle in the university students.

**Key words:**

Psychological capital.
Lifestyle. University students.

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## INTRODUCCIÓN

El estilo de vida (EV) es un constructo difícil de definir; no obstante, hay coincidencia en que está conformado por variables psicológicas, sociales, culturales y económicas que se relacionan con la salud. Psicológicamente se refiere a los patrones cognitivos, afectivos-emocionales y conductuales que tienen consistencia en el tiempo bajo condiciones similares y que pueden convertirse en factores de riesgo o protección, dependiendo de su naturaleza (1). Así, el estilo de vida saludable (EVS), por un lado, se puede entender como la disminución del consumo de alcohol, tabaco y otras drogas; y por otro, la instauración o aumento de conductas que favorezcan la condición física, los hábitos alimenticios, la recreación, el manejo del tiempo libre, el autocuidado, las indicaciones médicas y el sueño (2).

Consecuentemente, es importante mencionar que, desde la Psicología, se ha intentado identificar aquellas variables psicosociales que pudieran explicar el fenómeno de la no adopción de un EVS. Por ejemplo, en un estudio que tenía como objetivo probar un modelo de las relaciones entre el autoconcepto y algunas conductas saludables (consumo de alimentos sanos y práctica deportiva) y otras de riesgo (consumo de tabaco, alcohol y cannabis y alimentos insanos) en adolescentes españoles, se encontró que dimensiones del autoconcepto (como adecuación conductual, aceptación social y amistad íntima), predicen conductas de riesgo para la salud en adolescentes españoles (3). Como señalan Arrivillaga y Salazar (4) es necesario que en los programas de promoción de la salud se contemplen distintos procesos psicosociales como el aprendizaje, la cognición, la motivación y la emoción. No obstante, para lograr que los universitarios tengan un EVS es fundamental identificar las variables psicosociales asociadas.

Para tener un EVS se requiere que las personas sean proactivas, que puedan identificar sus habilidades para iniciar, desarrollar y mantener hábitos saludables. Por ello, es que en las últimas décadas la psicología positiva ha puesto su atención en variables que hacen a las personas aumentar su nivel de salud y bienestar psicológico.

Entonces, con base en lo anterior, se considera benéfico considerar en los programas de salud aspectos cognitivos y afectivos que impulsen un EVS. En este sentido, el capital psicológico (CapPsi) se convierte en una herramienta que puede impulsar estos aspectos, debido a que está formado por elementos como la autoeficacia, esperanza, resiliencia y optimismo que podrían favorecer el EVS. Para Luthans y Youssef (5) el capital psicológico se define como:

"El estado psicológico positivo de desarrollo de un individuo caracterizado por:

- Tener confianza (autoeficacia) para asumir y poner el esfuerzo necesario para tener éxito en tareas desafiantes.
- Hacer una atribución positiva (optimismo) sobre tener éxito ahora y en el futuro.
- Perseverar hacia las metas y cuando sea necesario, redireccionar los caminos hacia ellas (esperanza) con el fin de tener éxito.
- Cuando acosado por problemas y adversidad, mantenerse y recuperarse e incluso más allá (resiliencia) para alcanzar el éxito". (p. 3).

Por lo descrito anteriormente se entiende la definición del CapPsi como el conjunto de factores que forman a una persona con un comportamiento proactivo, lo cual favorece la formación de hábitos saludables. Considerando que desarrollar un EVS es complejo debido a que los universitarios tienen demandas psicosociales en su vida cotidiana que pueden entorpecer el desarrollo de un EVS, el CapPsi pudiera ser una variable que explique su instauración y/o mantenimiento. Además, es necesario considerar que el CapPsi ha demostrado ser más un estado que un rasgo de personalidad, motivo por el cual es susceptible de desarrollarse (6).

## OBJETIVO

Determinar la relación entre el CapPsi y el EV de estudiantes universitarios mexicanos. Particularmente se analizaron las diferencias por sexos.

## MÉTODO

### DISEÑO

Se realizó un estudio transversal, descriptivo y correlacional. Con una muestra no probabilística por cuotas.

### PARTICIPANTES

La muestra fue de 320 universitarios del Centro Universitario de los Valles de la Universidad de Guadalajara, de los cuales, 165 eran hombres (52%) y 155 (48%) mujeres. Eran estudiantes de las licenciaturas de Administración, Agronegocios, Contaduría, Derecho, Educación, Electrónica y Computación, Mecatrónica, Psicología, Sistemas de Información, Trabajo Social, Turismo y Tecnologías de la información.

### MÉTODOS ESTADÍSTICOS

El análisis estadístico se realizó mediante el programa SPSS versión 21 para Windows. Primeramente, se realizó una matriz de correlación con la r de Pearson. Debido a los coeficientes de correlación obtenidos se determinó realizar un análisis de regresión múltiple entre las variables CapPsi (predictora) y el EVS (dependiente).

### INSTRUMENTOS

#### Escala General de Autoeficacia (7)

Validada en población mexicana (8) obteniendo un alfa de Cronbach de .86. Es una escala tipo Likert de 10 ítems,

con 4 opciones de respuesta ("incorrecto", "apenas cierto", "más bien cierto" y "cierto").

### Escala de Esperanza para Adultos

Diseñada por Snyder (9) fue adaptada al castellano por Flores, Valdivieso y Martín (10). Es una escala tipo Likert de 12 ítems, con 8 opciones de respuesta que van de "totalmente falso" a "totalmente verdadero". La escala posee adecuados valores de consistencia interna y consistencia temporal. Las alfas de Cronbach oscilan entre 0,74-0,88 para toda la escala, alfas de entre 0,70-0,84 para la subescala *hope agency* y 0,63-0,86 para la subescala *hope pathways*. Su consistencia temporal es de 0,85 rango test-retest en tres semanas a 0,82 en 10 semanas. Posee apoyo de validez discriminatoria, así como validación convergente basada en manipulación experimental (11).

### Cuestionario de Resiliencia (12)

Es una escala tipo Likert de 32 ítems, con 5 opciones de respuesta que van de "siempre" a "nunca". Sus factores son:

- Factores protectores internos (FPI).
- Factores protectores externos (FPE).
- Empatía (E).

Las alfas de Cronbach son: FPI 0,80; FPE 0,73; E 0,78; en tanto que la de la escala total es de 0,91.

### Test de Orientación en la Vida (13)

Validada en México (14), se utilizó para medir optimismo. Es una escala tipo Likert de 10 ítems (6 sustantivos y 4 de relleno) con 4 opciones de respuesta que va de "Totalmente de acuerdo" a "Totalmente en desacuerdo". Tiene 2 factores: actitud optimista ante la vida (AOV) y pesimismo (P). Las alfas de Cronbach son de 0,78 para la dimensión AOVF y 0,45 para P.

### Cuestionario Fantástico (15)

Evalúa el estilo de vida. Es una escala tipo Likert de 25 ítems con 3 opciones de respuesta que van de "casi siempre" a "casi nunca". Sus factores son: familia y amigos, actividad, nutrición, tabaco y toxinas, alcohol, sueño, cinturón de seguridad y estrés, tipo de personalidad, interior y carrera. El Cuestionario está validado en población mexicana y el coeficiente de correlación test-retest reportado es de 0,91 ($p = 0,01$) para la escala total.

## PROCEDIMIENTO

Para la aplicación grupal de los instrumentos se entrenó a 5 estudiantes de Psicología. La aplicación se realizó durante el horario de clase en las distintas aulas durante diciembre del 2014. Primero, se solicitaba el permiso correspondiente al profesor y posteriormente se explicaba al grupo que la duración aproximada de la aplicación de los instrumentos era de 25 minutos. Se indicó que su participación era voluntaria y anónima y que incluso una vez iniciada su participación podían declinar si así lo deseaban. Se mencionó que aquellos que aceptaran participar necesitaban firmar el consentimiento informado, donde se explicaban los detalles de la investigación, los derechos de los participantes y los datos de contacto el investigador encargado. Los participantes no recibieron ninguna compensación económica ni académica por su participación en el estudio. Ningún participante se rehusó a contestar los cuestionarios.

## NORMAS ÉTICAS

Se cumplieron todas las normas éticas del trabajo con seres humanos, de acuerdo con la Declaración de Helsinki. Además de los supuestos señalados en la Ley General de Salud de los Estados Unidos Mexicanos en su Título Quinto "Investigación para la Salud" Capítulo Único Artículo 100; así como lo establecido en el Código Ético del Psicólogo que emite la Sociedad Mexicana de Psicología.

## ANÁLISIS ESTADÍSTICO

Los resultados obtenidos se analizaron estadísticamente mediante el paquete informático IBM SPSS Statistics, versión 21.0. La comparación entre las medias de las variables que conforman el CapPsi y el EVS entre hombres y mujeres se realizó utilizando la T de Student. Para identificar si las variables que conforman el CapPsi se relacionan con el EVS se utilizó una regresión múltiple, una vez identificadas las correlaciones a través de la R de Pearson. Para todos los ensayos se utilizó un nivel de significancia $p \leq 0,05$.

## RESULTADOS

El promedio de edad fue de 21,21 años (DE = 5,02). De los 320 participantes, el 28,4% (n = 91) tuvo un nivel de EV excelente; el 57,8% (n = 185) bueno; 12,8% (n = 41) regular; y el 0,9% (n = 3) bajo. No se identificaron diferencias significativas en el EV, en el CapPsi o algunos de sus factores por sexo, como se observa en la tabla I.

Se hizo una correlación entre el CapPsi y el EVS. De las variables que conforman el capital psicológico, la resiliencia fue la que obtuvo el coeficiente de correlación más alto ($r = 0,505$, $p < 0,01$) con el EVS; seguida de la esperanza ($r = 0,432$, $p < 0,01$); el optimismo ($r = 0,412$, $p < 0,01$), y finalmente la autoeficacia ($r = 0,400$, $p < 0,01$).

El 33,3 de la varianza total del estilo de vida es explicado por el CapPsi ($R^2 = 0,333$). El análisis de la varianza estimada señala

**Tabla I.** Valores medios en hombres y mujeres de nuestro estudio, para estilo de vida y capital psicológico

| Variable | Hombre (n = 165) | Mujer (n = 155) |
|---|---|---|
| Estilo de vida | 36,9 ± 6,1 | 36,5 ± 5,8 |
| Autoeficacia | 33,0 ± 4,8 | 32,0 ± 5,0 |
| Esperanza | 52,2 ± 6,9 | 51,9 ± 7,0 |
| Agencia | 25,6 ± 3,9 | 25,3 ± 4,0 |
| Medios | 26,5 ± 3,7 | 26,5 ± 3,7 |
| Resiliencia | 140,5 ± 14,9 | 139,8 ± 15,6 |
| Factores protectores internos | 61,8 ± 6,9 | 61,1 ± 7,4 |
| Factores protectores Externos | 48,8 ± 5,5 | 48,8 ± 5,9 |
| Empatía | 29,8 ± 4,2 | 29,8 ± 4,2 |
| Optimismo | 18,1 ± 2,8 | 18,3 ± 2,9 |

la existencia de un adecuado ajuste del modelo (F = 39,352; p = < 0,0001), como se observa en la tabla II.

Dentro del análisis de confiabilidad que se realizó se encontró que el Cuestionario Fantástico tuvo un alfa de Cronbach de 0,76; para la Escala General de Autoeficacia 0,85; para la Escala de Esperanza para Adultos 0,60; para el Cuestionario de Resiliencia 0,93 y; para la Test de Orientación en la Vida 0,52.

## DISCUSIÓN

Las correlaciones previas del CapPsi con el EV permitieron definir el diseño y el ajuste posterior del modelo de regresión utilizado (F = 39,352; p = < 0,0001); así este trabajo provee evidencia de que el CapPsi favorece el EVS. No se encontraron diferencias significativas entre hombres y mujeres respecto al CapPsi; lo cual, facilita el desarrollo de intervenciones para su fomento sin necesidad de particularizarlas por sexo. Sin embargo, los estilos de vida, de personas que tienen sobrepeso y obesidad, son diferentes en hombres y mujeres. Por ello, es necesario hacer más estudios para identificar particularmente las variables que podrían influir en el EV de personas con sobrepeso y obesidad (16).

Los universitarios constituyen una población de la que se espera tengan un EVS. Sin embargo, recientemente han atravesado la etapa de la adolescencia (12 y 17 años) en donde, en las últimas décadas, es común que desarrollen hábitos poco saludables; por ejemplo, es común observar que la mayoría realiza poca actividad física, omite el desayuno y prefiere consumir en la escuela comida rápida, lo cual incrementa el riesgo de padecer obesidad (17). Así, este trabajo, aporta evidencia de como el CapPsi puede ayudar a la adopción de un EVS.

No debe soslayarse que, aunque este grupo etario tiene mucha información y creencias favorables respecto a los beneficios de tener un EVS (18) no parece ser suficiente para la adopción de comportamientos saludables. Por ejemplo, Lumbreras y cols. (19) en un estudio en el cual se evaluaron a 2,659 universitarios mexicanos, el 23% tenía sobrepeso, el 6% obesidad; el 63% no realizaba ninguna actividad física; el 20,1% fumaba cotidianamente; el 22,6% consumía bebidas alcohólicas frecuentemente y; el 1,2% consumía drogas ilícitas regularmente. Además, encontraron que, producto del uso excesivo de la computadora, el 11% padecía trastornos visuales y el 8% problemas músculo-esqueléticos, así como que el 18% tenía trastornos psicológicos. Estos ponen de manifiesto la necesidad de trabajar en el desarrollo de habilidades psicosociales.

El problema es complejo si consideramos que incluso los universitarios que estudian en las áreas de la salud, no tienen el EVS esperado. Por ejemplo, Grimaldo (20) identificó que estudiantes de posgrado de ciencias de la salud, tenían un EVS que se ubicada en un nivel medio; además se ha identificado un desequilibrio nutricional y cierto riesgo de sufrir patologías cardiovasculares en el futuro de no modificar su EV (21,22). A esta problemática se le suma que las actitudes respecto a los problemas de salud, tampoco son las esperadas; por ejemplo, hay estudiantes de las áreas de la salud que rechazan a las personas con obesidad (23). Entonces, si los mismos estudiantes no tienen hábitos saludables, su labor de promoción de la salud puede que no sea eficaz (24). De esta manera, resulta conveniente que futuras investigaciones analicen a detalles si hay diferencias en cuanto a cómo el CapPsi influye en particular en cada factor de EV, por ejemplo, en la alimentación, la actividad y/o ejercicio físico, los hábitos de sueño; además de indagar en cómo y cuánto el CapPsi influye en la adopción y/o mantenimiento del EVS.

El estilo de vida ha sido asociado a diversas variables psicológicas y de personalidad (25). Se aporta evidencia de que variables psicológicas relacionadas con las capacidades individuales como el CapPsi también predicen parcialmente el EVS.

Aunque una limitación del estudio es que los datos fueron obtenidos mediante las auto-percepciones de los participantes, esto, no resulta arbitrario tal como se ha señalado en diversos trabajos (26-28).

**Tabla II.** Resumen del modelo de regresión múltiple

| Modelo | R | R cuadrado | R cuadrado corregida | Error tip. de la estimación | Cambio en R cuadrado | Cambio en F | gl1 | gl2 | Sig. Cambio en F |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 0,577[a] | 0,333 | 0,325 | 4,921 | 0,333 | 39,352 | 4 | 315 | 0,000 |

*[a]Variables predictoras: (Constante), Resiliencia, Optimismo, Autoeficacia, Esperanza. [b]Variable dependiente: estilo de vida.*

Pese a que todos los instrumentos tuvieron alfas de Cronbach aceptables, se recomienda que en futuras investigaciones se pueda realizar la validación en población mexicana de la escala de Esperanza para Adultos de Snyder para aumentar la solidez de los resultados. Además, futuras investigaciones podrían analizar la confiabilidad del Test de orientación en la vida, cuya alfa de Cronbach en el presente estudio fue baja.

Además, es necesario que futuras investigaciones consideren otras formas de recolección de los datos, así como realizar estudios similares con estudiantes de otras universidades.

Este trabajo amplía el campo de estudio del CapPsi, pues predominantemente es un constructo que se estudia en el ámbito de la Psicología Organizacional por lo que faltan más investigaciones que puedan comprobar su utilidad y aplicación en la Psicología de la Salud.

## CONCLUSIONES

El presente estudio aporta evidencia de que el CapPsi está relacionado con la práctica de un EVS; por ello, es necesario que los programas de promoción de la salud y prevención de la enfermedad incorporen técnicas y estrategias psicológicas que lo favorezcan.

Es necesario fomentar un EVS en los universitarios y los profesionales de la salud, pues además del beneficio directo para ellos, también se requiere que funjan como modelos para la población en general (7).

## AGRADECIMIENTOS

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Nutrición Hospitalaria

Trabajo Original

Otros

# Factores de riesgo relacionados con los hábitos de vida en pacientes con patología osteomuscular

*Risk factors related with lifestyle in patients with musculoskeletal disorders*

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## Resumen

**Introducción:** las enfermedades osteomusculares (EOM) engloban una serie de patologías discapacitantes con alta incidencia y prevalencia, representando un alto costo económico y social. Es fundamental su prevención, por lo que es de gran interés determinar factores de riesgo modificables, como son los relacionados con los hábitos de vida.

**Métodos:** se realizó un estudio descriptivo y trasversal en 91 pacientes seleccionados mediante muestreo aleatorio sistemático y que fueron distribuidos en tres grupos experimentales según la causa y evolución de su EOM (cervicalgia, gonalgia y lumbalgia). Se realizó una medición biométrica, evaluación nutricional, de la actividad física y laboral, del balance muscular y del estado oxidativo.

**Resultados:** el sexo femenino es el más afectado por la presencia de lesiones osteomusculares como cervicalgia y lumbalgia. En conjunto, la mayor parte de los pacientes (67,4%) tiene normopeso, el 24,41% sobrepeso y tan solo un 8,1% obesidad tipo I. Los pacientes con cervicalgia son el grupo que realiza menos actividad física y peor balance muscular presentan. El estrés oxidativo fue superior en pacientes con gonalgia que en los otros grupos. Con respecto a la dieta consumida, se observan diferencias entre grupos experimentales en el contenido mineral (Zn, Mn, Se y I) y vitamínico (folato y ácido ascórbico).

**Conclusiones:** la ingesta de colecalciferol y vitaminas A y D es inferior a las recomendadas en todos los sujetos, lo que favorece la dolencia muscular. La ingesta de folato está por debajo de las recomendaciones, incidiendo en la mayor susceptibilidad al estrés oxidativo. La obesidad y estrés oxidativo se relacionan con la prevalencia de los diferentes tipos de EOM estudiados.

**Palabras clave:**

Enfermedad osteomuscular (EOM).
Consejo nutricional.
Micronutrientes.
Estrés oxidativo.

## Abstract

**Background:** Musculoskeletal disorders (MSDs) encompass a series of debilitating diseases with high incidence and prevalence, representing a high economic and social cost. Prevention is crucial, so is of great interest to determine modifiable risk factors, such as those related to lifestyle.

**Methods:** A descriptive cross-sectional study was performed in 91 patients selected by systematic random sampling and were divided into three experimental groups according to the cause and evolution of its MSD (neck pain, knee pain and back pain). A biometric measurement, nutritional assessment, physical and occupational activity, muscle balance and oxidative status was performed.

**Results:** The female is the most affected gender by the presence of musculoskeletal injuries such as neck pain and back pain. Overall, most patients (67.4%) had normal weight, overweight 24.41% and only 8.1% were obese type I. Patients with neck pain are the group doing less physical activity and worse muscular balance present. Oxidative stress was higher in patients with knee pain than in the other groups. Regarding the consumed diet, differences between experimental groups on the mineral content (Zn, Mn, Se and I) and vitamins (folate and ascorbic acid) are observed.

**Conclusions:** Cholecalciferol intake and vitamins A and D is less than those recommended in all subjects, which promotes muscle disease. Folate intake was below recommendations, increasing susceptibility to oxidative stress. Obesity and oxidative stress related to the prevalence of the different types of MSDs studied.

**Key words:**

Musculoskeletal disease (MSD).
Nutritional counseling.
Micronutrients.
Oxidative stress.

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## INTRODUCCIÓN

Las enfermedades osteomusculares (EOM) engloban una serie de patologías clínicas específicas que incluyen afectaciones de los músculos, tendones y vainas tendinosas, síndromes de atrapamiento nervioso, alteraciones articulares y neurovasculares. Son ampliamente conocidas, comunes y potencialmente discapacitantes, representando un alto costo social y económico que se traduce en incapacidades, tratamientos costosos, repercusión en la producción de la empresa y aumento de carga física (1).

Entre las EOM más prevalentes destacan la cervicalgia, lumbalgia y gonalgia. La cervicalgia se considera el cuarto dolor incapacitante a nivel mundial (2), afectando del 30 al 50% de la población en general (3). En España, el dolor crónico cervical afecta al 9,6% de hombres y al 21,9% de mujeres y la lumbalgia crónica afecta al 14,3% de la población masculina y al 22,8% de la femenina, siendo la causa más común de absentismo laboral en individuos menores de 45 años. Entre un 65% y 90% de la población sufrirá un episodio de lumbalgia en algún momento de su vida (4). La gonalgia afecta a más de la mitad de individuos de cincuenta años por periodos de más de un año, estando asociado a una reducción persistente de la capacidad funcional del individuo (5).

Las EOM tienen una alta incidencia (35%) y prevalencia (48%) dentro de las enfermedades profesionales en España (1) y representan la tercera causa de incapacidad temporal en trabajadores sobre todo del sector terciario y del industrial, con edades entre los 25-50 años, y debidas a procesos dolorosos de la columna vertebral y lesiones mecánicas de rodilla (6). Detrás quedan otras como enfermedades de la piel, respiratorias, alteraciones mentales o de tumores malignos por exposición a riesgos laborales (1). Es, por tanto, fundamental la prevención de las EOM mediante el control de factores de riesgo modificables, por lo que es de gran importancia definirlos.

La patología osteomuscular se caracteriza por la existencia de inflamación, que es una parte de la respuesta inmune de un organismo a infecciones, traumatismos y enfermedades posisquémicas, tóxicas o autoinmunes (7). La inflamación genera una cascada de reacciones metabólicas que dan lugar a un estrés oxidativo que, a su vez, estimula a los mediadores inflamatorios (8). La producción de los radicales libres es controlada por los sistemas antioxidantes endógenos, pero cuando los radicales libres provienen además de fuentes exógenas, tales como alimentos ricos en grasas, consumo excesivo de alcohol, exposición a diversos químicos, ejercicio físico, etc., pueden ser nocivos. Se ha postulado el estrés oxidativo como factor etiológico de las EOM (9) y es interesante comprobar si los hábitos de vida que lo incrementan, inciden también en una mayor prevalencia de EOM.

Estudios epidemiológicos (10) han mostrado que la obesidad es un factor predictor para el desarrollo y progresión de osteoartritis de rodilla, asociado a 9-13% de incremento de riesgo para el inicio de la enfermedad por cada kilogramo de aumento de peso. La obesidad además se ha relacionado con artritis reumatoide y agravamiento del dolor de espalda (11), por tanto la obesidad se presenta como otro factor de riesgo asociado a EOM.

El grado de actividad física es otro hábito de interés en el estudio de EOM, ya que estas patologías han aumentado en las últimas décadas entre los adolescentes y se ha descrito una alta probabilidad de dolores musculoesqueléticos asociados al sedentarismo y malos hábitos de vida (12).

Diversos estudios encuentran una asociación entre el comportamiento sedentario, el peso y la calidad de la dieta (13) Una mala alimentación puede disminuir la respuesta del sistema inmunológico, alterar el desarrollo físico y mental e incrementar la vulnerabilidad a las enfermedades, entre ellas las EOM. La prevención de la obesidad, el seguimiento de hábitos de vida saludables y dieta equilibrada en estas patologías podría ser beneficiosa para su rehabilitación y mejora de síntomas, ya que la disminución de la masa ósea y muscular puede deberse a un aumento de la adipogénesis, que causa una osteoblastogénesis reducida y una osteoclastogénesis aumentada por la producción de citocinas proinflamatorias y un exceso de secreción de leptina o adiponectina que reducen la absorción de calcio, empeorando el pronóstico de las EOM (7).

Dada alta prevalencia de las EOM y la importancia de la prevención sobre las mismas, consideramos de interés estudiar la posible relación entre factores de riesgo (obesidad y estrés oxidativo) relacionados con los hábitos de vida (dieta, tabaquismo y ejercicio físico) con la prevalencia de diferentes tipos de EOM para poder planificar estrategias de prevención de las mismas.

## MATERIAL Y MÉTODOS

### MUESTRA

El estudio, de tipo transversal, valoró simultáneamente la exposición y la patología en una población bien definida en un momento determinado del tiempo. Este tipo de estudio epidemiológico se utiliza fundamentalmente para conocer la prevalencia de una enfermedad o de un factor de riesgo (14). La fase de reclutamiento de candidatos se inició tras la aplicación de los criterios de selección. A los sujetos que cumplían los criterios de inclusión se les explicó el motivo del estudio y se les aportó un informe con las preguntas más frecuentes, procediendo a firmar el consentimiento informado si estaban dispuestos a participar.

El estudio se realizó en 91 pacientes seleccionados, entre hombres y mujeres de 20 a 59 años, mediante muestreo aleatorio sistemático, entre aquellos que asistían por patología osteomuscular a una clínica de rehabilitación en Granada, España. Los criterios de inclusión fueron: que presentasen dolor cervical (cervicalgia), lumbar (lumbalgia) o de rodilla (gonalgia). Los criterios de exclusión fueron: pacientes menores de 20 años, embarazo, rechazo del paciente a participar en el estudio, procesos álgicos de origen infeccioso, neoplásico, metástasis, osteoporosis, artritis inflamatorias o fracturas, deterioro cognitivo de cualquier etiología, intolerancia al ejercicio o la actividad física e índice de masa corporal (IMC) mayor de 35. Todos fueron explorados por el médico de la clínica para determinar el tipo de patología y se les realizó radiografía o resonancia magnética nuclear según las necesida-

des de cada paciente. De todos los pacientes seleccionados, 36 presentaban cervicalgia (75% mujeres y 25% hombres), 25 lumbalgia (72% mujeres y 28% hombres) y 24 gonalgia (28%mujeres y 72% hombres) (Fig. 1).

## ANTROPOMETRÍA

La medición biométrica se hizo mediante los parámetros antropométricos de las directrices de International Society of Avancement of Kinanthropometry (ISAK) y utilizada por el Grupo Español de Cineantropometría (15).

### Control de hábitos de vida (dieta, tabaquismo, alcohol)

Se realizó una encuesta recordatorio de 24 horas sobre el consumo de alimentos, que permite identificar la ingesta de alimentos de un pasado reciente tanto cualitativa como cuantitativamente. Se registraron tres días, incluyendo uno festivo. La cumplimentación del cuestionario validado se realizó mediante entrevista personal con nutricionista. Para ayudar al paciente encuestado a cumplimentar este cuestionario y recoger datos de la manera más fiel posible, se utilizó un manual fotográfico que incluye modelos de tamaños de alimentos, platos elaborados y medidas caseras (16). Los datos de la encuesta fueron procesados a través del programa Nutriber (17), que permite conocer la cantidad de energía, macro y micronutrientes que consumen los sujetos y compararlos con las ingestas recomendadas para la población española (18).

También se realizó una encuesta de frecuencia de consumo de alimentos que nos indica los alimentos que el paciente consume con mayor frecuencia durante una semana.

Se valoró mediante cuestionario del ensayo PREDIMED (Prevención con Dieta Mediterránea) (19) la adherencia a la dieta mediterránea de los pacientes y un control de hábitos de vida para poder identificar factores de riesgo relacionados con la EOM.

### Balance muscular

Se determinó aplicando la resistencia de forma manual. Esta prueba, realizada por el médico rehabilitador de la clínica, nos permite ver el estado de fuerza del músculo que valoramos en base a factores de gravedad (peso del segmento como resistencia patrón), resistencia (por parte del examinador) y fatiga. La cuantificación muscular analítica se basa en una escala de seis niveles que consta de 6 grados (20).

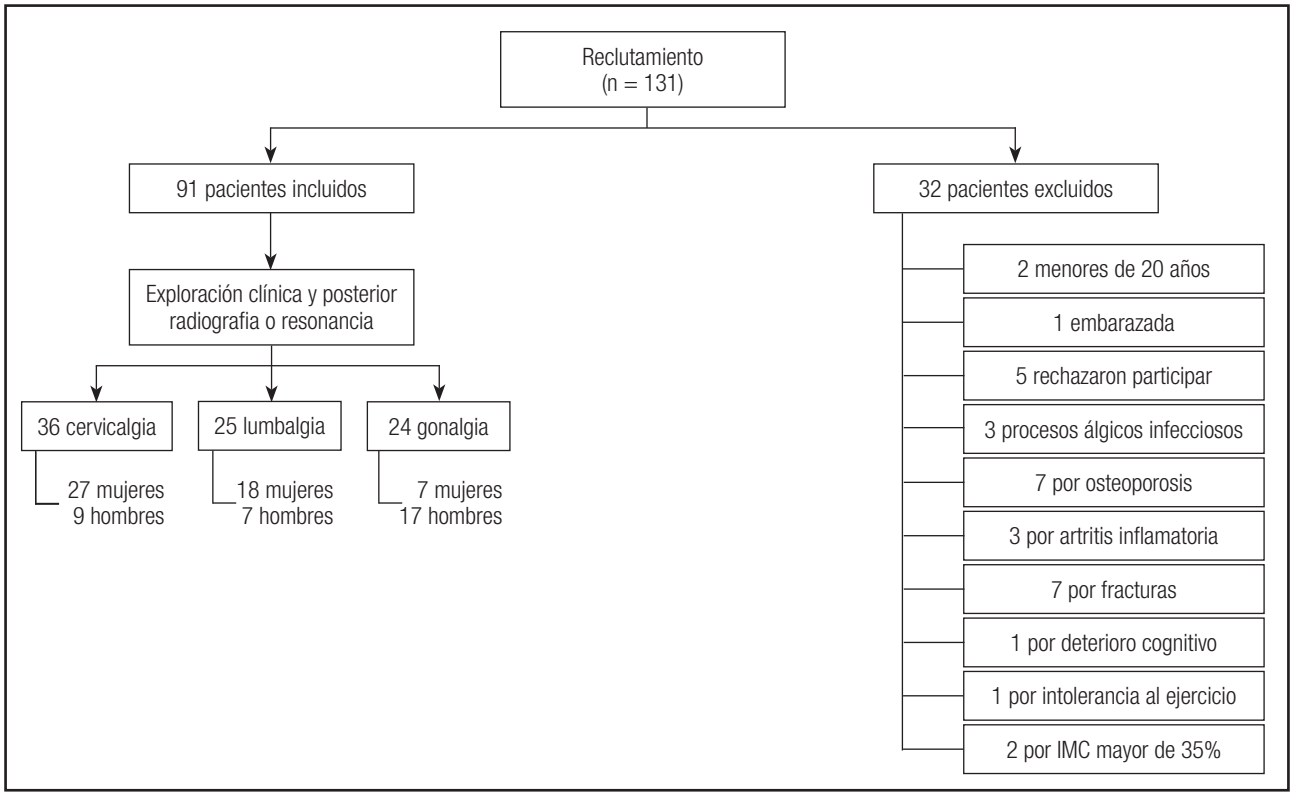


**Figura 1.**

Diagrama de flujo de los sujetos que participaron en el estudio.

### Actividad física

El nivel de actividad física fue estimado por medio del Cuestionario Internacional de Actividad Física (IPAQ) (21),que permite conocer la clase de actividad física que la gente realiza como parte de su vida diaria (en el trabajo y en el tiempo libre) y cuantifica todas las actividades realizadas en equivalentes metabólicos (MET).

### Estrés oxidativo

Se extrajo muestra de sangre a todos los pacientes en ayunas y se centrifugó a 1750 g durante 15 min a 4 °C en una centrífuga Beckman GS-6R (Beckman, Fullerton, CA, USA) para obtener el plasma. La actividad de la catalasa (CAT) se determinó mediante el método de Aebi (22). La actividad de la superoxidodismutasa (SOD) se determinó mediante el método descrito por Crapo y cols. (23). La actividad de la Glutationperoxidasa (GPx) fue determinada indirectamente por el método de Flohé y Gunzle (24). El grado de estrés oxidativo, medido como peroxidación lipídica, fue evaluado determinando la concentración de especies reactivas al ácido tiobarbitúrico (TBARS), siguiendo el método descrito por Yagi (25) y Ohkawa y cols. (26).

## ANÁLISIS ESTADÍSTICO

Antes de realizar el tratamiento estadístico, se comprobó la normalidad (con corrección de Lilliefors) de las variables y la varianza homogénea usando los test de Kolmogorov-Smirnov y Levene respectivamente. Para el análisis de los datos se aplicó una prueba de comparación de medias (*t* de Student). El nivel de significación estadística se estableció en $p < 0,05$. Para la realización de los cálculos estadísticos se utilizó el programa informático SPSS StatisticalPackagefor Social Sciences versión 20.0 (SPSS Inc., Chicago, IL, USA.) En el apartado de Resultados se presentan las tablas con el valor medio y error estándar de la media (EEM), dado el reducido número de sujetos por grupo.

## RESULTADOS

La edad media de los sujetos estudiados fue de 37,2 ± 10,3 años los pacientes con cervicalgia, 38,6 ± 9,2 años los pacientes con lumbalgia y 34,9 ± 10,3 años los de gonalgia**.** La media de peso de los pacientes con gonalgia es mayor (73,3 ± 14,5 kg), aunque no estadísticamente significativa, que la del grupo con cervicalgia (69,4 ± 14,2 kg) y con lumbalgia (67,8 ± 13,1 kg). No existe diferencia en la altura de los pacientes siendo la media 167 ± 8,6 cm de los que sufren cervicalgia, 168 ± 8,5 cm en los de lumbalgia y 173,6 ± 7,9 cm en pacientes con gonalgia. En conjunto, la mayor parte de los pacientes tiene normopeso (67,4%), un gran porcentaje (24,41 %) tienen sobrepeso y tan solo un 8,1 % tiene obesidad tipo I. No encontramos ningún paciente con obesidad tipo II. Si analizamos la muestra por patologías, se observa que en los pacientes con cervicalgia, la mayoría tiene normopeso (64,7%), el 26,5 % tienen sobrepeso y un 8,8 % tiene obesidad tipo I. Entre los que sufren lumbalgia, el 70,8% tiene normopeso, el 25,0 % presenta sobrepeso y solo un 4,2 % tiene obesidad tipo I. En los pacientes con gonalgia, el 66,7% tiene un peso normal, el 20,8 % presenta sobrepeso y un 12,5 % tiene obesidad tipo I.

Respecto a la encuesta de hábitos de vida, los pacientes que más fuman (más de un paquete de tabaco al día) son los que padecen lumbalgia, con respecto a los de cervicalgia ($p < 0,01$) y gonalgia ($p < 0,001$). Los que más consumen alcohol (más de 400 ml al día) son los pacientes con gonalgia, con respecto a cervicalgia ($p < 0,001$) y lumbalgia ($p < 0,01$).

Sobre el consumo de energía y macronutrientes no se han encontrado diferencias significativas entre las patologías estudiadas. Los sujetos de estudio presentan una dieta normocalórica. El porcentaje de proteínas consumidas por los hombres se encuentra en torno al 15% y los glúcidos 51%. Respecto al perfil lipídico, el aporte de grasa total es de un 33% con un nivel de ácidos grasos saturados de 8,5%, ácidos grasos monoinsaturados 18,04% y ácidos grasos poliinsaturados de 4,56%. En el caso de los sujetos de estudio mujeres, presentan un consumo de proteínas de un 16% y de glúcidos de un 49%. En su perfil lipídico, el aporte de grasa total corresponde a un 34% con un nivel de ácidos grasos saturados de 9%, ácidos grasos monoinsaturados 19,04% y ácidos grasos poliinsaturados de 4,40%.

Con respecto a los minerales ingeridos (Tabla I) se observan diferencias en contenido mineral de la dieta entre grupos experimentales para el Zn, Mn, Se y I. El consumo de Zn fue más bajo en el grupo de lumbalgia con respecto a cervicalgia ($p < 0,001$) y gonalgia ($p < 0,05$). El consumo de Mn también fue más bajo en el grupo de lumbalgia con respecto a cervicalgia ($p < 0,001$) y gonalgia ($p < 0,001$). El consumo de Se fue superior en el grupo de gonalgia en comparación con el de cervicalgia ($p < 0,05$) y lumbalgia ($p < 0,05$). El consumo de I también fue superior en el grupo de gonalgia en comparación con el de cervicalgia ($p < 0,05$) y lumbalgia ($p < 0,05$).

El contenido vitamínico de la dieta se muestra en la tabla II. El contenido en folato de la dieta de los pacientes con gonalgia fue superior a los de cervicalgia ($p < 0.01$) y lumbalgia ($p < 0,01$). La ingesta de ácido ascórbico fue inferior en pacientes con lumbalgia. Con respecto a los de cervicalgia ($p < 0,05$) y gonalgia ($p < 0,05$). El contenido de colecalciferol de la dieta de los pacientes con gonalgia fue superior a los de cervicalgia ($p < 0,001$) y lumbalgia ($p < 0,001$).

En la tabla III se expresan los resultados de frecuencia de consumo de alimentos. Solo el 68%, 54,5% y 68,2% de los pacientes con cervicalgia, lumbalgia y gonalgia, respectivamente, consumen fruta a diario siendo menor el consumo de los pacientes con lumbalgia ($p < 0,01$). El consumo de bollería es mayor en el grupo cervicalgia respecto al grupo lumbalgia y gonalgia ($p < 0,05$).

Los resultados del cuestionario del ensayo PREDIMED, que indica el grado de adherencia a la dieta mediterránea, muestran que hay una distribución homogénea entre alta y baja adheren-

**Tabla I.** Contenido mineral de la dieta en sujetos que sufren cervicalgia, lumbalgia o gonalgia

| | Cervicalgia | Lumbalgia | Gonalgia |
|---|---|---|---|
| Na (mg) | 3128,42 ± 121,22a | 2159,98 ± 146,48b | 2479,71 ± 171,54b |
| K (mg) | 2451,20 ± 139,58a | 2609,19 ± 101,91a | 2871,28 ± 114,79a |
| Ca (mg) | 968,28 ± 132,33a | 876,76 ± 213,68a | 1022,90 ± 197,11a |
| Mg (mg) | 313,92 ± 22,76a | 296,27 ± 22,92a | 334,91 ± 26,63a |
| P (mg) | 1164,81 ± 124,18a | 1180,00 ± 147,79a | 1279,83 ± 194,52a |
| Fe (mg) | 41,29 ± 6,23a | 43,64 ± 7,21a | 43,93 ± 4,47a |
| Cu (mg) | 1,60 ± 0,72a | 1,28 ± 0,55a | 1,15 ± .0,60a |
| Zn (mg) | 17,33 ± 3,16a | 8,76 ± 2,33b | 11,87 ± 2,29c |
| Cl (mg) | 1901,10 ± 168,31a | 1985,50 ± 161,33a | 2082,23 ± 122,82a |
| Mn (mg) | 15,63 ± 2,58a | 3,01 ± 1,28b | 8,21 ± 1,87c |
| Se (µg) | 67,09 ± 3,40a | 70,16 ± 2,06a | 79,87 ± 2,38b |
| I (µg) | 74,43 ± 4,58a | 75,36 ± 4,50a | 84,11 ± 5,08b |

*Datos expresados como Media ± EEM. a, b, c: valores con letras distintas indican diferencias significativas mediante el test de la t de Student (p < 0,05).*

**Tabla II.** Contenido vitamínico de la dieta en sujetos que sufren cervicalgia, lumbalgia o gonalgia

| | Cervicalgia | Lumbalgia | Gonalgia |
|---|---|---|---|
| Tiamina (mg) | 2,21 ± 1,12a | 3,11 ± 1,00a | 2,54 ± 0,45a |
| Riboflavina (mg) | 1,81 ± 0,28a | 1,57 ± 0,26a | 1,66 ± 0,46a |
| Piridoxina (mg) | 1,57 ± 0,56a | 1,83 ± 0,60a | 2,02 ± 1,03a |
| Cianocobalamina (µg) | 9,62 ± 1,21a | 9,62 ± 1,76a | 8,25 ± 1,43a |
| Folato (µg) | 347,60 ± 33,08a | 262,86 ± 23,07b | 243,55 ± 23,86b |
| Niacina (mg) | 28,04 ± 0,98a | 28,25 ± 1,06a | 28,06 ± 0,84a |
| Ác. ascorbico (mg) | 165,72 ± 22,16a | 103,67 ± 298,33b | 178,56 ± 33,74a |
| Ác. pantoténico (mg) | 3,80 ± 1,10a | 4,07 ± 1,26a | 4,38 ± 1,27a |
| Biotina (mg) | 6,77 ± 1,17a | 8,22 ± 1,03a | 8,08 ± 1,36a |
| Retinol (µg) | 699,17 ± 19,21a | 661,45 ± 21,56a | 697,14 ± 31,39a |
| Colecalciferol (µg) | 4,98 ± 0,78a | 4,68 ± 0,79a | 7,02 ± 6,78b |
| Tocoferol (mg) | 10,19 ± 1,60a | 9,63 ± 1,86a | 10,45 ± 1,75a |

*Datos expresados como Media ± EEM. a, b: valores con letras distintas indican diferencias significativas mediante el test de la t de Student (p < 0.05).*

**Tabla III.** Frecuencia de consumo de alimentos en sujetos que sufren cervicalgia, lumbalgia o gonalgia

| | Cervicalgia | Lumbalgia | Gonalgia |
|---|---|---|---|
| Frutas a diario | 68% | 54,5% | 68,2% |
| Verduras a diario | 44% | 63,6% | 63,6% |
| Pescado 2-3 veces/semana | 76% | 59,1% | 68,2% |
| Bollería 2-3 veces/semana | 36% | 13,6% | 18,2% |

*Datos expresados como porcentaje.*

cia en todos los grupos experimentales. El 45,5% de pacientes con cervicalgia presentan una baja adherencia y un 54,5% alta adherencia. Respecto a los pacientes con lumbalgia, un 45,8% presentan baja adherencia y un 54,2% alta adherencia. Un 52,2% de los pacientes con gonalgia tienen baja adherencia a la dieta mediterránea y un 47,8% alta adherencia.

En la tabla IV se expresan los resultados correspondientes al grado de contracción de los músculos flexores en los distintos pacientes. El grado de contracción muscular es mayor entre los pacientes con gonalgia con un 33,3% grado 5 y un 66,7% grado 4.

Los resultados de la encuesta IPAQ, que indica el nivel de actividad física en MET, muestra que los pacientes con cervicalgia realizan menos actividad física que aquellos con lumbalgia o gonalgia ($p < 0,001$) (Tabla V). Los pacientes con gonalgia realizan actividades físicas más vigorosas con respecto a los que tienen cervicalgia ($p < 0,001$) y lumbalgia ($p < 0,01$).

Los parámetros de estrés oxidativo se muestran en la tabla VI. La producción de TBARS fue superior en pacientes con gonalgia con respecto a los de cervicalgia ($p < 0,001$) y lumbalgia ($p < 0,001$). Los niveles de SOD fueron menores en pacientes con gonalgia con respecto a los de cervicalgia ($p < 0,001$) y lumbalgia ($p < 0,05$).

## DISCUSIÓN

En los pacientes con EOM evaluados, los factores de riesgo estudiados, relacionados con los hábitos de vida, son altamente prevalentes. El sexo femenino resulta ser el más afectado por la presencia de lesiones osteomusculares como cervicalgia y lumbalgia; probablemente debido a que existen diferencias en la exposición a factores de riesgo según el sexo. El sexo femenino suele desempeñar trabajos estáticos, que obligan a mantener posturas fijas y prolongadas, lo cual puede ocasionar problemas a nivel de la espalda (27-31) mientras que los hombres suelen tener trabajos que requieren mayor esfuerzo físico. Además, los factores de riesgo más frecuentes en las mujeres trabajadoras son de tipo psicosocial: el alto nivel de exigencia, la monotonía, el sedentarismo, las posturas forzadas, la necesidad de rapidez y destreza en el puesto de trabajo, la poca cualificación y responsabilidad, la acumulación de tareas y la inseguridad de mantenimiento del puesto (32).

En el grupo de gonalgia encontramos un mayor porcentaje de pacientes con obesidad. Diversos estudios han demostrado que la obesidad aumenta 3 veces el riesgo para el desarrollo de procesos degenerativos en rodilla (33,34), y se ha observado que el aumento de 5 kilogramos de peso incrementa un 35% el riesgo

**Tabla IV.** Grado de contracción muscular de músculos flexores (%)

| | Cervicalgia<br>Flexores de cuello | Lumbalgia<br>Flexores lumbares | Gonalgia<br>Flexores de rodilla |
|---|---|---|---|
| Grado 3 | 14,7% | 21,7% | - |
| Grado 4 | 73,5% | 26,1% | 66,7% |
| Grado 5 | 11,8% | 52,2% | 33,3% |

*Datos expresados como porcentajes.*

**Tabla V.** Actividad física (MET) de sujetos que sufren cervicalgia, lumbalgia o gonalgia

| | Cervicalgia | Lumbalgia | Gonalgia |
|---|---|---|---|
| Baja | 682,77 ± 149,28a | 806.83 ± 160,15b | 1390,22 ± 118,26c |
| Moderada | 245,11 ± 133,38a | 866.83 ± 117,51b | 779,00 ± 176,30b |
| Vigorosa | 362,35 ± 171,13a | 955,33 ± 169,37b | 1326,66 ± 170,05c |

*Datos expresados como Media ± EEM. a, b,c: valores con letras distintas indican diferencias significativas mediante el test de la t de Student ($p < 0.05$).*

**Tabla VI.** Parámetros de estrés oxidativo plasmático en sujetos que sufren cervicalgia, lumbalgia o gonalgia

| | Cervicalgia | Lumbalgia | Gonalgia |
|---|---|---|---|
| TBARS (nmol/mg proteína) | 0,681 ± 0,082a | 0,722 ± 0,095a | 1,171 ± 0,095b |
| SOD (U/mg proteína) | 0,691 ± 0,085a | 0,503 ± 0,062b | 0,401 ± 0,056b |
| CAT (U/mg proteína) | 4,51x10-6 ± 0,61x10$^{-6}$ a | 4,74x10-6 ± 0,55x10$^{-6}$ a | 4,84x10-6 ± 0,59x10$^{-6}$ a |

*Datos expresados como Media ± EEM. a, b: valores con letras distintas indican diferencias significativas mediante el test de la t de Student ($p < 0.05$).*

para presentar procesos degenerativos en la rodilla, produciendo una limitación en la función articular (35), por tanto el sobrepeso está íntimamente relacionado con la artrosis de rodilla (36,37). El peso corporal es el mayor predictor modificable de EOM, ya que mientras caminamos el peso se transfiere entre 3 y 6 veces a través de la articulación de la rodilla, incidiendo sobre el desarrollo de osteoartritis. El estudio de Chingford demostró que cada dos unidades añadidas al IMC, la *odds ratio* para padecer osteoartritis radiológica de rodilla aumentaba en 1,36 (38). Rosemann y col. (39) estudiaron a 978 pacientes diagnosticados de gonalgia, clasificados según su IMC y test de calidad de vida; encontraron una mayor prevalencia de EOM en pacientes con sobrepeso u obesidad y confirmaron la hipótesis de que la calidad de vida de los pacientes obesos está inversamente correlacionada con el IMC.

Nuestros resultados muestran que los pacientes con gonalgia son los que mayor actividad física vigorosa realizan y tienen mayor grado de contracción muscular. La actividad física mejora el rendimiento físico en general, pero por otro lado, posee diversos factores de riesgo que pueden dar lugar a lesiones, entre ellos, cuando se realiza un elevado entrenamiento o un entrenamiento no adaptado al deportista y sus cualidades físicas (40,41). A nivel de la articulación de la rodilla el ejercicio físico en personas sin factores de riesgo, no supone una degeneración del cartílago excepto aquellas actividades que requieran una flexión excesiva de la articulación. Quizás, el ejercicio vigoroso realizado por los pacientes con gonalgia, ha podido influir en aparición de la lesión, bien por no tener las cualidades físicas oportunas o porque la ejercicio físico no ha sido adaptada a sus cualidades físicas.

Los pacientes con cervicalgia son los que menos actividad física presentan junto con un peor grado de contracción muscular. En otros estudios queda patente que la afectación muscular y el dolor, como en el caso de las cervicalgias, afectan al control motor lo que posiblemente conlleva a déficits funcionales (42). En las cervicalgias crónicas los cambios incluyen alteraciones en el control motor y una gran activación de la musculatura accesoria del cuello. Por otra parte, se ha encontrado un retraso en la activación de la musculatura cervical y un déficit en el control automático de la propiocepción de la columna cervical, haciendo al cuello vulnerable a los microtraumatismos acumulativos y al dolor (43). Varios estudios han informado de la pérdida de fuerza muscular en pacientes con cervicalgia crónica en comparación con personas sanas. Barton y cols. (44) encontraron una pérdida del 50% de fuerza máxima en la musculatura flexora en pacientes con cervicalgia comparado a los controles sanos. Jordan y col. (45) observaron que la fuerza de flexión y extensión era un 50% menor en pacientes con cervicalgias crónicas comparado con los controles sanos. Además, en este mismo estudio (45) también se encontró una diferencia estadísticamente significativa en la máxima fuerza isométrica de la musculatura flexora y extensora entre pacientes con cervicalgia e individuos sanos, encontrando la mayor pérdida de fuerza en el grupo muscular extensor, por otra parte, también se encontró una reducción significativa de la resistencia isométrica en la musculatura extensora en la mayoría de pacientes. En el estudio de Harris y col. (46) se observó que los pacientes con cervicalgia tenían una menor resistencia de la musculatura flexora del cuello en comparación a los sujetos sanos del estudio.

Por otra parte es también conocido que una dieta rica en hidratos de carbono aumenta los parámetros de daño muscular (47). Por otra parte, también se ha observado que un aumento de la carga glucémica en individuos no diabéticos, incrementa la producción de especies reactivas de oxígeno *in vitro*, con la consiguiente lesión celular oxidativa y el desencadenamiento final de respuestas inflamatorias (48), con lo cual el bajo consumo de hidratos de carbono reducirá la señalización proinflamatoria en los tres grupos estudiados.

Respecto al perfil de la dieta ingerida, encontramos que es normocalórica y ligeramente baja en hidratos de carbono para los tres tipos de pacientes. Sin embargo, nuestros pacientes tienen una ingesta inferior a las recomendadas en pescado, frutas y verduras, pues son muchos los que no las consumen diariamente. La OMS recomienda unos 400g de frutas y verduras al día, sin contar patatas y tubérculos (49). El pescado posee ácidos grasos omega -3 que disminuyen los marcadores inflamatorios (50,51) y mitigan el daño muscular después del ejercicio intenso (52). Por tanto, el bajo consumo de pescado encontrado en los tres grupos de pacientes estudiados, puede influir negativamente en el desarrollo de las enfermedades osteomusculares, por no ejercer los beneficios comentados a estos pacientes (50).

Los resultados de la valoración de micronutrientes de la dieta muestran que los pacientes con lumbalgia presentan la ingesta más baja de Zn seguidos de los de gonalgia y cervicalgia. Los sujetos con lumbalgia y gonalgia presentan una deficiencia en la ingesta recomendada (que es de 15 mg/día) (18). Una de las consecuencias más importantes de la deficiencia de Zn es la inhibición del crecimiento lineal. El Zn es cofactor de la enzima antioxidante $SOD_1$ (53) que participa en la neutralización de radicales libres derivados del metabolismo celular hecho que adquiere gran importancia en el caso de los sujetos que sufren patologías osteomusculares, dada la elevada tasa de generación de especies reactivas del oxígeno durante los procesos inflamatorios (54). Esta disminución en la ingesta de Zn de ambos pacientes puede explicar la disminución de la actividad de la SOD y por tanto la mayor susceptibilidad a la peroxidación lipídica encontrada en el presente estudio (aumento de especies reactivas al ácido tiobarbitúrico). Por otro lado, se ha postulado el estrés oxidativo como factor etiológico de las EOM (7). Dentro de las EOM estudiadas, la que cursa con un proceso inflamatorio más acusado a la vista del estrés oxidativo inducido es la gonalgia en la que hay una disminución de la SOD y un aumento de la peroxidación lipídica en comparación con las otras patologías estudiadas. Además, es conocido que el Mn es cofactor de la $SOD_2$ (54) por lo tanto la actividad neta de la enzima también se ve afectada en el caso de la lumbalgia y gonalgia por la baja ingesta de Mn en ambos grupos. Todos los pacientes en general cumplen los requerimientos de minerales excepto en el caso del I cuyas ingestas son inferiores a las recomendaciones (18).

La ingesta de folato está por debajo de las recomendaciones de 300 µg/día (18) en los grupos de lumbalgia y gonalgia. Este hecho cobra gran importancia y explica también la mayor susceptibilidad

al estrés oxidativo en los grupos de lumbalgia y gonalgia, ya que el ácido fólico es una vitamina hidrosoluble y cofactor en el metabolismo intermediario que puede regular distintas rutas metabólicas, actuando como neutralizador de radicales libres y ejerciendo un claro efecto antioxidante (55). En este sentido, los folatos reducen los niveles de homocisteína en 25% y una deficiencia de ellos se relaciona con el aumento en la concentración plasmática de este aminoácido, que actúa como es inductor de estrés oxidativo: debido a su capacidad de oxidarse) (56).

La ingesta de ácido ascórbico fue inferior en pacientes con lumbalgia. La vitamina C constituye una de las principales defensas neutralizando radicales orgánicos altamente dañinos, formados por la acción de especies reactivas del oxígeno, que se acumulan induciendo estrés oxidativo (57) y además la baja ingesta de vitamina C induce daño muscular (58). Algunas especies reactivas del oxígeno se han señalado como las causantes del daño muscular tras ejercicios con contracciones excéntricas, por lo que el suministro de sustancias que reducen la existencia de radicales libres, como el ácido ascórbico, podría mejorar la disminución de la fuerza que se observa tras un esfuerzo extenuante.

Los tres grupos estudiados también presentan una baja ingesta de colecalciferol con respecto a las ingestas recomendadas (18) hecho que incide de manera negativa en las dolencias de tipo muscular, dado el papel de la vitamina D en el metabolismo del músculo esquelético. Además, la deficiencia de vitamina D se asocia con dolor musculoesquelético crónico y óseo generalizado (59). Se cree que la vitamina D puede disminuir el dolor musculoesquelético, disminuyendo la sensibilidad de las fibras nerviosas en los músculos (60,61). Algunos estudios también han investigado las concentraciones de vitamina D y los marcadores para la inflamación y el dolor. En un análisis retrospectivo, Hong y cols. 2014 (62) evaluaron la correlación entre las concentraciones de vitamina D y las citoquinas inflamatorias en pacientes con artritis reumatoide. Los pacientes con concentraciones más bajas de vitamina D tenían significativamente más síntomas de la enfermedad, tales como hinchazón, rigidez y dolor en las articulaciones. Además, las concentraciones de vitamina D se asociaron negativamente con la presencia de citoquinas inflamatorias. La baja ingesta de vitamina D en la población de nuestro estudio puede estar relacionada con el dolor inespecífico que presentan estos pacientes. El aporte de vitamina D induce rápidos cambios en el metabolismo del Ca de la célula muscular, que actúa directamente su membrana, activando varias vías de segundos mensajeros (cAMP, diacilglicerol, inositoltrifostato y ácido araquidónico), lo que potencia la entrada de Ca en escasos minutos (63). Por tanto un bajo consumo de vitamina D, no solo afecta de manera negativa al *turnover* óseo sino al metabolismo muscular pudiendo empeorar las dolencias de los tres grupos de pacientes.

La dieta mediterránea se caracteriza por un perfil alimentario moderado en el que adquieren protagonismo algunos grupos de alimentos típicos de la región mediterránea: cereales, legumbres, pescado, aceite de oliva, frutas, frutos secos, verduras, hortalizas y vino. La adhesión a la dieta mediterránea, como modelo alimentario saludable, puede cuantificarse mediante diferentes índices en los que se puntúa positivamente los alimentos y nutrientes que contribuyen beneficiosamente a proteger y preservar la salud. En nuestro caso usamos el cuestionario PREDIMED (19) y observamos que tan solo la mitad de cada grupo de pacientes, aproximadamente, tenía una alta adherencia a la dieta mediterránea, por lo tanto habría que realizar una educación nutricional para promover la mayor adherencia en estos pacientes.

Respecto a los hábitos de vida, el grupo con lumbalgia es el que más fuma y el grupo con gonalgia es el que más alcohol consume. Los efectos nocivos del humo del tabaco en nuestro organismo, provocan un aumento de radicales libres e interactúan en las reacciones enzimáticas del sistema antioxidante endógeno, dando lugar a una inflamación por la transcripción de citoquinas proinflamatorias (64). Por otro lado, el grupo gonalgia es el que más alcohol consume y también es el que más porcentaje de obesos presenta, a pesar de que su actividad física es más vigorosa, hecho que podemos explicar debido a la estrecha relación entre la ingesta de alcohol y el incremento de peso (65), además del consumo de alcohol con fines recreativos tras sesiones de ejercicio físico.

Finalmente, son muchos los estudios recientes que demuestran que un estilo de vida saludable previene las patologías osteomusculares, entre otras enfermedades. Así, no fumar, no consumir alcohol, realizar ejercicio físico adaptado a cada persona y una dieta equilibrada, entre otros factores, reducen el riesgo de padecer estas enfermedades (66-69).

Entre las limitaciones del presente estudio podemos citar la necesidad de incluir un grupo control sin patología osteomuscular y el modesto tamaño de la muestra poblacional dada la dificultad para la captación de pacientes.

## CONCLUSIÓN

En nuestro estudio existe una clara relación entre los factores de riesgo estudiados y la incidencia de EOM y el sexo femenino resulta ser el más afectado con la presencia de lesiones osteomusculares como cervicalgia y lumbalgia. Los pacientes con cervicalgia son los que menos actividad física presentan junto con un peor grado de contracción muscular. Los pacientes con lumbalgia presentan la ingesta más baja de Zn y Mn, seguidos de los de gonalgia y cervicalgia, lo que puede explicar la disminución de la actividad de la SOD encontrada en el presente estudio. La ingesta de folato está por debajo de las recomendaciones en los grupos de lumbalgia y gonalgia, incidiendo en la mayor susceptibilidad al estrés oxidativo en ambos grupos. Los tres grupos estudiados también presentan una baja ingesta de colecalciferol, hecho que incide de manera negativa en las dolencias de tipo muscular, dado el papel de la vitamina D en el metabolismo del músculo esquelético. Dada la alta incidencia de las EOM y las repercusiones sociales y económicas de éstas, es necesario realizar un plan de prevención y/o tratamiento que incluya la posibilidad de orientar a cada individuo a desempeñar el trabajo que realice dentro de las medidas ergonómicas adecuadas, a adaptar a la actividad física a las necesidades de éste y advertirle que dieta es la más adecuada para la prevención y/o tratamiento de su o

sus patologías. De este modo, podremos evitar o disminuir las recidivas o posibles futuras lesiones.

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Trabajo Original

Otros

# Composition and diversity of acaroids mites (Acari: Astigmata) community in the stored rhizomatic traditional Chinese medicinal materials

*La composición y la diversidad de ácaros (Acari: Astigmata) en productos de la medicina tradicional china*

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## Abstract

**Objective:** To investigate the species and breeding density of acaroid mites in the stored rhizomatic traditional Chinese medicinal materials in Anhui province, China, in order to supply evidences for control and prevention of such species.

**Methods:** The stored traditional Chinese medicinal materials of root-stock origins were collected in 30 herb stores and warehouses in 17 cities across Anhui province. Mites were collected by using Tullgren funnel and directicopy, and identified under microscopy.

**Results:** Twenty-two species of acaroid mites, belonging to 15 genera under 5 families, were identified from the total 47 stored samples, in which *Tyrophagus putrescentiae, Acarus farinae*, *Carpoglyphus lactis*, and *Cologlyplus berlesei* were predominant.

**Conclusion:** Breeding density of acaroid mites was high in the stored rhizomatic traditional Chinese medicinal materials in Anhui province. This indicates that the traditional Chinese medicinal herbs of root-stock origins in storage are seriously contaminated by the acaroid mites, and such infestation should be positively controlled to reduce the potential harm to public health.

**Key words:**

Stored Chinese medicinal materials. Acaroid mites. Habitat. Allergic diseases.

## Resumen

**Objetivo:** investigar las especies y densidad de especies de ácaros en los productos a bases de raíces de la medicina tradicional china en la provincia de Anhui, China, con el fin de proporcionar evidencias para el control y la prevención de tal infestación.

**Métodos:** se recogieron muestras de productos procedentes de raíces usados en la medicina tradicional china en 30 tiendas y almacenes de 17 ciudades de la provincia china de Anhui. Se recogieron las muestras mediante el embudo de Tullgren y la directicopia y los ácaros fueron identificados bajo microscopia.

**Resultados:** se identificaron 22 especies de ácaros, pertenecientes a 15 géneros menores de 5 familias a partir de 47 muestras almacenadas, en las que *Tyrophagus putrescentiae, Acarus farinae, Carpoglyphus lactis* y *Cologlyplus berlesei* eran predominantes.

**Conclusión:** la densidad de ácaros fue alta en el las muestras a base de raíces en el material almacenado para usarse como remedio en la medicina tradicional china en la provincia de Anhui. El control de esta infestación puede reducir el daño potencial para la salud pública.

**Palabras clave:**

Medicina tradicional china. Ácaros. Hábitat. Alergia.

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## INTRODUCTION

Allergic disease is recognized by the World Health Organization (WHO) as one of the four major noninfectious diseases for targeted prevention in the 21st century, and it annually affects 10% to 30% of global population and is growing an important public health concern (1,2). Allergen is one of the causative factors for development of allergic disorders. Particularly, allergens of mite sources are widely recognized as a primary initiator to induce hypersensitive reaction (3-6). As an aspiration allergen widely extant in nature, mite allergen has long received special attention for its universality and particularity (7-10). Therefore, it's of great significance to understand the diverse habitats and breeding materials of acaroid mites in the prevention and treatment of allergic asthma. During November 2009 and 2011, we undertook an investigation on breeding status of acaroid mites in 47 species of the stored rhizomatic traditional Chinese medicinal materials collected from 47 stores and warehouses for traditional Chinese medicinal herbs throughout 17 cities in Anhui province. The present study was aimed at reporting our findings on the mite breeding in the total 47 samples detected.

## MATERIALS AND METHODS

### SAMPLE COLLECTION

Herbal samples were collected from traditional Chinese medicine store and warehouses in compliance with the breeding habits of acaroid mites, ecological instruments were used to obtain relevant information. The samples were primarily included *Radix rehmanniae, Radix puerariae, Bulbus lilii, Radix angelicae sinensis, Radix salviae miltiorrhizae,* etc. Apart from that, dusts in the investigated places were also sampled. All of the stored rhizomatic traditional Chinese medicinal materials were stored over 6 months on average. And 10 aliquots of the samples were obtained from each of the stored rhizomatic traditional Chinese medicinal materials, separately sealed in sampling bag and transported to the laboratory, where each sample was measured with the balance by 10 g for each. Sieve shaker was used to separate the dusts from physical samples before final isolation of the acaroid mites.

### SEPARATION AND CLASSIFICATION OF ACAROID MITES

Mites in the physical samples were isolated using Tullgren funnel and directicopy, while those in the dusts were extracted with waternacopy and redricopy (11). The mite slides were prepared as previous description from the specimens isolated to undergo light microscopic observation of the morphology and species identification as well as count. Classification of the acaroid mites was in compliance with the taxonomic system described by Hughes (12,13).

### INFORMATION ANALYSIS

The number of acaroids mites in different samples of stored material was counted, and the breeding density of acaroid mites was calculated in accordance with the formula ($D = N/T \times 100\%$) (N represents the number of acaroid mites; T, the sample quality; and D, the breeding density of acaroid mites). Richness index of species was shown in Margalef index by formula $Rmargalef = (S-1)/lnN$ (where S stands for the number of species; N, total number of every individual species). Diversity index of species was denoted by Shannon-Wiener index in formula $H' = -\Sigma PilnPi$) ($Pi = Ni/N$, or the proportion of individuals belonging to the *i*th species). Evenness index of species was represented by Pielou's evenness as formula $J = H'/Hmax$ ($Hmax = lnS$).

## RESULTS

### SPECIES AND DENSITY OF ACAROID MITES IN DIFFERENT STORED RHIZOMATIC TRADITIONAL CHINESE MEDICINAL MATERIALS

Species and density of acaroid mites in 47 sorts of stored traditional Chinese medicinal materials of root-stock origins are shown in table I, which demonstrates that different species of acaroids mites differ in ecological habits and habitats. Different species of acaroid mites varied to a certain degree in their habitats, feedings and ecological habits as well as in the stored rhizomatic traditional Chinese medicinal materials by breeding densities. A total of 20 species of acaroid mites were separated from 47 kinds of rhizomatic traditional Chinese medicinal materials, belonging to 15 genus and 5 families of the acaridae respectively (Table II). The results indicate a diversity of the acaroid mites in the stored medicinal materials in Anhui area.

### ECOLOGICAL PARAMETERS FOR ACAROID MITES IN THE STORED RHIZOMATIC TRADITIONAL CHINESE MEDICINAL MATERIALS

The top five rhizomatic traditional Chinese medicinal materials in the 47 samples with highest breeding density of acaroid mites were involved sequentially in *Radix et rhizoma rhei, Rhizoma dioscoreae, Pseudobulbus cremastrae seu pleiones*, *Radix puerariae*, and *Rhizoma chuanxiong*. The breeding density, number of species, richness index, diversity index, and evenness index are shown in table III, demonstrating diverse ecological habits and habitats for different species of acaroids mites. The highest breeding density was found in *Radix et rhizoma rhei,* while the highest richness index, diversity index and evenness were seen *Pseudobulbus cremastrae seu pleiones.* These findings suggested serious contamination of the rhizomatic traditional Chinese medicinal materials withacaroid mites by diverse species and a relatively stable species class.

**Table I.** Breeding density of acaroid mites in the stored rhizomatic traditional Chinese medicinal materials

| Sample | Weight/g | Species of Breeding Acaroid Mites |
|---|---|---|
| *Radix et rhizoma rhei* | 77.61 | *T. putrescentiae, C. berlesei, Lepidoglyphus michaeli* |
| *Rhizoma dioscoreae* | 54.11 | *T. putrescentiae, G. ornatus, Dermatophagoides farinae* |
| *Pseudobulbus cremastrae seu pleiones* | 51.32 | *T. putrescentiae, C. lactis, G. domesticus, A. ovatus* |
| *Rhizoma homalomenae* | 31.23 | *C. lactis, C. berlesei, E. maynei* |
| *Radix aconiti* | 30.15 | *T. putrescentiae, C. lactis, G. domesticus* |
| *Rhizoma chuanxiong* | 41.18 | *T. putrescentiae, Suidasia nesbitti, Suidasia medanensis, C. berlesei* |
| *Bulbus fritillariae cirrhosae* | 36.62 | *G. domesticus, C. lactis, Cologlyplus berlesei* |
| *Radix pseudostellariae* | 28.16 | *T. palmarum, C. berlesei* |
| *Radix ginseng rubra* | 28.13 | *G. domesticus, G. ornatus, B. tropicalis* |
| *Rhiaoma cimicifugae* | 19.48 | *C. lactis, G. ornatus, D. farinae* |
| *Radix salviae miltiorrhizae* | 29.36 | *T. putrescentiae, C. lactis, G. ornatus* |
| *Radix linderae* | 28.36 | *T. putrescentiae, Gohieria fuscus, C. berlesei* |
| *Radix morindae officinalis* | 19.17 | *Tyrophagus putrescentiae, Carpoglyphus lactis, Euroglyphus maynei* |
| *Radix glycyrrhizar* | 18.67 | *L. destructor, C. lactis, C. berlesei* |
| *Rhizoma acori tatarinowii* | 15.47 | *S. nesbitti, S. medanensis, C. berlesei* |
| *Rhizoma bletillae* | 14.31 | *Glycyphagus domesticus, T. putrescentiae* |
| *Rhizoma atkactylodis macrocephalae* | 10.27 | *C. lactis, G. domesticus, Acarus siro* |
| *Radix paeoniae alba* | 16.63 | *G. domesticus, T. putrescentiae* |
| *Rhizoma bletillae striatae* | 15.38 | *T. putrescentiae, Tyrophagus longior, C. lactis* |
| *Radix angelicae dahuricae* | 17.58 | *G. domesticus, C. lactis, G. ornatus* |
| *Radix pulsatillae* | 19.27 | *G. domesticus, Glycyphagus ornatus, C. lactis* |
| *Radix scrophulariae* | 9.83 | *G. domesticus, C. lactis, C. berlesei* |
| *Rhizoma pinelliae* | 15.63 | *T. putrescentiae, T. longior* |
| *Radix rehmanniae* | 18.76 | *C. lactis, G. domesticus, T. putrescentiae* |
| *Radix sanguisorbae* | 17.41 | *C. lactis, C. berlesei, S. nesbitti* |
| *Coritex lycii* | 14.49 | *Lardoglyphus konoi, T. putrescentiae, E. maynei* |
| *Bulbus lilii* | 18.23 | *T. putrescentiae, G. domesticus, Glycyphagus bicaudatus* |
| *Radix angelicae sinensis* | 9.68 | *D. pteronyssinus, T. longior* |
| *Radix saposhnikoviae* | 6.85 | *T. longior, C. lactis, G. domesticus* |
| *Radix ophiopogonis* | 10.71 | *C. berlesei, E. maynei* |
| *Rhizoma atractylodis* | 6.64 | *C. lactis, G. domesticus, Dermatophagoides pteronyssinus* |
| *Radix polygoni multielori* | 5.22 | *C. lactis, A. siro* |
| *Radix isatidis* | 7.85 | *G. domesticus, C. lactis, Tyrophagus palmarum* |
| *Rhizoma anemarrhenae* | 8.97 | *G. domesticus, T. putrescentiae* |
| *Radix adenophorae* | 34.13 | *G. domesticus, D. pteronyssinus* |
| *Radix clematidis* | 24.48 | *T. putrescentiae* |
| *Radix peucedani* | 14.63 | *T. longior* |
| *Radix gentianae macrophyllae* | 16.51 | *T. putrescentiae, E. maynei* |
| *Rhizoma curcumae* | 30.13 | *Lardoglyphus konoi, T. putrescentiae* |
| *Radix platycodi* | 20.62 | *C. lactis, G. domesticus, A. ovatus* |
| *Radix bupleuri* | 21.17 | *C. lactis, G. ornatus* |
| *Radix codonopsis* | 27.93 | *S. nesbitti, S. medanensis, Histiostoma feroniarum* |
| *Radix scutellariae* | 31.43 | *Lepidoglyphus destructor, T. longior* |
| *Radix astragali* | 29.38 | *A. siro, B. tropicalis* |
| *Radix puerariae* | 48.68 | *Gohieria fuscus, A. ovatus, C. berlesei* |
| *Radix asteris* | 25.13 | *D. farinae, D. pteronyssinus, Rhizoglyphus robini* |
| *Rhizoma ligustici* | 26.27 | *G. bicaudatus, G. domesticus, C. lactis, T. palmarum* |

**Table II.** Species of acaroid mites in the stored rhizomatic traditional Chinese medicinal materials

| Genus | Family | Species |
|---|---|---|
| | *Acarus* | *A. siro* |
| | *Tyrophagus* | *T. putrescentiae* |
| | | *T. longior* |
| | | *T. palmarum* |
| *Acaridae* | *Aleuroglyphus* | *A. ovatus* |
| | *Rhizoglyphus* | *R. robini* |
| | *Suidasia* | *S. nesbitti* |
| | | *S. medanensis* |
| | *Cologlyplus* | *C. berlesei* |
| | *Lardoglyphus* | *L. konoi* |
| | *Glycyphagus* | *G. ornatus* |
| *Lardoglyphidae* | | *G. domesticus* |
| *Glycyphagidae* | | *G. bicaudatus* |
| | *Blomia* | *B. tropicalis* |
| | *Lepidoglyphus* | *L. destructor* |
| | | *L. michaeli* |
| | *Gohieria* | *G. fuscus* |
| *Carpoglyphidae* | *Carpoglyphus* | *C. lactis* |
| | *Dermatophagoides* | *D. farinae* |
| *Pyroglyphidae* | | *D. pteronyssinus* |
| | *Euroglyphus* | *E. maynei* |
| *Histiostomidae* | *Histiostoma* | *H. feroniarum* |

## SEASONAL CHANGES OF ACAROID MITES IN THE STORED RHIZOMATIC TRADITIONAL CHINESE MEDICINAL MATERIALS

In order to examine the community fluctuation of acaroid mites in the rhizomatic traditional Chinese medicinal materials in different month, we performed analysis on the average breeding density, diversity, richness index and evenness index in the samples collected in April, January, July and October, respectively, and found highest breeding species richness index and diversity index in July. Yet the average breeding density was highest in October, and maximal uniform index, in April (Table IV).

## SEASONAL CHANGES FOR THE 47 SPECIES ACAROID MITES IN THE STORED RHIZOMATIC TRADITIONAL CHINESE MEDICINAL MATERIALS

By the previous results, we included *Radix et rhizoma rhei, Rhizoma dioscoreae and Pseudobulbus cremastrae seu pleiones* for further investigation through cultivation under artificial environment. The observation showed that *T. putrescentia*, *C. berlesei* and other species of acaroid mites were increased to 53%, 36% and 11%, respectively, after 2-week of cultivation, and the number of *T. putrescentia* climbed to 15.71 individuals/g at week 4 from 12.47 individuals/g at week 2 and peaked at week 8 by 23.63 individuals/g. By 12$^{th}$ week, the number was decreased to 19.54 individuals/g. Cthe number of *C. berlesei* was declined to 5.71 individuals/g at week 8 and zero at week 12 from 8.54 individuals/g at 2$^{nd}$ week.

## DISCUSSION

House dust mites and stored product mites are ubiquitous and wide in species, and in category of Acarida, Oribatida, Aetinedida and Gamasida. Mites belonging to Acarida include 7 families, namely, *Acaridae, Lardoglyphidae, Glycyphagidae, Chortoglyphidae, Carpoglyphidae, Histiostomidae,* and *Pyroglyphidae* (14-18). Acaroid mite is a tiny arthropod widely distributed around the world, most of which live on themselves, feed on organic orts of animals or plants. Their ideal habitats includes grains, Chinese medicinal materials, dry fruits and vegetables in storages, as well as textile fabric and dust in human dwellings (18-20). Distribution and density of this species are commonly affected by rainfall and seasonal change. Emergence of it may be quantity in temperature of 15 °C to 16 °C, particularly in summer and autumn with an average temperature of 29-33 °C and humidity of around 68%-76%. Chao-pin LI (21) once investigate on the composition and

**Table III.** Ecological parameters for acaroid mites in the stored rhizomatic traditional Chinese medicinal materials

| Ecological parameters | Stored rhizomatic traditional Chinese medicinal materials | | | | |
|---|---|---|---|---|---|
| | ***Radix et rhizoma rhei*** | ***Rhizoma dioscoreae*** | ***Pseudobulbus cremastrae seu pleiones*** | ***Radix puerariae*** | ***Rhizoma chuanxiong*** |
| Breeding density | 77.61 | 54.11 | 51.32 | 48.68 | 41.18 |
| Richness index | 1.33 | 1.54 | 2.01 | 0.87 | 1.64 |
| Diversity index | 1.38 | 1.70 | 2.70 | 1.71 | 1.99 |
| Evenness index | 0.92 | 0.90 | 0.94 | 0.94 | 0.92 |

**Table IV.** Seasonal parameter change in acaroid mites community in the stored rhizomatic traditional Chinese medicinal materials

| Month | Average breeding density (No./g) | Richness index | Diversity index | Evenness index |
|---|---|---|---|---|
| January | 6.73 ± 3.25 | 2.145 ± 0.037 | 1.351 ± 0.210 | 0.927 ± 0.041 |
| April | 5.69 ± 3.00 | 1.531 ± 0.115 | 1.073 ± 0.110 | 0.955 ± 0.034 |
| July | 10.35 ± 2.53 | 6.131 ± 0.021 | 3.259 ± 0.082 | 0.811 ± 0.053 |
| October | 11.68 ± 2.21 | 5.509 ± 0.011 | 2.939 ± 0.075 | 0.841 ± 0.022 |

diversity of stored acaroid mites in Anhui province, and found that the average breeding density, species richness and diversity in southern Anhui areas (including Wuhu area) were higher than those of Huaibei Plain, Jianghuai hilly regions, and plain areas in central Anhui.

In order to understand the acaroid mites in rhizomatic traditional Chinese medicinal materials as well as the growth and decline of this species community in different months, such as indexes on the average breeding density, diversity, , richness and evenness in the same storage, we respectively examined the indexes in January, April, July and October, and found that the highest richness index and diversity index were present in July, while the highest average breeding density was in October, and the maximal evenness index in April. Previous studies described that the distribution of acaroid mites was influenced by humity, temperature, illumination, eating habits of the mites, human interference and other factors (22-24), which were identical to our results that the acaroid mites bred in large quantity in the storages, because of the average relative humidity being 75.6% and mean temperature being 31 °C in July. Besides, the storages sampled were in closure for long time without excellent ventilation and air exchange as well as planned cleaning. Although sampling in October, when the temperature and humidity remained at 25 °C and 66%, demonstrated relative decline of richness and diversity of the acaroid mites, yet the density was maximal. This may be associated with long breeding season, for the mites don't breed until the autumn after female acaroid mites lay their eggs in summer. Even if lower temperature in Spring doesn't favor to the breeding of acaroid mites, those with lower need of temperature and humidity , such as *T. putrescentiae*, can still easily live and breed. This is why our results demonstrated the highest evenness of the mites in April. As discussed above, we concluded that the average breeding density, diversity index, and richness index of the community as well as evenness index are closely related to humiture without considering the human and food factors, since higher indexes of average density, evenness and diversity were observed in samples collected in summer and autumn seasons. Whereas the acaroid mites would exist in hypopus when the temperature and humidity are unfavorable to its breeding (25).

Relatively higher average breeding density of acaroid mites was found in *Radix et rhizoma rhei, Rhizoma dioscoreae, Pseudobulbus cremastrae seu pleiones*, *Radix puerariae*, and *Rhizoma chuanxiong*, in which *T. putrescentiae* and *C. berlesei* are predominant. In order to understand change patterns, particularly the living habits and living environment for *T. putrescentiae* and *C. berlesei*, we cultivated *Radix et rhizoma rhei, Rhizoma dioscoreae and Pseudobulbus cremastrae seu pleiones* in the laboratory by artificially setting the temperature at 20 °C and humidity at 76%. Sampling by every other two weeks showed that the number of *C. berlesei* were decreasing, while *T. putrescentiae* continued to breed and peaked at 8$^{th}$ week when the number of species was in saturated state. Subsequently the number of *T. putrescentiae* was declined somewhat at week 10 and week 12 as a result of emerging of other species that led to insufficient food supply in the same community. These changes are involved in the living habits of acaroid mites and interspecies predominance, because only one predominant species of mites can survive in the same community, and distinctly affect the community population and environment. Besides, higher quantity of emerged mites would lead to higher biomass and stronger survival in the stored materials, eventually resulting in restraining other species of mites from breeding (26-28). However, as *Cheyletus eruditus*, the predator of acacoid mites breeding to a certain quantity emerges, the community will be dynamically balanced (29,30).

Our work suggests that acaroid mites breed extensively in stored rhizomatic traditional Chinese medicinal materials in Anhui province, and their quantity is large in *Radix et rhizoma rhei, Rhizoma dioscoreae, Pseudobulbus cremastrae seu pleiones* and *Radix puerariae. G. domesticus* and *T. putrescentiae* were detected in the traditional Chinese medicinal materials of root-stock origins. Higher richness index, diversity index and breeding density of acaroid mites seen in July showed that breeding of this species are affected by humiture. We observed the growth and decline of *C. berlesei* and *T. putrescentiae* under artificial circumstances, and found a sharp decline in the number of *C. berlesei,* while the number of *T. putrescentiae* tended to grow before decrease. Although this tendency may be associated with changes in the local environment and climate, yet it remains further investigation.

The species of acaroid mites in the samples may be over our real recordings, because we exclusively identified part of the samples and left other species uncounted. Besides, it is hard to completely isolate entire mites from the samples. The breeding density of sampled mites was represented by the number of mites in the overall samples, and calculated indirectly in proportional samples, for which only mirrors the gross breeding density in various samples. Nevertheless, previous studies indicated that acaroid mites would move and spread around when their breeding density increases to a certain extent in stored rhizomatic traditional Chi-

nese medicinal materials. Migration of the mites tends to spread various microorganisms like bacterium and fungus. Therefore, the dust and the herbal residues in storages should be well deposited in order to prevent transmission of acaroid mites.

In conclusion, we conducted a preliminary investigation on the species, density and diversity of acaroid mites breeding in the stored rhizomatic traditional Chinese medicinal materials. These findings may be additional data for systematic research on the mites in stored products, and supply theoretical evidences for prevention and control of the acaroid mite contamination in the stored rhizomatic traditional Chinese medicinal materials.

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Nutrición Hospitalaria

Trabajo Original

Otros

# *Trematode Aspidogastrea* found in the freshwater mussels in the Yangtze River basin

## Trematodos Aspidogastrea *encontrados en los mejillones de agua dulce en la cuenca del río Yangtze*

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## Abstract

**Objective:** To investigate the prevalence of trematode Aspidogastrea in the freshwater mussels in the Yangtze River basin within Anhui province, China.

**Methods:** We initially harvested the freshwater mussels living in the Yangtze River running through Anhui area, and labeled them with corresponding number. Then the samples were dissected for isolating the flukes, which were identified by conventional staining.

**Results:** Infection rate of trematode Aspidogastrea in freshwater mussels in the Yangtze River basin within the territory of Anhui province was 30.38% (103/339) in general, and a total of 912 flukes of Aspidogastrea were detected in the 103 mussels, with average infection rate of 8.85 for each mussel.

**Conclusion:** Trematode *Aspidogastrea* is prevalent in the freshwater bivalves living in the Yangtze River basin running through Anhui area, and the treamatode was identified as *Aspidogaster* sp. belong to *Aspidogaste* under Aspidogastridae of Aspidogastrea.

**Key words:**

Freshwater mussels. Aspidogastrea. Trematode.

## Resumen

**Objetivo:** investigar la prevalencia de trematodos *Aspidogastrea* en mejillones de agua dulce en la cuenca del río Yangtze en la provincia de Anhui, China.

**Métodos:** se recogieron mejillones de agua dulce en el río Yangtze a su paso por la provincia de Anhui y se etiquetaron con su número correspondiente. Posteriormente se disecaron para aislar los trematodos por medio de tinción convencional.

**Resultados:** la tasa de infección de trematodos en mejillones de agua dulce en la cuenca del río Yangtze, en el territorio de la provincia de Anhui fue 30,38% (103/339), en general, y un total de 912 trematodos fueron detectados en 103 mejillones, con tasa promedio de infección de 8,85 por cada mejillón.

**Conclusión:** el trematodo *Aspidogastrea* es frecuente en los bivalvos de agua dulce que viven en la cuenca del río Yangtze, en la región de Anhui, y el trematodo fue identificado como *Aspidogaster* sp. pertenecen a la familia *Aspidogaste* bajo el género Aspidogastridae de Aspidogastrea.

**Palabras clave:**

Mejillones de agua dulce. *Aspidogastrea*. Trematodo.

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## INTRODUCTION

The Aspidogastrea, a small group of flukes belonging to the Trematoda, are parasites of freshwater and marine molluscs or vertebrate host, and were reported in the mussels in Fujian province and Heilongjiang areas of China (1,2). However, few reports are available on aspidogastrean infection with the freshwater mussels living in the Yangtze River basin running through Anhui province of China. In order to investigate the prevalence of Aspidogastrea, we conducted a survey in April of 2014 on the freshwater mussels living in the Yangtze River basin across Anui area. This paper was undertaken to report our findings.

## MATERIALS AND METHODS

### SAMPLE COLLECTION

The sample species of freshwater bivalves were collected from areas of Anqing, Chizhou, Tongling, Chaohu, Wuhu and Ma'anshan, the coastal cities along the Yangtze River across Anhui province. All bivalve mollusks, regardless of male or female, were wild growth with a life of 3 to 5 years. The samples were labeled with number and sampling location, and brought back to the laboratory for examination.

### ISOLATING THE TREMATODE

The instrument and tools for isolation of the flukes included dissecting microscope, wax disc, scalpels, scissors and small-sized tweezers. Isolation of the flukes was performed by: a) opening the bivalve in the wax disc with a scalpel cutting through the occlusor; b) the soft bodies, visceral mass, were totally separated from either inner valve and placed onto the plate; c) the mantle was stripped with a scalpel under the microscope and the pericardial cavity was cut open; d) the fluke detected was transferred with a sucker into another small dish containing small amount of clean water; and e)sufficient amount of saline was added into the dish to rinse the species by gently shaking it. The flukes were counted by individual bivalve mollusks and preserved in 70% alcohol for following identification.

### SPECIMEN PREPARATION

Specimens were prepared in accordance with the technique by Chaopin Li (2008) (3), and cleansed and stained in the carmalum. After initial decolorization with 1% hydrochloric acid solution, the specimens were rinsed in clean water, and then subjected to gradient elution in alcohol and dehydration in 70% alcohol. When pressed to flat and thin, the specimens were fixed with Bowen's fixative, and gradiently dehydrated till concentration of 95% alcohol (repeated staining may be required as appropriate). After final twice dehydration in 100% alcohol, the specimens were treated with wintergreen oil and transferred onto the slide that was mounted with Canada balsam after adjusting the posture, and dried in a thermostat cabinet for following use. The flukes were measured by unit of millimeter, and all samples were preserved in the Department of Medical Parasitology, Wannan Medical College.

### IDENTIFICATION OF THE SPECIES

The parasite species were morphologically identified under a microscope or dissecting microscope, with reference to related literatures (2,4,5).

## RESULTS

### TREMATODE INFECTIONS

Of the 339 freshwater mussels collected, 103 were infected with aspidogastrean species, and the infection rate was 30.38%. A total of 912 aspidogastreans were recovered from the 103 mussels infected, in which the number in each individual varied from 2 to 61, with an average of 8.85 flukes. The aspidogastreans isolated from the bivalve mollusks comprised larvae and adults in which large number of eggs was seen.

### ADULT MORPHOLOGY

Under stereomicroscope, the live adult aspidogastreans present with light red color tegument and active telescopic swimming. The fluke specimens are laterally expanded ton an oval to oblong shape, and the body size varies a lot for each individual. The mouth is located at the anterior tip of the body and trumpet-shaped. The pharynx presents with oval shape, followed by a single tubular intestinal caecum that extends to the posterior body end. The testis is found in the middle body approximately posterior to the ventral side, where a spermatic duct runs into the cirrus sac that is placed in the middle line at the anterior edge of ventral sucker, and the penis occurs in the cirrus sac. The ovary arises anteriorly at the testis and is ovally shaped. The vitellarium presents with follicular figure and posteriorly arranges at either side of the body. The ventral disc, shaping like a shield plate, extends along most of the body by ventral aspect.

### IDENTIFICATION OF ASPIDOGASTREA

We conducted an identification on the Aspidogastrea in terms of its morphology and classification referring to Faust and Tang (1936) (5), and recognized that this species belongs to *Aspidogaster* under the Aspidogastridae of subclass Aspidogastrea, by currently naming it as *Aspidogaster* sp. due to few information is available.

## DISCUSSION

Although the Aspidogastrea is small group of flukes comprising only two subclasses Aspidogastrea and Digenea, and appears to be archaic species of freshwater bivalves. None of the species has any economic importance, but the group is of very great interest to biologists in research of the evolution of parasites (4). Previous literatures reported the distribution of Aspidogastrea in areas of Fujian, Heilongjiang, Hubei and Sichuan, China, and that Aspidogaster conchicola is most prevalent in Fuzhou area, and hosted generally in the pericardial cavity of mussel (1,2,6,7). The freshwater bivalve mollusks are the most optimal host of the Aspidogastrea. Tang Zhongzhang (1980) described six species of Aspidogastrea in China, including *Aspidogaster conchicola Baer* (1827), *Aspidogaster amurensis* Achmerov (1956), *Aspidogaster ijimai* Kawamura (1913), *Aspidogaster indica* Dayal (1943), *Cotylaspis sinensis* Faust and Tang (1936), and *Lophotaspis orientalis* Faust and Tang (1936) (4). The site that flukes parasitize in a host is primarily associated with pericardial cavity of the freshwater bivalves, yet the infection occasionally occurs in the kidney (2,4). Apart from the hosts of Aspidogastrea previously described, Yao et al. (1996) found that the water-snail, intermediate host of *Schistosoma japonicum,* was infected with Aspidogastrea (8), and Wei et al. (2001) once recovered the *Aspidogaster chongqingensis* in the body of *Spinibarbas sinensis* (6).

The Yantze River in Anhui areas start from the outlet of Poyang Lake of Jiangxi province and runs a total of 416 km through the coastal cities of Anqing, Chizhou, Tongling, Wuhu and Ma'anshan, where are the subtropical transition zone with adequate light, mild climate, abundant rainfall and distinct four seasons. Sufficient water resources, various landform and soils in the basin along the Yangtze River make it possible for the aquatic lives to grow in large quantity, including a variety of snails and bivalves. The mussels used in our experiment are mostly occurring in the rivers, lakes and pools in those areas, and our investigation showed that the freshwater bivalves living in Yangtze River basin are infected with aspidogastrean species, which belongs to *Aspidogaster* of Aspidogastridae under Aspidogastrea. Although the species remains accurate identification, our findings will fill the gaps in research of the trematode Aspidogastrea in the basin of the Yangtze River in Anhui, and supply valuable information for policies in freshwater aquaculture, including freshwater bivalve mollusks and pearls.

Wang Lizhen (1995) conducted a survey on the Aspidogastrea infection with mussels living in the Lake Dian (in Yunnan province of China), and found that the pericardial cavity of mussels were infected with aspidogastrean species in large quantity and death of the bivalves was attributed to the existence of such parasites (9). However, our results showed that the freshwater mussels can lively survive the infection, though more than 300 aspidogastreans were detected in individual bivalve. What exactly leads to the death of the freshwater mussels remains further investigation.

The Aspidogastrea detected in the freshwater bivalves collected in the basin of the Yangtze Rive in Anhui areas is preliminarily identified in terms of the classification by Liu et al. (10) as *Mollusca, Bivalvia, Unionida, Unionidae, Anodontinae, Anodonta*. We found that both larvae and adults were omnipresent in the mussels, suggesting that the mussels may potentially re-infect with the flukes.

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Trabajo Original

Otros

# Diet and liver apoptosis in rats: a particular metabolic pathway

*La dieta y la apoptosis hepática en ratas: una ruta metabólica particular*

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## Abstract

**Introduction:** Various studies have indicated an association between modification in dietary macronutrient composition and liver apoptosis.

**Objective:** To explain how changes in metabolic pathways associated with a high-protein, high-fat, and low-carbohydrate diet causes liver apoptosis.

**Methods:** Two groups of rats were compared. An experimental diet group (n = 8) using a high-protein (59.46%), high-fat (31.77%), and low-carbohydrate (8.77%) diet *versus* a control one (n = 9) with American Institute of Nutrition (AIN)-93-M diet. Animals were sacrificed after eight weeks, the adipose tissue weighed, the liver removed for flow cytometry analysis, and blood collected to measure glucose, insulin, glucagon, IL-6, TNF, triglycerides, malondialdehyde, and β-hydroxybutyrate. Statistical analysis was carried out using the unpaired and parametric Student's t-test and Pearson's correlation coefficients. Significance was set at $p < 0.05$.

**Results:** Animals from the experimental group presented less adipose tissue than dose of the control group. Percentage of nonviable hepatocytes in the experimental group was 2.18 times larger than the control group ($p = 0.001$). No statistically significant differences were found in capillary glucose, insulin, glucagon, IL-6, or TNF-α between two groups. Plasmatic β-hydroxybutyrate and malondialdehyde of the experimental group expressed higher levels and triglycerides lower levels compared with the control group. The results show a positive and significant correlation between the percentage of nonviable hepatocytes and malondialdehyde levels ($p = 0.0217$) and a statistically significant negative correlation with triglycerides levels ($p = 0.006$).

**Conclusion:** Results suggest that plasmatic malondialdehyde and triglyceride levels are probably good predictors of liver damage associated with an experimental low-carbohydrate diet in rats.

**Key words:**

Apoptosis.
Gluconeogenesis.
Liver damage.
Ketogenic diet.
Nutrition.

## Resumen

**Introducción:** varios estudios han indicado una asociación entre la modificación de la composición de macronutrientes de la dieta y la apoptosis hepática.

**Objetivo:** el objetivo fue explicar cómo los cambios en las rutas metabólicas provoca la apoptosis hepática.

**Métodos:** se evaluó un grupo de 17 ratas. Un grupo (n = 8) con dieta experimental: proteínas (59,46%), grasas (31,77%) e hidratos de carbono (8,77%) y otro (n = 9) con dieta control (AIN-93-M). Los animales se sacrificaron después de ocho semanas, y se pesó el tejido adiposo, se retiró el hígado para su posterior análisis por citometría de flujo, y en la sangre recogida se midieron glucosa, insulina, glucagón, IL-6, TNF, triglicéridos, malondialdehído y β-hidroxibutirato. El análisis estadístico utilizó la prueba t no pareada y paramétrica de Student, y la correlación de Pearson; significación se fijó en $p < 0,05$.

**Resultados:** no se encontraron diferencias estadísticamente significativas en la glucosa capilar, insulina, glucagón, IL-6, TNF-α o en el grupo de la dieta experimental frente al control. El β-hidroxibutirato y malondialdehído se expresaron en los niveles más altos y los triglicéridos en los niveles más bajos en el grupo experimental. El porcentaje de células no viables en el grupo de dieta experimental era 2,18 veces mayor que la del grupo control. Había menos tejido adiposo de ratas alimentadas con la dieta experimental que la dieta control. Los resultados muestran una correlación positiva y significativa entre el porcentaje de células viables y malondialdehído y una correlación negativa estadísticamente significativa con los triglicéridos.

**Conclusión:** malondialdehído y los niveles de triglicéridos en plasma son probablemente buenos predictores de daño hepático.

**Palabras clave:**

Apoptosis.
Gluconeogénesis.
Daño en el hígado.
Dieta cetogénica.
Nutrición.

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*Institutional review board statement: The study was authorized and approved by the Director of Nutrition College of Fluminense Federal University and by the professor responsible for the Experimental Nutrition Laboratory of the same institution.*

*Institutional animal care and use committee statement: The study received prior approval by the Institutional Review Board for Animal Research (CEUA), Fluminense Federal University, case number 648, February 27, 2015. It was designed based on the determinations of the Brazilian law for research with animals (law number 11.794, October 2008).*

*Animal care and use statement: The animal protocol minimized pain and discomfort to the rats.*

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## INTRODUCTION

Various studies have indicated an association between modification in dietary macronutrient composition and liver apoptosis, but the exact mechanism in the development of apoptosis under these circumstances is not entirely understood (1-4).

Apoptosis is an innately programmed process responsible for the death of unwanted cells. It occurs mainly during embryogenesis or in tissues with the capacity for regeneration such as the liver (5). Senescent and mutagenic cells that have completed their mission are eliminated by apoptosis, and new cells are formed when necessary to replace them (6). Dysregulation occurs when the regenerative capacity is lower than the apoptosis rate, and the physiological pathway becomes pathological.

Apoptosis leads to the development of numerous diseases such as cancer, autoimmune diseases, viral or bacterial infections, alcoholic liver disease, viral hepatitis, cholestatic liver disease, hepatocellular carcinoma, Wilson's disease, and nonalcoholic steatohepatitis (5).

There are two forms of triggered apoptosis. The first is mediated by agents that penetrate the cell directly, and the second occurs with the participation of mediators like tumor necrosis factor (TNF) (1). Heat shock, stress, free radicals, ultraviolet radiation, drugs, synthetic peptides, toxins, and numerous enzymes are examples of agents in the first process (6). Zhang et al. demonstrated for the first time that apoptosis was induced by TNF-$\alpha$ in an *in vitro* steatotic hepatocyte model (1).

Cells are complex genetic machines that once activated directly or indirectly enter into an apoptotic cycle. The cycle begins with the activation of a caspase –a cysteine protease that mediates intracellular proteolytic cascade and cleaves the cellular substrate and activates transcription factors (7). Once active, the transcription factors engender the expression of specific genes that determine the production of pro-apoptotic and anti-apoptotic factors (5).

In liver, excess fatty acid mobilization or lipid transport leads to apoptosis. Palmitate, a saturated fatty acid, has well-studied lipotoxic effects. The inability to convert fatty acid to triglycerides raises the risk of hepatocyte apoptosis and can probably be avoided by the use of an antioxidant. Hepatocytes are injured because the liver receives more fatty acids than can be oxidized or transported by VLDL (8-11). Hepatocyte damage begins with modification in mitochondrial morphology from fission to fusion, which decreases cellular adenosine triphosphate (ATP) levels and increases reactive oxygen species (ROS) (12).

Oxidative stress results from an imbalance between substances that promote oxidation and others with antioxidant effects; the consequence is a cellular lesion when pro-oxidants predominate (13). ROS are pro-oxidant substances that are responsible for intracellular lipid peroxidation that produces malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE). It alters the protein, lipid, polysaccharide, and DNA synthesis (14,15).

The objective of this study is to discuss if and how modifications in a metabolic pathway due to a high-protein, high-fat, and low-carbohydrate diet can increase liver damage.

## METHODS

### ANIMALS

The study received prior approval by the Institutional Review Board for Animal Research (CEUA), Fluminense Federal University, case number 648, February 27, 2015. The study was conducted in the Experimental Nutrition Laboratory of the School of Nutrition, Fluminense Federal University (UFF), Niterói, RJ, Brazil. Animals were obtained from the Laboratory Animal Facility of the Oswaldo Cruz Foundation, Ministry of Health, Rio de Janeiro, Brazil.

After five days of adaptation, the rats were separated into two groups: the control diet group (CDG) (n = 9) and the experimental diet group (EDG) (n = 8). They were housed in individual polypropylene cages with controlled temperature (24 ± 2 °C) and humidity (60 ± 10%) and an alternating light-dark cycle (06:00 AM to 18:00 PM and 18:00 PM to 06:00 AM).

### DIETS

Pragsoluções Biociências Comércio e Serviços, LTD, Jaú, São Paulo, Brazil handled the preparation of the diets. The control diet (AIN-93-M) had the following composition: carbohydrate (76.98), protein (13.56), and fat (9.46%). The experimental diet was based on the Atkins formula, with carbohydrate (8.77%), protein (59.46%), and fat (31.77%). Tert-butylhydroquine was calculated as 0.002 mg/1 g fat. The diets had the same amounts of vitamins, minerals, L-cystine, choline, and fiber, based on AIN-93-M specifications (16). The animals received diet and water ad libitum for eight weeks.

### EXPERIMENTAL PROCEDURES AND SAMPLE COLLECTION

The estrous cycle phase was investigated, and animals in estrus were separated and fasted for eight hours. The animals were anesthetized by intraperitoneal injection of a solution containing 11.5 mg/100 g body mass of ketamine and 0.1 mg/100 g body mass of xylazine (17).

A capillary blood sample was drawn from the tails and blood samples from cardiac puncture. Samples were separated into two tubes: one with sodium heparin and the other with 0.7% EDTA with 4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride (AEBSF) 1 mg/mL of blood from Sigma-Aldrich, USA. The blood was centrifuged for 20 minutes at 314 rad.s-1 and stored at -80 °C for analysis.

The livers were removed and washed with saline solution, and flow cytometry analysis was performed immediately using the FITC Annexin V Apoptosis Detection Kit I components: 10X Annexin V Binding Buffer; FITC Annexin V; Propidium Iodide Solution from BD Pharmingen™; and flow cytometer FACF-CALIBUR BD model.

Intra-abdominal adipose tissue was carefully removed and weighed with a BioPrecisa® precision scale.

## ANALYTIC METHODS

Capillary blood samples were collected for glucose measurement using the handheld Johnson & Johnson OneTouch®, Ultra Mini™ meter. Plasma triglycerides in heparinized tubes were measured using automatic analysis (Vitalab Selectra E) with commercial kits from BioSystems Reagents & Instruments in the Multidisciplinary Research Support Laboratory (LAMAP), School of Medicine, UFF, Niterói, RJ, Brazil. The β-hydroxybutyrate and MDA in heparinized tubes were measured using the Beta-Hydroxybutyrate (beta HB) Assay Kit (ab83390) and Lipid Peroxidation (MDA) Assay Kit (ab118970), respectively, from Abcam®, USA. The plasma was filtered through 10 kDa Spin Filter (ab93349) from Abcam®, USA, to remove interfering substances, and quantified colorimetrically for MDA $\lambda = 532$ nm and β-hydroxybutyrate $\lambda = 450$ nm with a SpectraMax Plus 384 Microplate Reader. The analyzes were done at the Multidisciplinary Research Support Laboratory, School of Medicine, UFF, Niterói, RJ, Brazil. Insulin, glucagon, IL-6, and TNF-α in EDTA tubes were measured using Multiplex Biomarker Immunoassays for Luminex xMAP technology (Millipore, Billerica, MA, USA) lot number 2634193. Measurements were performed three times. The analyses were performed at the Specialized Laboratory for Clinical Analyses, São Paulo, Brazil.

## STATISTICAL ANALYSIS

Data are presented as means ± standard deviations. Differences between the groups were analyzed using the Student's t-test, and the values were considered unpaired and parametric. An F-test was used to compare variances. Correlations between MDA and triglycerides and nonviable liver cells were analyzed with Pearson's correlation coefficient. Statistical significance was set at $p < 0.05$. The software package was GraphPad-Prism version 6.0e for Mac OS X, 2015.

## RESULTS

No statistically significant differences were found between the groups for capillary glucose, insulin, glucagon, IL-6, or TNF-α. The β-hydroxybutyrate and MDA were expressed at the highest levels ($p = 0.001$ and $p = 0.009$, respectively) and triglycerides at the lowest levels ($p = 0.005$), in the experimental group. The percentage of nonviable cells in the experimental diet group was 2.18 times that of the control group ($p = 0.001$) (Table I).

The adipose tissue of rats fed on the experimental diet weighted less than the adipose tissue of rats that received the control diet. Mean EDG weight was 6.926 ± 1.118 g and mean CDG weight was 12.10 ± 1.849 g ($p = 0.0339$).

The results show a positive and significant correlation between the percentage of nonviable cells and MDA nmoL/mL levels (95% confidence interval, $p = 0.0217$) and a statistically significant negative correlation with triglycerides (TGA) mg/dL ($p = 0.006$) (Fig. 1).

## DISCUSSION

Although the macronutrients composition of the experimental diet is not adequate for rats, it is carbohydrate content that regulates gluconeogenesis (18). Pichon et al. considered carbohydrate levels the most important factor in lipid metabolism (19) (Fig. 2).

The results showed no statistically significant differences in glucose, insulin, or glucagon levels between the groups. The glucose levels are preserved by gluconeogenesis (20). Low insulin and high glucagon may not occurs when gluconeogenesis is associated with high protein amounts that increases the secretion of insulin and glucagon (21-23). Our results are similar to the datas observed by Blouet et al. (23). Bielohuby et al. found low fasting glucose and low insulin levels associated with low carbohydrate and protein, and high fat diet (24). Westman et al. reported lower glucose, insulin, and C-peptide in humans receiving high fat versis high carbohydrate diet (20).

**Table I.** Results of analytical methods and flow cytometry

| Data | EDG* | CDG** | p‡*** |
|---|---|---|---|
| Glucose (mg/dL) | 83.00 ± 3.746 | 85.22 ± 3.398 | 0.666 |
| Insulin (pg/mL) | 1207.75 ± 300.7 | 1451.78 ± 308.6 | 0.582 |
| Glucagon (pg/mL) | 40.68 ± 17.89 | 43.50 ± 15.35 | 0.906 |
| IL-6 (pg/mL) | 174.00 ± 54.54 | 151.00 ± 33.11 | 0.717 |
| TNF-α (pg/mL) | 6.80 ± 0.6866 | 6.56 ± 0.7203 | 0.812 |
| β-hydroxybutyrate (nmoL/mL) | 11.32 ± 1.127 | 4.06 ± 1.472 | 0.001# |
| MDA† (nmoL/mL) | 13.18 ± 1.386 | 7.63 ± 1.225 | 0.009# |
| TGA (triglycerides) (mg/dL) | 51.00 ± 4.645 | 104.00 ± 14.82 | 0.005# |
| Inviable cells‖ (%) | 29.29 ± 2.41 | 13.40 ± 1.59 | 0.001# |

**Experimental diet group n = 8; **Control diet group n = 9; ***Each value expressed as mean ± SD with statistical signficance p < 0.05; and †Malondialdehyde; ‖Corresponds to % apoptosis + % non-apoptotic death; #Statistical significant.*

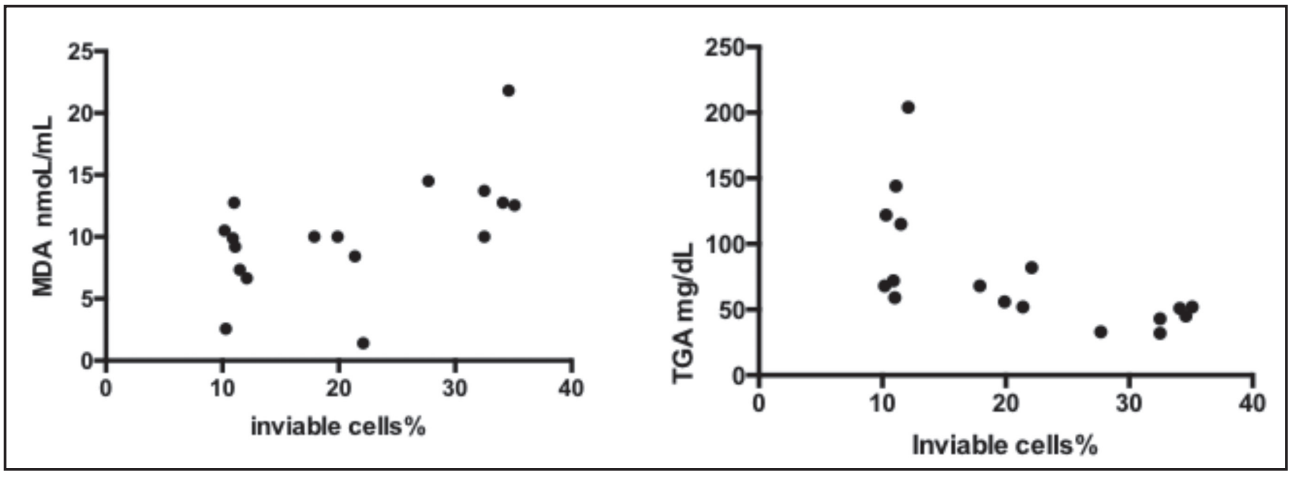


**Figure 1.**

Pearson's correlation coefficient between: MDA and inviable cells with r = 0,5517, $R^2$ = 0,3044 and p = 0,0217 and TGA and inviable cells with r = - 0,5956, R = 0,3548 and p = 0,0056.

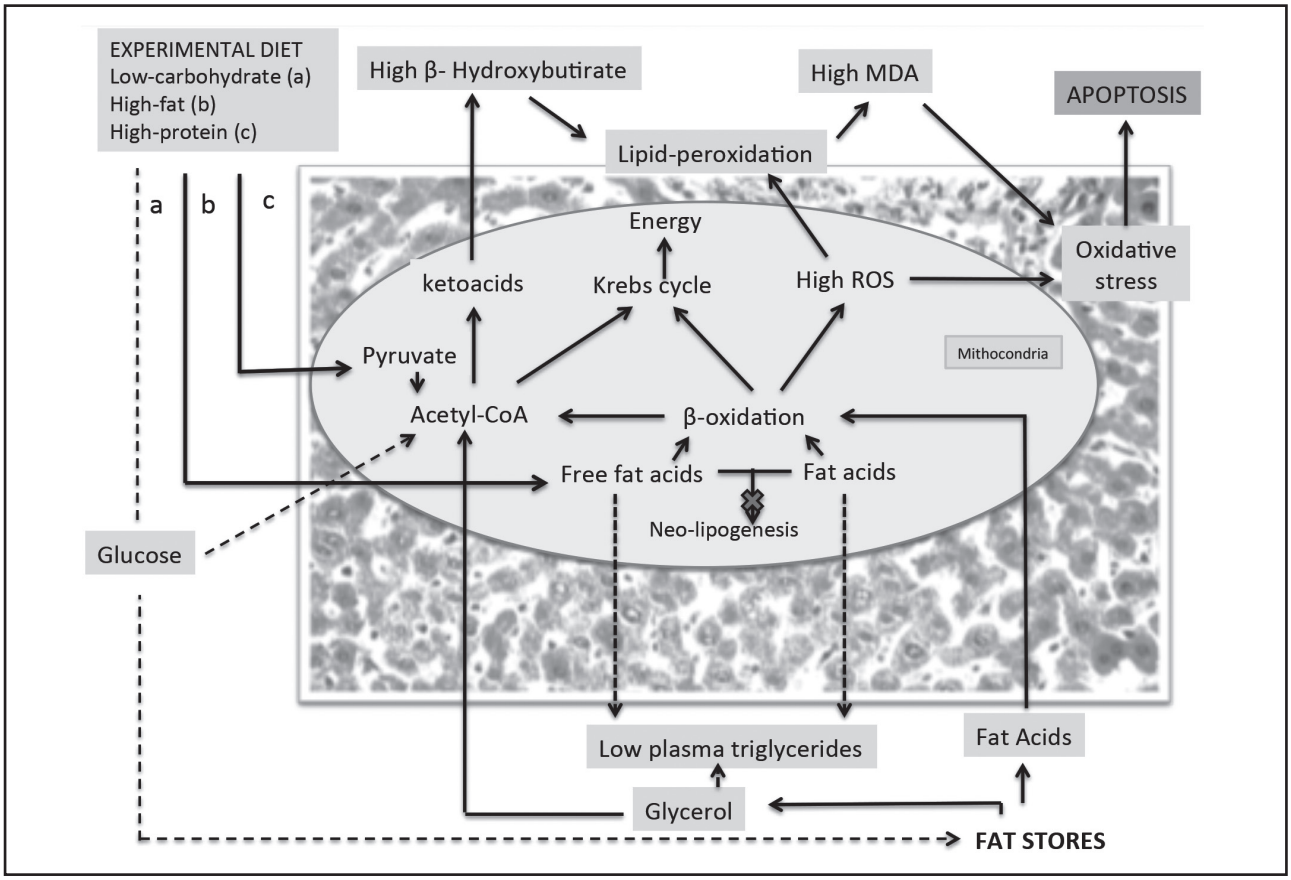


**Figure 2.**

The metabolic pathway responsible for hepatic damage associated with low-carbohydrate diet, high protein and high fat diet.

Corroborating previous studies, the adipose tissue weight was lower in the experimental diet than in the control (19,21,23,25,26). Low-carbohydrate decreased fat reserves and high-protein increased energy expenditure as protein needs more energy for digestion and metabolism (26,27). In adipose tissue, the lipolysis of triglyceride occurs with the supply of glycerol that will be converted to glucose, and fatty acids (28). In the liver, the fatty acids enter in the mitochondria, but are not stored as triglycerides, in the cytoplasm, because lipogenesis is inhibited (10,21,29). Botion et al. showed that rats fed with high-protein and carbohydrate free diet had a reduction of fat acids synthesis and low triglycerides in liver and plasma (30). Monteiro et al. demonstrated that hepatic steatosis was not found in rat livers that received high-fat, high-protein and low-carbohydrate diet. The diet composition was the same as the present work (31).

The plasma triglyceride levels in the present work are lower in the experimental group than the controls (Fig. 2). Kennedy et al. reported decreased plasma and hepatic triglycerides associated with a low-carbohydrate diet in rats fed on a ketogenic diet (32). Westman et al. conducted a thematic review with humans and found similar results (20).

In the mitochondria, fatty acids from the adipose tissue and the high-fat diet are broken down to produce energy through β-oxidation. When the concentration of acetyl-CoA is elevated, it is converted to ketoacids that can be used as fuel for the brain, muscle, and heart (33). The pyruvate formed by an excess supply of amino acids from a high-protein diet enters the hepatocytes by a carrier-mediated transport. In the mitochondria, the pyruvate is converted to oxalacetate that may take two metabolic pathways –one to glucose be formed (the main one) or another to acetyl-CoA. When the offer of amino acids is elevated the second pathway becomes the mainly one (34). These data confirm this: the β-hydroxybutyrate level was 2.7 times higher in the experimental diet group than controls. This result supports the conclusion that gluconeogenesis is the main metabolic process and that low-carbohydrate diet is a ketogenic diet.

Kim et al. reported that when β-oxidation is abnormal (uncontrolled), levels of intermediate products increase and lead to inadequate energy production with a decrease in the NAD/NADH ratio and ATP. Consequently, lipid peroxidation occurs. This biochemical cascade leads to cellular membrane damage via the formation of reactive oxygen species (ROS), causing mitochondrial damage, oxidative stress and apoptosis (35). The elevated levels of β-hydroxybutyrate are another cause of lipid peroxidation and its consequences (36).

In our research the plasma MDA levels were higher in experimental diet *versus* the AIN-93M diet demonstrating the presence of lipid peroxidation (Fig. 2). The current study showed a positive correlation between the percentage of nonviable liver cells (apoptosis + non-apoptotic death) and MDA levels and a negative correlation with TGA levels (Fig. 1). This result suggests plasma MDA and triglycerides as probable indicators of hepatocyte damage.

Malondialdehyde (MDA) may reach distant tissues and extend cellular damage causing an increase in pro-inflammatory cytokines such as IL-6 and TNF-α (14). Here, plasma IL-6 and TNF-α levels did not differ significantly between the two groups. Oarada et al. found similar results when they fed rats on a low-carbohydrate, high-protein diet (37). Ellenbroek et al. showed that rats receiving a low-carbohydrate diet for 12 weeks had increased plasma IL-6. The diet in this study consisted of low protein and high fat (93.1%) (38).

In conclusion the metabolic pathway leads to modifications on plasma MDA and triglycerides doing them indicators of liver damage in rats fed with an experimental Atkins-type diet containing 59.46% of protein, 31.77% of fat and 8.77% of carbohydrate.

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Revisión

# Los antioxidantes en el proceso de patologías oculares

## The antioxidants in the process of ocular pathology

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## Resumen

**Introducción:** la influencia de los antioxidantes en los procesos oculares ha tomado en los últimos años una relevancia importante por sus efectos en la salud visual. El estrés oxidativo es un factor implicado en el desarrollo de las principales patologías tales como cataratas, glaucoma y degeneración macular asociada a la edad (DMAE).

**Objetivo:** establecer la evidencia científica que existe sobre los distintos tipos de antioxidantes y sus efectos en procesos patológicos oculares mediante una revisión sistemática.

**Métodos:** búsqueda bibliográfica en MEDLINE, Scielo y Cochrane de estudios que evalúan la utilización de antioxidantes en la prevención y/o tratamiento de las enfermedades oculares. Se seleccionaron ensayos clínicos controlados y aleatorizados publicados en los últimos 7 años.

**Resultados:** la relación entre distintos tipos de antioxidantes, vitamina E, C, betacaroteno, zinc, luteína, antocianinas y carotenoides, sugiere una relación positiva ante el riesgo y progresión de DMAE y parámetros del glaucoma, indicando un menor riesgo de la enfermedad ante un mayor consumo de antioxidantes en la dieta. Informes iniciales sugieren un papel potencial para la modificación de la dieta en el tratamiento de la degeneración macular asociada a la edad y glaucoma principalmente, no evidenciándose para la prevención de la catarata.

**Conclusiones:** promover el consumo adecuado de antioxidantes en la dieta puede prevenir y proteger frente a patologías oculares de gran prevalencia. Los antioxidantes del grupo de vitaminas son los más estudiados hasta el momento en las patologías oculares. Es necesario llevar a cabo más ensayos clínicos para establecer de forma más precisa estas relaciones.

**Palabras clave:**

Antioxidante. Glaucoma. Degeneración macular. Cataratas. Eficacia.

## Abstract

**Introduction:** The influence of antioxidants on ocular processes has taken on a significant importance in recent years for its effects on visual health. Oxidative stress is a factor involved in the development of major pathologies such as cataracts, glaucoma and age-related macular degeneration (AMD).

**Objective:** To establish the scientific evidence that exists about the different types of antioxidants and their effects on ocular pathological processes through a systematic review.

**Methods:** Literature search in MEDLINE, Scielo and Cochrane for studies evaluating the use of antioxidants in the prevention and/or treatment of eye diseases. Selected randomized controlled clinical trials over the past 7 years were selected.

**Results:** The relationship between different types of antioxidants, vitamin E, C, beta carotene, zinc, lutein, anthocyanins and carotenoids, suggests a positive relationship with the risk and progression of AMD and glaucoma parameters, indicating a lower risk of the disease due to an increased consumption of antioxidants in the diet. Initial reports suggest a potential role for diet modification in the treatment of age-related macular degeneration and glaucoma primarily, not evidencing for the prevention of cataract.

**Conclusions:** Promoting adequate consumption of antioxidants in the diet can prevent and protect against highly prevalent eye diseases. The antioxidants of the group of vitamins are the most studied so far in the ocular pathologies. More clinical trials are needed to establish these relationships more precisely.

**Key words:**

Antioxidant. Glaucoma. Macular degeneration. Cataract. Effectiveness.

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## INTRODUCCIÓN

Los problemas oculares presentan grandes complicaciones en la calidad de vida y aumentan las situaciones de dependencia. En el mundo hay aproximadamente 285 millones de personas con discapacidad visual. Entre las patologías oculares más importantes destacamos el glaucoma, que ha alcanzado proporciones epidémicas de hasta 66,9 millones de personas en el mundo, presentando 6,7 millones ceguera bilateral. Se estima que en el año 2020 el número de personas en el mundo afectadas por el glaucoma alcanzará los 79,6 millones (1). Otra enfermedad a destacar es la degeneración macular asociada a la edad (DMAE), que se ha convertido en un problema importante de salud pública. Es una de las primeras causas de baja visión y de ceguera legal. La prevalencia aumenta con la edad, las mujeres tienen mayor riesgo de presentar formas graves de esta enfermedad (2). En España se estimó que para el 2015 unas 400.000 personas españolas sufrirían DMAE y más de 1 millón de personas pueden estar en riesgo (3). Actualmente esa cifra estimada ha llegado a 700.000 personas (1,5% de la población actual), casi el doble de la que se estimó (4).

Un reto de salud pública y para los profesionales sanitarios es realizar una detección precoz de los diagnósticos visuales a través de la medición de la presión intraocular (PIO) y realización de un fondo de ojo e incidir sobre la importancia de hábitos saludables. Entre estos últimos, cada vez toma más fuerza la influencia de los alimentos y el ejercicio. Los factores de riesgo asociados a patologías oculares como glaucoma, DMAE y cataratas no solo se centran en la edad, sexo, raza, herencia y salud cardiovascular sino también en el estado nutricional. El efecto de una alimentación equilibrada y rica en antioxidantes sobre distintos niveles de la retina, e incluso parámetros de control y seguimiento de signos y síntomas, hacen que estudios sobre su eficacia sean relevantes en distintos procesos patológicos del ojo.

El estrés oxidativo (EO) es uno de los factores implicados en las enfermedades oculares. En la DMAE el exceso de radicales libres (RL) ataca a los fotorreceptores de la retina, cuyas células están sujetas al EO por la exposición combinada a la luz y el oxígeno. El resultado final es la incapacidad del epitelio pigmentario de la retina para disminuir estas moléculas dañadas, dando lugar a acumulación de materiales de desecho en la porción basal del epitelio. Los tejidos oculares son sensibles a los efectos de los radicales libres oxigenados que causan el EO, sobre todo en el cristalino y la retina (5).

En el glaucoma, los RL que ocasionan un EO, producen un daño al ADN en la malla trabecular del ojo humano, pudiendo comprometer el flujo de salida del humor acuoso y, consecuentemente, aumentar la presión intraocular y dañar las células ganglionares de la retina (6). Las especies reactivas de oxígeno (EROx), que constituyen los radicales libres, si se acumulan, también pueden dañar a las células y a los tejidos (Tabla I). Tanto el EO como las EROx, forman parte de los mecanismos lesivos de enfermedades como el Alzheimer, Parkinson, cáncer y enfermedades del sistema visual (7).

**Tabla I.** Roles de los radicales libres (RL) en el organismo humano (8,9)

| *Acciones beneficiosas* |
|---|
| Mantener el sistema inmunológico activo |
| Oxidación de etanol |
| Factor endotelial de relajación |
| Fagocitosis |
| Reacciones de oxidación, carboxilación e hidroxilación |
| Producción de eicosanoides |
| *Acciones nocivas* |
| Estrés oxidativo relacionado con hiperglucemia |
| Peroxidación de lípidos |
| Daño al ADN, proteínas, enzimas y carbohidratos |

El objetivo es encontrar un equilibrio entre la cantidad de radicales libres y el nivel de antioxidantes en nuestro organismo (10). La influencia de los antioxidantes a través de la dieta o mediante suplementos orales puede contrarrestar los efectos nocivos de los RL. Actualmente la creciente preocupación por llevar a cabo investigaciones que muestren un posible efecto coadyuvante de antioxidantes con los tratamientos farmacológicos oculares (11) se debe, principalmente, a que han pasado de ser considerados desde simples atrapadores de RL a moléculas cuyo consumo puede suponer sinónimo de salud (12).

La influencia de ciertos antioxidantes en la salud ha quedado demostrada, como que la combinación de antioxidantes con el zinc reduce la progresión a formas avanzadas de DMAE y que una dieta rica en vitaminas C y E, carotenoides y polifenoles puede contribuir a reducir el riesgo de padecerla (13). Los polifenoles están presentes en una amplia gama de frutas, verduras y productos de origen vegetal, tales como el cacao, el té o el vino (14). La ingesta de las dietas ricas en polifenoles (fruta y verdura) también se asocia inversamente con el riesgo de varias enfermedades crónicas, tales como patologías cardiacas, cáncer y trastornos neurodegenerativos. Otros estudios han examinado el potencial de las dietas como una intervención de primera línea en la prevención y el tratamiento de patologías oculares (15,16).

Sin embargo, revisiones anteriores al presente estudio realizadas por Trumbo y cols. (17) y por Evans y cols. (18) sobre la relación entre una dieta rica en vitaminas antioxidantes (carotenoides, vitamina E y C) y minerales (selenio y zinc) y la reducción de la propensión a padecer DMAE, concluyeron que no existía evidencia suficiente que hiciese suponer una correspondencia clara entre la suplementación con vitamina E y betacarotenos y la prevención de la DMAE.

En la catarata se ha investigado si las hojas de "Cassia tora" pueden prevenir su aparición en ratas recién nacidas, sugiriendo que el consumo de estas hojas puede ofrecer una protección a la lente por su acción antioxidante, lo que plantea un nuevo enfoque terapéutico contra la catarata de forma preventiva (19). Aunque no es objeto de esta revisión los ensayos en animales, creemos que es importante esta aportación para posibles y futuras investigaciones.

Por todo ello planteamos que el efecto de los antioxidantes en el proceso patológico de las enfermedades oculares requiere de una revisión actual. El objetivo de este trabajo es, mediante una revisión sistemática, establecer una comparación entre las escasas evidencias científicas de los antioxidantes y sus efectos en procesos patológicos oculares más prevalentes: glaucoma, DMAE y cataratas.

## MATERIALES Y MÉTODOS

### CRITERIOS DE INCLUSIÓN

La presente revisión consideró como criterios de inclusión para la selección de los estudios que fueran ensayos clínicos aleatorizados, con un seguimiento mínimo de 4 semanas. En los estudios se debían incluir personas mayores de 18 años de ambos géneros y que estuviesen relacionadas con alguna de las siguientes patologías: DMAE, glaucoma y/o catarata; utilizar al menos en un grupo de intervención (GI), en caso de existir varios, cualquier tipo de antioxidante y tener un grupo placebo (GP) en el que se interviniese de cualquier forma de administración sin antioxidante. Los estudios incluidos debieron ofrecer, como mínimo, el dato de la existencia o no de significación estadística, entre ambos grupos, y su efecto en los parámetros medidos (Tabla II).

### ESTRATEGIA DE LA BÚSQUEDA Y CALIDAD METODOLÓGICA

Se realizó una búsqueda bibliográfica en bases de datos de MEDLINE (PubMed; enero de 2009-noviembre 2016), Scielo y fuentes adicionales de artículos sin restricción de idioma. Se seleccionaron artículos de revisión sobre el tema, así como ensayos clínicos controlados y aleatorizados publicados que evalúen la utilización de suplementos de antioxidantes para la prevención o tratamiento de las enfermedades oculares.

Para obtener los estudios en base a los criterios establecidos anteriormente y centrándonos en nuestra estrategia de evidenciar la relación entre salud ocular y antioxidantes, hemos utilizado una estrategia de búsqueda de las tres patologías establecidas para esta revisión (glaucoma, DMAE y catarata). Para el glaucoma fue la siguiente: *(glaucoma)) OR ((glaucoma) AND antioxidants)) AND clinical trial) AND controlled clinical trial) AND randomized controlled trial.* Para la DMAE: *(macular degeneration)) OR ((macular degeneration) AND antioxidants)) AND clinical trial) AND controlled clinical trial) AND randomized controlled trial.* Y para la catarata: *(cataract)) OR ((cataract) AND antioxidants)) AND clinical trial) AND controlled clinical trial) AND randomized controlled trial.*

Ante la inexistencia de estudios que utilizasen el mismo tipo de antioxidante y que, a su vez, midiesen los mismos parámetros, se optó por incluir todos los parámetros medidos. También se buscaron otros estudios aportados que aportaran revisiones sistemáticas previas, en Cochrane, y revisiones bibliográficas sobre antioxidantes en patologías oculares recientes.

La calidad metodológica de los estudios fue analizada mediante el CASPe *(Clinical Appraisal Skills Programme Español),* herramienta de lectura crítica mediante 11 preguntas relacionadas con el análisis de ensayos clínicos en las que contienen: preguntas de eliminación, preguntas de detalle en cuanto al modo de llevar a cabo el ensayo y, por último, preguntas relacionadas con los resultados y el interés del estudio (Tabla III). Los motivos exactos de su exclusión pueden verse en la tabla IV. No se pudo realizar metaanálisis por la heterogeneidad en el uso de tan variados antioxidantes en las intervenciones y los parámetros y medidas de resultado, no pudiéndose obtener una estimación global del efecto.

## RESULTADOS

La estrategia de búsqueda en MEDLINE y en Scielo 75 reportaron un total de 140 estudios más 38 de otras fuentes adicionales Tras la primera revisión de duplicidad obtuvimos 78 estudios (Fig. 1). Tras el análisis de la calidad metodológica de los mismos, obtuvimos un total de 11 estudios para nuestra revisión. De estos, 3 estudios son relevantes en los últimos años sobre antioxidantes y DMAE, 6 sobre el glaucoma y 2 sobre cataratas.

Los estudios incluidos en la revisión sistemática así como sus características más relevantes y variables recogidas en cada uno se resumen en la tabla V.

**Tabla II.** Listado de criterios de selección para la realización de la revisión

| | **Criterios de selección** |
|---|---|
| **Tipo de diseño** | **Ensayos clínicos controlados y aleatorizados** |
| Perfil de sujetos | Raza humana<br>Mayores de 18 años<br>Cualquier estadio de enfermedad ocular: DMAE, glaucoma y/o cataratas<br>Sin hospitalizar<br>Sujetos asignados para la investigación |
| Periodo de tiempo | Últimos 7 años |
| Idioma del estudio | Sin restricción de idiomas |

**Tabla III.** Evaluación de la calidad metodológica y el riesgo de sesgo con la escala CASPe

| Estudio | P1 | P2 | P3 | P4 | P5 | P6 | P7 | P8 | P9 | P10 | P11 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Christen et al., 2015 (21) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | 10 |
| Fogagnolo et al., 2013 (22) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | 10 |
| Galbis et al., 2013 (38) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | 10 |
| Jabbarpoor et al., 2014 (39) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | 11 |
| Yoshida et al., 2013 (26) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | 11 |
| Egorov et al., 2013 (31) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | 10 |
| García et al., 2015 (29) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | 10 |
| Falsini et al., 2009 (37) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | 11 |
| Chew et al., 2013 (AREDS) (23) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | 10 |
| Chew et al., 2013 (AREDS II) (24) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | 11 |
| Murray et al., 2013 (27) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | (+) | 11 |

*(-): no; (+): sí; CASPe: criterios de calidad metodológica. P1-P2-P3: se refieren a las tres preguntas clave de la escala CASPe (claridad de la pregunta -P1, adecuación de la aleatorización -P2, y adecuación del seguimiento -P3). P4-P5-P6: se refieren a las tres preguntas de detalle (enmascaramiento -P4, similitud de los grupos al inicio del ensayo -P5, tratamiento similar de los grupos de comparación -P6). P7-P8: se refieren a los resultados (efecto del tratamiento medido -P7, precisión del efecto –P8). P9-P10-P11: se refieren a la posible ayuda de los resultados para nuestro objetivo (posibilidad de aplicar los resultados al objetivo –P9, se tuvieron en cuenta los resultados de importancia clínica –P10, los beneficios a obtener justifican los costes y riesgos –P11).*

**Tabla IV.** Relación de estudios excluidos y razón(es) para su exclusión

| Autores/as | Año | Razón(es) de exclusión |
|---|---|---|
| Akuffo et al. (28) | 2015 | No hay grupo placebo-controlado |
| Wu et al. (30) | 2015 | Se trata de un estudio de cohortes, no ensayo clínico |
| Volchergoski et al. (32) | 2012 | No se dispone del estudio completo y hay escasa información para completar los objetivos de la revisión |
| Kubota et al. (33) | 2010 | Los participantes eran de origen animal; ratas, criterio de exclusión para la revisión |
| Pintea et al. (34) | 2011 | El procedimiento es *in vitro* |

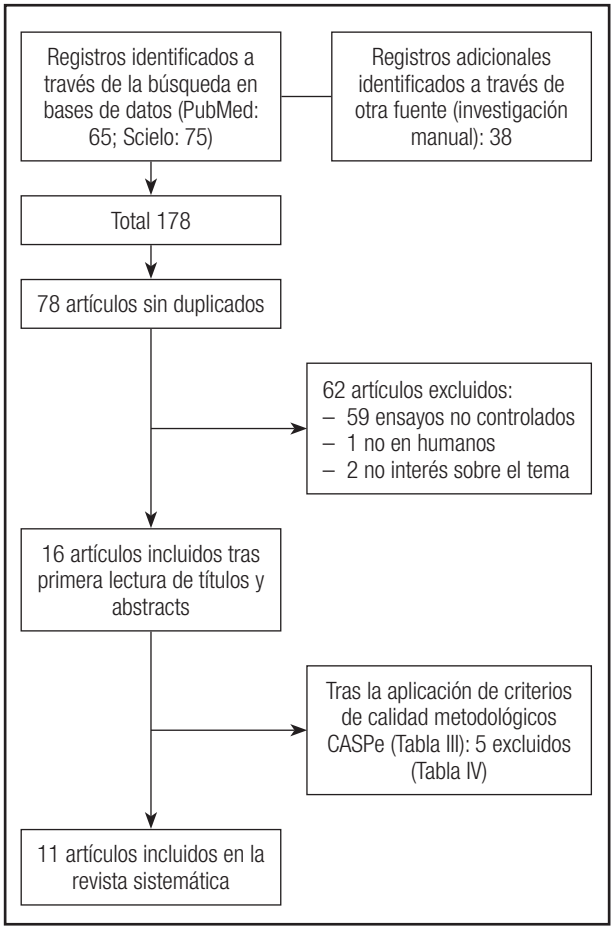


**Figura 1.**
Diagrama de flujo del proceso de selección de estudios.

## EVIDENCIAS CIENTÍFICAS DE LOS ANTIOXIDANTES EN LAS ENFERMEDADES OCULARES

### Vitaminas antioxidantes

La vitamina E es un antioxidante liposoluble por lo que actúa especialmente sobre los ácidos grasos poliinsaturados de las membranas celulares e inhibiendo la peroxidación de las partículas de LDL. También se encarga de retrasar el envejecimiento celular ocasionado por la oxidación, protegiendo a las células de

**Tabla V.** Estudios relacionados con la eficacia de los antioxidantes en patologías oculares

| Autores | Diseño/Duración | Participantes/ Edad | Grupos intervención antioxidantes/Placebo | Enfermedad ocular/Variables estudiadas | Resultados/Valor p | Efecto |
|---|---|---|---|---|---|---|
| Christen et al., 2015 (21) | Ensayo clínico aleatorizado/5,6 años | 11.267 / edad > 50 | GI1: vitamina E (400 IU/ día)<br>GP1: con placebo<br>GI2: selenio + vitamina E (200 mg y 400 UI/día)<br>GP2: solo selenio (200 mg/día) | Desarrollo de catarata | Diferencia no significativa entre grupos con antioxidante y placebo (p > 0,05)<br>GI1 y GP1: p = 0,37<br>GI2 y GP2: p = 0,84 | No beneficioso |
| Fogagnolo et al., 2013 (22) | Ensayo clínico aleatorizado/9 meses | 40 / edad no disponible | GI: coenzima Q10 tras cirugía<br>GP: solución salina sin antioxidante | Catarata: recuperación más rápida tras la cirugía de la densidad de los nervios sub-basales corneales | Diferencia significativa entre grupos tras cirugía de catarata( p<0,02) | Beneficioso |
| Galbis et al., 2013 (38) | Ensayo clínico aleatorizado/3 meses | 97 / edad 25-80 | GI1: antioxidantes (AOXs/EPUFAs)[1] (2 cápsulas/día)<br>GP: sin antioxidante | Glaucoma: acción de mejora de signos y síntomas de ojo seco por tratamiento de glaucoma | Diferencia significativa entre grupos con antioxidantes respecto al grupo placebo (p < 0,0002) | Beneficioso |
| Jabbarpoor et al., 2014 (39) | Ensayo clínico aleatorizado/1 mes | 34 / edad 51-79 | GI: azafrán (30 mg/día)<br>GP: sin antioxidante | Glaucoma: acción de mejora de PIO (presión intraocular) | Diferencia significativa de la PIO en el grupo experimental en comparación con el grupo control (p = 0,001) | Beneficioso |
| Yoshida et al., 2013 (26) | Ensayo clínico aleatorizado/24 meses | 38 / edad no disponible | GI: antocianinas de grosella negra (100 mg/día)<br>GP: sin antioxidante | Glaucoma: acción de mejora de parámetros de control y aumento del flujo sanguíneo para el retraso de glaucoma | Diferencia significativa en el aumento de flujo sanguíneo entre grupos (p < 0,005) | Beneficioso |
| Egorov et al., 2013 (31) | Ensayo clínico aleatorizado/1 mes | 50 / edad 18-75 | GI1: Mexidol 100 mg; Picamilon (150 mg /día)<br>GI2: Mexidol 300 mg: Picamilon (150 mg /día)<br>GP: sin antioxidante solo Picamilon (150 mg/día) | Glaucoma : acción de mejora del campo visual (AV) | Diferencia significativa entre grupos con antioxidantes respecto al grupo placebo<br>GI1 y GI2: p < 0,05<br>GP: p > 0,05 | Beneficioso |
| García et al., 2015 (29) | Ensayo clínico aleatorizado/24 meses | 117 / edad >40 | GI1: ICAPS®[2]<br>GI2: OFTAN MACULA®[3]<br>GP: sin antioxidante | Glaucoma: acción de mejora campo visual (CV) y espesor de la capa de fibras nerviosas de la retina (CFNR) , pérdida de las células ganglionares maculares (CGM) | Diferencia no significativa para el CV/CFNR/CGM<br>GI1 p = 0,83; p = 0,45; p = 0,39<br>GI2 p = 0,81; p = 0,39; p = 0,31<br>CP p = 0,97; p = 0,93; p = 0,99<br>Diferencia no significativa para todas las comparaciones (p > 0,05) | Neutro |
| Falsini et al., 2009 (37) | Ensayo clínico aleatorizado/6 meses | 20 / edad 25-60 | GI: galato de epigalocatequina (EGCG) (200 mg/día)<br>GP: sin antioxidante | Glaucoma: acción de mejora de AV y patrón electrorretinograma (PERGs) | Diferencia significativa entre grupo con antioxidante y grupo placebo (p < 0,05) | Beneficioso |

*(Continúa en la página siguiente)*

**Tabla V (Cont.).** Estudios relacionados con la eficacia de los antioxidantes en patologías oculares

| Autores | Diseño/Duración | Participantes/ Edad | Grupos intervención antioxidantes/Placebo | Enfermedad ocular/Variables estudiadas | Resultados/Valor p | Efecto |
|---|---|---|---|---|---|---|
| Chew et al., 2013 (AREDS) (23) | Ensayo clínico aleatorizado/6,3 años | 3.640 / edad 55-80 | GI1: antioxidantes: vitamina C (500 mg) vitamina E (400 IU) y betacaroteno (15 mg)/día<br>GI2: óxido cúprico (2 mg) + zinc (80 mg)/día<br>GI3: antioxidantes + zinc<br>GP4: placebo | DMAE: acción de mejora en la AV y desarrollo de la enfermedad | Disminución en la pérdida de AV ($p = 0,007$) y disminución de la progresión de la enfermedad ($p < 0,001$) para el GI1 | Beneficioso |
| Chew et al., 2013 (AREDS II) (24) | Ensayo clínico aleatorizado/5 años | 1.608 / edad 50-85 | GI1: fórmula AREDS[4]<br>GI2: DHA[5] (350 mg) + EPA[6] (650 mg)<br>GI3: luteína + zeaxantina + DHA + EPA<br>GP4: placebo | DMAE: acción de mejora en la AV y desarrollo de la enfermedad | Diferencia no significativa en la progresión de la DMAE ($p > 0,05$) respecto al grupo control y no diferencias en cambio en la AV ($p > 0,40$) | Neutro |
| Murray et al., 2013 (27) | Ensayo clínico aleatorizado/12 meses | 72 / edad media 70,5 | GI: luteína (10 mg/día)<br>GP: sin luteína | DMAE: acción de mejora de pigmento macular óptico (MPOD) y AV | Diferencia significativa con mejora de AV en el grupo de antioxidantes ($p < 0,05$)<br>La suplementación con antioxidantes aumenta los niveles de MPOD en las primeras etapas de la DMAE ($p < 0,001$) | Beneficioso |

[1]*Antioxidantes (AOXs/EPUFAs)*: ácido docosahexaenoico (350 mg), ácido eicosapentaenoico (42,5 mg), ácido docosapentaenoic (30 mg), vitamina A (133 mg), vitamina C (26,7 mg), vitamina E (4 mg), tirosina (10,8 mg), cisteína (5,83 mg), el glutatión (2 mg), zinc (1,6 mg), cobre (0,16 mg ), manganeso (0,33 mg), selenio (9,17 g).*

[2]*ICAPS®*: vitamina A (800 mcg), vitamina B (B1: 1,4 mg, B2: 1,6 mg, B3: 18 mg, B6: 2 mg, B9: 100 mcg, B12: 1 mcg), vitamina C (60 mg), vitamina E (10 mg), lutenina (6 mg), zeaxantina (0,3 mg), ácidos grasos omega-3; DHA:* 96 mg, EPA: *85 mg, zinc (10 mg), selenio (40 mg), manganeso (2 mg).*

[3]*OFTAN MACULA®*: vitamina A (800 mcg), vitamina B (B1: 1,4 mg, B2: 1,6 mg, B3: 18 mg, B6: 2 mg, B9: 100 mcg, B12: 1 mcg), vitamina C (60 mg), vitamina E (6,7 mg), lutenina (6 mg), zeaxantina (0,5 mg), zinc (7,5 mg), selenio (25 mcg), manganeso (1 mg).*

[4]*Fórmula AREDS*: vitamina C (500 mg), vitamina E (400 UI), betacaroteno (15 mg), zinc (80 mg) y cobre (2 mg, como óxido cúprico).*

[5]*DHA*: indica ácido docosahexaenoico.*

[6]*EPA*: indica ácido eicosapentaenoico.*

la acción de los RL y previniendo las enfermedades crónicas. La vitamina C (ácido ascórbico), potente antioxidante hidrosoluble, entre otros, actúa sobre el sistema inmunitario, mientras que los betacarotenos actúan combinando con otras para mantener la función depurativa del óxido nítrico en las células.

Los antioxidantes suelen actuar de manera conjunta, ya que de esa forma consiguen incrementar su efecto, incluso son capaces de regenerar su efecto antioxidante cuando lo han perdido, como le sucede a la vitamina E con la vitamina C y el selenio (20).

Respecto a su utilización a largo plazo (5-6 años) para la prevención de cataratas no tiene efecto significativo (21). En otro ensayo clínico se evaluó el uso de la coenzima Q10 junto con la vitamina E de nuevo en las cataratas; durante 9 meses, asociándose la Q10 con la regeneración del nervio más rápidamente influyendo en la integridad de la superficie ocular (22). Se deduce que existe controversia en cuanto al suplemento vitamínico y catarata, aunque parece razonable mencionar que la eficacia es más notable cuando el suplemento es a corto plazo que a largo plazo ya que en este último es más neutral.

En el glaucoma, se han demostrado grandes beneficios utilizando suplementos vitamínicos A, E y C junto con otros tipos de antioxidantes, evidenciando la mejoría de los efectos adversos que sufren los pacientes con glaucoma con el tratamiento tópico hipotensor como es el ojo seco (38). Según las evidencias de estudios en humanos se encuentra un efecto protector vitamínico en cuanto al riesgo de desarrollar glaucoma y aconsejan un consumo alto de frutas y verduras (16).

En la DMAE el estudio de Chew y cols. (AREDS) (23), pudo confirmar, con un seguimiento a largo plazo entre 6 y 10 años, que con la suplementación de antioxidantes: vitamina C, vitamina E, betacaroteno y zinc, se disminuye el desarrollo de DMAE avanzada, ya que los resultados obtenidos fueron estadísticamente significativos ($p > 0,001$). También se observó una disminución en el desarrollo de pérdida de visión moderada. Sin embargo, la segunda parte de este estudio evaluó si añadiendo luteína, zeaxantina y ácidos grasos omega-3 (EPA y DHA) a la formulación de antioxidantes de la primera parte del estudio se disminuía aún más el riego de desarrollar DMAE avanzada, sin encontrar efecto, pudiendo ser este resultado atribuible a la falta de eficacia de los nutrientes añadidos en la segunda parte del estudio, pero también al uso de dosis o formas inadecuadas de dichos nutrientes (24).

## Polifenoles

Los polifenoles se suman las patologías oculares, principalmente a la enfermedad del glaucoma (25). Las antocianinas tienen propiedades antitumorales, antimicrobianas y neuroprotectoras (7). Se ha demostrado que su uso tiene un efecto beneficioso para paliar la progresión del glaucoma ya que mejoran la circulación sanguínea ocular por normalizar los valores de ET-1 (endotelina-1, 10 veces más vasoconstrictor que la angiotensina II) (26).

## Carotenoides

Los resultados muestran asociación entre un mayor aporte de carotenoides, mediante suplementación y una mejora en el desarrollo de la DMAE. Las dos variables estudiadas han sido la agudeza visual (AV) y la densidad del pigmento macular (DPM). Se han evidenciado efectos positivos en cuanto a la mejora de la agudeza visual con suplementos de luteína de 10 mg/día durante 12 meses en el estudio de Murray y cols., mostrando un resultado estadísticamente significativo ($p < 0,001$) (27). El estudio de Akuffo y cols., no incluido en la revisión sistemática por no contener grupo de control, evidencia una mejoría en el pigmento macular en todos los grupos de intervención con la suplementación de luteína, zeaxantina y meso-zeaxantina en personas con DMAE precoz (28). La actividad biológica de estos carotenoides en la retina se basa en dos tipos de mecanismos de acción, no excluyentes, actuar como filtros de luz azul (la zona luminosa del espectro visible de mayor energía) reduciendo su efecto oxidativo, y como antioxidante, limitando el estrés oxidativo resultante del metabolismo y de la luz. Por estos mecanismos de acción se podría explicar su papel beneficioso en relación con la DMAE, ya que entre las principales hipótesis etiológicas de esta enfermedad está la hipótesis oxidativa y la de insuficiencia vascular (en la circulación coroidal) resultando una gran protección macular.

Para el glaucoma los estudios revisados no coinciden en cuanto al aporte de carotenoides y sus efectos positivos, como ocurre con la DMAE. Las variables medidas en cada uno de los estudios difieren, por lo que mostramos cada una de ellas. La administración de suplemento de luteína (6 mg) y zeaxantina (0,5 mg) junto con otros antioxidantes en la fórmula ICAPS® muestran efectos neutros tanto en la mejora del campo visual (CV) en el grupo de intervención ($p = 0,97$) como en el espesor de la capa de fibras nerviosas de la retina (CFNR) ($p = 0,57$) y en la pérdida de las células ganglionares maculares (CGM) ($p = 0,29$) (29). Además al comparar la fórmula anteriormente nombrada con otra en la que añadían omega-3, no se evidencian diferencias significativas en cuanto a la mejora de estos parámetros de control y seguimiento del glaucoma.

## Otros antioxidantes

Algunos minerales como el cobre, el manganeso, el selenio y el zinc, tienen propiedades antioxidantes; sin embargo no podemos afirmar sus efectos beneficiosos en prevención y/o control de patologías oculares ya que entre los analizados no hemos encontrado evidencias de sus beneficios (21,30). Otros estudios (31,32) muestran que el uso del antioxidante Mexidol (derivado del ácido succínico y 3-hidroxipiridina) en el tratamiento de los pacientes con glaucoma primario de ángulo abierto mejora la agudeza visual y el aumento progresivo de la velocidad de flujo sanguíneo arterial de la retina, por lo que disminuye el riesgo de obstrucción, y con ello, que las células se degeneren y puedan causar la pérdida de visión.

Es necesario también destacar que la utilización del resveratrol, antioxidante presente en varias plantas y especialmente en la piel de las uvas rojas, las grosellas, las moras y los cacahuetes (33) y también el empleo del trans-resveratrol previene el daño retiniano debido a la exposición a la luz, con lo que normalmente previene la disfunción, el daño y la muerte celular en el ojo con DMAE (34). Tiene un efecto protector significativo frente a la citotoxicidad inducida por el peróxido de hidrógeno en el epitelio pigmentario de la retina (EPR). Se ha demostrado que reduce la acumulación intracelular de EROx inducida por peróxido de hidrógeno en las células epiteliales del cristalino en el hombre. Este también puede ser eficaz en la microcirculación del ojo debido a sus propiedades de mejora vascular. Sin embargo no han sido incluidos por no ajustarse a los criterios de inclusión.

## DISCUSIÓN

A la vista de la evidencia científica recogida en los trabajos de investigación analizados, puede apoyarse la suplementación de distintos tipos de antioxidantes con efectos beneficiosos en determinadas patologías oculares, la DMAE y el glaucoma. Reafirmamos que hay que tener precaución con generalizar cualquier antioxidante ya que no todos pueden evidenciar su efecto positivo coincidiendo con lo evidenciado también por Hollman y cols. (35). Por los resultados de la revisión podemos valorar la posibilidad de que los antioxidantes a nivel ocular tengan un efecto más positivo a corto que a largo plazo (11).

Tras la revisión podemos sugerir para la disminución en la progresión del glaucoma la administración de los antioxidantes y sus efectos a distintos niveles. Podemos recomendar que la administración de antocianinas como la grosella negra con dosis de 100 mg/día durante 24 meses, puede tener un efecto beneficioso en la mejora de la función y aumento del flujo sanguíneo de la retina demostrado significativamente (26). Además sería interesante exponer que ante la cirugía filtrante de glaucoma, donde la inflamación se asocia a fibrosis y por tanto al fracaso de la misma, sería conveniente realizar futuros ensayos clínicos del papel de las antocianinas como coadyuvantes (36).

La administración de galato de epigalocatequina (EGCG) (200 mg/día durante 6 meses) mejora el patrón electrorretinograma y el campo visual en el glaucoma ($p < 0,05$) (37). También la terapia combinada con el antioxidante Mexidol® (100mg /día durante 1 mes) mejora la agudeza visual, coincidiendo con otro estudio en el que emplearon el ácido succínico, cuyo derivado también es el Mexidol® (31,32).

La suplementación con vitamina A, C y E mejora los signos y síntomas del ojo seco (38) que aparecen por la administración de medicación de forma continuada para el tratamiento de esta patología ($p < 0,05$). Sin embargo no podemos recomendar dosis aproximadas por la variedad de antioxidantes y minerales empleados, pero sí podemos afirmar su influencia positiva en la disminución de la progresión del glaucoma, utilizando el test de Schimer como herramienta para observar su efectividad (38). Por el contrario, en la patología ocular de la catarata, aún no se evidencia el uso beneficioso de la vitamina E, existiendo actualmente una controversia sobre los suplementos vitamínicos y las cataratas en cuanto al tiempo de administración, aunque parece razonable mencionar que la evidencia es más notable cuando el suplemento es a corto plazo y más neutral cuando es a largo plazo; pero no lo suficiente para poder afirmarlo (21,22).

En el glaucoma se evidencia que el azafrán tiene efecto hipotensor ocular, debido a los derivados de carotenoides, presente en el extracto del azafrán, recomendando 30 mg/días durante 1 mes (39). Además puede ser muy útil como coadyuvante en el tratamiento de la hipertensión ocular, uno de los factores de riesgo más importantes del glaucoma.

En cuanto a la DMAE, el estudio Age-Related Eye Disease Study (AREDS II) (24), del National Eye Institut, en EE. UU., clarifica que tanto la luteína y la zeaxantina, como los ácidos grasos poliinsaturados de cadena larga omega-3, pueden añadir una reducción adicional al riesgo de progresión de la enfermedad, ya observada con otros antioxidantes (vitaminas C, E y betacaroteno) más el zinc, cuyos resultados fueron significativos ($p < 0,001$). Aunque no se ha determinado una dosis exacta, podemos afirmar que la luteína y la zeaxantina al reducir el número de radicales libres muestran una relación con la salud ocular. A pesar de que no existe una ingesta diaria recomendada de luteína y zeaxantina, estudios recientes (27,40) muestran un beneficio saludable al suplementarse con 10 mg/día de luteína y 2 mg/día de zeaxantina produciendo un aumento general sobre la densidad óptica del pigmento macular y la agudeza visual en pacientes con DMAE con resultados estadísticos significativos ($p < 0,05$) (27).

Estos resultados pueden apoyarse con los obtenidos en otro estudio (30) de cohortes prospectivo publicado en 2015 que investigó si había asociación, entre los niveles de carotenoides (luteína y zeaxantina) y el riesgo de DMAE avanzada, concluyendo que existe asociación entre un mayor consumo en la ingesta, a través de los alimentos de luteína y zeaxantina a largo plazo, y un menor riesgo de DMAE (RR = 0,59; IC del 95%, 0,48 a 0,73; $p < 0,001$). Además, dado que otros carotenoides ($\beta$-criptoxantina, $\alpha$-caroteno y $\beta$-caroteno) también se asociaron a un menor riesgo para esta enfermedad ($p < 0,001$), es recomendable promover estrategias de salud pública destinadas a aumentar el consumo de frutas y verduras ricas en carotenoides para reducir la incidencia de esta enfermedad (14,41). Actualmente, un estudio *in vitro* ha demostrado que el aporte de trans-resveratrol puede ser eficaz en la microcirculación del ojo debido a sus propiedades de mejora vasculares (34), siendo un paso importante para comenzar posibles ensayos en humanos. En conjunto los estudios científicos tanto con suplementos, como a través del consumo adecuado de alimentos ricos en antioxidantes, llegan a la conclusión su factor protector en la prevención de la DMAE.

Para finalizar este apartado debemos destacar que el uso de suplementación nutricional en oftalmología no está exento de controversias, en cuanto al tiempo de suplementación y la combinación de múltiples tipos de antioxidantes. Sin embargo, para la DMAE existe más evidencia científica, aunque centrada principalmente en dos grandes estudios (23,27). En el glaucoma

son estudios recientes los que están evidenciando la eficacia y las dosis de los antioxidantes; sin embargo consideramos que es pronto para poder recomendar a los profesionales unas pautas en cuanto a la duración. Esto último puede ser debido a la escasez de estudios existentes sobre la administración de antioxidantes y glaucoma a largo plazo (más de 5 años), que podrían mostrar otros resultados.

Otra controversia importante es la falta de estudios que comparen el mismo tipo de antioxidantes y contrasten su administración a largo plazo con parámetros, dosis y tiempo para una misma patología ocular. Para una mayor calidad, hubiera sido interesante poder trabajar con un número mayor de registros, sin embargo tampoco se pretendía ampliar el límite de años para no distorsionar la actualización y evidencia de esta revisión. De momento podemos coincidir con las recomendaciones que se inclinan a la importancia de una dieta variada, alta en frutas y vegetales, no fumar, evitar el exceso de exposición al sol y a las radiaciones ultravioletas (42), aunque ya encontramos evidencias científicas de sus efectos a nivel ocular mediante la suplementación.

## LIMITACIONES DEL ESTUDIO

La metodología de este estudio tiene como limitaciones, como por ejemplo escasa información del rol de los antioxidantes sobre la catarata, no pudiendo mostrar una evidencia concluyente para esta patología, así como la variedad de distintos tipos de antioxidantes y la falta de estudios que reproduzcan el efecto con mismas dosis, plazos de administración y mismos tipos de antioxidante. Tampoco se compara la administración del antioxidante con las edades de consumo, el grado de dependencia y la eficacia de los mismos a más largo plazo para el glaucoma y catarata concretamente. Por tanto, sugerimos la necesidad de realizar estudios más homogéneos en las distintas patologías oculares respecto al tipo de antioxidante, dosis y llevarlos a cabo a más largo plazo.

## CONCLUSIONES

- La administración de antocianinas y de EGCG, con dosis superiores a 100 mg/día pueden ser útiles como coadyuvantes del glaucoma retrasando y/o disminuyendo su progresión.
- La suplementación con vitaminas A, C y E mejora la iatrogenia del tratamiento del glaucoma, aunque establecen efectos neutros en catarata y para el glaucoma con administración prolongada en 2 años. Sin embargo las vitaminas C y E, junto con los betacarotenos mejora su acción en la agudeza visual para la DMAE.
- La luteína y la zeaxantina, son los dos carotenoides más potentes con efecto beneficioso para reducir el riesgo de progresión de la DMAE.

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Nutrición Hospitalaria

Revisión

# Insatisfacción con la imagen corporal en niños y adolescentes: revisión sistemática

*Body-image dissatisfaction in children and adolescents: a systematic review*

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## Resumen

**Introducción:** la diferencia de la percepción entre la silueta percibida y la deseada se ha definido como insatisfacción con la imagen corporal (IMCO).

**Objetivo:** evaluar los métodos utilizados para medir la IMCO y la frecuencia de la IMCO en niños y adolescentes.

**Metodología:** se buscaron artículos registrados en las bases de datos de PubMed, EBSCOhost y Scielo, de estudios transversales en inglés y español, que valoraran la IMCO en niños y adolescentes publicados de abril de 2010 al mes de abril de 2015. Se registraron, edad, sexo, tamaño muestral, estado de peso, tipo de método para valorar la IMCO y estimación de la IMCO.

**Resultados:** cumplieron con los criterios de inclusión 16 estudios que valoraron la IMCO en niños y adolescentes de 5 a 19 años de edad. De los artículos analizados se encontraron 9 métodos de valoración de la IMCO. En la mayoría se realizaron pruebas de estabilidad temporal y validez. La frecuencia de IMCO por tener sobrepeso u obesidad, osciló de 44% a 83% y por bajo peso, de 1,7% a 37%. La IMCO aumentó de acuerdo al IMC, y en algunos estudios se asoció con la edad. Fue más frecuente en las mujeres, y en algunos casos se presenta IMCO en los niños delgados.

**Conclusión:** la IMCO se presenta con mayor frecuencia en el sexo femenino y se asocia positivamente con el IMC. A pesar de la variedad de métodos utilizados para evaluar la IMCO, los resultados son consistentes.

**Palabras clave:**

Insatisfacción imagen corporal. Escalas de valoración. Índice de masa corporal. Niños. Adolescentes. Revisión sistemática.

## Abstract

**Background:** The difference in the perception between the perceived silhouette and the desired silhouette has been defined as body image dissatisfaction (BID).

**Objective:** To review the type of methods for measuring BID, the frequency of BID among children and adolescents.

**Method:** We searched studies through electronic databases (PubMed, Scielo and EBSCOhost), from cross-sectional studies published in English or Spanish. Eligible studies assessing BID in children and adolescents published in Spanish and English, from April 2010 to April 2015. Age, sex, weight and method or scale used to evaluate the BID and the self- perception of body weight were assessed.

**Results:** Sixteen studies met the inclusion criteria, and included children and adolescents aged 5 to 19 years. Nine types of measurement methods of BID were found. In most of the studies, temporal stability and validity test were performed. In BID studies where frequency was reported, ranged from 44% to 83% for overweight or obese and 1.7% a 37% for underweight. In some studies, BID was associated with age and was more frequent among girls. BID was also present in thin boys.

**Conclusion:** BID was more frequent among girls and was positively associated with BMI. Despite the variety of methods used, the results are consistent.

**Key words:**

Body image dissatisfaction. Assessment scales. Body mass index. Children. Adolescents. Systematic review.

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## INTRODUCCIÓN

Varios estudios han mostrado que desde los cinco años de edad los niños y las niñas reportan insatisfacción, preocupación y percepción inexacta de la imagen corporal (1,2). La imagen corporal, según Baile es un constructo psicológico complejo, que se refiere a cómo la autopercepción del cuerpo genera una representación mental compuesta por un esquema corporal perceptivo, por las emociones, los pensamientos y las conductas asociadas (3). El componente perceptual implica la exactitud de la estimación de la forma del cuerpo y la actitud y sentimientos que tienen hacia su cuerpo (4). Sin embargo, no existe un consenso científico sobre qué es la imagen corporal, o cómo se evalúa, ni cómo se manifiesta una alteración de ella (3).

La autopercepción se ha clasificado como correcta, subestimación y sobrestimación, y esta a su vez podría generar la satisfacción o insatisfacción corporal. Algunos autores consideran que la distorsión perceptiva es la alteración de la percepción que se manifiesta por una incapacidad para estimar con exactitud el tamaño corporal (5).

La insatisfacción se puede originar por la distorsión perceptiva, por la discrepancia entre el cuerpo percibido y el ideal o, simplemente, por el disgusto con el propio cuerpo y puede originarse por un entorno adverso a ciertas figuras ideales establecidas por la sociedad (6). La frecuencia de la insatisfacción de la imagen corporal (IMCO) puede ser explorada en diferentes grupos como el género, la edad, la sexualidad, las clases sociales, los grupos étnicos o culturales. Las causas de la IMCO pueden deberse a factores sociales y psicológicos. Algunos investigadores han explorado los factores sociales, como los medios de comunicación (7-9), la cultura (10,11), las amistades (7,12) y la familia (13,14) y dentro de los factores psicológicos se encuentran los sentimientos causados por los factores sociales (15); así mismo, se han estudiado las creencias generadas por la influencia de los padres (13,16) y la cultura (17).

La insatisfacción con la imagen corporal, la restricción alimentaria, así como los comportamientos para la pérdida de peso durante la infancia son considerados factores de riesgo, que asociados a elementos biopsicosociales (18) contribuyen a problemas como la dependencia al ejercicio y a los trastornos alimenticios. En un estudio realizado en Galway, Irlanda (19), no se encontraron diferencias sustanciales en la IMCO entre sexos, sin embargo, los que seguían conductas para bajar de peso tuvieron más IMCO comparado con los que no las seguían ($p < 0,001$); quienes tenían sobrepeso y obesidad tenían menos riesgo de IMCO al compararlo con el grupo que no tenía sobrepeso. La IMCO se asoció positivamente con la conducta para bajar de peso (OR 9,17, 95%, CI 6,99-12,02) ($p < 0,001$). La revisión sistemática más reciente valoró la IMCO en niños y preadolescentes, incluyó artículos publicados de 1990 a 2011, solamente describió los métodos para evaluar la IMCO y las variables asociadas; sin embargo, no reportó la magnitud de la IMCO (20). Esta revisión describe que diversos estudios han explorado la IMCO en diferentes países y en diferentes grupos de edad, y lo han realizado con diferentes métodos y escalas. Estas diferencias dificultan hacer comparaciones entre culturas y países, por lo que el propósito de este estudio fue revisar los diferentes métodos para medir la IMCO, así como la frecuencia de la IMCO entre niños y adolescentes, en publicaciones realizadas en español o en inglés de 2010 a 2015.

## METODOLOGÍA

Se realizó una búsqueda de artículos publicados en inglés y español en las bases de datos de PubMed, EBSCOhost y Scielo del 18 de abril de 2010 al 18 de marzo de 2015, utilizando los términos MeSH: "body dissatisfaction" OR "body image dissatisfaction" OR "body shape dissatisfaction" OR "insatisfacción" OR "imagen" AND "corporal" NOT "review" AND ("2010/04/18": "2015/04/18" AND "humans" AND (English(lang) OR Spanish(lang)) AND "child").

Los criterios de inclusión fueron estudios transversales realizados en menores de 19 años, sin algún trastorno mental identificado, publicados en inglés o español, publicados del 18 de abril de 2010 al 18 de abril de 2015, y que reportaran la IMCO. Se incluyeron todos los estudios que cumplían con los criterios de inclusión. Se excluyeron estudios en los que se valorara la IMCO con alguna enfermedad física y/o mental, lesiones, alteraciones hormonales y/o prácticas parentales y donde se incluyera algún tipo de dieta para bajar de peso.

Se realizaron dos diferentes búsquedas electrónicas, en las cuales se encontraron un total de 314 estudios de los cuales fueron descartados 70 por ser duplicados, quedaron 244, posteriormente se eliminaron 179 porque eran revisiones sistemáticas, porque no cumplían con los criterios de inclusión, como eran el período de publicación y las publicaciones en inglés o español. Se revisaron 65 artículos, de los cuales 48 no cumplían con todos los criterios de inclusión. Se analizaron 16 artículos en la revisión sistemática (Fig. 1).

Se registraron los siguientes datos de cada estudio: autores, año, país de publicación, número de participantes, edad, género, frecuencia del estatus del peso, criterios y métodos para evaluar la insatisfacción corporal y otros indicadores de adiposidad. También se registró la validación y confiabilidad del método utilizado; la frecuencia de la IMCO, en sus dos niveles (por percibirse muy delgado o muy gordo), la subestimación y la sobrestimación del peso, y la media del puntaje obtenido en toda la población.

## RESULTADOS

De abril de 2010 a marzo de 2015 se encontraron 16 estudios que cumplieron con los criterios de inclusión.

En la tabla I se presentan las características de la población estudiada, los métodos de evaluación y los resultados de la evaluación de la imagen e insatisfacción corporal. El grupo de edad evaluado fue de los 5 a los 19 años de edad, aunque solamente un estudio (1) incluyó niños de 5 a 7 años de edad, el tamaño de las poblaciones estudiadas oscilaba de 50 hasta 9.000, y en la mayoría de estudios se evaluó la insatisfacción en ambos sexos.

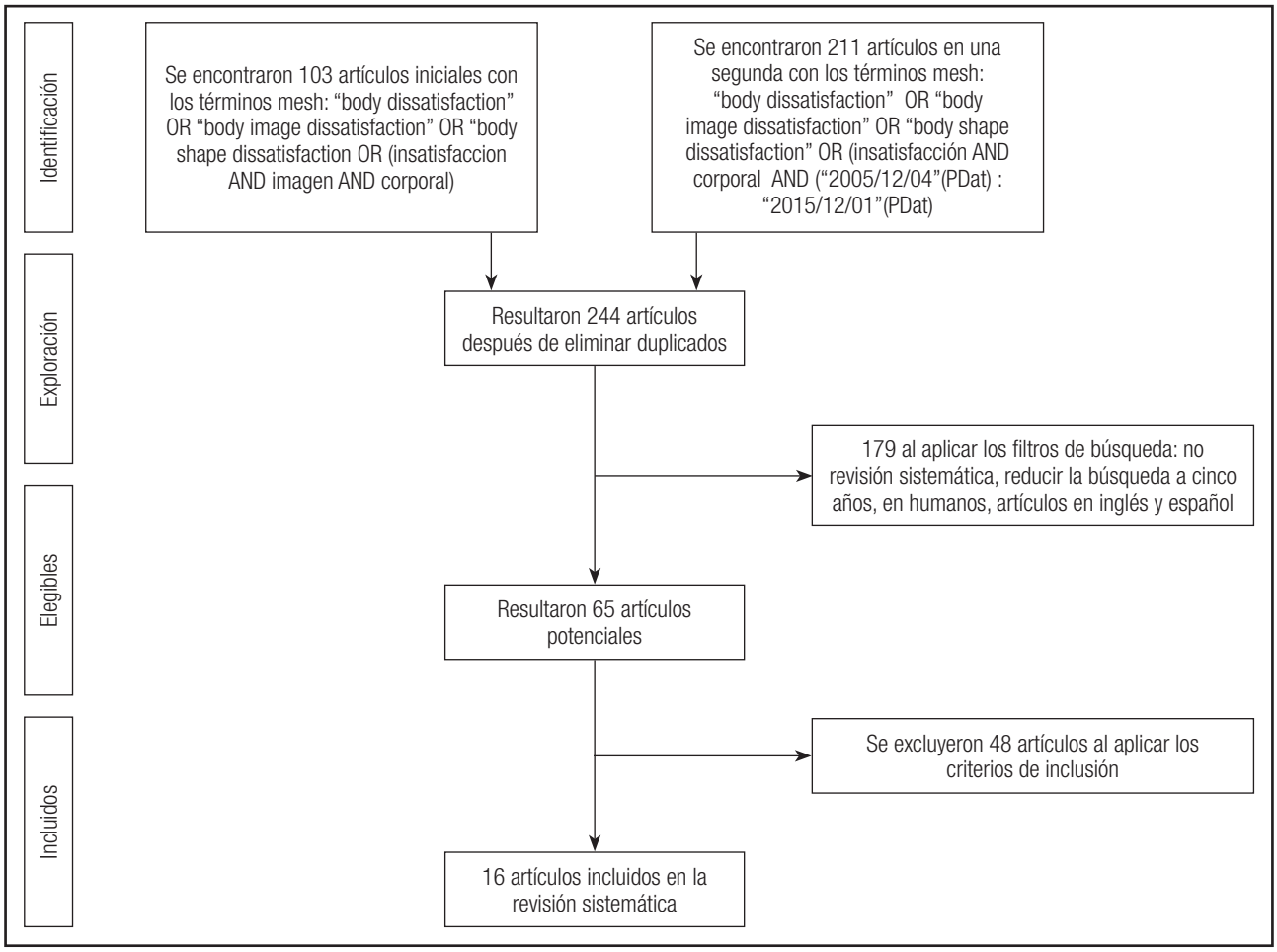


**Figura 1.**

Búsqueda de acuerdo a PRISMA.

Se utilizaron 9 métodos de evaluación de la IMCO (inventarios, escalas, cuestionarios). En la mayoría de los estudios se analizó la confiabilidad test-retest y/o la confiabilidad interna y se utilizaron instrumentos adaptados y traducidos al país donde se realizaron los estudios. En la tabla I se presentan los resultados de cada trabajo. En dos estudios (1,21) utilizaron el método de las figuras de Collins y clasificaron a los niños de acuerdo al IMC.

Otros 2 estudios utilizaron el "Body Shape Questionnaire" (22,23).

En el Reino Unido se realizaron 2 estudios que utilizaron el método desarrollado por Wardle en el 2002, basado en los pictogramas de Stunkard (24,25).

Cuatro de los estudios (26-29) evaluaron la insatisfacción corporal por medio de la subescala de insatisfacción corporal con el Eating Disorder Inventary (EDI, por sus siglas en ingles). Algunos presentan variantes adaptadas al contexto del país en el que fueron utilizadas (Estados Unidos, Países Bajos, Hungría, Reino Unido y España).

Dos estudios más utilizaron la subescala (30,31) "Body Dissatisfaction", "Body Importance" y "Body Image Concern" de la escala de "Body Image and Body Shape Questionnaire".

Un estudio (32) utilizó la "Children Figure Rating Scale". Por otro lado un estudio multicultural (11) en donde incluía países como Australia, Chile, Grecia, Indígenas Figi, Indo-Figi, Malasia y Tonga, utilizó algunas preguntas de la subescala de "Body Image Dissatisfaction" del inventario "Body Image and Body Change and Body Change Inventory". Otro estudio (33) utilizó algunos reactivos del "Body Image Subescale" de la "Body Investment Scale". Otro estudio (34) evaluó la IMCO en una investigación realizada en Alemania por medio de preguntas sobre la autopercepción.

En solamente 3 estudios se reportó la frecuencia de IMCO por percepción de gordo o muy gordo que osciló de 44% a 61% y por bajo peso varió de 5,7% a 37%. La media de la IMCO se reportó en 14 estudios, que no fueron comparables porque se realizaron con diferentes métodos.

**Tabla I.** Estudios incluidos, características de los instrumentos para evaluar la IMCO y resultados obtenidos

| Autor/es, (año), país (referencia) | Edad (años) Media o rango | n | Estado de peso | Método/ escala de BP/BD | Validación/ confiabilidad | Descripción de la escala de la IMCO | Subestimación (%) | Sobrestimación (%) | Frecuencia de la IMCO % | Media del score de IMCO | Asociaciones |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pallan MJ (2011), Reino Unido (1) | 5-7 | m = 296 f = 278 | Bajo peso: m: 1,7 f: 3,7 Peso normal: m: 82,0 f: 72,0 Sobrepeso: m: 5,8 f: 9,1 Obesidad: m: 10,5 f: 15,3 | Figuras de Collins adaptadas por Rand y Resnick | Coeficientes de confiabilidad del instrumento en el test-retest de 3 días | Puntajes negativos o positivos indican que el niño/a se percibe más delgado o con más sobrepeso que el ideal | m: 40 f: 35 | m: 41 f: 48 | Bajo peso: 36,7 Peso normal: 40,9 Sobrepeso: 40,2 Obesidad: 43,85 | Bajo peso: 0,33 (DE 2,26); Peso normal: - 0,05 (DE 2,35); Sobrepeso/ obesidad: 1,86 (DE 2,38) ($p < 0,001$) | Puntuación de IMCO se asoció con el aumento de IMC z-score y con el aumento de la edad |
| Morano M (2011), Italia (21) | 12.6 | m = 162 | Peso normal: 52,5 Sobrepeso: 32,1 Obesidad: 15,4 | Figuras de Collins | Moderada a alta confiabilidad y validez del test-retest en niños | La IMCO se calculó como la discrepancia de "uno mismo - el ideal". Los resultados negativos y positivos indican un deseo de tener mayor o menor peso | | | | *Peso normal:* deportes individuales: - 0,1 (-1,0, 2,0) deportes en equipo: - 0,5 (-3,0, 1,0) *Sobrepeso:* deportes individuales: 0,9 (-1,0, 2,5) deportes en equipo: 0,5 (-1,0, 2,0) | Los niños con sobrepeso presentan más IMCO en comparación con los niños de peso normal |
| Santana ML (2013), Brasil (22) | 11-17 | m = 646 f = 852 | Bajo peso: m: 10,4 f: 6,2 Peso normal: m: 73,4 f: 80,1 Sobrepeso: m: 9,2 f: 8,5 Obesidad: m: 7 f: 5,2 | "Body Shape Questionnaire" (BSQ) | El BSQ fue validado en adolescentes brasileños: Cronbach alfa: 0,96 | Satisfecho con la imagen corporal (puntuaciones ≤ 80); poco insatisfechos (puntuaciones de 81 a 110); moderadamente insatisfechos (puntuaciones de 111 a 140), seriamente insatisfechos (puntuaciones > 140) | m: peso normal 20,2 sobrepeso 57,6 obesidad 26,6 f: peso normal 17 sobrepeso 37,5 obesidad 22,7 | m: bajo peso 31,3 peso normal 4,2 sobrepeso 42,4 f: peso normal 17,9 | m: bajo peso 6 peso normal 5,7 sobrepeso 22,0 obesidad 44,4 ($p < 0,001$) f: bajo peso 5,7 peso normal 22,7 sobrepeso 58,3 obesidad 61,4 ($p < 0,001$) | | Mayor porcentaje de IMCO en mujeres que en hombres. La IMCO fue superior entre los/ las adolescentes con sobrepeso u obesidad. |

*(Continua en la página siguiente)*

**Tabla I (Cont.).** Estudios incluidos, características de los instrumentos para evaluar la IMCO y resultados obtenidos

| Autor/es, (año), país (referencia) | Edad (años) Media o rango | n | Estado de peso | Método/ escala de BP/BD | Validación/ confiabilidad | Descripción de la escala de la IMCO | Subestimación (%) | Sobrestimación (%) | Frecuencia de la IMCO % | Media del score de IMCO | Asociaciones |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fortes L de S (2013), Brasil (23) | 10-19 | m = 163 f = 199 | La media de IMC fue normal en todas las categorías | "Body Shape Questionnaire" (BSQ), auto-reporte | El BSQ fue validado en adolescentes brasileños. Consistencia interna ($\alpha = 0,96$). Confiabilidad fue IC ($r = 0,91$, $p < 0,001$), Conti et al. (2009) | Las puntuaciones superiores a 80 indican insatisfacción con su apariencia física | | | | m: 60 (35-178) f: 78 (35-172) ($p = 0,001$) | Las niñas tenían valores más altos de IMCO |
| Farrow CV (2011), Reino Unido (25) | 7-14 | m = 195 f = 175 | | Escala desarrollada por Wardle et al. y basada en el "figure rating scale" Stunkard, Sorenson- y Schlusinger's (1983) | Confiabilidad interna ($\alpha = 0,78$). En esta muestra, el alfa de Cronbach fue de 0,80 | Alta puntuación indica mayor nivel de insatisfacción | | | | 8,23 (DE 6,15) m: 7,08 (DE 5,95) f: 9,37 (DE 6,20) $p < 0,01$ | Mayor IMCO en mujeres. La IMCO está correlacionada con la ingesta restringida de comida y los síntomas emocionales |
| Farrow (2011), Reino Unido (24) | 10,5 | m = 75 f = 78 | Media del IMC z-score: 0,32 (1.57) m: -0,20 f: -0,45 | Escala desarrollada por Wardle et al., basada en el "figure rating scale", desarrollado por Stunkard et al. (1983) | | La IMCO se calcula restando la figura ideal de la imagen que creían que en realidad parecían | | | | 0,42 (1,02) m: 0,30 f: 0,54 | No diferencias en la IMCO entre niños y niñas |

*(Continua en la página siguiente)*

**Tabla I (Cont.).** Estudios incluidos, características de los instrumentos para evaluar la IMCO y resultados obtenidos

| Autor/es, (año), país (referencia) | Edad (años) Media o rango | n | Estado de peso | Método/escala de BP/BD | Validación/ confiabilidad | Descripción de la escala de la IMCO | Subestimación (%) | Sobrestimación (%) | Frecuencia de la IMCO % | Media del score de IMCO | Asociaciones |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Xanthopoulos M (2011), EUA (26) | 4to-6to grado | n = 1.212 | Bajo peso: 2,1<br>Peso normal: 57,1<br>Sobrepeso: 16,7<br>Obesidad: 24,3 | Subscala "body dissatisfaction" del EDI-2, rango (0-36) | El Cronbach alfa global de la subescala de IMCO de 9 reactivos fue de 0,79. La consistencia interna fue comparable entre las niñas (0,81) y los niños (0,76), así como entre los grupos raciales/étnicos: Asia (0,79), afroamericanos (0,77), hispanos (0,80), de raza caucásica (0 0,84) y otros (74), lo que indica que el instrumento era fiable y se comportó de manera similar en el sexo y grupos raciales/ étnicos | Puntuaciones ≤ 7 indican "baja" insatisfacción, mientras que las puntuaciones 8-30 sugieren insatisfacción "moderada" y > 30 sugieren "elevada" insatisfacción | | | | m: 8,8 (DE 0,5)<br>f: 10,0 (DE 0,5)<br>($p < 0,03$)<br>Bajo peso: 6,9 (DE 1,4)<br>Peso normal: 6,7 (DE 0,3)<br>Sobrepeso: 9,8 (DE 0,5)<br>Obesidad: 14,3 (DE 0,5)<br>($p < 0,001$) | El estado de peso, la raza/ etnia y el sexo fueron el predictor más fuerte de IMCO. Las niñas tenían una mayor IMCO que los niños |
| Papp I (2013), Hungría (27) | 10-16 | m = 145<br>f = 225 | Bajo peso: 10,3<br>Peso normal: 75,1<br>Sobrepeso y obesidad: 14,6 | Subescala de "body dissatisfaction" de 9 reactivos del "Eating Disorder Inventory" (EDI) versión húngara (Túry et al., 1997). Percepción corporal del "Health Behavior in School-aged Children" (HBSC) | La consistencia interna fue de 0,93 para el EDI-BD para muestras combinadas de personas con trastornos alimenticios y mujeres controles no ricos al., 1997) | Escala de 6 puntos desde 1 (nunca) a 6 (siempre) | 13,8 | 28,9 | | m: 23,2 (DE 9,78)<br>f: 27,0 (DE 10,89)<br>$p < 0,001$ | Las niñas presentaron más IMCO por exceso de peso que los niños |
| Quested E (2011), Reino Unido (28) | Media 18,7 | m = 96<br>f = 293 | | Subescala de "body dissatisfaction" de 9 reactivos del "Eating Disorders Inventory" | La validez y confiabilidad buena en poblaciones atléticas y no atléticas | Escala de 27 puntos desde 1 (nunca) a 6 (siempre) | | | | 10,43 (DE 7,38) | Baja insatisfacción corporal (10,43 en una escala de 27 puntos) |

*(Continua en la página siguiente)*

**Tabla I (Cont.).** Estudios incluidos, características de los instrumentos para evaluar la IMCO y resultados obtenidos

| Autor/es, (año), país (referencia) | Edad (años) Media o rango | n | Estado de peso | Método/escala de BP/BD | Validación/ confiabilidad | Descripción de la escala de la IMCO | Subestimación (%) | Sobrestimación (%) | Frecuencia de la IMCO % | Media del score de IMCO | Asociaciones |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Bully P (2011), España (29) | 10-18 | m = 484 f = 451 | | Escala de "body dissatisfaction" dentro del Eating Disorder Inventory y por el indicador índice de masa corporal ideal (IMCi) | En estudios de validación presentó una alta consistencia interna. Cronbach alfa: 0,89 y 0,95 dependiendo del trastorno alimenticio | 10 reactivos: 1 (nunca) a 6 (siempre) codificados en 0-4 | | | | m: 7,93 (DE 8,28) f: 12,40 (DE 10,17) 10-12 años: m: 8,3 (DE 9,2) f: 9,0 (DE 9,2) 13-14 años: m: 8,1 (DE 8,9) f: 12 (DE 10.8) 15-16 años: m: 7,2 (DE 7,7) f: 15,6 (DE 10,6) 17-18 años: m: 8,1 (DE 8,4) f: 13,1 (DE 10) | La IMCO aumentó con la edad solo en las niñas ($p < 0,001$). Las medias de IMC fueron más elevadas en los varones que en las mujeres y las diferencias entre sexos aumentaron con la edad. El IMC fue altamente predictivo del IMCO |
| McCabe MP (2010), Australia (30) | 11-16 | m = 344 f = 246 | Peso normal: m: 45,42 f: 35,25 Sobrepeso: m: 12,88 f: 6,44 | Dos escalas: "Body Dissatisfaction" y "Body Importance" del "Body Image and Body Change Questionnaire" (Ricciardelli & McCabe, 2002) | Alfa Cronbach para insatisfacción corporal: peso normal en niños 0,74 sobrepeso en niños 0,80 peso normal en niñas 0,71 obesidad en niñas 0,76 | Las puntuaciones van de 5 a 25, y las puntuaciones más altas indican mayor niveles de IMCO | | | | m: 11,6 (EEM 0,19) f: 12,0 (EEM 0,27) Peso normal: 10,7 (EEM 0,14) Sobrepeso: 12,8 (SEM = 0,29) ($p < 0,001$) | Adolescentes con sobrepeso reportaron mayor insatisfacción |
| Xu X (2010), China (31) | 12-16 | m = 219 f = 298 | Bajo peso: m: 16,4 f: 10,4 Peso normal: m: 74 f: 86,2 Sobrepeso: m: 9,6 f: 3,4 | Versión modificada de la subescala "Body Image Concern" del "Body Image and Body Change Questionnaire" (McCabe & Ricciardelli, 2004) | Alfa Cronbach: 0,88-0,94. Test-retest: r = 0,70 a 0,85 en adolescentes | Las puntuaciones oscilaron de 5 a 25, las puntuaciones más altas indican una mayor insatisfacción corporal | | | | m: 13.8 (DE 4,21) f:15.3 (DE 4,1) ($p = 0,041$) Bajo peso: 13,19 (DE 4,05) Peso normal: 14,8 (DE 4,2) Sobrepeso: 16,19 (DE 4,47) ($p = 0,001$) | Insatisfacción corporal fue mayor en las mujeres y en las personas con sobrepeso que en los niños y en los adolescentes de peso normal |

*(Continua en la página siguiente)*

**Tabla I (Cont.).** Estudios incluidos, características de los instrumentos para evaluar la IMCO y resultados obtenidos

| Autor/es, (año), país (referencia) | Edad (años) Media o rango | n | Estado de peso | Método/escala de BP/BD | Validación/ confiabilidad | Descripción de la escala de la IMCO | Subestimación (%) | Sobrestimación (%) | Frecuencia de la IMCO % | Media del score de IMCO | Asociaciones |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fuller M (2012), multicultural (11) | 11-18 | m = 1.758 f = 2.247 | Bajo peso: 0,3 Peso normal: 76,95 Sobrepeso: 16,6 Obesidad: 6,2 | Versión de cinco reactivos de la subescala "Body Image Dissatisfaction" del "Body Image and Body Change Inventory" (Ricciardelli & McCabe, 2002) | Alfa Cronbach global fue de 0,86 | Puntuación varió de 1 a 5. La puntuación total se obtiene del promedio de las respuestas de los cinco reactivos | | | | m: 1,42 f: 1,66 | Las niñas tenían más IMCO que los niños dentro de la misma cultura, con las excepciones de los participantes de Indi-Fiji y Malasia. El nivel de IMCO fue bajo. Se observó variabilidad en las puntuaciones de la IMCO, dentro y en todos los grupos |
| Anschutz (2011), Alemania (32) | 9-12 | n = 60 | Sobrepeso: 18,3 Obesidad: 1,7 | "The Children Figure Rating Scale" (Tiggemann & Wilson-Barret, 1998) | Validez en niños y test retest adecuado | Las diferencias absolutas entre las figuras corporales ideales y las percibidas se utilizaron como medida de IMCO. El IMCO se midió después de la exposición al ideal delgado, telenovela y videoclip neutral | | | | 0,69 (DE 1,05) 4to grado: 0,44 (DE 0,93) 5to grado: 0,71 (DE 1,0) 6to grado: 0,92 (DE 1,2) después del videoclip de delgados 1,24 (DE 1,4) (p = 0,001) | Las niñas de 6to grado tuvieron niveles más altos de insatisfacción cuando fueron expuestas al video del ideal delgado |

*(Continua en la página siguiente)*

**Tabla I (Cont.).** Estudios incluidos, características de los instrumentos para evaluar la IMCO y resultados obtenidos

| Autor/es, (año), país (referencia) | Edad (años) Media o rango | n | Estado de peso | Método/escala de BP/BD | Validación/ confiabilidad | Descripción de la escala de la IMCO | Subestimación (%) | Sobrestimación (%) | Frecuencia de la IMCO % | Media del score de IMCO | Asociaciones |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Iannotti RJ (2013), EUA (33) | 11-16 | n = 9,206 | Bajo peso: m: 4,3, f: 3,2 Peso normal: m: 61,9 f: 69,0 Sobrepeso: m: 18,3, f: 16 Obesidad: m: 15,4, f :12 | Cinco reactivos de la subescala de "the body image" del "Body Investment Scale" (Orbach & Mikulincer, 1998) | | Insatisfacción corporal fue evaluada en una escala de 5 puntos. Una puntuación más alta indica una mayor IMCO | | | | 2,2 m: 1,9 f: 2,45 Modelo saludable: m: 1,9 f: 2.37 Poco saludable: m: 1.87 f: 2,39 Modelo típico: m: 2,00 f: 2,53 | Mayor IMCO en mujeres. El grupo típico reportó mayores niveles de IMCO |
| Finne E (2011), Alemania (34) | 11-17 | n = 6.813 | % grasa corporal: m: 19,39 (SE 0,2) f: 26,26 (SE 0,18) | "Entrevistas de Salud y Encuesta Alemana" (KiGGS), preguntas relacionadas con la imagen corporal: si se consideraban "demasiado delgados", "un poco delgados", "exactamente en el peso adecuado", "un poco gordos", o "demasiado gordos" | | La insatisfacción corporal se clasificó como "demasiado delgado", "un poco delgado", "exactamente en el peso", "un poco gordos" o "demasiado gordos" | | | Demasiado delgados: m: 3,1 f: 1,7 Un poco delgados: m: 17,1 f: 7,2 Peso normal: m: 44,5 f: 36,4 Un poco gordos: m: 30,6 f: 44,5 Demasiado gordos: m: 4,7 f: 10,1 (p < 0,001) | | Asociación independiente de IMCO con menores niveles de actividad física. Los niños tenían mayor IMCO por ser delgados y las niñas por mayor peso |

*IMCO: insatisfacción de la imagen corporal; IMCi: índice de masa corporal ideal; m: masculino; f: femenino; PC: percepción corporal; DE: desviación estándar.*

## DISCUSIÓN

Los resultados de esta revisión indican que en niños y adolescentes de 5 a 19 años se han utilizado una gran variedad de métodos para evaluación de la IMCO, y que tanto la subestimación de la imagen corporal como la IMCO son consistentes. En segundo lugar, se ha observado que en la mayoría de los estudios hay una asociación positiva entre el IMC y la IMCO, que la IMCO aumenta con la edad y es más frecuente en las mujeres que en los hombres. En el caso de los hombres se ha reportado la IMCO como resultado de bajo peso. Además, en los 3 estudios que reportan la frecuencia de IMCO, se observó que en los niños con obesidad la IMCO osciló de 44% a 61% y por bajo peso de 6% a 36%; estas frecuencias indican un estado de alarma por la alta frecuencia de IMCO y sus implicaciones en este grupo de edad, lo que permite subrayar la necesidad de mediciones más homogéneas y medidas de prevención de la IMCO.

La variedad de métodos utilizados dificulta comparaciones sobre la situación actual y las tendencias entre grupos de edad, regiones de un país y entre países, lo que complica la valoración de la situación real y de la efectividad de las medidas para prevenir la IMCO y sus consecuencias.

En esta revisión se observó que la mayor frecuencia de la IMCO se presenta en las niñas (11,22,23,25,26,28,31) y aumenta con la edad (1,25,29), lo que podría indicar que la presión ejercida por diferentes los entornos, entre los que se incluyen la familia, los padres, las compañeras, los anuncios de la televisión, las modas, el cine, etc., es mayor en las mujeres que en los hombres (1,22,29,31), incluso a temprana edad, aunque aumenta al llegar a la adolescencia. Esos resultados podrían explicar el aumento en la frecuencia de la anorexia nerviosa, bulimia y atracones en las mujeres más que en los hombres (27,35,36) y la alta demanda para la reducción del peso. Debido a esto, entre otras implicaciones indirectas de los resultados de esta revisión, podrían estar la reducción en la calidad de vida, el aumento en los riesgos de bulimia, la anorexia nerviosa, los atracones, los sentimientos de culpa y la obesidad. Algunos autores sugieren que la IMCO puede ser un síntoma para identificar algún problema o trastorno futuro, como anorexia, bulimia, trastorno por atracón, entre otros (37). Además, la IMCO debido a exceso de peso, también puede provocar ansiedad, baja autoestima y episodios de depresión.

También es importante destacar que niños y adolescentes presentaron IMCO en menores puntajes que las niñas (22-27,29-31), lo que sugiere que los entornos también están afectando la satisfacción de la imagen corporal de los varones (38,39). Esta IMCO puede ser de dos tipos: la de quienes desean una imagen corporal mayor, que indique fuerza y musculatura, y las que desean una imagen más delgada (39). En la presente revisión los puntajes de IMCO en jóvenes por bajo peso fueron bajos, a excepción de un estudio (34), mientras que en otro estudio (22) se presentó un mayor puntaje de IMCO en los niños con obesidad.

En la revisión sistemática realizada por Rees y cols. (40), también ser observa que a una imagen de mayor tamaño le atribuyeron características negativas.

Las implicaciones que tienen estos resultados sobre la salud pueden ser de relevancia. En los medios de comunicación, algunos gobiernos y académicos destacan la necesidad de que la reducción de la obesidad puede realizarse solamente con cambios de estilos de vida, lo que implica que quien tiene exceso de peso no tiene un estilo de vida saludable y es negligente. Sin embargo, las evidencias de programas de prevención e intervención en niños y adolescentes no demuestran qué reducciones de peso son consistentes ni significativas para la reducción del sobrepeso y la obesidad (41).

Se recomienda, para reducir la IMCO, la moderación sobre los mensajes de los gobiernos, medios de comunicación y académicos en relación a la obesidad y resaltar la necesidad de cambios de múltiples entornos para disminuir la obesidad. Centrarse en la voluntad individual o en un peso ideal inalcanzable para ciertos grupos vulnerables, debido a factores genéticos, pre y posnatales y ambientales, puede ocasionar daños no deseables. La discriminación por el peso o la imagen corporal ignora el origen multifactorial de la obesidad en algunos programas de prevención y tratamiento. Se sugieren estudios que evalúen el efecto a largo plazo de la IMCO sobre la salud y el desarrollo social.

Entre las limitaciones de esta revisión está la gran variedad de métodos y escalas utilizadas. Sin embargo, se observa de manera consistente una mayor IMCO con el aumento de IMC. Además, en algunos estudios no se valora la exactitud de la percepción del tamaño corporal. Otra limitación importante es la falta de estudios en diversos países y en poblaciones de diferentes etnias, culturas, nivel de educación y socioeconómico.

Dentro de las fortalezas de la revisión se puede indicar que la mayoría de estudios incluía a muestras grandes que permiten generalizar los resultados a los grupos de edad estudiados, y a que se revisaron estudios realizados en los últimos cinco años.

En conclusión**,** a pesar de que se encontró gran variedad de métodos para evaluar la IMCO, se observó una mayor IMCO con el aumento del IMC. Se puede observar que la IMCO se presenta desde los cinco años, es más frecuente en las mujeres y aumenta con la edad en niños y adolescentes. Se recomienda homogeneizar criterios de evaluación de la IMCO para poder hacer comparaciones internacionales y regionales.

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Nutrición Hospitalaria

Revisión

# Ingestas de energía y nutrientes recomendadas en la Unión Europea: 2008-2016

*Recommended energy and nutrients intakes in the European Union: 2008-2016*

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## Resumen

Esta revisión tiene por objeto reflejar los cambios producidos en la legislación de la Unión Europea y los dictámenes de la Autoridad Europea de Seguridad Alimentaria en relación al etiquetado nutricional de los alimentos, a los valores de referencia de energía, macronutrientes y micronutrientes, y a los niveles máximos de ingesta tolerable.

La vigente legislación europea utiliza los valores de referencia para el etiquetado establecidos por el Comité Científico de la Alimentación Humana en 2003. Sería aconsejable una actualización de los mismos a partir de los valores de referencia establecidos por dicha autoridad europea para vitaminas y minerales. Igualmente sería positiva la inclusión de valores de referencia para el etiquetado de ácidos grasos poliinsaturados, fibra alimentaria y colina, y para el etiquetado específicamente referido a niños de 6 a 36 meses.

Para vitaminas y minerales sería deseable una revisión de los niveles máximos de ingesta tolerable y el establecimiento de cantidades máximas permitidas en los alimentos enriquecidos y en los complementos alimenticios en la Unión Europea; su ausencia puede representar un peligro de ingesta excesiva e insegura de determinados minerales y vitaminas en algunos grupos de población.

**Palabras clave:**

Ingestas recomendadas de energía y nutrientes. Etiquetado nutricional. Valores de referencia. Nivel máximo de ingesta tolerable. Cantidades máximas permitidas.

## Abstract

The aim of this document is to reflect the changes happened in the European Union legislation and the opinions of the European Food Safety Authority in relation to the nutritional labeling on food, the reference values for energy, macronutrients and micronutrients, and the tolerable upper safe levels.

The European legislation in force uses the labeling reference values established by the Scientific Committee on Food in 2003. There would be advisable an update of them from the reference values for vitamins and minerals established by the European Food Safety Authority. Equally, there would be good to include reference labeling values for polyunsaturated fatty acids, dietary fiber and choline, and specific reference labeling values for children from 6 to 36 months.

For vitamins and minerals there would be desirable the revision of tolerable upper safe levels and the establishment of maximum amounts allowed in fortified food and food supplements in the European Union; its absence might represent a risk in some population groups for an excessive and unsafe intake of certain minerals and vitamins.

**Key words:**

Recommended intakes for energy and nutrients. Nutritional labelling. Reference values. Tolerable upper safe levels. Maximum amounts allowed.

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## INTRODUCCIÓN

Las recomendaciones nutricionales han ido evolucionando de acuerdo con los conocimientos científicos de los aspectos fisiológicos y bioquímicos sobre las necesidades de nutrientes del organismo humano en situaciones de salud y enfermedad. La definición de nutrientes esenciales y de los requerimientos nutricionales proporcionó la estructura científica para las recomendaciones basadas en nutrientes.

En revisiones anteriores realizadas en España (1-4) se han analizado las recomendaciones hechas en diversos países europeos, incluyendo España y la Unión Europea (UE), en Estados Unidos (EE. UU.) y por la FAO/OMS. En ellas se han mostrado diferentes datos y conceptos, destacando:

- Cantidades diarias recomendadas (CDR: UE).
- Valores de referencia de la dieta (DRV: UE).
- Aporte dietético recomendado (RDA: EE. UU.).
- Ingesta de referencia de la dieta (DRI: EE. UU.).
- Ingesta de nutrientes recomendada (RNI: FAO/OMS).
- Ingesta (o intervalo de ingesta) adecuada o aceptable (AI).
- Intervalo de ingesta de referencia para los macronutrientes (RI).
- Umbral mínimo de ingesta (LTI).
- Requerimiento medio (AR).
- Ingesta de referencia para la población (PRI).
- Valores de referencia para el etiquetado (RLV).
- Nivel máximo de ingesta tolerable (UL).
- Nivel inferior de observación de efectos adversos (LOAEL).
- Nivel de no observación de efectos adversos (NOAEL).
- Factor de incertidumbre (UF).
- Cantidades máximas de vitaminas y minerales permitidas en alimentos.
- Encuestas de ingesta alimentaria.

El objetivo principal de este documento es revisar la legislación de la UE y los dictámenes de la Autoridad Europea de Seguridad Alimentaria (EFSA) que se han publicado en los últimos 9 años, los cuales han modificado sustancialmente la situación anterior.

**Tabla I.** Cantidad diaria recomendada (CDR) UE 2008 y valor de referencia de nutrientes (VRN) UE 2011

| Nutriente | Unidad | CDR-VRN |
|---|---|---|
| Vitamina A | µg | 800 |
| Vitamina D | µg | 5 |
| Vitamina E | mg | 12 |
| Vitamina K | µg | 75 |
| Vitamina C | mg | 80 |
| Tiamina | mg | 1,1 |
| Riboflavina | mg | 1,4 |
| Niacina | mg | 16 |
| Vitamina $B_6$ | mg | 1,4 |
| Ácido fólico | µg | 200 |
| Vitamina $B_{12}$ | µg | 2,5 |
| Biotina | µg | 50 |
| Ácido pantoténico | mg | 6 |
| Potasio | mg | 2000 |
| Cloruro | mg | 800 |
| Calcio | mg | 800 |
| Fósforo | mg | 700 |
| Magnesio | mg | 375 |
| Hierro | mg | 14 |
| Zinc | mg | 10 |
| Cobre | mg | 1 |
| Manganeso | mg | 2 |
| Fluoruro | mg | 3,5 |
| Selenio | µg | 55 |
| Cromo | µg | 40 |
| Molibdeno | µg | 50 |
| Yodo | µg | 150 |

## LEGISLACIÓN DE LA UNIÓN EUROPEA

La Directiva 2008/100/CE (5) se basó en los RLV establecidos por el Comité Científico de la Alimentación Humana (SCF) de la UE en 2003 (6) con el fin de modificar para algunos nutrientes las CDR establecidas en la Directiva 90/496/CE (7) e introducir nuevas CDR para algunos nutrientes que no la disponían anteriormente. Se aumentó las CDR de las vitaminas E, C y $B_{12}$ y del magnesio, se disminuyó las CDR de tiamina, riboflavina, niacina, vitamina $B_6$, biotina, fósforo y zinc, y se introdujeron nuevas CDR para vitamina K, potasio, cloruro, cobre, selenio, manganeso, cromo, molibdeno y fluoruro. El sodio siguió sin contar con una CDR. Estas CDR están recogidas en la tabla I.

Para el calcio y el ácido fólico las CDR se deberían haber aumentado de acuerdo con los RLV establecidos por el SCF en 2003, para el calcio de 800 a 1000 mg/día y para el ácido fólico de 200 a 400 µg/día, pero se prefirió mantener para ellos las CDR de la Directiva 90/496/CE. En el caso del calcio se debió probablemente al hecho de que para que se pudiera efectuar la declaración nutricional de "fuente de" el alimento debía contener por 100 g o por 100 ml al menos el 15% de la CDR. Como la leche de vaca no enriquecida tiene un contenido en calcio de 120 mg/100 ml, ello equivale al 15% si la CDR es de 800 mg; si la CDR se hubiera aumentado a 1000 mg los 120 mg equivaldrían al 12%, lo que hubiera impedido hacer tal declaración nutricional para la leche no enriquecida y, en consecuencia, declaraciones de propiedades saludables basadas en la presencia de calcio, en aplicación del Reglamento (CE) 1924/2006 (8).

Estas mismas CDR de la Directiva 2008/100/CE se reprodujeron íntegramente en el Reglamento (UE) 1169/2011 (9), Anexo XIII, parte A, bajo la denominación de "Valores de referencia de nutrientes (VRN)" para vitaminas y minerales (adultos). Este Reglamento, en

el caso de las bebidas, disminuyó del 15% al 7,5% el porcentaje mínimo necesario para la consideración de "fuente de". Ello hubiera permitido el aumento de la CDR (= VRN) de calcio de 800 mg a 1000 mg, ya que el 7,5% de 1000 mg son 75 mg y por tanto un nivel inferior al contenido en calcio de la leche no enriquecida. Pero desgraciadamente no se aprovechó esta oportunidad y así la leche no enriquecida pasó de un día a otro de ser "fuente de" calcio a "alto contenido" de calcio (≥ 15% CDR en bebidas).

En dicho Reglamento tampoco se revisaron al alza los 5 µg de la CDR para la vitamina D, muy inferior a los valores de EE. UU. del 2011 (RDA vitamina D 15 µg y para > 70 años 20 µg, RDA calcio 1000 mg y para hombres > 70 años y mujeres > 50 años 1200 mg) (10) y del reciente dictamen de la EFSA para la vitamina D (AI 15 µg), ambos bajo mínima síntesis cutánea de vitamina D.

Como respuesta a las ingestas de referencia para el etiquetado de energía, grasas totales, grasas saturadas, hidratos de carbono y sal (en lugar de sodio) propuestas por la Comisión Europea, el Panel de Productos Dietéticos, Nutrición y Alergias (NDA) de la EFSA emitió un dictamen (11). Debido a su relación con la salud, las ingestas recomendadas para grasas totales, grasas saturadas, azúcares y sal están basadas en los límites superiores, mientras que para los hidratos de carbono se basa en el límite inferior. Estos valores, junto con una ingesta de 50 g de proteínas, fueron incorporados como "Ingestas de referencia del valor energético y de los nutrientes seleccionados distintos de las vitaminas y minerales" (macronutrientes en adultos) en el Reglamento (UE) 1169/2011, Anexo XIII, parte B, y se reflejan en la tabla II.

En cuanto al sodio, en este Reglamento se sustituyó el término "sodio" por el de "sal", a fin de que el consumidor pudiera entender fácilmente la información proporcionada en el etiquetado, a pesar de que una gran parte del sodio presente en los alimentos no está en forma de sal común (cloruro sódico) y que las normas FAO/OMS y de EE. UU. utilizan el sodio y no la sal en el etiquetado nutricional. Desde 1990, año de publicación de la Directiva 90/496/CE, en el etiquetado nutricional –hasta 2016 generalmente voluntario- de los alimentos se declaraba el contenido de sodio y no su equivalente en sal. Dado que el 40% de la sal común es sodio, la ingesta de referencia de 6 g para la sal equivale a 2,4 g de sodio.

**Tabla II.** Ingesta de referencia (IR) para el etiquetado del valor energético y de macronutrientes, UE 2011

| Valor energético o nutriente | Unidad | IR |
|---|---|---|
| Valor energético | kJ/kcal | 8400/2000[a] |
| Grasas (totales) | g | 70 |
| - Grasas saturadas | g | 20 |
| Hidratos de carbono | g | 260 |
| - Azúcares | g | 90 |
| Proteínas | g | 50 |
| Sal | g | 6 |

*[a]Corresponde a mujeres moderadamente activas, correspondiente a un nivel de actividad física (PAL) de 1.6.*

Además, la Comisión Europea solicitó a la EFSA las ingestas de referencia para el etiquetado de ácidos grasos poliinsaturados n-3 y n-6. El Panel NDA emitió un dictamen sobre las mismas (12) pero sus valores, basados en consideraciones de salud cardiovascular y reseñados en la tabla III, no fueron incorporados al Reglamento (UE) 1169/2011, Anexo XIII, parte B.

Este Reglamento prevé que la Comisión Europea pueda adoptar "actos de ejecución" sobre la indicación en el etiquetado de ingestas de referencia para grupos de población específicos. Tal es el caso de los niños de 6 a 36 meses, que ya tienen unos VRN específicos para vitaminas y minerales en la legislación de los preparados de continuación. Lamentablemente, las conocidas popularmente como "leches de crecimiento", dirigidas a niños de 1 a 3 años, no pueden aplicar en su etiquetado VRN específicos para su edad pues solo están reguladas por la legislación general aplicable a todos los alimentos.

La Directiva 2002/46/CE (13) sobre complementos alimenticios y el Reglamento (UE) 1925/2006 (14) sobre alimentos enriquecidos prevén el establecimiento de unas cantidades máximas (diarias y/o por una determinada cantidad de alimento) permitidas para los minerales y vitaminas contenidos en los mismos, tomando en consideración sus UL para distintos grupos de población y su ingesta a partir de otras fuentes de la dieta, así como sus valores de referencia. Después de más de una década, la Comisión Europea no ha iniciado todavía el proceso para fijar dichas cantidades máximas, por lo cual se han establecido cantidades máximas heterogéneas en algunos países europeos, por ejemplo en Francia, Italia, Bélgica y Dinamarca para los complementos alimenticios y en Bélgica y Dinamarca para los alimentos enriquecidos. Una cantidad muy elevada de algunos minerales o vitaminas en la dosis diaria recomendada en complementos alimenticios y/o su ingesta excesiva (por contenido elevado y/o alto consumo diario) en alimentos enriquecidos, sumados a su ingesta a partir de otras fuentes de la dieta, comporta el riesgo de exceder el UL de determinados minerales y vitaminas en algunos grupos de población.

## VALORES DE REFERENCIA

La Comisión Europea solicitó a la EFSA que revisara los RLV establecidos en 2003 por el SCF para energía, nutrientes y otras

**Tabla III.** Ingestas de referencia (IR) para el etiquetado de ácidos grasos poliinsaturados n-3 y n-6, EFSA 2009

| Nutriente | Unidad | IR |
|---|---|---|
| Ácidos grasos n-3 | | |
| - α-linolénico (ALA) | g/d | 2 |
| - EPA+DHA | mg/d | 250 |
| Ácidos grasos n-6 | | |
| - Linoleico (LA) | g/d | 10 |

*EPA: ácido eicosapentaenoico. DHA: ácido docosahexaenoico.*

sustancias con un efecto nutricional o fisiológico, en el contexto de una dieta equilibrada y un estilo de vida saludable, a fin de que mediante una nutrición óptima contribuyan a una buena salud. Dado que los requerimientos nutricionales difieren con la edad, el sexo y la situación fisiológica, la EFSA (15) propuso ofrecerlos por tramos de edad, sexo y situaciones de embarazo y lactancia materna, a excepción de los 6 primeros meses de vida para los cuales el modelo de referencia es la leche materna. Y decidió derivar para ellos 5 tipos de "Valores de referencia de la dieta (DRV)":

- Ingesta de referencia para la población (PRI).
- Requerimiento medio (AR).
- Umbral mínimo de ingesta (LTI).
- Ingesta adecuada (AI).
- Intervalo de ingesta de referencia para macronutrientes (RI).

## ENERGÍA

El Panel NDA (16) publicó los AR, expresados como MJ/día, para las distintas edades o tramos de edad de ambos sexos, así como los incrementos producidos en los 3 trimestres de embarazo y en el primer semestre de lactancia materna. Para ello, al gasto energético basal (REE) se le añade la energía adicional para atender los distintos niveles de actividad física (PAL) y las necesidades de crecimiento de los niños y adolescentes.

## GRASAS

La EFSA emitió su dictamen sobre los DRV para grasas (17), incluyendo los ácidos grasos saturados, monoinsaturados, poliinsaturados, *trans* y colesterol, los cuales pueden verse en la tabla IV. No estableció DRV para los ácidos grasos saturados, monoinsaturados, *trans*, ácido linoleico conjugado (CLA) y colesterol, pero recomendó mantener lo más baja posible la ingesta de ácidos grasos saturados y *trans*.

Respecto a los ácidos grasos poliinsaturados n-3 de cadena larga, dictaminó una AI de 250 mg para la suma de los ácidos eicosapentaenoico (EPA) y docosahexaenoico (DHA). Durante el embarazo y la lactancia materna recomendó una ingesta adicional (a la de 250 mg de EPA + DHA) de 100-200 mg de DHA para compensar las pérdidas oxidativas de DHA y facilitar su acumulación por el lactante. Para los niños de 6 a 24 meses de edad fijó una AI de DHA de 100 mg.

**Tabla IV.** Intervalo de ingesta de referencia (RI) o ingesta adecuada (AI) de grasas, EFSA 2010

| Nutriente | RI o AI | Unidad | Cantidad |
|---|---|---|---|
| Total grasas | RI | % energía total | 20 - 35 |
| Ácidos grasos n-3 | | | |
| - $\alpha$-linolénico (ALA) | AI | % energía total | 0,5 |
| - EPA+DHA | AI | mg/d | 250 |
| Ácidos grasos n-6 | | | |
| - Linoleico (LA) | AI | % energía total | 4 |

*EPA: ácido eicosapentaenoico. DHA: ácido docosahexaenoico.*

## HIDRATOS DE CARBONO Y FIBRA ALIMENTARIA

Los DRV para hidratos de carbono y fibra alimentaria (18) están resumidos en la tabla V.

El Panel NDA no pudo establecer un UL para los azúcares añadidos, pero advirtió que un exceso de los mismos puede contribuir a la ganancia de peso, a incrementar las concentraciones séricas de triglicéridos y colesterol, y afectar negativamente la respuesta en los niveles de glucosa e insulina. Tampoco se pronunció sobre el índice glucémico y la carga glucémica, si bien reconoció que una reducción de ambos puede tener efectos favorables sobre factores de riesgo metabólico, tales como los lípidos séricos.

Para la fibra estableció una AI de 25 g en la población adulta, nivel adecuado para una laxación normal. Sin embargo, reconoció que cantidades superiores reducen el riesgo de enfermedades coronarias y de diabetes tipo 2, y mejoran el mantenimiento del peso. En el caso de los niños la AI es de 2 g/MJ, equivalente a 8,4 g/1000 kcal. La AI de fibra alimentaria de 25 g en adultos no fue incorporada a las ingestas de referencia de macronutrientes del Reglamento 1169/2011, Anexo XIII, parte B.

## PROTEÍNAS

Para la población adulta la EFSA (19) estimó un AR de 0,66 g/kg peso y una PRI de 0,83 g/kg de peso. Durante la infancia y la adolescencia los AR y PRI por kilo de peso son superiores a dichos niveles, descendiendo progresivamente la PRI desde 1,31 g/kg de peso a los 6 meses de vida hasta los 0,83 g a los 18 años. Para llegar a las PRI/día multiplicó las PRI/kg de peso por los teóricos "Pesos de referencia" para cada edad, tanto de hombres como de mujeres. Para el embarazo estimó una PRI/día adicional de 1 g en el primer trimestre, de 9 g en el segundo y de 28 g en el tercero, y en la lactancia materna una PRI/día adicional de 19 g en el primer semestre y de 13 g después.

**Tabla V.** Intervalo de ingesta de referencia (RI) o ingesta adecuada (AI) de hidratos de carbono y fibra alimentaria, EFSA 2010

| Nutriente | RI o AI | Unidad | Cantidad |
|---|---|---|---|
| Hidratos de carbono | RI | % energía total | 45 - 60 |
| Fibra alimentaria | | | |
| - Niños > 1 año | AI | g/MJ | 2 |
| - Adultos | AI | g/d | 25 |

Como comparación con la ingesta de referencia de 50 g de proteínas del Reglamento 1169/2011, Anexo XIII, parte B, el PRI para mujeres adultas es de 52 g y en mujeres de ≥ 60 años es de 55 g, mientras que en los hombres adultos es de 62 g y en los hombres de ≥ 60 años es de 61 g.

Las ingestas medias de proteínas en Europa superan frecuentemente la PRI de 0,83 g/kg de peso, habiéndose observado ingestas (percentil 95 en los hombres holandeses) de 1,7 g/kg de peso o 27% de la energía, si bien no se han detectado inconvenientes o ventajas aparentes. En lactantes debe evitarse un exceso de proteínas a fin de no afectar negativamente al balance hídrico.

## AGUA

En la tabla VI se indican las AI de agua (20) para los distintos grupos de edad de ambos sexos y los incrementos debidos a la gestación o la lactancia materna. Dichos AI se aplican solo en condiciones moderadas de temperatura ambiental y de actividad física. En caso de darse condiciones extremas puede ser necesaria una ingesta mucho más elevada. No estableció un UL para el agua, pero el Panel NDA advirtió que una ingesta muy elevada puede conducir a una hiponatremia por intoxicación hipo-osmolar de agua.

## VITAMINAS Y COLINA

La EFSA hasta ahora ha determinado unas PRI o, en su defecto, AI de 11 vitaminas (21-31): A, D, E, C, tiamina, niacina, $B_6$, folato, $B_{12}$, ácido pantoténico y biotina. Faltan todavía los DRV para vitamina K y riboflavina. En el año 2017 se publicará la AI para la vitamina K (borrador EFSA: 1 µg/kg de peso en los distintos tramos de edad, siendo de 70 µg/d para los adultos con inclusión de embarazo y lactancia materna). Para la vitamina E se propone solo como $\alpha$-tocoferol una AI diaria, en lugar de como equivalentes de $\alpha$-tocoferol que incluía 4 tocoferoles y 4 tocotrienoles ($\alpha$, $\beta$, $\gamma$, $\delta$) en proporción con la ingesta de ácidos grasos poliinsaturados (6). Para la niacina se ofrecen los datos como equivalente de niacina, es decir añadiendo, a la niacina preformada de la dieta, la cantidad teórica de niacina que puede sintetizarse a partir del triptófano de las proteínas ingeridas. Para el folato, expresado como equivales de folato en la dieta, se usa una mayor ponderación para el suplementado que para el contenido de forma natural en los alimentos. Los DRV se refieren a la ingesta diaria absoluta de cada vitamina, salvo de tiamina y niacina de las cuales su PRI está en función de la cantidad de energía diaria expresada en MJ.

En cuanto a la colina (32), excepción hecha al nivel exigido legalmente en los preparados para lactantes, por primera vez se la considera como nutriente esencial para todas las edades, tal como ya se reconocía en EE. UU.

Los DRV de 11 vitaminas y la AI de la colina están recopilados en la tabla VII.

## MINERALES

Hasta el presente la EFSA ha establecido unas PRI o, en su ausencia, AI de 12 minerales (33-44): potasio, calcio, fósforo, magnesio, hierro, zinc, cobre, yodo, selenio, manganeso, molibdeno y fluoruro, las cuales se encuentran en la tabla VIII. Quedan pendientes de fijación los DRV de sodio y cloruro. Para el hierro se distingue las PRI de las mujeres en edad fértil de la que tienen las postmenopáusicas. Se ha tenido en cuenta el efecto inhibitorio de la cantidad de fitato de la dieta sobre la absorción de zinc, a la hora de fijar su PRI.

El Panel NDA afirmó que no existe evidencia de efectos beneficiosos asociados a la ingesta de cromo en personas sanas con una glucemia normal. Por ello consideró inapropiado el establecimiento de una AI (45).

## NIVELES MÁXIMOS DE INGESTA TOLERABLE

Primero el SCF (2000-2003) y luego la EFSA (2004-2005) dictaminaron sobre los UL de las 13 vitaminas (y además del $\beta$-caroteno) y de 20 minerales (incluyendo boro, silicio, níquel, vanadio y estaño), asignándoles o no asignándoles un UL. Estos UL fueron compilados en 2006 por la EFSA (46).

**Tabla VI.** Ingesta adecuada (AI) de agua, EFSA 2010

| Edad/situación | Unidad | Hombres | Mujeres |
|---|---|---|---|
| Lactantes < 6 meses | ml/kg de peso | 100-190 | 100-190 |
| Lactantes > 6 meses | ml/d | 800-1000 | 800-1000 |
| 2-3 años | ml/d | 1300 | 1300 |
| 4-8 años | ml/d | 1600 | 1600 |
| 9-13 años | ml/d | 2100 | 1900 |
| ≥ 14 años | ml/d | 2500 | 2000 |
| Embarazo | ml/d | | +300 |
| Lactancia materna | ml/d | | +700 |

**Tabla VII.** Ingesta de referencia para la población (PRI) o ingesta adecuada (AI) para 11 vitaminas y colina, EFSA 2013-2016

| Edad, sexo y situación | A µg ER/d PRI | D µg/d AI | E mg α-T/d AI | C mg/d PRI | $B_1$ mg/MJ PRI | Niacina mg EN/MJ PRI | $B_6$ mg/d PRI | Folato µg EFD/d PRI | $B_{12}$ µg/d AI | $B_5$ mg/d AI | $B_8$ µg/d AI | Colina mg/d AI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7-11 meses | 250 | 10 | 5 | 20 | 0,1 | 1,6 | 0,3 (AI) | 80 (AI) | 1,5 | 3 | 6 | 160 |
| 1-3 años | 250 | 15a | 6 | 20 | 0,1 | 1,6 | 0,6 | 120 | 1,5 | 4 | 20 | 140 |
| 4-6 años | 300 | 15a | 9 | 30 | 0,1 | 1,6 | 0,7 | 140 | 1,5 | 4 | 25 | 170 |
| 7-10 años | 400 | 15a | 9 | 45 | 0,1 | 1,6 | 1,0 | 200 | 2,5 | 4 | 25 | 250 |
| 11-14 años H | 600 | 15a | 13 | 70 | 0,1 | 1,6 | 1,4 | 270 | 3,5 | 5 | 35 | 340 |
| 11-14 años M | 600 | 15a | 11 | 70 | 0,1 | 1,6 | 1,4 | 270 | 3,5 | 5 | 35 | 340 |
| 15-17 años H | 750 | 15a | 13 | 100 | 0,1 | 1,6 | 1,7 | 330 | 4 | 5 | 35 | 400 |
| 15-17 años M | 650 | 15a | 11 | 90 | 0,1 | 1,6 | 1,6 | 330 | 4 | 5 | 35 | 400 |
| ≥ 18 años H | 750 | 15a | 13 | 110 | 0,1 | 1,6 | 1,7 | 330 | 4 | 5 | 40 | 400 |
| ≥ 18 años M | 650 | 15a | 11 | 95 | 0,1 | 1,6 | 1,6 | 330 | 4 | 5 | 40 | 400 |
| Embarazo | 700 | 15a | 11 | +10 | 0,1 | 1,6 | 1,8 | 600 (AI) | 4,5 | 5 | 40 | 480 |
| Lactancia materna | 1300 | 15a | 11 | +60 | 0,1 | 1,6 | 1,7 | 500 | 5 | 7 | 45 | 520 |

*[a]Bajo condiciones de mínima síntesis de vitamina D. En presencia de dicha síntesis el requerimiento es menor e incluso puede ser cero.*

*H: hombres. M: mujeres. $B_1$: tiamina (0,1 mg/MJ = 0,42 mg/1000 kcal). $B_5$: ácido pantoténico. $B_8$: biotina.*

*ER: equivalentes de retinol. 1 µg ER = 1 µg retinol = 6 µg β-caroteno = 12 µg otros carotenoides provitamina A.*

*α-T: α-tocoferol, solo se considera esta forma de vitamina E.*

*EN: equivalentes de niacina (1 mg EN = 1 mg niacina = 60 mg triptófano de la dieta). 1,6 mg EN/MJ = 6,7 mg EN/1000 kcal.*

*EFD: equivalente de folato en la dieta. 1 µg EFD = 1 µg folato en la dieta = 0,6 ácido fólico suplementado si se consume con alimentos = 0,5 µg ácido fólico si el suplemento se toma en ayunas. Ingesta combinada de folato en la dieta y ácido fólico: µg EFD = µg folato en la dieta + (1,7 x µg ácido fólico).*

**Tabla VIII.** Ingesta de referencia para la población (PRI) o ingesta adecuada (AI) para 12 minerales, EFSA 2013-2016

| Edad, sexo y situación | K mg/d AI | Ca mg/d PRI | P mg/d AI | Mg mg/d AI | Fe mg/d PRI | Zn mg/d PRI | Cu mg/d AI | I µg/d AI | Se µg/d AI | Mn mg/d AI | Mo µg/d AI | F mg/d AI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7-11 meses | 750 | 280(AI) | 160 | 80 | 11 | 2,9 | 0,4 | 70 | 15 | 0,02-0,5 | 10 | 0,4 |
| 1-3 años | 800 | 450 | 250 | 170 | 7 | 4,3 | 0,7 | 90 | 15 | 0,5 | 15 | 0,6 |
| 4-6 años | 1100 | 800 | 440 | 230 | 7 | 5,5 | 1,0 | 90 | 20 | 1,0 | 20 | 1,0 H-0,9 M |
| 7-10 años | 1800 | 800 | 440 | 230 | 11 | 7,4 | 1,0 | 90 | 35 | 1,5 | 30 | 1,5 H-1,4 M |
| 11-14 años H | 2700 | 1150 | 640 | 300 | 11 | 10,7 | 1,3 | 120 | 55 | 2,0 | 45 | 2,2 |
| 11-14 años M | 2700 | 1150 | 640 | 250 | 11-13 | 10,7 | 1,1 | 120 | 55 | 2,0 | 45 | 2,3 |
| 15-17 años H | 3500 | 1150 | 640 | 300 | 11 | 14,2 | 1,3 | 130 | 70 | 3,0 | 65 | 3,2 |
| 15-17 años M | 3500 | 1150 | 640 | 250 | 13 | 11,9 | 1,1 | 130 | 70 | 3,0 | 65 | 2,8 |
| 18-24 años H | 3500 | 1000 | 550 | 350 | 11 | 9,4-16,3[b] | 1,6 | 150 | 70 | 3,0 | 65 | 3,4 |
| 18-24 años M | 3500 | 1000 | 550 | 300 | 16[a] | 7,5-12,7[b] | 1,3 | 150 | 70 | 3,0 | 65 | 2,9 |
| ≥ 25 años H | 3500 | 950 | 550 | 350 | 11 | 9,4-16,3[b] | 1,6 | 150 | 70 | 3,0 | 65 | 3,4 |
| ≥ 25 años M | 3500 | 950 | 550 | 300 | 16[a] | 7,5-12,7[b] | 1,3 | 150 | 70 | 3,0 | 65 | 2,9 |
| Postmenopausia | 3500 | 950 | 550 | 300 | 11 | 7,5-12,7[b] | 1,3 | 150 | 70 | 3,0 | 65 | 2,9 |
| Embarazo | = | = | = | = | 16 | +1,6 | 1,5 | 200 | = | = | = | = |
| Lactancia materna | 4000 | = | = | = | 16 | +2,9 | 1,5 | 200 | 85 | = | = | = |

*[a]Estas PRI cubren el requerimiento de hierro de aproximadamente el 95% de las mujeres premenopáusicas.*

*[b]Estas PRI de zinc aumentan con la cantidad de fitato de la dieta (300 y 1200 mg/d respectivamente para ambos extremos de las horquillas), debido a su efecto inhibitorio sobre la absorción de zinc.*

*H: hombres. M: mujeres.*

**Tabla IX.** Nivel máximo de ingesta tolerable (UL) de vitamina D y calcio, EFSA 2012

| Edad, sexo y situación | Vitamina D µg/d | Calcio mg/d |
|---|---|---|
| 0-12 meses | 25 | No establecido |
| 1-10 años | 50 | No establecido |
| 11-17 años | 100 | No establecido |
| ≥ 18 años | 100 | 2500 |
| Embarazo | 100 | 2500 |
| Lactancia materna | 100 | 2500 |

Posteriormente el Panel NDA solo ha revisado los UL de vitamina D (47) y calcio (48) previamente establecidos, los cuales se detallan en la tabla IX. En el caso de vitamina D se ha doblado el UL anterior, pasando de 25 a 50 µg/d en los niños de 1 a 10 años y de 50 a 100 µg/d en personas mayores de 10 años, y no han variado los 25 µg/d en los lactantes. Para el calcio se mantiene el UL de 2500 mg/d para adultos, incluyendo gestación y lactancia materna, y siguen sin fijar los UL para los lactantes, niños y adolescentes, aunque para estos grupos de edad no se ha identificado un riesgo con el nivel más elevado de ingesta de calcio. Las ingestas más elevadas de calcio en los hombres europeos se acercan mucho al UL.

La EFSA emitió un dictamen (49) sobre los ácidos grasos poliinsaturados n-3 de cadena larga, que incluyen los ácidos eicosapentaenoico (EPA, C20:5), docosahexaenoico (DHA, C22:6) y docosapentaenoico (DPA, C22:5). Los datos disponibles no le permitieron establecer un UL pero consideró que es improbable que ingestas suplementarias conjuntas de EPA y DHA de hasta 5 g/día, o bien individuales de hasta 1,8 g de EPA o 1 g de DHA, induzcan cambios en las funciones inmunitarias que puedan implicar en la población general un riesgo de infecciones o de activación inapropiada de la respuesta inflamatoria. No se pronunció sobre dosis suplementarias individuales de DPA, el cual suele acompañar en pequeña cantidad la suplementación de EPA y DHA.

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Nutrición Hospitalaria

# Nota Clínica

## Catheter traction and gastric outlet obstruction: a repeated complication of using a Foley catheter for gastrostomy tube replacement

*Migración del catéter y obstrucción de la salida gástrica: una complicación repetida del uso de catéteres de tipo Foley para substitución de la sonda de gastrostomía*

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## Abstract

**Background:** Percutaneous endoscopic gastrostomy (PEG) is a safe procedure and major morbidity is unusual. However, the number of PEG fed patients is increasing all over the world and complications may become more and more frequent.

**Case report:** We describe a 73 years old woman with persistent vomit after replacement of the standard PEG tube with a Foley catheter. An upper GI endoscopy showed the catheter pulled into the duodenum causing gastric outlet obstruction. It was removed and replaced by a suitable standard PEG tube, allowing PEG feeding to be resumed.

**Discussion:** Previous reports pointed the risk of this complication, almost always associated with insertion of a Foley-type catheter. Replacement of PEG tubes should be performed by experienced teams using standard PEG tubes and the use of Foley-type catheters for this purpose should be banned from routine practice.

**Key words:**

Gastrostomy.
Foley catheter.
Enteral nutrition.
Complications.

## Resumen

**Introducción:** la gastrostomía endoscópica percutánea (PEG) es un procedimiento seguro con una morbilidad poco común. Sin embargo, el número de pacientes alimentados por PEG está aumentando en todo el mundo y las complicaciones pueden llegar a ser cada vez más frecuentes.

**Caso clínico:** se describe el caso de una mujer de 73 años que se presentó con vómitos persistentes después de la sustitución de la sonda PEG estándar por una sonda de tipo Foley. La endoscopia digestiva mostró el catéter situado en el duodeno causando obstrucción de la salida gástrica. La sonda Foley fue retirada y sustituida por una sonda PEG estándar adecuada, lo que permitió el reinicio de la alimentación por PEG.

**Discusión:** descripciones anteriores en la literatura señalaron el riesgo de esta complicación, casi siempre asociada a la inserción de un catéter de tipo Foley. La sustitución de sondas PEG debe ser realizada por equipos experimentados; el uso de catéteres de tipo Foley para este fin debe ser evitado en la práctica clínica habitual.

**Palabras clave:**

Gastrostomía. Foley.
Nutrición enteral.
Complicaciones.

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## BACKGROUND

All over the world and most strikingly in developed countries, population is aging. In 2010, world elderly population (above 65 years old) should represent about 8% of total world population, which corresponds to more than 500 million people (1). In 2050, it is expected that this elderly population reach about 1.500 million, 16% of total world population. The increase number of older citizens is creating new social and clinical problems. Neurologic disorders increase with age. Also, most cancers, including head and neck cancer, are more frequent in elderly patients. Neurologic disorders and head and neck cancer share an important clinical feature: they both cause dysphagia and long standing dysphagia is the major clinical indication for percutaneous endoscopic gastrostomy (PEG) (2). This aging population in developed countries is creating an increasing number of PEG fed patients.

Endoscopic gastrostomy is generally considered a safe procedure with very low mortality and unusual severe morbidity (3). Some complications may eventually occur and becoming more and more frequent due to the high number of patients usually fed through the gastrostomy for months and years (3). Migration of the PEG tube is considered a rare complication of long term enteral feeding. Indeed, standard PEG tubes have external bumpers that prevent migration into the stomach and duodenum. Most of the rare cases of migration into the duodenum were reported with Foley-type tubes that, unlike standard PEG tubes, do not have external bumpers. Nevertheless, Foley tubes are still used because they are cheaper than standard PEG tubes and widely available in nursing homes and other health facilities.

## CASE REPORT

A 73 years old woman was admitted in the emergence room with a two days history of vomiting. She suffered a stroke two years before and she was fed using an endoscopic gastrostomy. Since the discharge after the stoke, the patient was followed in the Artificial Nutrition Outpatient Consultation of our Hospital. Gastrostomy tubes were regularly changed each 4-6 months. One week before the vomiting episode, the patient accidentally pulled out her PEG tube. A Foley catheter was passed in order to replace the PEG tube and the patient was fed through this catheter for a few days. Two days before hospital admission she started vomiting after each meal. At the same time, the Foley catheter was pulled into the stomach leaving just the proximal tip in the PEG gastrocutaneous tract (Fig. 1). An upper GI endoscopy was performed showing the catheter pulled into the duodenum (Fig. 2) where the balloon caused obstruction. The balloon was deflated and removed. A 24Fr PEG tube was passed and the patient resumed gastrostomy feeding immediately without any problem.

## DISCUSSION

Inadvertent removal of PEG tube occurs in 1.6% to 4.4% of patients (3). In order to maintain the feeding access and prevent spontaneous closure of the gastrocutaneous tract, the tube must be replaced as soon as possible. A large percentage of PEG fed patients is bedridden or has major motility impairment, living in nursing homes or other institutions. These patients are difficult to move to a hospital where experience enteral feeding teams can provide adequate tube replacement. In many occasions, replacing the PEG tube by a Foley catheter is appealing. Furthermore, some articles support this option. In a 1994 study, 46 patients were randomized for replacement with standard PEG tubes or Foley catheters. They used both tubes during several weeks and neither the Foley catheter nor the standard replacement gastrostomy tube migrated into duodenum (4). To the best of our knowledge, there was no other prospective study evaluating the replacement of PEG tubes with Foley-type catheters but some teams kept advocating this procedure (5). That is not

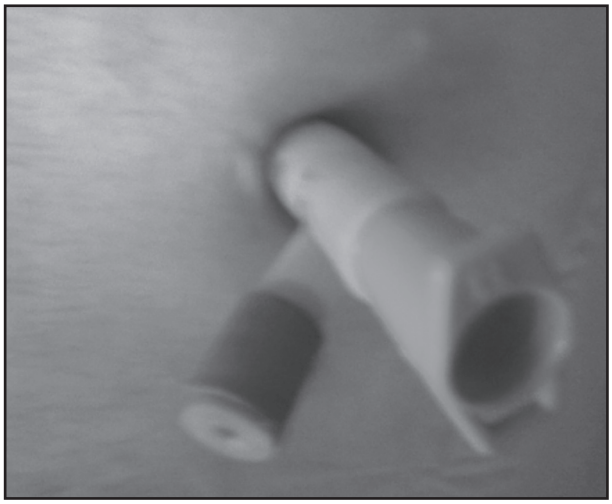

**Figure 1.**
Proximal tip of the Foley catheter in the PEG gastrocutaneous tract.

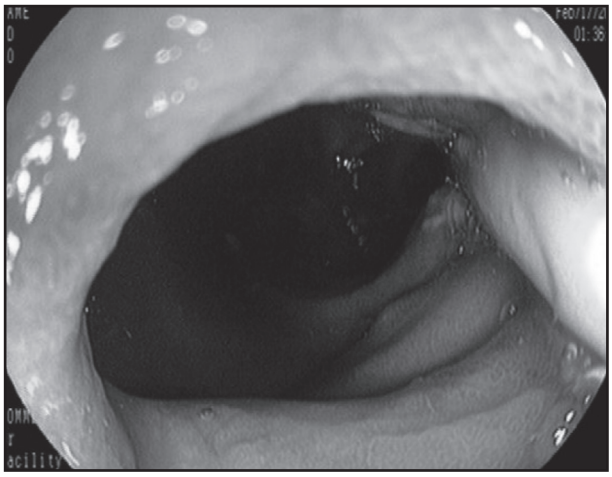

**Figure 2.**
Foley catheter in the duodenum.

the experience of our enteral feeding team as over the years we had several cases of tube migration with duodenal obstruction, like the one described above, and others previously reported in literature (6-8). This is not only our experience since over the years a large number of migrations were also reported, including in children (9) and occasionally causing pancreatitis (10). Most of these duodenal migrations are caused by Foley-type catheters (3). Each hospital or institution should have an optimal protocol for PEG tube replacement (11). Replacement of PEG tubes using Foley catheters in institutions without experienced teams and established protocols increases the risks of severe complications.

## CONCLUSION

Replacement of PEG tubes should be performed by experienced teams in institutions with comprehensive protocols and always using standard PEG tubes. According with our experience, the use of Foley-type catheters that may migrate into the duodenum and cause obstruction is occasionally performed in institutions with little experience, nevertheless this strategy is dangerous and should be banned.

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