Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):181-192
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisiones

Impacto de la nutrición en la evolución de la enfermedad inflamatoria intestinal

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Resumen

La enfermedad inflamatoria intestinal es una entidad de etiopatogenia aún no bien conocida, con importantes implicaciones nutricionales y metabólicas, por la alta prevalencia de malnutrición que conlleva; por la posible implicación de factores dietéticos en su patogenia; y por la hipótesis de que la intervención nutricional pudiera ser un tratamiento primario de la enfermedad. Algunos nutrientes, además de su función exclusivamente nutricional, podrían inducir un bajo estímulo antigénico, regular respuestas inflamatorias e inmunológicas y estimular el trofismo de la mucosa intestinal. La evidencia disponible actual apoya el empleo de nutrición enteral en enfermedad de Crohn como terapia primaria en adultos si el tratamiento con corticoides no es posible (fracaso o contraindicación) (grado de recomendación A) o bien en terapia combinada con fármacos en pacientes malnutridos y estenosis inflamatoria del intestino. En los pacientes en remisión clínica duradera no se ha demostrado beneficio de la nutrición enteral o suplementos en ausencia de déficits nutricionales. No se recomienda el uso de fórmulas elementales ni modificadas (glutamina, ácidos grasos omega 3). En colitis ulcerosa, no se ha demostrado la influencia de la nutrición sobre la actividad de la enfermedad, aunque disponemos de datos prometedores sobre el papel de los ácidos grasos w3 con cubierta entérica y de un posible papel de los probióticos. En el tratamiento y profilaxis de la pouchitis crónica, el empleo de probióticos puede tener un papel (VSL#3). La nutrición debe considerarse un componente integral en el manejo de los pacientes con EII.

(*Nutr Hosp*. 2010;25:181-192)

DOI:10.3305/nh.2010.25.2.4295

Palabras clave: *Enfermedad inflamatoria intestinal. Enfermedad de Crohn. Colitis ulcerosa. Probióticos. Nutrición enteral.*

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Recibido: 2-IX-2009.
Aceptado: 6-XI-2009.

IMPACT OF NUTRITIONAL TREATMENT IN THE EVOLUTION OF INFLAMMATORY BOWEL DISEASE

Abstract

Inflammatory bowel disease is an entity with not well-known pathogenesis, and important nutritional and metabolic implications because of the high prevalence of malnutrition, the possible implication of dietary factors in its pathogenesis and because of the hypothesis that nutritional intervention could be a primary treatment for the disease. Some nutrients could induce a low antigenic stimuli, regulate inflammatory and immunological responses and stimulate intestinal mucosal trophism. Present available evidence supports enteral nutrition in Crohn´s disease as a primary treatment if treatment with steroids is not possible (failure or contraindication) (grade of recommendation A) or either combined treatment with drugs in malnourished patients or those with inflammatory bowel stenosis. In those patients with sustained clinical remission, no benefit of either enteral nutrition or supplements in the absence of nutritional deficits has been shown. Elemental or modified formula (glutamine, omega 3 fatty acids) could not be recommended. In ulcerative colitis, nutritional influence over the activity of the disease has not been shown, although there are some promising results regarding enteric coated W3 fatty acids and a possible role for probiotics. In the treatment and prevention of pouchitis, there could be a role for probiotics (VSL#3). Nutritional treatment should be considered an integral component in the Management of patients with inflammatory bowel disease.

(*Nutr Hosp*. 2010;25:181-192)

DOI:10.3305/nh.2010.25.2.4295

Key words: *Inflammatory bowel disease. Chron's disease. Ulcerative colitis. Probiotics. Enteral nutrition.*

La enfermedad inflamatoria intestinal (EII) engloba un grupo de enfermedades caracterizadas por la inflamación crónica y recidivante de la mucosa intestinal de etiología desconocida, y que están representadas fundamentalmente por dos entidades clínicopatológicas: la colitis ulcerosa (CU) y la enfermedad de Crohn (EC). La CU afecta exclusivamente al colon, con mayor o menor extensión, siendo la lesión limitada a la mucosa y submucosa y de forma continua. Su inicio tiene lugar en el recto (proctitis ulcerosa) desde donde el proceso inflamatorio puede extenderse de forma variable en sentido proximal a otros segmentos del colon (proctosigmoiditis, colitis ulcerosa izquierda, colitis ulcerosa extensa y pancolitis ulcerosa). Por el contrario la EC puede afectar a cualquier parte del tubo digestivo, desde la boca al ano, de forma segmentaria, siendo las zonas de localización más frecuentes el íleon distal y el colon ascendente. Las lesiones son transmurales pudiendo afectar todas las capas de la pared intestinal, de ahí su tendencia a la fistulización. La incidencia en España de CU es de 8 por 100.000 habitantes/año y de EC de 5,5 por 100.000 habitantes/año[1]. Alrededor de un 25% de los pacientes se diagnostican en la infancia o adolescencia. La EII es una entidad de etiopatogenia aún no bien conocida, aunque se piensa que es el resultado de una activación inapropiada y mantenida del sistema inmune de la mucosa intestinal motivado por la presencia de flora intestinal normal y/o otros antígenos luminales. Esta respuesta aberrante está facilitada muy probablemente por defectos tanto en la función de barrera del epitelio intestinal como en el sistema inmune de la mucosa intestinal[2].

Cualquiera de los tipos de EII tiene importantes implicaciones nutricionales y metabólicas, que podemos considerar desde distintas perspectivas: a) por la alta prevalencia de malnutrición que conlleva la enfermedad; b) por la posible implicación de factores dietéticos en su patogenia, aunque los estudios diseñados para buscar la vinculación entre la exposición del tracto gastrointestinal a diversos componentes dietéticos y la EII no han resultado concluyentes hasta ahora; c) por la hipótesis de que la intervención nutricional pudiera ser un tratamiento primario de la enfermedad, al menos en algunos tipos de pacientes[3]. La nutrición debe considerarse un componente integral en el manejo de los pacientes con EII[4]. La prevalencia de malnutrición en la EII es alta, entre el 20 y el 85%, dependiendo del grado de actividad en los pacientes estudiados y de su situación ambulatoria u hospitalización[5]. En la figura 1 pueden verse las principales causas de malnutrición en EII. Además, dado el distinto curso clínico de la CU y la EC (generalmente a brotes agudos en la primera y más crónico e insidioso en la segunda) los pacientes con CU suelen presentar formas agudas de desnutrición energético-proteica, mientras que en la EC predominan las formas marasmáticas o mixtas de malnutrición[6].

Sin embargo, será el último punto, el posible impacto de la nutrición sobre la evolución de la EII, el objetivo de la presente revisión, habiendo sido tratados los otros dos puntos en excelentes revisiones recientes[6-8]. El trata-

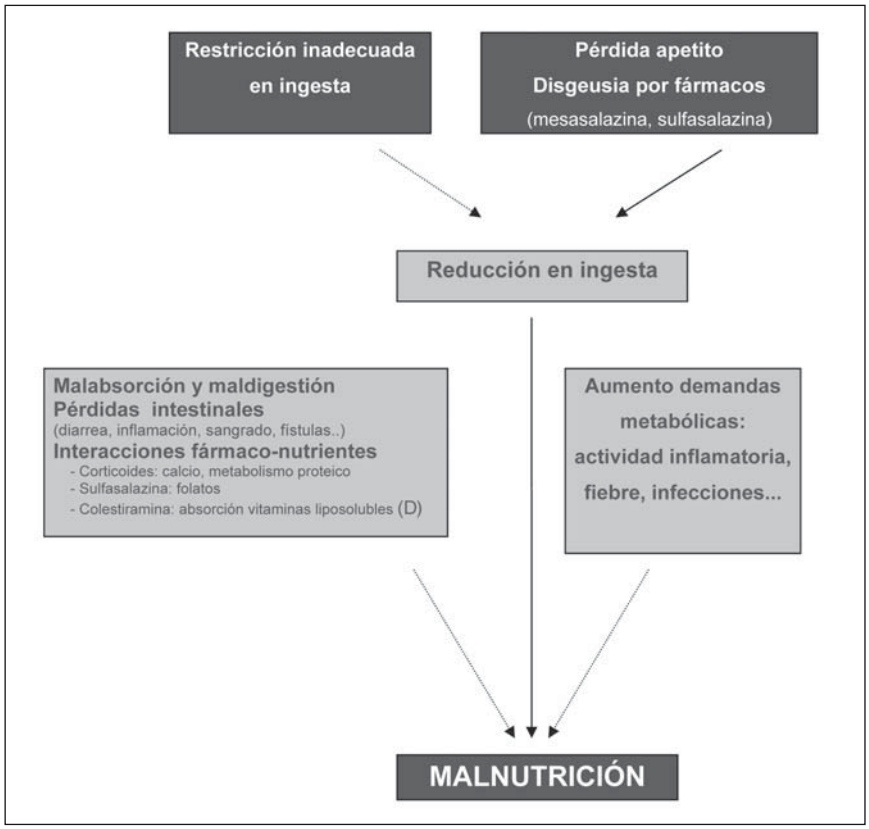

Fig. 1.—Causas de malnutrición en EII.

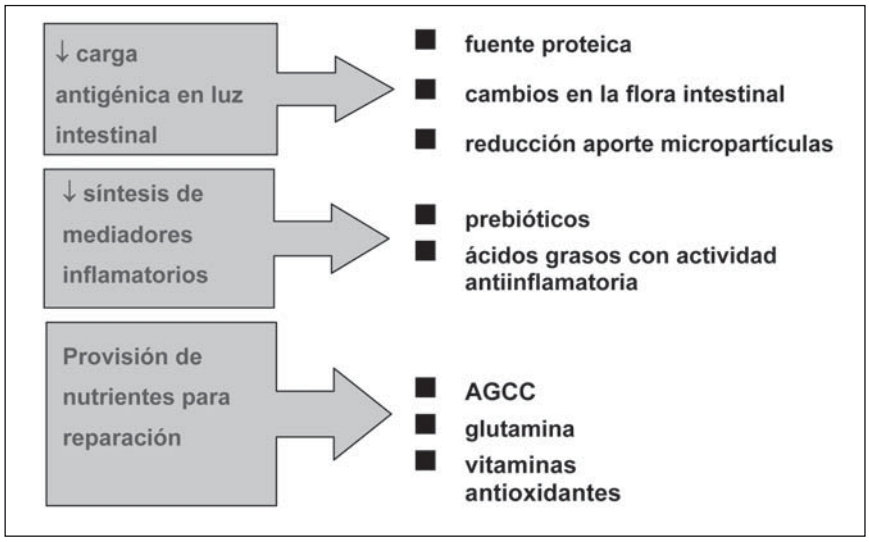

Fig. 2.—Posibles mecanismos de NE como tratamiento primario en EII.

miento de las enfermedades con nutrientes específicos, basándose en las posibles propiedades "farmacológicas" de éstos (en este caso antiinflamatorias) se conoce como fármaconutrición, y representa un reto que actualmente está en pleno desarrollo para algunas patologías, especialmente gastrointestinales. En EII, algunos nutrientes, además de su función exclusivamente nutricional, podrían inducir un bajo estímulo antigénico, regular respuestas inflamatorias e inmunológicas y estimular el tropismo de la mucosa intestinal[9].

Nutrición parenteral como tratamiento primario en EII

En los años 60 y 70, varios autores comunicaron que la nutrición parenteral (NP) podría mantener y/o mejorar la situación nutricional de los pacientes en brote agudo de EII mientras se esperaba el efecto del tratamiento médico o de forma previa a la cirugía en aquellos refractarios a tratamiento convencional. Se postuló entonces que el "reposo intestinal" podría ser per se un tratamiento primario de la enfermedad y la NP se convirtió en un tratamiento habitual durante la fase aguda. Sin embargo, un estudio prospectivo aleatorizado de Greenberg y cols.[10] en 1988 en pacientes refractarios a tratamiento médico invalidó la teoría del reposo digestivo para la inducción de remisión en EII, dando lugar a un editorial con el "sugerente" título de "Total parenteral nutrition as primary treatment in Crohn's disease—RIP?"[11], y redujo las indicaciones de NP a algunas complicaciones de la enfermedad, como la obstrucción o el síndrome de intestino corto.

Nutrición enteral como tratamiento primario en EII

Los mecanismos por los que el tratamiento con nutrición enteral puede ser eficaz en la EII aún son desconocidos. Se ha postulado que la disminución de la carga antigénica en la luz intestinal, en función de la fuente proteica, la fuente de grasa o con relación a cambios en la flora intestinal o a la reducción del aporte de micropartículas[12,13], podría jugar un papel. Otros factores implicados se relacionan con la disminución de la síntesis de mediadores inflamatorios intestinales por la administración en la NE de prebióticos o de ácidos grasos con actividad antiinflamatoria, así como con la provisión de nutrientes importantes para la reparación de las lesiones mucosas, como ácidos grasos de cadena corta, glutamina o vitaminas antioxidantes, como E y C[8] (fig. 2).

Inducción de remisión en enfermedad de Crohn

Desde el estudio pionero de O'Morain y cols., en 1984[14] que comparaba esteroides con una dieta elemental en el tratamiento del brote agudo de la enfermedad de Crohn, ha existido un debate sobre el posible efecto antiinflamatorio de la nutrición enteral y su papel como tratamiento primario en la inducción de la remisión. Una revisión de la Biblioteca Cochrane[15] estudió este tema, encontrando seis ensayos que compararon NE frente a esteroides (192 pacientes NE y 160 con esteroides) y que supusieron un odds ratio agrupado de 0,33 a favor del tratamiento esteroideo (IC 95%: 0,21 a 0,53). Otros tres metanálisis habían establecido previamente esta superioridad de los corticoides[16-18], aunque es necesario destacar que la tasa global de respuesta a la nutrición enteral total fue del 60%, una cifra muy superior a la respuesta esperada con un placebo (alrededor de un 20-30%)[6]. Es más, si se evalúa a los pacientes con buen cumplimiento terapeútico y que no presentaron intolerancia a la dieta enteral, las tasas de remisión aumentan hasta el 70-79%, lo que apoyaría el concepto de que la nutrición enteral puede ser un tratamiento efectivo cuando es bien tolerada, aunque serían deseables nue-

Tabla I
Indicaciones para el tratamiento con nutrición enteral en EII

En adultos
– Intolerancia a corticoides.
– Rechazo del paciente a tratamiento esteroideo.
– NE en combinación con corticoides en paciente desnutrido.
– Pacientes con estenosis inflamatoria de intestino delgado.
En edad pediátrica: condiciones ideales
– Enfermedad de Crohn.
– Primer episodio.
– Afectación del íleon terminal y el colon ascendente.
– Importante afectación nutricional.
– Retraso puberal o de crecimiento.
– Ausencia de enfermedad perianal.
– Rechazo a la toma de corticoides.

vos estudios que confirmaran este punto[6]. Por otra parte, aunque los corticoides alcancen con mayor frecuencia la remisión clínica, no inducen la curación de la mucosa, lo que se ha demostrado con nutrición enteral en algunos estudios pequeños no controlados y que pudiera ser considerado un mejor paradigma de control de la enfermedad en el futuro[19]. Teniendo en cuenta todo lo anterior y siguiendo las guías de nutrición enteral de ESPEN, el papel de la NE en la EC en el momento actual se recoge en la tabla I.

Son desconocidos los mecanismos por los que la NE podría ejercer su acción terapéutica primaria. La revisión Cochrane comentada[15] también comparó distintos tipos tipos de NE. El metanálisis de diez ensayos que incluían 334 pacientes no demostró diferencias en la eficacia de la fórmula elemental *versus* la fórmula no elemental (OR 1,10; IC 95%: 0,69 a 1,75), lo que contradice la hipótesis de la utilidad de la dieta elemental en virtud de su baja antigenicidad. Las comparaciones entre cualquier combinación de diferentes *fuentes de las proteínas* no mostraron diferencias significativas en cuanto a la efectividad, ni tampoco el enriquecimiento con glutamina reveló diferencias en las tasas de remisión (OR 0,64; IC del 95%: 0,10 a 4,11). Este último ensayo, además, incluyó a sólo 18 pacientes pediátricos, y aunque no hubo diferencias en la tasa de remisión *con o sin glutamina* (4/9 *vs* 5/9 pacientes), la mejoría en el índice de actividad fue significativamente mayor con la dieta no enriquecida[20]. El *factor transformador del crecimiento TGF-β-2* es una citokina presente de forma natural en la leche humana y en la leche de vaca, con propiedades antiinflamatorias (inhibitorias de la respuesta tipo Th 1 en la mucosa intestinal) y "curativas" de la mucosa. En estudios no controlados en niños, las fórmulas enterales enriquecidas con TGF β han demostrado una reducción de la inflamación de la mucosa y una disminución de las citoquinas proinflamatorias en el íleon y colon[21,22], aunque no disponemos de estudios controlados randomizados que valoren diferencias en las tasas de remisión.

Cerrado el debate sobre dieta elemental vs polimérica y la posible implicación de la fuente proteica de la dieta, el interés se ha centrado en el *tipo de grasa,* por su posible papel en la modulación de la respuesta inflamatoria[23]. Las dietas ricas en ácido linoleico (ω6), precursor del ácido araquidónico, podrían aumentar la respuesta inflamatoria debido a la producción de eicosanoides proinflamatorios, mientras que los ácidos grasos poliinsaturados ω3, abundantes en los aceites de pescado, inhiben la producción de araquidónico y también la actividad protein kinasa C necesaria para la liberación de TNF por los macrófagos. A pesar de estos fundamentos, no disponemos de estudios que apoyen un papel de los ω3 en la inducción de remisión en EC, aunque posteriormente comentaremos las evidencias disponibles para el mantenimiento de la remisión y en colitis ulcerosa[24]. El análisis de la Biblioteca Cochrane[15] de otros 7 ensayos con 209 pacientes tratados con fórmulas de diferente *contenido de grasa* (bajo en grasa: < 20 g/1000 kcal *versus* alto en grasa: > 20 g/1.000 kcal) no demostró diferencias estadísticamente significativas en cuanto a eficacia (OR 1,13; IC del 95%: 0,63 a 2,01). Se investigó el efecto de un contenido muy bajo de grasa (< 3 g/1.000 kcal) o el tipo de grasa (triglicéridos de cadena larga), pero sólo se demostró una tendencia no significativa que favorecía el contenido muy bajo de grasa y muy bajo de triglicéridos de cadena larga, aunque los autores señalan que este resultado debe interpretarse con cuidado, por la heterogeneidad y el tamaño de la muestra pequeño.

Por otra parte, un estudio multicéntrico europeo que evaluó el efecto de dos dietas poliméricas con composición lipídica diferente, en comparación con esteroides, en la inducción de la remisión clínica en la EC activa tampoco demostró un claro efecto beneficioso del *tipo de grasa*[25]. Curiosamente, en el análisis por intención de tratar, la tasa de remisión fue 20% para la dieta rica en grasa monoinsaturada, 52% para la dieta rica en grasa poliinsaturada ω6, y de 79% para los esteroides, lo que los autores atribuyeron a un probable exceso de grasa monoinsaturada (79% de la grasa total) y la ausencia de triglicéridos de cadena media en la composición lipídica de la dieta y a que la fuente de grasa monoinsaturada fue trioleína sintética, mientras que en anteriores estudios se utilizó aceite de oliva, por lo que no se puede descartar que otros componentes de este aceite pudieran ejercer un efecto antiinflamatorio[26].

Inducción de remisión en enfermedad de Crohn en niños

En el caso de los niños y adolescentes, si se tiene en cuenta tanto las tasas de remisión como el balance riesgo/beneficio del tratamiento primario con nutrición enteral frente al tratamiento con glucocorticoides, puede estar justificado plantearse la nutrición enteral como tratamiento primario alternativo en la EC activa. Otra revisión Cochrane sobre intervenciones frente al retraso del crecimiento en niños con EC valoró 2 estudios controlados y aleatorizados, con un número

pequeño de pacientes, en los que una fórmula elemental administrada durante 4-6 semanas supuso una mejoría en la velocidad de crecimiento a los 6 meses frente a esteroides[27]. Un metanálisis reciente[28] no encontró diferencias significativas en la tasa de remisión entre NE y esteroides en niños (RR 0,97, IC 95% 0,7-1,4), aunque un ensayo demostró que la NE total frente a parcial, sí aumentó la tasa de remisión (RR 2,7, IC 95% 1-7,4). No se han encontrado diferencias entre dieta elemental y polimérica[29,30].

Podemos referirnos a las guías británicas de tratamiento de EII, que reconocen un grado de recomendación A para el tratamiento nutricional como terapia primaria en niños o adolescentes. Desde el punto de vista clínico, parece que aquellos pacientes pediátricos que más pueden beneficiarse de un tratamiento con nutrición enteral son los que cumplen las condiciones descritas en la tabla I[31]. Para inducir la remisión, se recomienda NE con dieta polimérica[32] o elemental[33] > 6 semanas, preferentemente por vía oral fraccionada y, si no se tolera, por sonda nasogástrica, para cubrir 140-150% de los requerimientos calóricos para edad y altura, o 50-70 kcal/kg de peso ideal[33]. Si la indicación se refiere al fallo de crecimiento, puede emplearse NE polimérica 3 meses por año. Para evitar recaídas en niños, también se han recomendado pautas intermitentes de NE nocturna, bien por sonda nasogástrica o gastrostomía, 4 semanas cada 4 meses, un total de 3 ciclos o 5/7 noches por semana o de forma exclusiva 1 mes/4 meses[31].

Mantenimiento de la remisión en EC

La prevención de la recaída es una cuestión fundamental en el tratamiento de la enfermedad de Crohn. Azatioprina, infliximab, adalimumab y natalizumab han demostrado su efectividad, pero pueden causar eventos adversos importantes y aumentan el riesgo de infección. Los corticosteroides, 5-AAS, anti-micobacterias, probióticos o ciclosporina no son efectivos para el mantenimiento de la remisión. El efecto de la nutrición enteral a largo plazo y de los ácidos grasos w3 de cubierta entérica se apoya en estudios pequeños[34].

También la Biblioteca Cochrane ha revisado el impacto de la *nutrición enteral en el mantenimiento de la remisión en EC*[35], encontrando tan solo 2 estudios en adultos que no pudieron estudiarse conjuntamente desde el punto de vista estadístico porque las intervenciones de control y la manera en que se evaluaron los resultados difirieron enormemente entre ambos. En un estudio[36], los pacientes que recibieron la mitad de las necesidades calóricas diarias totales como dieta elemental y la otra mitad con una dieta normal presentaron una tasa de recaída significativamente inferior en comparación con los pacientes que recibieron una dieta normal sin restricción (nueve de 26 *versus* 16 de 25; OR 0,3; IC del 95%: 0,09 a 0,94). En el otro estudio[37], se comparó la suplementación con dieta elemental *vs* polimérica (que proporcionaban entre 35 y 50% del aporte calórico previo al ensayo de los pacientes además de alimentos normales sin restricción) y fueron igualmente efectivos para el mantenimiento de la remisión y permitieron retirar el tratamiento con esteroides (ocho de 19 *versus* seis de 14; OR 0,97; IC del 95%: 0,24 a 3,92). Por tanto, la suplementación con nutrición enteral puede ser eficaz para el mantenimiento de la remisión en la enfermedad de Crohn, como una opción o como un complemento de la farmacoterapia de mantenimiento, aunque son necesarios estudios más amplios para confirmar estos hallazgos.

Respecto al papel de nutrientes específicos, el estudio multicéntrico randomizado y controlado EPIC[38] ha comprobado recientemente que la administración oral de 4 g/d en cápsulas en gelatina de ácidos grasos w3 no mejoró la tasa de recaídas (31,6% a 1 año *vs* 35,7% placebo, p = 0,30). Otra revisión sistemática[39] evaluó cuatro estudios en el mantenimiento de la remisión en EC encontrando un efecto no significativo (RR 0,64; IC 95% 0,4 a 1,03; P = 0,07), aunque los estudios eran muy heterogéneos, y sí se observó un efecto beneficioso en los ω3 que emplearon cápsulas con recubrimiento entérico frente a las de gelatina (RR 0,49; IC 95% 0,35 a 0,69); número necesario a tratar para evitar una recaída en un año: 3 (IC 95% 2 a 5).

Colitis ulcerosa

No disponemos de suficientes datos que apoyen la influencia del tratamiento nutricional sobre la actividad inflamatoria en la CU, por lo que no se recomienda el empleo de NE ni en la inducción ni en el mantenimiento de la remisión[40]. Un ensayo controlado con semillas de Plantago ovata *vs* mesalazina ha estudiado el posible papel terapeútico de la fibra fermentable, ya que en su fermentación colónica da lugar a butirato, que podría tener propiedades antiinflamatorias, pero las tasas de recaída a 1 año fueron similares[41]. También se ha evaluado el empleo de aceite de pescado (ω3) en la inducción de la remisión de la CU. La Colaboración Cochrane[42] encontró sólo seis estudios, que no pudieron agruparse para el análisis debido a las diferencias en los resultados y la metodología de los estudios incluidos. Un estudio pequeño reveló un beneficio positivo para la inducción de la remisión (RR 19,00; IC del 95%: 1,27 a 284,24), pero los resultados necesitan interpretarse con cuidado debido al reducido tamaño del estudio y la calidad deficiente del mismo. Por ello, los autores concluyen que los datos actuales no permiten una conclusión definitiva para recomendar el aceite de pescado. Tampoco los estudios realizados para el mantenimiento de la remisión han demostrado la eficacia de los ω3. Los tres estudios incluidos en una revisión Cochrane reciente[43] utilizaron diferentes formulaciones y dosis de ácidos n-3, aunque ninguno utilizó cápsulas de cubierta entérica. El análisis agrupado reveló una tasa similar de recaída en los pacientes trata-

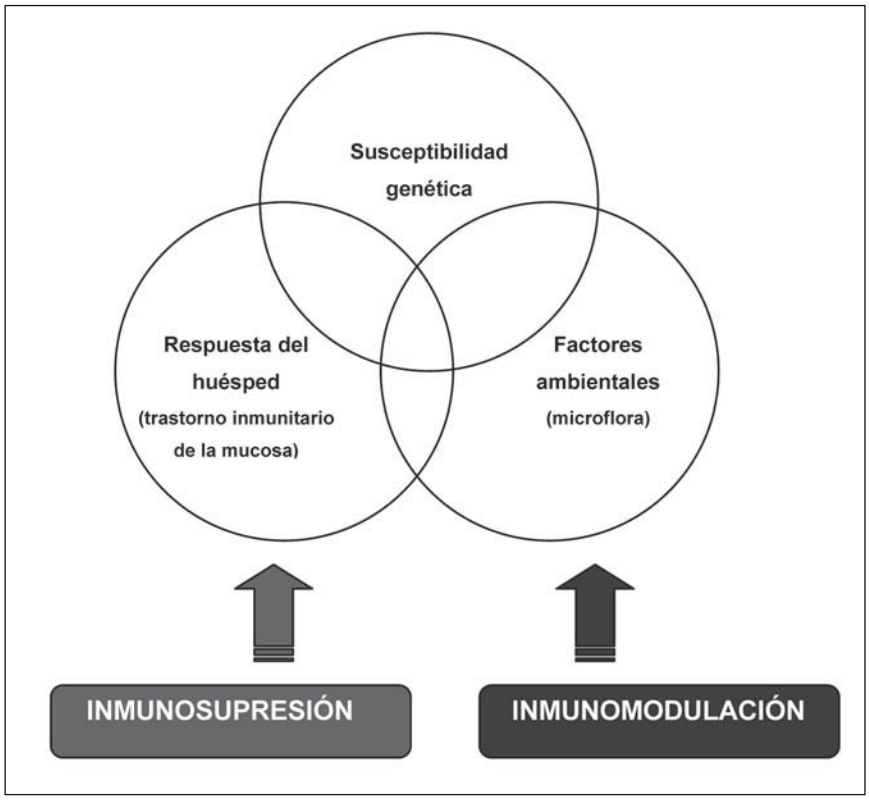

Fig. 3.—Fisiopatología de la enfermedad inflamatoria intestinal y enfoques terapéuticos.

dos con ácidos ω-3 y en los controles (RR 1,02; IC del 95%: 0,51 a 2,03; p = 0,96). También algunos ensayos pequeños o series de casos han sugerido efectos de aloe vera o bromelinas derivadas de piña en la actividad de la colitis ulcerosa, pero los datos que lo apoyan son insuficientes hasta el momento[44].

Probióticos en enfermedad inflamatoria intestinal

Como se ha comentado, aún es desconocido el origen de la enfermedad inflamatoria intestinal, pero parece que es la interacción de varios factores, del huésped y del ambiente, lo que provoca la inflamación intestinal[45]. Se ha demostrado la existencia de un trastorno en la inmunidad de la mucosa[46], probablemente determinado genéticamente (NOD2 está implicado en el reconocimiento de péptidos bacterianos específicos y en la consiguiente activación de la respuesta inmune), que origina una inmunorreactividad anormal o exagerada contra elementos ambientales como la propia flora comensal[47]. Esto induce daño inflamatorio a la mucosa y perpetúa las lesiones hacia la cronicidad. Ocurre, por tanto, una alteración en el contenido bacteriano intestinal y en la interacción huésped-flora bacteriana que se conoce como disbiosis[48].

Si bien hasta el momento, la estrategia clínica utilizada ha sido la modificación del trastorno de la inmunidad mediante fármacos inmunosupresores, la actuación terapéutica sobre este estado de disbiosis mediante antibióticos, prebióticos o simbióticos puede ser una alternativa terapéutica atractiva (fig. 3). Los prebióticos y los probióticos constituyen una alternativa terapéutica que permite influir sobre la composición del complejo ecosistema intestinal sin los efectos adversos de los antibióticos, como la falta de especificidad, el riesgo de sobrecrecimiento y el desarrollo de resistencias. Se han postulado varios mecanismos por lo que el empleo de probióticos puede ser eficaz en EII[49] y se muestran en la tabla II.

Probióticos en la enfermedad de Crohn

Son escasas las evidencias que apoyan el empleo de *probióticos como tratamiento del brote agudo* en la enfermedad de Crohn[50]. Sólo disponemos de un ensayo aleatorizado controlado[51] con 11 pacientes, de los que sólo 5 terminaron el ensayo, que no demostró un beneficio de *Lactobacillus rhamnosus GG* en la inducción de la remisión. En el *mantenimiento de remisión,* una revisión reciente de la Biblioteca Cochrane[52] sólo encontró 7 estudios pequeños y muy diferentes entre sí en relación con el probiótico empleado, calidad metodológica y pauta de fármacos. No encontró beneficio estadísticamente significativo de *E. coli Nissle*[53] ni de *Lactobacillus GG* para reducir el riesgo de recaída frente a placebo tras una remisión inducida médicamente. En el *mantenimiento de remisión inducida tras*

Tabla II
Mecanismos de acción de probióticos en EII (modificado de Sartor R[83])

- Actividad antimicrobiana y supresión de crecimiento de patógenos.
  - Disminución pH luminal.
  - Secreción de proteínas bactericidas.
  - Resistencia a colonización (ocupan nicho ecológico).
  - Bloqueo de unión al epitelio.
  - Inhibición de invasión del epitelio.
- Reforzamiento de la actividad de barrera intestinal
  - Producción de ácidos grasos de cadena corta, incluido butirato.
  - Aumento en producción de moco.
  - Aumento en integridad de la barrera.
- Inmunomodulación y/o estimulación de respuesta inmune
  - Inducción de expresión y secreción de IL-10 y TGF.
  - Estimulación producción IGA secretora.
  - Disminución expresión factor de necrosis tumoral.
  - Inducción de apoptosis de células T.

cirugía, tampoco la administración de L rhamnosus GG o Lactobacillus johnsonii ha demostrado efecto en la prevención de la recurrencia clínica y endoscópica tras cirugía[54-56]. En conclusión, en pacientes con *enfermedad de Crohn,* tanto activa como inactiva, se han realizado diversos estudios con varios probióticos *(Escherichia coli* Nissle, *Lactobacillus* GG, Lactobacillus johnsonii LA1, *Saccharomyces boulardii* y VSL#3) pero todos ellos incluyen pocos pacientes y en *ninguno se han observado diferencias significativas a favor del probiótico* (tabla III).

Probióticos en la colitis ulcerosa

En *colitis ulcerosa activa,* la administración de la cepa no patógena de *Escherichia coli Nissle 1917,* en un ensayo aleatorizado frente a mesalazina en 116 pacientes[57], obtuvo una tasa de remisión equivalente en un tiempo similar (tabla IV). Un estudio piloto aleatorizado controlado de Kato y cols.[58] con leche fermentada con *Bifidobacterias* durante 12 semanas ha sugerido mejoría estadísticamente significativa a los 3 meses en el grupo suplementado con bifidobacterias, que presentó mejores índices de actividad clínica e histológica. Sin embargo, se trata de un estudio piloto con escaso número de pacientes. En 2005, otro estudio piloto con *Bifidobacterium longum*[59], esta vez como simbiótico en asociación con un prebiótico (Synergy 1, inulina-oligofructosa) también pudo demostrar mejoría significativa en algunos aspectos en sólo un mes. Guslandi y cols.[60] estudiaron el efecto de *Saccharomyces boulardii* en un estudio no controlado en pacientes no aptos para tratamiento esteroideo con un brote leve a moderado encontrando remisión en 17 de 25 pacientes. Otro probiótico estudiado en colitis ulcerosa activa, VSL#3, mezcla probiótica de cuatro lactobacilos, tres bifidobacterias y *Streptococcus thermophilus,* durante 6 semanas demostró remisión en 53% y respuesta parcial en 24%[61], pero también se trata de un estudio no controlado.

En el *mantenimiento de remisión,* también *Escherichia coli Nissle 1917* ha demostrado ser similar a mesalazina[57,62,63]. Se han publicado dos estudios aleatorizados y controlados con *bifidobacterias,* como suplemento nutricional en forma de *leche fermentada con bifidobacterias* (Bifidobacterium bifidum YIT 4007, B. breve YIT 4065 y L. acidophilus YIT 0168) añadido al tratamiento con-

Tabla III
Principales estudios con probióticos en el mantenimiento de la remisión en enfermedad de Crohn

Estudio	*N*	*Control*	*Tratamiento*	*P*
Mantenimiento de remisión tras tratamiento médico				
Malchow y cols., 1997[53] Remisión a 12 meses (activo)	28	Prednisona + placebo 33%	Prednisona + E coli Nissle 63%	ns
Schultz y cols., 2004[51] Remisión a 6 meses (activo)	11	Prednisona + placebo 2/6	Prednisona + Lactobacillus GG 2/5	ns
Guslandi y cols., 2000[60] Remisión a 6 meses (inactivo)	32	Mesalacina 62%	Mesalacina + S boulardii 93%	ns
Mantenimiento de remisión tras tratamiento quirúrgico				
Prantera y cols., 2002[54] Remisión clínica a 12 meses Remisión endoscópica a 12 meses	45	Placebo 89% 65%	Lactobacillus GG 83% 40%	ns
Marteau P y cols., 2006[55] Recurrencia endoscópica a 6 meses	98	Placebo 64%	L johnsonii La1 49%	ns
Van Gossum y cols., 2007[56] Recurrencia endoscópica severa a 3 meses	70	Placebo 21%	L johnsonii La1 15%	ns

Tabla IV
Principales estudios con probióticos en inducción de remisión en colitis ulcerosa

Estudio	*N*	*Control*	*Tratamiento*	*P*
Rembacken y cols., 1999[57]	116	Mesalazina	E coli Nissle	
% Remisión		75%	68%	ns
Días hasta remisión (media)		44 días	42 días	
Kato y cols., 2004[58]	20	Mesalazina	Mesalazina + Leche fermentada con bifidobacterias 100 ml/d	
Indice de actividad clínica		5,8	3,7	
Respuesta a 3 meses		33%	70%	p < 0,01
Furrie y cols, 2005[59]	18	Placebo	Bifidobacterium longum + Sinergy 1	
Score actividad en sigmoidoscopia (0-6)		-1,3	+ 0,58	p = 0,06
Marcadores inflamatorios			↓mRNA beta defensinas 2, 3, 4	p = 0,016
			↓TNF-alfa, IL-1 alfa	p = 0,018
Guslandi y cols., 2003[60]	25	No controlado	Mesalazina + Saccharomyces boulardii	
Remisión clínica a 4 semanas			68%	–
Bibiloni y cols., 2005[61]	34	No controlado	VSL#3	
Remisión/respuesta a 6 semanas			77%	–

vencional con mesalazina. Aunque ambos estudios incluyen pocos pacientes, las bifidobacterias parecen ejercer un efecto beneficioso a la hora de mantener la remisión al menos similar al tratamiento convencional[58,64]. Un estudio publicado con *VSL#3,* aunque no controlado, ofrece también interesantes tasas de remisión de hasta 75% en 1 año en pacientes en remisión intolerantes a 5-ASA[65]. Otro estudio compara la eficacia de balsalacida (profármaco de mesalazina) aislada frente a balsalacida asociada a VSL#3 en pacientes con colitis ulcerosa activa, demostrándose sólo un ligero beneficio en cuanto a mayor rapidez de acción[66]. Por último, se ha publicado recientemente un ensayo con *Lactobacillus GG* 18 x 10^9 CFU/día, solos o en combinación con mesalazina[67], siendo las tasas de remisión similares con el probiótico sólo, combinado con mesalazina o mesalazina sola, aunque parece que Lactobacillus GG sí es efectivo para prolongar el tiempo de remisión(P < 0,05).

En conclusión, en *colitis ulcerosa activa* se ha sugerido que *E coli Nissle* podría ser equivalente a mesalazina en la *inducción de la remisión,* y también se ha observado mejoría clínica en estudios con menor número de pacientes con *Bifidobacterias*. Otros probióticos como *Saccharomyces boulardii y VSL#3* sólo han sido estudiados en ensayos no controlados, aunque sus efectos parecen prometedores. Una vez conseguida la remisión, *Escherichia coli Nissle 1917, Bifidobacterias y Lactobacillus GG* parecen ser tan eficaces como la mesalazina en el *mantenimiento de la remisión* en los pacientes con colitis ulcerosa, siendo VSL# 3 también similar a balsalacida.

Probióticos en la pouchitis o reservoritis

La pouchitis o reservoritis crónica es una inflamación recidivante de la mucosa del reservorio que aparece en el 5% a 15% de pacientes sometidos a colectomía y reconstrucción con anastomosis ileoanal. Su etiopatogenia es desconocida, aunque también parecen intervenir factores de desequilibrio bacteriano, ya que el tratamiento que mejores resultados ha ofrecido hasta ahora ha sido el uso de antibióticos[47]. El efecto de los probióticos en esta patología nos ofrece las mejores evidencias en EII. Tres estudios apoyan la eficacia del tratamiento en pacientes con pouchitis crónica con *VSL#3,* preparado probiótico que incluye 4 variedades de lactobacilli *(Lactobacillus casei, Lactobacillus plantarum, Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. Bulgaricus),* 3 de bifidobacteria *(Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium infantis)* y 1 *Streptococcus salivarius subsp. thermophilus*. En el primero, publicado en 2000 por Gionchetti[68], realizado en 40 pacientes durante 9 meses tras obtener la remisión mediante una tanda de un mes de antibióticos, los resultados son claramente favorables al probiótico *VSL#3* 6 g/d (5 x10^{11} bacterias liofilizadas viable por gramo), con el 85% de los pacientes en remisión a los 9 meses frente al 0% en el grupo placebo. El número necesario a tratar con tratamiento probiótico oral para evitar una recaída adicional fue de 2. Además, todos los pacientes en remisión en el grupo de VSL3 tuvieron una recaída en los primeros 4 meses tras suspenderse el tratamiento al final del ensayo. Los resultados fueron confirmados en 2004[69]. En un nuevo estudio publicado por el mismo grupo en 2003[70] el aporte de VSL-3 comenzó inmediatamente después de la anastomosis íleo-anal con la intención de prevenir el desarrollo de pouchitis, complicación que aparece al menos una vez en el 50% de pacientes con reservorio en los 10 años posteriores a la intervención[47]. Solamente 10% en el grupo tratado con VSL-3, frente a 40% en el grupo control desarrollaron pouchitis durante el primer año post-cirugía.

Tabla V
Principales estudios con probióticos en mantenimiento de remisión en colitis ulcerosa

Estudio	*N*	*Control*	*Tratamiento*	*P*
Rembacken y cols., 1999[57]	116	Mesalazina	E coli Nissle (200 mg/d)	
Recaídas a 12 meses		73%	67%	ns
Duración media de remisión		206 días	221 días	
Kruis y cols., 1997[62]	120	Mesalazina	E coli Nissle (100-200 mg/d)	
Recaídas a 3 meses		11,3%	16%	ns
Duración media de remisión		103 días	106 días	
Kruis y cols., 2004[63]	327	Mesalazina	E coli Nissle (100-200 mg/d)	
Recaídas a 3 meses		33,9%	36,4%	ns
Ishikawa y cols., 2003[64]	21	Mesalazina	Mesalazina + Bifidobacterias (leche fermentada)	
Remisión a 12 meses		10%	70%	p = 0,01
Kato y cols., 2004[58]	20	Mesalazina	Mesalazina + Bifidobacterias (leche fermentada)	
Remisión a 3 meses		33%	40%	ns
Venturi y cols., 1999[65]	20	No controlado	VSL#3	
Remisión a 12 meses			75%	–
Tursi y cols., 2004[66]	90	Balsalacida	VSL#3 + Balsalacida	
Remisión a 8 semanas		80%	77%	ns
Tiempo en obtener remisión		7,5 d	4 días	p < 0,01
Zocco y cols., 2006[67]	187	Mesalazina	Mesalazina + Lactobacillus GG	
			Lactobacillus GG	ns
Recaída a 12 meses		20%	16% y 15%	

El *Lactobacillus GG* (LGG) también se ha utilizado en dos estudios en pacientes con pouchitis. En el primero[71], 20 pacientes con historia previa de pouchitis y signos endoscópicos de inflamación se aleatorizaron para recibir LGG o placebo. No se observaron diferencias en la actividad de la enfermedad, anaerobios y aerobios totales en las biopsias de mucosa o en las heces después de 3 meses de tratamiento. El segundo estudio, como en el caso anterior, trató de reducir los episodios de pouchitis mediante la administración de LGG inmediatamente después de la construcción de anastomosis íleo-anales[72]; la comparación se hizo con controles "históricos": 2 de 39 (5,13%) *versus* 8 de 78 (10,25%) desarrollaron episodios de pouchitis ileal, 1 *versus* 12 sufrió episodios recurrentes de pouchitis y 0 *versus* 7 sufrió pouchitis crónica.

Por tanto, los probióticos obtienen las mejores evidencias sobre su empleo en EII en el tratamiento y profilaxis de la pouchitis, con excelentes resultados con *VSL#3,* y parecen prometedores los resultados en CU, aunque aún no disponemos de datos suficientes para su recomendación generalizada[73].

Prebióticos en enfermedad inflamatoria intestinal

Otro modo de promover la proliferación intestinal de bacterias probióticas es mediante la administración de prebióticos, sustancias que favorecen su crecimiento sobre el de otras especies. Los prebióticos modulan la composición de la flora colónica, disminuyendo el pH intraluminal y favoreciendo la proliferación de las bacterias acidolácticas probióticas e inhibiendo la de otras, incluidas probablemente algunas con potencial patógeno. Para considerar una sustancia como prebiótico: 1) No debe ser hidrolizado, absorbido ni digerido en estómago ni en intestino delgado; 2) debe ser un sustrato fermentable por un grupo o grupos de bacterias comensales beneficiosas colónicas, y estimular su crecimiento de manera selectiva; 3) debe alterar la microflora colónica, con predominio de lactobacillus y bifidobacterias, e inducir efectos beneficiosos luminales/ sistémicos en el huésped[74]. Esta definición más o menos se superpone con la de fibra dietética, salvo por la selectividad por ciertas especies. Esta selectividad se ha demostrado para las bifidobacterias con fructooligosacáridos (FOS) e inulina, galacto-oligosacáridos (GOS) y oligosacáridos de soja[75]. Además de su capacidad de promover el crecimiento de probióticos, ligado a su fermentabilidad, algunos de estos probióticos tienen por si mismos efectos biológicos saludables, como capacidad antioxidante o incremento en absorción de calcio[74]. Algunos tipos de fibra fermentable (como la de las semillas de *Plantago ovata),* precursores de los ácidos grasos de cadena corta, podrían contribuir a la reparación de la mucosa del colon y del intestino delgado distal, porque los ácidos grasos de cadena corta (como el acetato, el

Tabla VI
Principales estudios con probióticos en pouchitis

Estudio	*N*	*Control*	*Tratamiento*	*P*
Gionchetti y cols., 2000[68] Recaídas en 9 meses	40	Placebo 15%	VSL#3 100%	P < 0,001
Gionchetti y cols., 2003[70] Desarrollo de episodio de pouchitis	40	Placebo 40%	VSL#3 10%	P < 0,01
Mimura y cols., 2004[69] Recaídas en 12 meses	36	Placebo 15%	VSL#3 84%	P < 0,0001
Kuisma y cols., 2001[71] Actividad de la enfermedad tras 3 meses	20	Placebo	L. rhamnosus GG	n.s.
Gosselink y cols., 2004[72] Riesgo acumulado de primer episodio	117	Placebo 29	L. rhamnosus GG 7	P = 0,011

propionato y el butirato, resultantes de la fermentación anaerobia de los prebióticos), además de ser nutrientes específicos del epitelio intestinal, disminuyen la inflamación (el butirato bloquea la activación de la vía del NF-κB y disminuye la síntesis de citocinas proinflamatorias como IL-6 y 8). El tratamiento de la CU activa con enemas de ácidos grasos de cadena corta (y de butirato) ha producido resultados contradictorios, aunque algunos datos sugieren que podrían ser eficaces en algunos subgrupos de pacientes con CU, por lo que es necesaria la realización de ensayos clínicos controlados para su confirmación[76].

El empleo de prebióticos en EII aún está insuficientemente estudiado. En enfermedad de Crohn, un estudio no controlado en solo 10 pacientes y de 3 semanas de duración ha sugerido que FOS inducen una reducción significativa en los índices de severidad de la enfermedad y modifican la función de la células dendríticas de la mucosa[77]. Algunos ensayos preliminares no controlados también han sugerido efectos beneficiosos en la actividad en colitis ulcerosa leve-moderada con preparados alimenticios de cebada germinada, asociados al incremento fecal de Bifidobacterium spp. y Eubacterium limosum[78]. En pouchitis crónica, en un ensayo controlado randomizado, cruzado y doble ciego, la suplementación con 24 g/d de inulina durante 3 semanas a 20 pacientes redujo significamente los datos endoscópicos e histológicos de inflamación de mucosa, aumentó los niveles fecales de butirato y redujo el número de Bacteroides fragilis[79]. Finalmente, el empleo de simbióticos (Bifidobacterium longum + inulina enriquecida oligofructosa) también podría ser beneficioso en colitis ulcerosa leve-moderada[80]. Aunque no se trate estrictamente de un prebiótico, el empleo de fibra dietética en colitis ulcerosa *(Plantago ovata),* por su efecto en la producción colónica de butirato, ha demostrado ser equivalente a mesalazina en el mantenimiento de remisión[81].

Por tanto, aunque los datos clínicos y experimentales apoyarían la hipótesis de que prebióticos como inulina y oligofructosa pueden prevenir o mejorar la inflamación intestinal, aún son necesarios más estudios de suficiente calidad metodológica[82].

Conclusión

En conclusión, la evidencia disponible en el momento actual[40] apoya el empleo de NE en EC como terapia primaria en adultos si el tratamiento con corticoides no es posible (fracaso o contraindicación) (grado de recomendación A) o bien en terapia combinada con fármacos en pacientes malnutridos y en aquellos con estenosis inflamatoria del intestino. En los pacientes en remisión clínica duradera (desde hace más de 1 año) no se ha demostrado beneficio de la nutrición enteral o suplementos en ausencia de déficits nutricionales (grado de recomendación B). No se recomienda el uso de fórmulas elementales ni modificadas (glutamina, ácidos grasos omega 3) al no haberse encontrado beneficios (grado de recomendación A). En el caso de la colitis ulcerosa, no se ha demostrado la influencia de la nutrición sobre la actividad de la enfermedad, aunque disponemos de datos prometedores sobre el papel de los ácidos grasos ω3 con cubierta entérica y de un posible papel de los probióticos (E coli Nissle, Bifidobacterias, VSL 3...). En el tratamiento y profilaxis de la pouchitis crónica, el empleo de probióticos puede tener un papel (VSL#3). La nutrición debe considerarse un componente integral en el manejo de los pacientes con EII[4].

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):193-206
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisiones

Major diet-drug interactions affecting the kinetic characteristics and hypolipidaemic properties of statins

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Abstract

Concomitant administration of statins with food may alter statin pharmacokinetics or pharmacodynamics, increasing the risk of adverse reactions such as myopathy or rhabdomyolysis or reducing their pharmacological action. This paper reviews major interactions between statins and dietary compounds. Consumption of pectin or oat bran together with Lovastatin reduces absorption of the drug, while alcohol intake does not appear to affect the efficacy and safety of Fluvastatin treatment. Grapefruit juice components inhibit cytochrome P-4503A4, reducing the presystemic metabolism of drugs such as Simvastatin, Lovastatin and Atorvastatin. Follow-up studies on the therapeutic effect of statins in patients consuming a Mediterranean-style diet are necessary to assure the correct prescription because the oil-statin and minor oil compound-statin possible interactions have been only briefly studied. Preliminary study suggests that olive oil can increase the hypolipaemiant effect of Simvastatin with respect sunflower oil. The consumption of polyunsaturated rich oils, throughout the cytochrome P-450 activation could decrease the half-life of some statins and therefore their hypolipaemic effects. The statins and n-3 fatty acids combined therapy gives rise to pharmacodinamic interaction that improves the lipid profile and leads greater cardioprotection. Although statins are more effective in high endogenous cholesterol production subjects and plant sterols are more effective in high cholesterol absorption efficacy subjects, plant esterols-statins combined therapy generates very positive complementary effects. This review ends suggesting possible diet-stain interactions that require further investigations (e.g. types of olive oils, fruit juices other than grapefruit, fibre or consumption of alcoholic beverages rich in polyphenols or ethanol).

(*Nutr Hosp.* 2010;25:193-206)

DOI:10.3305/nh.2010.25.2.4405

Key words: *Statins. Diet-drug interactions. Fibre. Alcohol. Grapefruit juice. Oils. Plant sterols. N-3 fatty acids.*

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Recibido: 30-VI-2009.
Aceptado: 9-VII-2009.

PRINCIPALES INTERACCIONES DIETA-FÁRMACO QUE AFECTAN LA CINÉTICA Y PROPIEDADAS HIPOLIPEMIANTES DE LAS ESTATINAS

Resumen

La administración conjunta de estatinas y alimentos puede producir reacciones adversas, como miopatía o rabdomiolisis, o reducir su acción farmacológica. Este artículo revisa las interacciones más importantes entre estatinas y componentes dietéticos. El consumo de pectina o de salvado de avena junto con Lovastatina reduce la absorción del fármaco, mientras que la ingesta de alcohol no afecta la eficacia ni la seguridad del tratamiento con Fluvastatina. Algunos componentes del zumo de pomelo inhiben el citocromo P-450 A4, reduciendo el metabolismo presistémico de la Simvastatina, Lovastatina y Atorvastatina. Se necesitan estudios de seguimiento sobre los efectos terapéuticos de las estatinas en pacientes que consumen dieta Mediterránea para asegurar la correcta prescripción, ya que no existen estudios de posibles interacciones entre el aceite o sus compuestos minoritarios y las estatinas. Un estudio preliminar sugiere que el aceite de oliva respecto al de girasol incrementa la acción hipolipemiante de la Simvastatina. El consumo de aceites ricos en ácidos grasos poliinsaturados, a través de la activación de citocromo P-450, podría disminuir la vida media de las estatinas y, por tanto, sus efectos hipolipemiantes. La terapia combinada estatinas y ácidos grasos n-3 da lugar a una interacción farmacodinámica que mejora el perfil lipídico e induce mayor cardioprotección. Aunque las estatinas son más efectivas en individuos con alta producción endógena de colesterol y los esteroles de plantas en aquellos que presentan mayor absorción de colesterol, la terapia conjunta induce efectos complementarios muy positivos. Se concluye la revisión sugiriendo más estudios en aquellas interacciones entre alimentos (ej. tipos de aceite de oliva, de zumos, de fibra o el consumo de bebidas alcohólicas ricas en polifenoles o etanol) y estatinas.

(*Nutr Hosp.* 2010;25:193-206)

DOI:10.3305/nh.2010.25.2.4405

Palabras clave: *Estatinas. Interacciones dieta-fármacos. Fibra. Alcohol. Zumo de pomelo. Aceites. Fitosteroles. Ácidos grasos n-3.*

Introduction

Statins are drugs that inhibit the rate-limiting enzyme of cholesterol synthesis 3-hydroxy-3-methylglutaryl coenzyme A reductase, thus reducing intracellular hepatic cholesterol biosynthesis and decreasing intracellular cholesterol accumulation. The reduction in intracellular cholesterol levels stimulates synthesis of low density lipoproteins (LDL) receptors and their expression on the surface of liver cells. These receptors are responsible for the uptake of LDL in addition to that of their precursors, very low density lipoproteins (VLDL) and VLDL remnants, whose hydrolysis produces LDL. The more VLDL and VLDL remnants taken up by the receptors, the fewer LDL produced. This effect of statins on VLDL also explains their capacity to reduce triglyceride levels, although to a lesser degree and in a less consistent manner.[1] Nevertheless, statins may also produce adverse reactions, such as myopathy and rhabdomyolysis. Concomitant use of other drugs may lead to undesirable interactions and increase the risk of adverse reactions.[2] Of the various statins available, those that are presently marketed in Spain include Simvastatin, Lovastatin, Pravastatin, Atorvastatin and Fluvastatin (fig. 1).

The knowledge of structure and pharmacokinetic characteristics of these drugs will help to understand their pharmacokinetically-based interactions with certain food compounds. Table I summarises the pharmacokinetic characteristics of statins, as well as the principal transporters involved in their metabolism and elimination. All statins presently available display good intestinal absorption. Thus, Simvastatin and Lovastatin, which are lipophylic, easily cross the plasma membrane by means of passive diffusion, while other statins are recognised by specific transport systems. Pravastatin is the least lipophylic statin.[2,3] Simvastatin, Lovastatin, Pravastatin, Atorvastatin and Pitavastatin are P-glycoprotein (Pgp) substrates. The Pgp is a membrane glycoprotein which plays an important role during the cellular capture of drugs.[3]

The statins presently available are mainly eliminated by the liver. Except for Pravastatin, of which up to 47% is eliminated through urine in an unaltered form, urinary excretion of statins is limited (table I). Organic anion transporter OAT3 may be involved in renal Pravastatin uptake.[3]

Simvastatin, Lovastatin and Atorvastatin are metabolised by cytochrome P-450 3 A4 (CYP 3 A4), while Fluvastatin is metabolised by CYP 2 C9. Only small amounts of Pravastatin, Rosuvastatin and Pitavastatin are metabolised; their plasma clearance depends on transporters involved in hepatic uptake and bile excretion. Hepatic uptake by transporters also plays an important role in clearance of other statins administered in acid form (Fluvastatin and Atorvastatin).[3]

A pharmacological interaction is defined as an alteration of the pharmacodynamics and/or pharmacokinetics of a drug, produced by concomitant pharmacological treatment, dietary factors or social habits such as tobacco or alcohol.[4] Such interactions can affect statins as much as any other drugs resulting in higher risk of adverse reactions in some cases or lower pharmacological action in others. This review summarises major data available on nutritional interactions with statins, placing special emphasis on those interactions that produce an additive effect to statin treatment.

Statins and dietary fibre

Although the effects of fibre on cholesterol levels have been thoroughly investigated and its benefits proven,[5] studies have shown that its consumption together with Lovastatin reduces intestinal absorption of the drug. In one study[6] it was found that after addition of pectin (three patients) or oat/bran (two patients) to Lovastatin (80 mg/day), the LDL-c levels were increased after 4 weeks and returned to their previous values

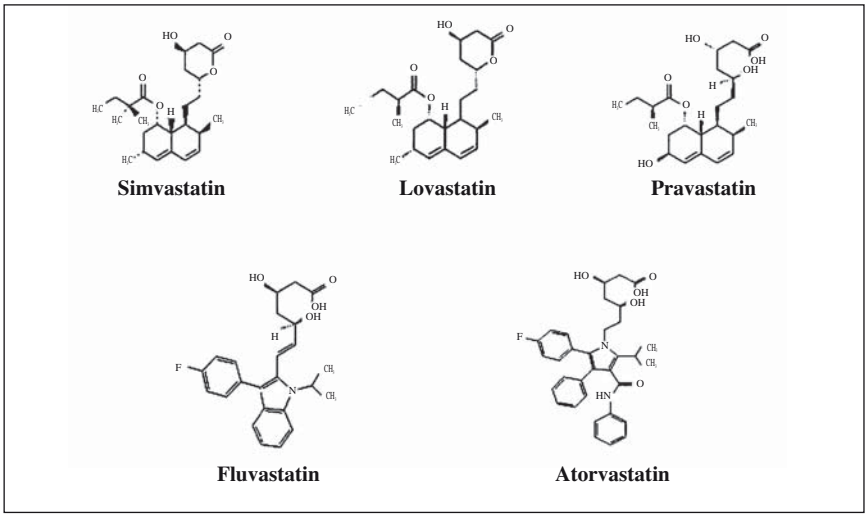

Fig. 1.—Chemical structure of main statins.

Table I
Pharmacokinetic characteristics of statins

Parameter	*Fluvastatin*	*Pravastatin*	*Lovastatin*	*Simvastatin*	*Atorvastatin*
Absorption (%)	98	34	30	60-80	30
Solubility	Fat soluble	Water soluble	Fat soluble	Fat soluble	Fat soluble
Bioavailability (%)	19-29	18	5	< 5	12
Prodrug	No	No	Yes	Yes	No
Proteins bind (%)	> 98	50	> 95	> 95	> 98
Main metabolic pathway	CYP2C9	Conjugation	CYP3A4	CYP3A4	CYP3A4
Active metabolites	No	No	Yes	Yes	Yes
Half-life (hrs)	< 1	1-3	2-4	2-3	11-14
Unmodified urinary excretion (%)	NS	47	10	NS	< 2
Transporters involved in liver uptake and bile excretion	BSEP	OATP1B1 OATP2B1 OAT3 BSEP BCRP MDR1 MRP2	OATP1B1	OATP1B1	OATP1B1

NS, Non-significant; BSEP, Bile salt exporting pump OATP, Organic anion transporting polypeptide system; OAT, Organic anion transporter; MRP, Multidrug resistance associated protein; MDR, Multidrug resistance protein; BCRP, Breast cancer resistance protein. Modified from Lennernas and Fager.[3]

after the consumption of fibre was stopped. Later, it was observed that the combination of Lovastatin with psyllium lowered LDL-c more than the statin alone. Agrawal et al.[7], in a 4-week parallel study involving 36 male adults, in which subjects consumed 20 mg of Lovastatin, 10 g of psyllium or 20 mg Lovastatin plus 10 mg psyllium, observed an additive effect of the combination, although the differences were not significant. In a 12-week blinded placebo-controlled study, patients were randomized to receive 20 mg of Simvastatin plus placebo, 10 mg of Simvastatin plus placebo, or 10 mg of Simvastatin plus 15 g of psyllium daily.[8] The effect on lipid profile was evaluated at 4 and 8 weeks. It was concluded that dietary psyllium supplementation in patients taking 10 mg Simvastatin is as effective in lowering LDL-c and ApoB as 20 mg of Simvastatin alone. Values of HDL-c and TG did not significantly vary by the fibre addition. In this context, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines recommend increase soluble fibre (10-25 g daily) as a therapeutic option to enhance LDL-c lowering.[9] Viscous fibre may have additional side effects reducing blood glucose. Besides, it is important to take into account the dietary fibre, because administration of Lovastatin with food is recommended as under those conditions plasma concentrations are 50% higher than at fasting conditions.[10]

Statins and alcoholic beverages

Moderate consumption of alcohol is known to have beneficial effects on cardiovascular disease, probably by increasing HDL-c levels. However, high consumption displays deleterious effects giving rise to hypertriglyceridaemia.[11]

Few studies have been carried out to determine the possible interactions between alcohol and statins (table II). A prospective crossover study investigated the effect of acute alcohol consumption together with a single 40 mg oral dose of Fluvastatin.[12] After being randomly divided into two groups, individuals in one group were given a total of 70 g of ethanol in separate doses diluted to 20% with orange juice, while those of the other group were given orange juice alone. Volunteers given alcohol showed that the half-life ($t_{1/2}$) of the single dose of Fluvastatin was significantly shorter than that of the controls, whereas the area under the curve (AUC), the maximum concentration (C_{max}), and the time to reach maximum concentration (T_{max}) did not differ from the control group. The alterations in the lipoprotein profile, measured after 8 hours, were observed when the statin was taken with alcohol. Triglyceride levels increased, total cholesterol and LDL-c levels decreased, possibly due to a pharmacokinetic interaction, and HDL-c and Apo A1 values slightly decreased.[12] In contrast, the lipoprotein profile measured after 8 hours in the control group did not vary and only a slight reduction in Apo A1 was observed.

To evaluate the long-term effect of alcohol consumption, a prospective, double-blind crossed study involving 26 individuals with primary hypercholesterolaemia and a control group was carried out.[13] Patients receiving Fluvastatin (40 mg/day) for 6 weeks were divided at random into two groups; one was given 20 g of alcohol diluted to 20% with lemonade while the other was given lemonade alone. Alcohol intake tended to increase the half life ($t_{1/2}$), the area under the curve (AUC) and the time to reach

Table II
Summary of results obtained in studies on the effect of simultaneous alcohol and fluvastatin intake

	Changes in pharmacokinetic parameters compared with control group values	*Lipoprotein profile changes*	
		Control group	*Study group*
Study 1 Single dose Fluvastatin plus alcohol or placebo	↓$t^{1}/_{2}$ No significant changes in AUC, t_{max} and C_{max}	Slight ↓ Apo A-1	↓ CT and LDL-c, slight ↓ HDL-c and Apo A-1 No significant changes in Triglycerides
Study 2 Daily dose Fluvastatin for 6 months plus alcohol or placebo	Tendency to $t^{1}/_{2}$, AUC, t_{max} No significant changes in C_{max}	↓ CT, LDL-c and Apo B No significant changes in HDL-c and Triglycerides	↓ CT, LDL-c and ApoB No significant changes in HDL-c, TG

Source, Smith et al.[12,13]

maximum concentration (T_{max}) compared with control values, while it did not appear to affect maximum concentration values (C_{max}). With regard to the lipoprotein profile, both groups displayed a decrease in total cholesterol, LDL-c and Apo B, and no significant differences between the decreases in the two groups were observed, while HDL-c and triglyceride levels displayed no significant changes. Although alcohol modifies the metabolism of the drug, it does not reduce its efficacy as a hypolipidaemic agent.[13]

In conclusion, alcohol consumption does not affect the efficacy and safety of Fluvastatin treatment, although the effect of large doses of alcohol over long periods of time requires further investigation. Moreover, the concomitant effect of minor compounds present on alcoholic beverages (e.g. trans-resveratrol in red wines) on statin pharmacokynetics have not yet been investigated.

Statins and grapefruit juice

The first article to report an interaction between grapefruit juice and a drug appeared in 1989. This accidental finding, made by Bailey et al.[14] while studying the haemodynamic effect of felodipine and ethanol, was due to the use of grapefruit juice to disguise the flavour of ethanol.

Grapefruit juice interacts with various drugs,[15] including calcium channel blockers, antihistamines, immunosuppressants, hypnotic benzodiazepines, and the HMG-CoA reductase inhibitors statins. The interaction mechanism is believed to be the irreversible inhibition that grapefruit juice produces on the intestinal cytochrome P-450 (CYP) 3A4, leading to a reduction of the presystemic metabolism of the drug, elevating its bioavailability. Alternative mechanisms of this interaction and the possible responsible compounds in the grapefruit juice are presented with more detail at the end of this section.

The pharmacokinetic effects of grapefruit juice on the various statins have been investigated in different studies carried out by Lilja et al.[16-18] (table III). In one two-phased crossover study,[16] 10 healthy volunteers, divided at random into two groups, drank 200 ml grapefruit juice or water three times a day for two days. On the third day, each volunteer took 40 mg of Simvastatin with 200 ml of grapefruit juice or water and another 200 ml of the same liquid 30 minutes and 90 minutes after Simvastatin intake. The results of this study show an increase in the Cmax and the AUC of Simvastatin in volunteers who drank grapefruit juice. C_{max} values and AUC also increased with the acid form of Simvastatin. The authors conclude that grapefruit juice increases serum concentrations of both, the lactone and acid form of Simvastatin, and suggest that the probable mechanism of action is the reduction of the presystemic metabolism of Simvastatin due to the inhibition of CYP 3A4. These findings indicate that concomitant administration of grapefruit juice and Simvastatin, at least in large quantities of the juice, should be avoided, or that the dose of Simvastatin should be reduced to avoid adverse reactions such as rhabdomyolysis.[16]

In a later study, the same research group[17] studied the effect of grapefruit juice on the pharmacokinetics of Atorvastatin and Pravastatin, using similar design as in the previous study. Grapefruit juice significantly increases serum concentrations of Atorvastatin, in both its acid and lactone forms. Thus, concomitant administration of Atorvastatin and grapefruit juice should be avoided, or the dose of Atorvastatin reduced proportionately.[16] Nevertheless, this juice does not appear to have any effect on the pharmacokinetics of Pravastatin due to its hydrosolubility. A Japanese study also confirmed the interaction of grapefruit juice with Atorvastatin but not with Pravastatin.[19] It has been also found that Pitavastatin, unlike Atorvastatin, appears to be scarcely affected by the CYP 3A4-mediated metabolism.[20]

However, there is a debate concerning duration of the inhibitory effect of grapefruit juice on CYP 3A4 and the real effect in hypercholesterolaemic patients. It should be considered, on one hand the amount of grapefruit juice, its concentration and frequency of consumption, and on the other that the variability of the individual response to the statin-fruit juice interaction is very high,[21-22] which may be explained by genetic variability.

Repeated consumption of high quantities of grapefruit juice has increased the AUC values of Simvastatin considerably.[16] However, drinking daily 250 ml of the juice 12 h apart from Lovastatin has a modest effect on the pharmacokinetic of the drug.[23]

Table III
Effect of grapefruit juice (GFJ) on statin pharmacokinetics and recommendations

Reference	*Statin*	*Treatments*	*Effects*	*Recommendations*
Lilja et al.[16]	Simvastatin	200 ml GFJ 3 times/day. On the third day 40 mg of Simvastatin with the first GFJ intake	↑ C_{max} and ↑ AUC of statins (lactone and acid forms)	Avoid concomitant use of GFJ and Simvastatin, or reduce Simvastatin dose
Lilja et al.[17] Fukazawa et al.[19]	Atorvastatin Pravastatin	200 or 250 ml GFJ 3 times/day. On the third day Atorvastatin (10 or 20 mg) or Pravastatin (10 mg) with the first GFJ intake	↑ C_{max} and ↑ AUC (0-48 h) of Atorvastatin No significant changes in Pravastatin pharmacokinetics	Use Pravastatin which presents little or not interaction with GFJ, or reduce Atorvastatin dose
Ando et al.[20]	Atorvastatin Pitavastatin	250 ml GFJ 3 times/day for 4 days. On each day 20 mg of Atorvastatin or 4 mg Pitavastatin with the first GFJ intake	↑ AUC of Pitavastatin acid was only 13% while that of Atorvastatin was 83%	Use Pitavastatin
Rogers et al.[23]	Lovastatin	250 ml GFJ once daily for 3 days 12 h apart from Lovastatin	No significant changes in Lovastatin pharmacokinetics. High variability in the individual response	Lovastatin taken 12 h apart form GFJpresents a modest interaction
Lilja et al.[18]	Simvastatin	200 ml GFJ once daily for 3 days. On the third day 40 mg of Simvastatin with the GFJ intake	↑ C_{max} and ↑ AUC (0-24 h)	Even one glass of GFJ increases Simvastatin plasma concentrations
Lilja et al.[24]	Simvastatin	200 ml double-strength GFJ 3 times/day for 3 days with 40 mg Simvastatin, or 1, 3, and 7 days after ingestion of the high-dose GFJ.	↑ C_{max} and ↑ AUC was lower when Simvastatin was taken after 24 h of GFJ intake, even less after 3 days, and not significant after 7 days	The interaction of large amounts of GFJ with Simvastatin disappears after 3-7 days

In a crossover study using 40 mg of Simvastatin with water (control period) and with high doses of grapefruit juice (200 ml three times a day for three days), or 1, 3 and 7 days after drinking the large quantities of grapefruit juice[24] it was observed that when Simvastatin was taken with grapefruit juice, Simvastatin C_{max} and AUC increased 12 and 13.5-fold, respectively, in comparison with control values. When Simvastatin was administered 24 hr after the last grapefruit juice intake, C_{max} and AUC increased 2.4- and 2.1-fold, respectively, compared with control values. When Simvastatin was given 3 days after the grapefruit juice, C_{max} and AUC increased 1.5- and 1.4-fold, respectively, in comparison with control values. There were no differences between C_{max} and AUC values of study participants who took Simvastatin 7 days after taking grapefruit juice and controls. Furthermore, when Simvastatin was taken 24 hours after large amounts of grapefruit juice the AUC is much lower that the one observed after a concomitant intake of both. The potential interaction of large amounts of grapefruit juice with CYP 3A4 disappears 3-7 days after the last intake of grapefruit juice.[24]

Given that Simvastatin, Lovastatin and Atorvastatin are metabolised by CYP 3A4 (table I), they are the only available statins affected by this particular interaction, for which reason one of the other statins (e.g. Pravastatin, Pitavastatin) can be taken as an alternative treatment.

However, a number of studies focus on other interaction mechanisms besides that of CYP 3A4. Grapefruit juice also inhibits P-glycoprotein, a transporter that carries drugs from the enterocyte back to the gut lumen, resulting in a further increase in the fraction of drug that is absorbed.[16,25] Grapefruit juice is also capable to inhibit human organic anion-transporting polypeptide B (OATP-B) *in vitro*.[25-26] This inhibition decreases the intestinal uptake and therefore the oral bioavailability of the drug, which is the opposite effect to that of CYP 3A4 inhibition. Nevertheless, it remains unclear the contribution to the bioavailability of statins affected by P-glycoprotein and OATP-B inhibition.

In 2007, Li et al.[27-28] described an estearase inhibition attribute of grapefruit juice as a new drug interaction. Lovastatin (a lactone) is known to be metabolized by CYP 3A4 but also by estearase to a hydroxyacid analog (active drug). The hydrolysis occurs in gut, liver and plasma and is considered its major metabolic pathway. The study carried out in rats and Caco-2 cells demonstrated that the grapefruit juice decreased Lovastatin hydrolysis in the gut, and thereby markedly increased the metabolic stability and permeability of the ester, leading to the enhancement of exposure to Lovastatin acid in rats. It was also found that the contribution of estearase inhibition was similar to that of CYP 3A, and that the estearase inhibition also affected Analapril (a prodrug for the treatment of hypertension) pharmacokinetics.

The potential interaction between specific grapefruit juice components has been also investigated.[28-29] In one study, it was observed that the most powerful inhibitor of P-glycoprotein was the furanocoumarin 6,7-epoxy-bergamottin, followed by 6,7-dihydroxybergamottin, while bergamottin did not display any inhibitory effect at concentrations of up to 10 μmol. Naringenin was 10 times more powerful than naringin. Concentrations of the flavonoids and furanocoumarins evaluated in this study were in the same range as those found in grapefruit juice. Therefore, the results obtained from this *in vitro* study suggest that the compounds present in grapefruit juice are able to inhibit P-glycoprotein modifying the bioavailability of drugs such as Simvastatin, Lovastatin, Pravastatin, Atorvastatin and Pitavastatin, which are substrates for that glycoprotein.[3] Heating grapefruit juice was recently found to decrease its concentrations of bergamottin and dihydroxybergamottin, thereby decreasing its interactions.[30] This finding could be very useful to those patients who wish to drink this juice but are taking one of the drugs that interact with it.

Concerning the juice components responsible of the estearase inhibition, the furanocumarins bergamottin, 6,7-dihydroxybergamottin, and bergapten, and the glycoside flavonoids naringin and hesperidin, did not present estearase inhibition at concentration found in grapefruit juice or higher.[28] However, the flavonoid aglycones morin, galangin, kaemferol, quercetin, and naringenin showed appreciable estearase inhibition. It should be pointed out that these compounds are widely distributed among fruit juices.

There are few studies on the possible interactions between fruit juices other than grapefruit and statins. Citrus juices have been found to interact with statins through the OATP mechanism.[31] Orange juice increases Pravastatin AUC, without affecting its excretion rate.[31] This effect could be related to higher intestinal absorption of the drug, mediated by the orange juice, but the mechanism is not clear and further studies are necessary. Orange juice does not alter Simvastatin pharmacokinetics.[32]

One report highlights the possible interaction between Rosuvastatin and pomegranate juice causing rhabdomyolysis in one patient.[33] The patient was treated for familiar hypercholesterolemia with Ezetimide 10 mg/day and Rosuvastatin 5 mg every other day for 17 months. Three weeks before urgent presentation, and after reading the consumer information on the antioxidant benefits of pomegranate juice, he began drinking 200 ml twice weekly. Although the precise influence of this juice was not studied since this was only a case report, this observation deserves further research, including the impact of the media on patient's choice. These data point out that health claims of food and ingredients should be thoroughly evaluated considering all aspects of the target population.

Statins and unsaturated fatty acids

Statins and unsaturated oils

Very little information exists on the possible relation between unsaturated oil intake and statin effects. This is surprising because culinary oils contribute with more than 50% of the consumed fat.[11] It has been known for many years that diets rich in fat and cholesterol tend to raise serum cholesterol.[34-36] Monounsaturated fatty acids (MUFA) are considered neutral because they do not raise or lower the plasma cholesterol. However, recent studies show that replacing saturated fatty acids (SFA) with either MUFA or polyunsaturated fatty acids (PUFA) lowers total and LDL-c.[37,38] Mattson and Grundy[35] found that oleic acid lowered plasma cholesterol as much as linoleic acid. According to Dietschy,[39] unsaturated fatty acids (oleic acid more than linoleic acid) increase gene expression of LDL receptors, maintaining the amount and activity of these receptors high and thus decreasing the concentration of serum LDL, while palmitic acid in the liver maintains gene expression of LDL-receptors low and, thus, serum LDL concentrations high. However, it is generally accepted a more prominent hypocholesterolemic effect of n-6 PUFA (e.g. linoleic acid) than of MUFA (e.g. oleic acid).[40,41] Nonetheless, oleic acid keeps HDL-c higher than linoleic acid does.[40,41]

Taking into consideration all these results, our research group[42] carried out a observational follow-up study in 25 men aged 45 to 65 years presenting according to the ATPIII protocol a cardiovascular risk higher than 20%. Twelve of the volunteers used daily, as the only culinary fat, olive oil; while the other thirteen volunteers used sunflower oil. After hypercholesterolaemia diagnosis, the participants were given statins for the first time. It was confirmed that statins, with independence of the consumed culinary oil, significantly reduced serum lipid and lipoprotein levels after 6 months of treatment. No significant differences on cholesterol, LDL-c, HDL-c and triglycerides were found at the start and six months later between the two oil groups. TC/HDL-cholesterol and the ATPIII 10-year risk percent significantly decreased more in the olive oil group. TC and the TC/HDL-cholesterol and the LDL-cholesterol/HDL-cholesterol ratios and the ATPIII 10-year risk percent decreased significantly more in the olive oil-group after BMI, energy and alcohol intakes were adjusted. Figure 3 shows the differences found in volunteers consuming Simvastatin and olive oil or sunflower oil. This result is relevant taken into account the predictive power of future cardiovascular risk of the TC/HDL-cholesterol ratio.[43]

At present no clear explanation can be drown taken into consideration the theoretical higher hypocholesterolaemic effect of linoleic acid than the oleic acid.[40,41] However, PUFA have been shown to activate CYP activity, while SFA exert lower cytochrome activation with MUFA exerting intermedium effect.[44] Thus, we

suggest that the half-life of statins could be reduced due to a cytochrome-activating effect when the drug is consumed by patients following a sunflower oil rich diet with respect to the same diet prepared with olive oil. Nonetheless, the possible potentiating effect of olive oil polyphenols on statin pharmakocynetic, due to an inhibition of CYP,[44,45] should not be ruled out. In the Sánchez-Muniz et al preliminary paper,[42] it was concluded that although Simvastatin was a very effective hypolipaemic drug, olive oil-diets in preference to sunflower oil-diets should be consumed in patients with high cardiovascular risk.

Statins and n-3 fatty acids

Humans cannot produce n-3 fatty acids, for which reason they are essential and must be obtained from the diet. Eicosapentaenoic acid (EPA) is the precursors of a group of eicosanoids, including prostaglandins (PGE3, PGD3), prostacyclins (PGI3), thromboxanes (TXA3) and leukotrienes (LTB5), with anti-inflammatory, antithrombotic, antiarrhythmic and vasodilating properties.[47] Numerous studies have demonstrated the cardioprotective effect of n-3 fatty acids,[48,51] throughout reduction of TXA2 formation,[11] and the increased synthesis of TXA3 and PGI3.[52,53] N-3 fatty acids decrease formation of serie 4-leukotrienes by monocytes and neutrophils, attenuating leukotriene-mediated chemotaxis and the adherence of neutrophils to endothelial cells. They also reduce the formation of platelet derived growth factor,[54] decreasing the proliferation of endothelial cells in the process of atherosclerosis, lower plasma fibrinogen levels[55] and arterial pressure in individuals with hypertension.[56]

Results of the ATTICA Study[57] showed that fish consumption was inversely related to all the inflammatory markers analysed, especially protein C reactive and interleukine-6, followed by tumour necrosis factor-α and the white blood cell count.

The anti-arrhythmic properties of n-3 fatty acids may constitute another protective mechanism against cardiovascular disease.[58] Fish intake reduced the risk of sudden cardiac death in some studies.[48,49] Moreover, n-3 fatty acids are able to alter cardiac electrophysiology and, thus, behave as pro or anti-arrhythmic agents, depending on the mechanism of the arrhythmia.[58] Statins also display anti-arrhythmic properties, as it is shown in different studies.[59-61] While this action mechanism of statins are not yet entirely clear, it appears that they may produce these effects due to their anti-inflammatory[62] or anti-oxidant properties.[63]

The cardiovascular protective role of statins can be explained by their capacity to inhibit HMGCo-A reductase and reduce LDL-c levels in blood. Moreover, HMGCo-A reductase inhibitors are also known to inhibit transendothelial migration of neutrophils, as well as to alter the chemotactic capacity of monocytes.[64] In addition, statins can also prevent cardiovascular disease through other mechanisms. These drugs inhibit synthesis of mevalonic acid, a precursor of cholesterol and other metabolites such as isopentenyl adenosines (which form part of tRNA) and dolichols (used in glycoprotein and CoQ10 synthesis). Furthermore, mevalonic acid metabolites, such as farnesyl pyrophosphate and geranyl pyrophosphate, mediate the prenylation of some specific proteins that intervene in transduction processes of cellular differentiation and proliferation. Thus, statins may protect against atherosclerosis by modulating cell function set into motion by the inhibition of protein prenylation.[2]

Statins and n-3 fatty acids have different but complementary effects on the lipid profile. While statins fundamentally reduce concentrations of cholesterol,[65-66] n-3 fatty acids reduce plasma triglyceride levels, especially in individuals with hypertriglyceridaemia.[67] A recent review of studies in humans[68] reported that 1.5 to 3.5 g/day of n-3 fatty acids reduce plasma triglyceride concentrations by 25-30%, and that the majority of studies found reductions in total cholesterol and increases in HDL-c while the results on LDL-c are not consistent. Therefore, the association of statins with n-3 fatty acids could be useful to treat dyslipaemias characterised by high cholesterol and triglyceride levels.

Administered together, statins and n-3 fatty acids have proven to be safe, effective and well tolerated in treatment of combined dyslipaemia (table IV). In a study undertaken by our group,[69,70] individuals having chronic statin therapy who consumed a fish-rich diet presented a better lipoprotein profile than those who ate a meat-based diet. In addition, a fish-rich diet is known to increase insulin sensitivity without the adverse effects of supplements containing high doses of n-3 fatty acids.[68]

In 32 patients with combined dyslipaemia,[71] the addition of n-3 fatty acids to Pravastatin produced lower triglyceride and Apo B levels than Pravastatin treatment alone, although the differences were not statistically significant. On the other hand, total cholesterol values were significantly lower when Pravastatin was used with fish oil than when fish oil was given alone. Another study concluded that Simvastatin and n-3 fatty acids have an additive effect and that their combined therapeutic use probably has beneficial clinical consequences.[72] When n-3 fatty acids were combined with Simvastatin treatment, total cholesterol and triglyceride levels decreased, while HDL-c concentrations were not affected. Apo A and Apo B values did not change, but Apo E concentrations decreased significantly.

The combined Simvastatin and n-3 fatty acid treatment reduced serum concentrations of total cholesterol, triglycerides and Apo E, as reported in previous studies.[72] During postprandial hyperlipaemia, which decreased with both treatments (although significantly more with the combined treatment), activation of coagulation factor VII was significantly lower, indicating that combined treatment may reduce the thrombotic

Table IV
Summary of the results obtained in studies on the combined use of statins and n-3 fatty acids

Reference	*Number of participants (n)*	*Dyslipemia*	*Treatment*	*Effects of combined treatment*
Contacos et al..[71]	32	Combined hyperlipaemia	Pravastatin plus n-3	↓ Triglycerides ↓ Apo B ↓ Total cholesterol
Nordøy et al.[72]	41	Combined hyperlipaemia	Simvastatin plus n-3	↓ Triglycerides ↓ Apo E ↓ Total cholesterol
Nordøy et al.[73]	41	Combined hyperlipaemia	Simvastatin plus n-3	↓ Triglycerides ↓ Apo E ↓ Total cholesterol ↓ Factor VII a
Nordøy et al.[74]	42	Combined hyperlipaemia	Atorvastatin plus n-3	↓ Factor VII a
Durrington et al.[75]	59	Coronary arterial disease and hypertriglyceridaemia	Simvastatin plus n-3	↓ Triglycerides ↓ VLDL-c

potential associated with intake of high-fat meals in these patients.[73] Similar studies were carried out in patients treated with Atorvastatin. Nordøy et al.[74] in a parallel-group, double-blind, placebo-controlled study found that postprandial levels of activated factor VII decreased with Atorvastatin treatment and diminished even further by the addition of n-3 fatty acids, which lowered the fasting and postprandial levels of activated factor VII, and its coagulant activity as well. Prothrombin fragment 1+2 increased during postprandial hyperlipaemia, but to a lesser degree after combined treatment with Atorvastatin and n-3 fatty acids. Therefore, although patients with combined hyperlipaemia present an elevated risk of activation of the coagulation system, especially during postprandial hyperlipaemia, combined statin and n-3 fatty acid therapy can significantly reduce this activation.[74] In another study, 59 patients with coronary heart disease who received Simvastatin (10-40 mg/day) were divided at random into two groups for a one-year period, during which time one group received n-3 fatty acids while the other was given placebo.[75] The addition of n-3 fatty acids significantly lowered serum triglyceride levels by 28% in 12 weeks, and by 35% after 48 weeks of treatment. In addition, VLDL-c concentrations significantly decreased and non-HDL-c levels dropped by 18% after 18 weeks of treatment.[75] Nordøy et al.[76] also concluded that the addition of low doses of n-3 fatty acids to Atorvastatin treatment could improve the cardiovascular disease risk profile in patients with combined hyperlipaemia.

Results regarding the efficacy of combined treatment with statins and n-3 fatty acids indicate that it is a useful therapeutic alternative in patients with hypertriglyceridaemia when LDL levels have decreased and statin monotreatment cannot lower hypertriglyceridaemia. As Simvastatin is extensively metabolised by CYP 3A4, McKenney et al.[77] designed a random and double-crossed study, with two 14-day-long treatment periods separated by a wash-out period, to determine the impact of administration of n-3 fatty acids on Simvastatin pharmacokinetics. Participants were randomly divided into groups that received 80 mg of Simvastatin together with a daily morning dose of n-3 fatty acids or alone. No statistically significant differences in pharmacokinetic parameters of Simvastatin or its metabolite β-OH-Simvastatin were observed when Simvastatin was administered with n-3 fatty acids, making it possible to conclude that repeated doses of n-3 fatty acids do not affect Simvastatin pharmacokinetic. Nevertheless, after the first dose of fatty acids, the AUC of Simvastatin increased slightly. The authors of this study concluded that concomitant treatment with n-3 fatty acids and Simvastatin did not significantly affect the pharmacokinetics of Simvastatin in the stationary state and was well tolerated in the population studied.[77]

Statins and phytosterols

Sterols are a group of components essential to the formation of animal and plant cell membranes. Phytosterols are plant sterols and are differentiated from cholesterol by their lateral chain (fig. 2). Stanols are saturated sterols that lack the double bond in position 5 of the B ring. The most abundant dietary phytosterols are β-sitosterol, campesterol and stigmasterol.[78]

After the discovery of free phytostanols and their application to reduce cholesterol levels, investigations of fat-soluble phytostanol esters began in 1991,[79] and phytostanol-enriched margarine became available to

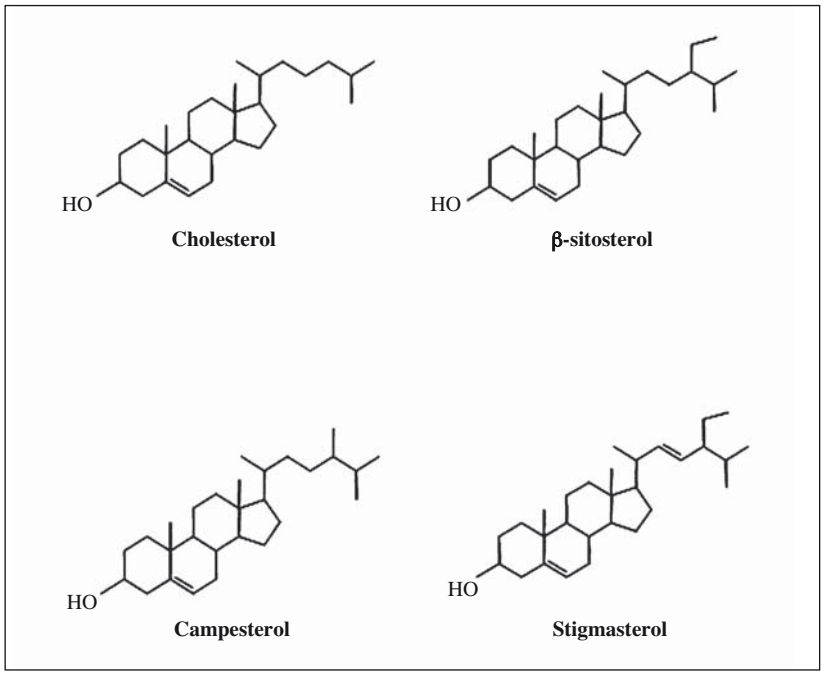

Fig. 2.—Chemical structure of cholesterol and main plant sterols.

the general public in 1995.[80] A 1992 study demonstrated that a dose of 1.5-3 g/day of phytosterols/phytostanols reduced total plasma cholesterol by 8-17% and LDL-c by 9-19%, while HDL-c levels were not affected.[81] A subsequent meta-analysis of 41 assays confirmed those findings and also demonstrated an additive effect when they were taken with cholesterol-reducing drugs.[82] The most important possible negative effect of phytosterol intake may be the reduction of fat-soluble vitamin plasma levels,[78,83] which can be avoided, at least partially, with a fruit and vegetable-rich diet.

Phytosterols impede cholesterol absorption while statins inhibit cholesterol synthesis. Both mechanisms work in a complementary manner to increase LDL receptor activity and LDL-c plasma clearance. Statins are most effective in individuals with high endogenous cholesterol production, while plant sterols act best in those with the most efficient cholesterol absorption.[82] The Scandinavian Simvastatin Survival Study (4S) demonstrated that individuals with the greatest cholesterol absorption efficiency and low cholesterol synthesis levels presented high blood phytosterol concentrations and were not able to reduce LDL-c levels or cardiovascular disease rates after 5 years of statin treatment.[84] Keeping in mind the effects of both, phytosterols and statins, the ideal therapy may include small doses of statins with phytosterols/phytostanols. The combined treatment will be most efficient in individuals with high cholesterol absorption efficiency.

Individual cholesterol absorption capacity and endogenous production varies due to genetic polymorphism. Response to statins may be determined by the Apo E genotype, by a possible effect on bile acid synthesis and/or by variability in the rate of CYP metabolism.[85] There are studies in patients with familial hypercholesterolaemia[86] and non-familiar hypercholesterolaemia[87] that suggest that statin treatment in those who display an E4 allele reduces LDL-c to a lesser degree than in individuals with E2 or E3 alleles. However, other studies have not been able to confirm this hypothesis.[87-90] Individuals with the Apo E4 allele do, nevertheless, absorb more cholesterol than those with other Apo E alleles.[91] In a study that measured cholesterol absorption and synthesis in a group of Finns, those with an E2 allele (E2/2, E2/3 or E2/4) absorbed less and synthesised more cholesterol than those with an E3 (E3/3) allele. Individuals with an E4 (E3/4 or E4/4) allele displayed the greatest absorption and lowest synthesis.[92] As well as by the Apo E genotype, inter-individual differences in absorption are influenced by polymorphisms of the ABC G5 and G8 genes.[91] Differences in the response to sterol esters in mild hypercholesterolaemics have been found to be dependently of ApoE polymorphisms.[83] Patients carrying the ApoE4 allele decreased less the total cholesterol, LDL-cholesterol and ApoB levels than their ApoE2 and ApoE 3 carrier counterparts.[83]

Statin treatment reduces cholesterol precursors and increases serum phytosterol levels,[93] particularly in individuals with a high absorption capacity for cholesterol and sterols in general. In the early 1990's, some studies with Pravastatin and Lovastatin reported increases in cholestanol and serum phytosterols,[94-96] while others described reductions.[97] Serum concentrations of phytosterols decrease with statin treatment for a variable period of time. Some studies indicate that this reduction depends on their pre-treatment absorption levels, treatment duration and the efficacy in inhibiting cholesterol synthesis.[85,97] Several studies deal with the effect of sterol and stanol treatment on LDL-c levels in individuals treated with statins (table V).[98] The first

Table V
Effect of phytosterols and phytostanols on LDL-c in individuals treated with statins

Reference	*Subjects (n)*	*Statins*	*Esters of*	*Dose (g/day)*	*Time (weeks)*	*Δ LDL-c (%) vs statin plus placebo*
Vanhanen[99]	FH (13) HC (14)	Pravastatin	Sitostanol	1,5	6	0
Gylling and Miettinen[100]	HC-NIDDM (8)	Pravastatin	Sitostanol	3	7	-6
Gylling et al.[101]	PMW-MI	Simvastatin	Sitostanol	3	7	-16(*)
Vuori et al.[102]	FH (12)	Simvastatin	Stanols	2,2	6	-20(*)
Blair et al.[103]	HC (148)	Various	Stanols	3	8	-10
Neil et al.[104]	FH (30)	Various	Sterols	2,5	8	-11
Simons.[105]	HC (75)	Cerivastatin	Sterols	2	4	-7
O'Neill et al.[106]	FH (25)	Various	Stanols	2,6	8	-7

FH, Familial hypercholesterolaemia; HC, hypercholesterolaemia; NIDDM, non-insulin-dependent diabetes mellitus; PMW-MI, postmenopausal women with a previous myocardial infarction; (*) uncontrolled studies. Udapted from Thompson.[98]

study that combined statins and stanols (1.5 g/day of sitostanol ester), reported no significant decrease in total cholesterol or LDL-c levels.[99] Results of a later study of individuals with non-insulin-dependent diabetes mellitus treated with Pravastatin displayed an additional 6% decrease in LDL-c levels when these patients were given sitostanol esters (3 g/day) in margarine, even when initial cholesterol absorption was already low.[100] Even greater reductions (16-20%) were observed in other studies although these were unblinded and uncontrolled.[101-102] Reductions in total cholesterol levels of 11% and of LDL-c levels of 16% were obtained in postmenopausal women who had previously suffered myocardial infarction and were taking Simvastatin after have been given a complementary treatment consisting of sitostanol ester (3 g/day) in margarine.[101] Serum LDL-c levels decreased by 20% in individuals with familial hypercholesterolaemia who were given Simvastatin together with 2.24 g/day of stanols.[102] LDL-c reductions of 7-11% were reported in four-to-eight-week-long placebo-controlled, double-blind random studies with phytosterol and/or phytostanol esters.[103-107] In one of these studies, 5.1 g/day of phytostanol ester in margarine in conjunction with a stable statin treatment further reduced total serum cholesterol levels by 7% and those of LDL-c by 10%.[91] Various studies have shown that phytostanols[103] and phytosterols[105] have an additive, not a synergic, effect when given together with statins to individuals with primary hypercholesterolaemia.[105] The four treatment options of this study were: placebo plus regular margarine, placebo plus phytosterol-enriched (2 g) margarine, cerivastatin (400 µg) plus regular margarine and cerivastatin (400 µg) plus phytosterol-enriched (2 g) margarine. Cerivastatin vs. placebo reduced LDL-c by 32% and enriched margarine vs. regular margarine reduced these levels by 8%. Phytosterol-enriched margarine taken together with cerivastatin induced a 39% reduction but no significant interactive effect between phytosterol and statin was observed. With regard to the reduction of cholesterol levels through phytosterol or phytostanol treatment some of the studies reviewed report no statistical differences between hypercholesterolaemic individuals treated with statins and non-treated hypercholesterolaemics[104] or normocholesterolaemic individuals.[105]

Few studies compare the efficacy of plant sterols and stanols. The majority, lasting for only 3-4 weeks, reflect insignificant differences in effectiveness. Differences were detected, however, between the administration of phytosterol esters (1.6 g/day) and phytostanol esters (1.6 g/day or 2.6 g/day) over a two-month-long period to healthy individuals and to others with familial hypercholesterolaemia receiving statin treatment.[106] The effect of the phytosterols decreased at the end of the study and LDL-c level was not significantly different from baseline. In addition, these individuals displayed an increase in serum phytosterol levels and decrease bile acid synthesis. In contrast, after the two-month-long treatment, phytostanol esters significantly decreased both LDL-c and phytosterol levels, without producing any effect on bile acid synthesis.[106]

Taking into account all the information previously reviewed, it is possible to conclude that phytostanol esters with respect to phytosterol esters should be preferred for long-term treatment of hypercholesterolaemia. Various studies have confirmed that the additive effect produced by combining phytostanols with a small dose of statins reduces LDL-c levels by approximately 10%,[84] this reduction is slightly greater than that achieved by doubling the dose of statins.[107] Furthermore, by lowering the dose of statins the risk of rhabdomyolysis, which appears to be dose-dependent, also decreases.[108] In addition, a triple therapy including stanol esters, statins and resins can reduce LDL-c by up to 67% and may be effective in the most resistant hypercholesterolaemias.[93]

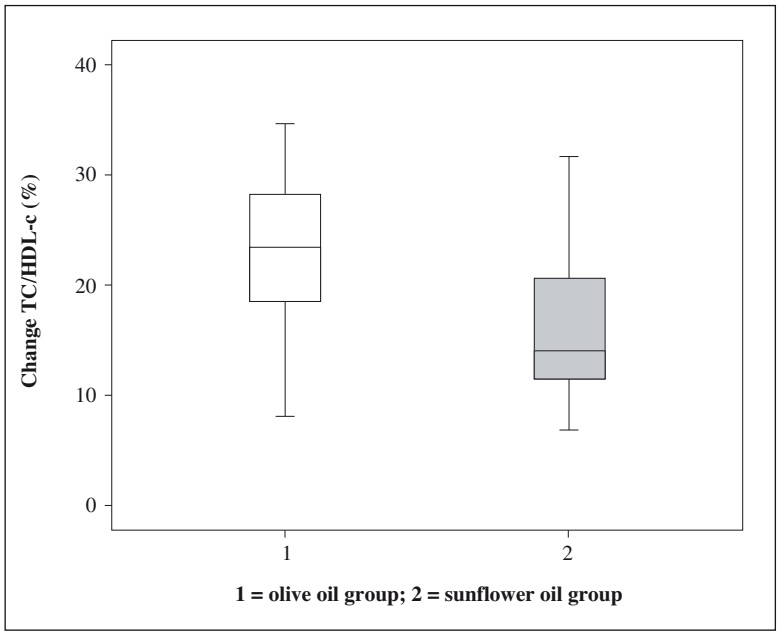

Fig. 3.—Change in the total cholesterol/HDL-cholesterol ratio (%) in patients with high cardiovascular risk after six month-treatment with statins and consuming diets prepared with olive oil or sunflower oil. N = 12, Olive oil group, N = 13, sunflower oil group. The effect was significantly higher (P < 0.05) in the olive oil group than in the sunflower oil one.[42]

Conclusions and future remarks

This article reviews some outstanding aspects of the interactions between statins and dietary components. The most relevant results were those obtained with grapefruit juice, oily fish and phytosterols. Given the risk of statin-induced adverse reactions (e.g. myopathy and rhabdomyolysis), a close monitorisation of patients receiving statin treatment is necessary. Concomitant administration of this group of drugs with certain foods can lead to a reduction (in the case of fibre) or an increase (with grapefruit juice, n-3 fatty acids, phytosterols) of their pharmacological action. Therefore, to optimise the pharmacological treatment, it is necessary to understand and adjust certain important aspects of the diet of these patients. Besides, follow-up studies of the therapeutic effects of statins in patients consuming a Mediterranean diet, which includes high levels of fibre, citric fruits, oily fish, phytosterols, olive oil rich in polyphenols and other minor components, are necessary to assure the correct prescription and dosage of statins in these individuals. To conclude, we emphasize that there are possible interactions that require further investigation, for example, different types of oils —e.g. poor and rich in minor compounds olive oils—, fruit juices or fibre, or the prolonged consumption of high doses of alcohol.

Acknowledgements

The authors are grateful to the Nutrition and Cardiovascular Disease PhD students for their interest in the problems of the nutrition and drug interactions. The study was partially granted by Projects PR248/01-10161 and AGL 2008-04892-C03-02.

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):207-223
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisiones

Distribución regional de la grasa corporal. Uso de técnicas de imagen como herramienta de diagnóstico nutricional

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Resumen

La masa grasa es el componente más variable en la composición corporal, tanto si se comparan varios individuos o se consideran los cambios de una persona a lo largo de la vida. La obesidad se caracteriza por un exceso de masa grasa que afecta a la salud y al bienestar de las personas. Los riesgos asociados al exceso de grasa se deben, en parte, a la localización de la grasa, más que a la cantidad total. Hoy se postula que las causas y consecuencias metabólicas de la distribución regional de la grasa tienen particular importancia clínica. Por ello, el ideal sería identificar un compartimento de tejido adiposo mórbido y poder actuar sobre él. En la presente revisión se evalúa la bibliografía existente sobre la localización y características de la grasa en el ser humano adulto. Nos centramos en la región abdominal, a la luz de los principios de las modernas técnicas de imagen disponibles como la tomografía computarizada y la resonancia magnética, considerando sus ventajas y limitaciones. El objetivo de esta revisión es valorar si es posible conocer la composición corporal y la distribución de la grasa basándonos en los métodos de imagen. La tomografía fue la primera técnica en aplicarse a estudios de obesidad, pero en la actualidad, debido a los inconvenientes de irradiar al paciente, esta técnica va cediendo paso a la resonancia magnética que, además de evitar las radiaciones, proporciona una calidad de imagen extraordinaria. Ambos métodos de imagen permiten subdividir los depósitos adiposos clásicos en otros más específicos. Así, el depósito graso subcutáneo puede ser superficial o profundo, mientras que el depósito graso visceral puede estar constituido por grasa mesentérica, omental o epiploica, retroperitoneal y perirrenal. Además, la utilización de estas técnicas de imagen modernas permite el estudio de la grasa muscular, considerada por algunos autores como el nuevo compartimento graso. La grasa muscular comprende los depósitos de grasa localizados entre las fibras musculares esqueléticas o

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Recibido: 1-VII-2009.
Aceptado: 9-VIII-2009.

REGIONAL DISTRIBUTION OF THE BODY FAT. USE OF IMAGE TECHNIQUES AS TOOLS FOR NUTRITIONAL DIAGNOSIS

Abstract

Fat mass is the most variable component in the human body, both when comparing several individuals and when considering changes in the same person throughout life. Obesity is characterized by an excess of body fat that affects health and well-being of individuals. Risk associated with excess body fat is due, in part, to location of fat rather than to total amount. Today is stated that causes and metabolic consequences of regional distribution of fat are of particular clinical importance. To identify a compartment of morbid adipose tissue and to be able to act on it is one of the main aims of the present research. In this review, we have revised the existing literature on location and characteristics of total body fat in human adult. We have focused on abdominal region, basing this review on the use of modern imaging techniques available nowadays, such as computerized tomography and magnetic resonance imaging, with their advantages and limitations. The purpose of this review is to assess whether it is possible to know the body composition and fat distribution on the basis of image methods. Computed tomography technique was first applied in studies of obesity, but today, due to the inconvenience of irradiating the patient, this technique is being replaced by magnetic resonance that, in addition to avoid radiation, provides images of extraordinary quality. Both methods allow to subdivide the classic general fat depots in others more specific. Subcutaneous fat depot can be superficial or deep, while visceral can be divided in mesenteric, omental or epiploic, retroperitoneal and perirrenal fat. In addition, these modern techniques of imaging permit to study muscular fat, considered by some authors asthe new fat compartment. Muscular fat includes fat located between skeletal muscle fibers, called extramyocellular fat, as well as lipids located within skeletal mucle fibers (intramyocellular fat). Its importance lies not only in size, similar to visceral fat, but on its pathophysiological implications. Finally, techniques of image analysis have prove to be extremely useful in studying the location and extent of abdominal fat compartments, becoming reference to

extramiocelulares, así como los lípidos localizados dentro de las fibras muculares esqueléticas o intramiocelulares. Su importancia radica, no sólo en su tamaño, similar a la grasa visceral, sino en sus posibles implicaciones fisiopatológicas. En definitiva, las técnicas de análisis de imagen han resultado ser sumamente útiles en el estudio de la localización y medida de los depósitos de grasa abdominal, pasando a ser la técnica de referencia para validar ecuaciones obtenidas a partir de los métodos denominados indirectos.

(*Nutr Hosp.* 2010;25:207-223)

DOI:10.3305/nh.2010.25.2.4406

Palabras clave: *Grasa cutánea. Grasa visceral. Grasa muscular. Tomografía computerizada. Resonancia magnética. Obesidad.*

validate equations obtained from the so-called "indirect methods".

(*Nutr Hosp.* 2010;25:207-223)

DOI:10.3305/nh.2010.25.2.4406

Key words: *Subcutaneous fat. Visceral fat. Muscle fat. Computed tomography. Magnetic resonance image. Obesity.*

Introducción

El estudio de la composición corporal, a pesar de no ser una disciplina nueva, despierta cada día más interés. Se refiere al estudio anatómico, molecular o tisular de los distintos componentes del cuerpo humano, y es precisamente en el campo de la nutrición donde se ha demostrado en mayor medida su aplicación clínica, tanto para la valoración del estado nutricional como para la evaluación de la respuesta a la intervención nutricional en patologías diversas.

La grasa es un componente del cuerpo humano que se acumula en forma de tejido graso o adiposo. En la actualidad se reconoce que el tejido adiposo (TA), además de ser la reserva de lípidos, es un órgano endocrino que produce una variedad de hormonas y citoquinas que regulan el metabolismo e influyen en la composición corporal[1]. Recientemente, el TA está surgiendo como fuente importante de células madre adultas[2].

La distinción entre grasa y TA en el lenguaje corriente es normalmente irrelevante, y los términos se usan indistintamente. Sin embargo, en el campo de la composición corporal y el metabolismo, "grasa" y TA son distintos términos, y la distinción semántica es importante cuando se determina la masa o se estudian las características metabólicas. Aunque muchas veces puedan considerarse como términos sinónimos, es importante recordar que, con la edad, el contenido de "grasa" del "TA" puede variar. Por ejemplo, el contenido de grasa del TA es del 66% en los recién nacidos y aumenta gradualmente hasta la edad adulta, siendo del 80% a partir de los 13 años de edad[3].

Desde el punto de vista de la histología, el TA es uno de los considerados tejidos conectivos o conjuntivos laxo.

La distribución anatómica del TA también muestra patrones de cambio con la edad y un dimorfismo sexual acentuado. En general, el grosor del TA subcutáneo aumenta en el tronco en los niños durante la adolescencia, y en la zona glúteo-femoral en las niñas, lo que conduce a fenotipos distintivos en la edad adulta que se han descrito como patrón de grasa androide frente a ginoide.

Otro factor a considerar es que la masa de TA es el elemento más variable de la composición corporal. Así, la variabilidad entre individuos puede oscilar desde alrededor del 6% hasta más del 60% del peso corporal total. La variabilidad en el mismo individuo (intra-individuo), puede ser también considerable a lo largo del tiempo si pasa por fases sucesivas de obesidad y delgadez.

La mayoría de los métodos que proporcionan datos por regiones anatómicas miden o estiman el TA, no determinan la grasa, que es un término químico, como ya hemos mencionado.

Nuestra especie presenta varios tipos de TA según la función que realice: el TA o grasa parda, marrón o multilocular y la grasa blanca, amarilla o unilocular, ambos con capacidad para almacenar grandes cantidades de lípidos, pero con diferentes papeles en el metabolismo energético. A continuación se revisan las características, importancia, función y distribución de estos dos tipos de tejido graso, interesantes desde el punto de vista de la nutrición.

TA pardo: grasa parda, marrón o multilocular

El TA marrón, también llamado grasa parda, porque su color varía del dorado al marrón rojizo, se caracteriza por presentar adipocitos o células grasas con un gran núcleo central, amplio citoplasma y mitocondrias muy numerosas, redondeadas con crestas muy juntas y bien desarrolladas. Estas mitocondrias contienen citocromos que les confieren ese color oscuro característico. En el citoplasma se encuentran dispersas varias gotas de ácidos grasos de distinto tamaño, que durante la preparación histológica rutinaria se pierden disueltas en los distintos alcoholes, proporcionando el aspecto agujereado característico al observarlo al microscopio. Los adipocitos son poligonales y grandes, aunque más pequeños que las células del TA blanco. Estas distin-

ciones no son absolutas, puesto que los adipocitos pueden ser uniloculares y tener un reducido número de mitocondrias cuando los niveles de termogénesis son bajos. La diferencia fundamental con el TA blanco, se basa en sus características bioquímicas, puesto que el TA pardo presenta una proteína desacoplada propia que falta en la grasa blanca[4].

El TA marrón se caracteriza por estar lobulado, recordando a una glándula. Tiene más capilares que el blanco, así como numerosas terminaciones nerviosas simpáticas. Después de un ayuno prolongado, las células adoptan un aspecto similar a un epitelio, acentuándose la semejanza con una glándula.

La función principal de la grasa parda es producir calor, bien para la termorregulación o en relación con la regulación del balance de energía, produciéndose grandes cambios en animales como respuesta al frío. Los ácidos grasos almacenados en la grasa parda se usan directamente por el tejido en el que están almacenados, aunque también pueden ser movilizados y utilizados en situaciones críticas por otros tejidos[4].

La grasa parda ejerce una importante función en el feto y recién nacido, llegando a representar el 2-5% del peso corporal. Este tipo de grasa se encuentra localizada entre las escápulas, en las axilas, en la nuca, y alrededor de los grandes vasos del tronco. La función principal es termogénica durante el primer año de vida, al final del cual se creía prácticamente desaparecida en su totalidad, transformándose en grasa blanca o amarilla[5]. Sin embargo, hoy ya se acepta su existencia también en la edad adulta.

Es fácil comprender que la relación entre superficie y volumen del cuerpo en nuestra especie es muy diferente a la de los animales pequeños, y que la termodispersión en humanos es mucho menor que en roedores. Los recién nacidos presentan una cantidad considerable de grasa parda. En el adulto, se han descrito adipocitos marrones dispersos entre los blancos en biopsias perirrenales en el 24% de casos, que alcanzaban valores de hasta el 50% si se excluían los pacientes mayores de 50 años. Se ha calculado la presencia de un adipocito marrón por cada 100-200 adipocitos blancos como media en los depósitos de grasa visceral de adultos delgados[6], también está descrito un aumento de adipocitos marrones en trabajadores al aire libre del norte de Europa[7]. La señal para la activación de los adipocitos marrones es una temperatura por debajo de la considerada neutra (34 ºC para los ratones, 28 ºC para las ratas y 20-22 ºC para los humanos). La dieta podría activar del mismo modo el TA marrón, que sería el responsable de la termogénesis inducida por los alimentos[8].

En animales de experimentación, el porcentaje relativo de adipocitos marrones y blancos es variable, dependiendo de la cepa, edad, sexo, condiciones ambientales y nutricionales. Las ratas poseen una evidente plasticidad que permite que adipocitos blancos retroperitoneales, a temperatura ambiente, se transformen en pardos en animales aclimatados al frío por transdiferenciación. Estos cambios histofisiológicos se producen a través de un estímulo adrenérgico, probablemente por la activación de los adrenoceptores beta-3, y esta conversión contribuye al tratamiento de la obesidad y diabetes en estos animales[9], abriendo una puerta al futuro tratamiento en humanos.

El desarrollo de técnicas de imagen cada vez más complejas aplicadas al estudio de trazadores de metástasis tumorales, como la FDG PET (tomografía por emisión de positrones con fluorodeoxyglucosa), ha proporcionado como hallazgo colateral y sorpendente, la visualización de áreas simétricas de gran actividad en la parte superior del cuerpo que corresponden a TA pardo. Los depósitos humanos son diferentes a los de roedores, el depósito principal se encuentra en las regiones supraclavicular y del cuello, con depósitos adicionales paravertebrales, mediastínicos o para-aórticos y suprarrenales, pero no interescapulares como los que existen en los recién nacidos[10] (fig. 1).

La utilización de la FDG PET tiene una dificultad todavía inexplicable, consistente en que cuando un paciente se examina varias veces, la presencia o ausencia del TA marrón no es reproducible, esta cuestión impide dar datos concretos sobre la prevalencia de depósitos de TA marrón en adultos. En un estudio rea-

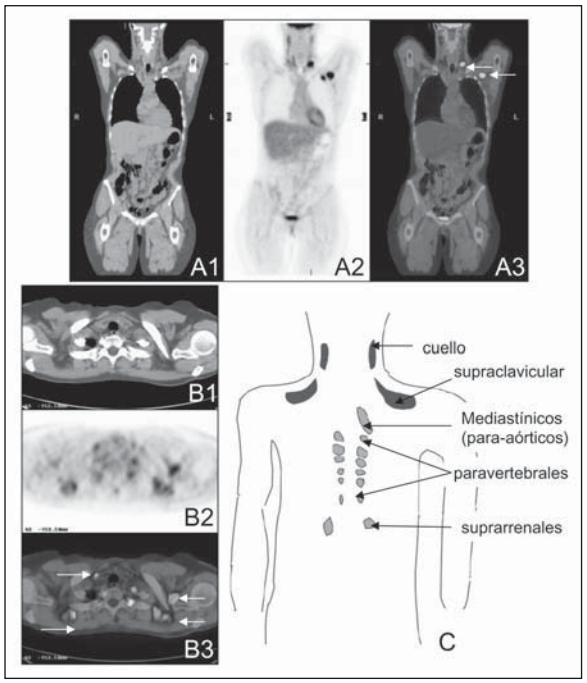

Fig. 1.—Localización del tejido adiposo pardo en el adulto. Ay B: Imagen de una tomografía computarizada (TC) del tronco (A1, plano coronal) y de la parte superior del tórax (B1, plano axial). En las imágenes equivalentes (A2 y B2) de tomografía por emisión de positrones (PET), las manchas oscuras representan los puntos de mayor actividad metabólica. Superposición de las dos imágenes anteriores (A3 y B3) en las que las manchas blancas corresponden a los puntos de mayor actividad, como el cerebro, la vejiga y la grasa de la base del cuello (flechas). C: Esquema de la localización de los distintos depósitos de tejido adiposo pardo en el adulto. Los depósitos del cuello y supraclavicular (color marrón oscuro) aparecen con mayor frecuencia que los mediastínicos, paravertebrales o suprarrenales (color amarillo).

lizado en 33 mujeres que fueron examinadas con éxito en cinco ocasiones sucesivas durante el período de tratamiento anticancerígeno[11], se observó que del total de mujeres, 6 no parecían tener TA marrón marcado en alguno de los cinco exámenes, y solamente una lo presentó en las cinco ocasiones. En el resto de pacientes, la intensidad de señal era diferente en todos los casos. La prevalencia de TA marrón estimada en esta pequeña población era del 80%, aunque los investigadores destacan que una única medida puede infravalorar enormemente la verdadera prevalencia de TA marrón debido a su variabilidad en la detección. Recientemente, revisando las historias clínicas de 1972 pacientes, se han encontrado depósitos de TA pardo en 7,5% de las mujeres frente al 3,1% de varones, en una relación 2:1 de mujeres/hombres[12].

Estos porcentajes aumentarían durante la exposición al frío y no en condiciones termoneutras, con actividad significativamente menor en personas con sobrepeso y obesas frente a las delgadas[13,14].

Actualmente se acepta que la presencia de TA pardo en adultos jóvenes es alta, pero su actividad es reducida porque se relaciona inversamente con el IMC, y el porcentaje de grasa corporal[13], especialmente en las personas mayores[12]. El TA pardo puede ser metabólicamente importante en humanos, y el hecho de que esté reducido, aunque todavía presente en la mayoría de las personas con sobrepeso u obesas puede ser fundamental para el tratamiento de la obesidad.

TA blanco: grasa blanca, amarilla o unilocular

La grasa blanca recibe esta denominación por contraposición a la grasa de color pardo o marrón. En este tejido, el color depende en parte de la dieta: en los primates, grupo al que pertenece nuestra especie, el color amarillo se debe a los carotenos, entre otras sustancias. En preparaciones histológicas rutinarias, los adipocitos aparecen con una gran vacuola o espacio vacío en posición central que corresponde a una única y gran gota de ácidos grasos que se ha disuelto durante la preparación y que hace que el citoplasma quede reducido a una fina película en la parte periférica, con un núcleo de menor tamaño, el número de mitocondrias es reducido y con escasas crestas. El tamaño de los adipocitos puede ser muy grande, con diámetros superiores a las 100 micras. El TA blanco posee una escasa vascularización e inervación.

Las funciones de la grasa blanca pueden resumirse en cuatro principales: sintetizar lípidos a partir de excedentes de hidratos de carbono o proteínas; responder a estímulos hormonales y nerviosos; secretar sus propias hormonas (leptina, TNF-alfa, adiponectina, etc.); y la más clásica de todas, actuar como reservorio de energía, formando, almacenando y descomponiendo ácidos grasos en equilibrio con la concentración correspondiente en el torrente sanguíneo[15], aunque recientemente el TA está surgiendo como fuente importantísima de células madre adultas[2].

En el ayuno prolongado, los adipocitos liberan gradualmente los lípidos almacenados y la vacuola central disminuye de tamaño, siendo reemplazada por numerosas gotas de lípidos más pequeñas. Si se moviliza todo el lípido almacenado, las células se asemejan a fibroblastos. Una excepción a esta regla son los acúmulos grasos que se localizan alrededor de los riñones, las órbitas oculares, algunas articulaciones como la rodilla o la cadera, las palmas de las manos o las plantas de los pies, cuyas células adiposas, en situaciones de ayuno, no liberan los lípidos acumulados. En estas regiones, la función principal del tejido graso parece ser de tipo mecánico, es decir, amortiguar golpes y servir de sostén a los distintos órganos[5].

El número de células de grasa se puede determinar de forma aproximada cuando tenemos una medida de la grasa corporal total y una estimación del tamaño celular medio. La grasa corporal total en un individuo normopeso es del orden de 10 a 20 kg lo que corresponde aproximadamente a 3 x 1.010 adipocitos. El número de adipocitos en individuos obesos fluctúa generalmente entre 4-6 x 1.010 y aunque aumenta más rápidamente en la infancia y en la adolescencia, en la actualidad se sabe que el número de adipocitos también puede aumentar en la edad adulta[16,17].

Desde el punto de vista de las características histológicas del TA, clásicamente la obesidad se define en función del tamaño y número de adipocitos. Así, se considera obesidad hiperplásica o hipercelular, aquella con número de adipocitos > 5 x 1.010 y generalmente se presenta en la infancia[18]. En la edad adulta esta hiperplasia celular se produce normalmente en aquellos individuos con más del 75% de su peso deseable (IMC > 35 kg/m^2) y se asocia en general con la obesidad ginoide[19]. Cuando la obesidad se implanta en la edad adulta o durante el embarazo, se le llama obesidad hipertrófica e implica un aumento del tamaño de las células de grasa. La obesidad hipertrófica tiende a correlacionarse con una distribución androide o troncal de la grasa y está a menudo asociada con desórdenes metabólicos tales como intolerancia a la glucosa, hiperlipidemia, hipertensión y enfermedades cardiovasculares[19]. Se considera obesidad hipertrófica aquella en la que el peso de los adipocitos es > 0,42 mg en individuos menores de 35 años y > 0,82 mg en individuos de más de 35 años[18].

En realidad, hoy en día sabemos que el TA muestra habitualmente características mixtas de hipertrófia-hiperplásia, pero en situaciones extremas puede hacerse más manifiesto el predominio de la hipertrofia sobre la hiperplasia o viceversa, siendo la primera forma más típica de la obesidad severa del adulto y la segunda de la del niño.

Clasificación del TA blanco

A pesar del aumento de interés en el conocimiento de los distintos compartimentos de TA, todavía no

Tabla I
Clasificación anatómica del tejido adiposo (Shen y cols.)

1. Tejido adiposo total: La suma de tejido adiposo, generalmente excluyendo la médula ósea y el tejido adiposo de la cabeza, las manos y los pies.
2 Tejido adiposo subcutáneo: La capa que se encuentra entre la dermis y la aponeurosis y fascia de los músculos. Incluye el tejido adiposo mamario.
   2.1. Tejido adiposo subcutáneo superficial: La capa que se encuentra entre la piel y un plano de fascia en la parte inferior del tronco y la región de la cadera y glúteos.
   2.2. Tejido adiposo subcutáneo profundo: la capa que se encuentra entre la fascia muscular y un plano fascial en la parte inferior del tronco y la región de la cadera y glúteos.
3. Tejido adiposo interno: Tejido adiposo total menos tejido adiposo subcutáneo.
   3.1. Tejido adiposo visceral: tejido adiposo dentro del tórax, abdomen y pelvis.
      3.1.1. Tejido adiposo intratorácico:
         – Intrapericárdico
         – Extrapericárdico.
      3.1.2. Tejido adiposo intrabdominopélvico:
         – Intraperitoneal: omental y mesentérico
         – Extraperitoneal:
         – intrabdominal: preperitoneal y retroperitoneal.
         – intrapélvico: parametrial, retropúbico, paravesical, retrouterino, pararrectal, retrorrectal.
   3.2. Tejido adiposo interno no visceral: tejido adiposo interno menos el tejido adiposo visceral.
      3.2.1. Tejido adiposo intramuscular: tejido adiposo dentro de un músculo (dentro de las fascias).
      3.2.2. Tejido adiposo perimuscular: tejido adiposo dentro de la fascia del músculo (fascia profunda), excluyendo el tejido adiposo intramuscular.
         – Tejido adiposo intermuscular: tejido adiposo entre los músculos.
         – Tejido adiposo paraóseo: Tejido adiposo en la interface entre músculo y hueso (por ejemplo, paravertebral).
      3.2.3. Otros tejidos adiposos no viscerales: Tejido adiposo de la órbita, tejido adiposo aberrante asociado a condiciones patológicas (por ejemplo, lipomas).

existe un consenso sobre la nomenclatura de estos depósitos. La anatomía clásica ha dejado de lado un tejido que no era considerado como "un órgano", y que además molestaba a la hora de preparar las disecciones para el estudio de otras estructuras consideradas "nobles". Esta situación explica que en la mayoría de los textos de anatomía falte una clasificación detallada del TA, considerando simples categorías tales como: TA subcutáneo o fascia superficial (sería la capa comprendida entre la dermis y las fascias y aponeurosis musculares); TA que rodea órganos y que puede recibir un nombre específico del órgano que rodea (TA perirrenal); TA intersticial o infiltrado entre otros tejidos, de tal forma que es imposible disecar como una estructura continua, o el TA de la médula ósea.

Esta clasificación fue útil para los anatomistas en el pasado, principalmente porque el enfoque se centraba en los órganos y había escasa patología atribuida o relacionada directamente con el compartimento del TA. Sin embargo, en la actualidad se considera que el TA no es un compartimento homogéneo único, sino que tiene depósitos regionales específicos con importantes propiedades metabólicas. Por tanto, hoy en día, a la luz de los nuevos conocimientos, el estudio de los depósitos de TA requiere una clasificación más exhaustiva y una localización anatómica precisa, ya que estos compartimentos adiposos individuales podrían tener mayor asociación con procesos fisiológicos y patológicos que la masa de TA total.

El término distribución de la grasa se refiere a la cantidad relativa de grasa en los compartimentos principales en donde se almacena TA y grasa en el cuerpo. El perfeccionamiento de los métodos de valoración de la composición corporal ha hecho posible medir la grasa en sitios de tejido no adiposo como el músculo o el hígado, constituyendo la llamada grasa ectópica.

Clasificación del TA propuesta por Shen y cols.[20]

Desde el punto de vista anatómico Shen y colaboradores[20] han realizado una clasificación exhaustiva del TA blanco (tabla I). Esta clasificación es de gran interés por ser extremadamente detallada y precisa, permitiendo caracterizar cada región anatómica del TA en el humano, proponiendo una nomenclatura de consenso para los distintos depósitos, rescatando del olvido algunos tradicionalmente no considerados. La clasificación que propone es, además, un híbrido entre regiones y propiedades funcionales, puesto que es especialmente exhaustiva respecto al TA visceral.

El estudio del TA, adquiere especial relevancia cuando se refiere al individuo obeso. Por ello, y teniendo en cuenta aspectos relativos a la distribución topográfica de la grasa corporal, Vague en 1947 clasificó la obesidad como de tipo androide y ginoide. En la tabla II se representa la clasificación de la distribución del tejido adiposo en el individuo obeso según la Sociedad Española del Estudio de la Obesidad (SEEDO)[21].

Distribución topográfica de la grasa abdominal

En la presente revisión, vamos a estudiar la distribución del TA abdominal siguiendo básicamente la clasificación propuesta por Shen y colaboradores[20], considerando además aspectos metabolicos y fisiopatológicos del TA. Hemos escogido la región abdominal debido a la abundante bibliografía y gran interés existente en los depósitos de grasa abdominal, pues incluso los estudios antropométricos incluyen la medida de la cintura y

Tabla II
Clasificación de la SEEDO[21]

- *Obesidad androide* más marcada en el segmento superior, con mayor celularidad y volumen adipocitario a nivel del área del deltoides respecto al área trocantérea, se caracteriza por un excesivo acúmulo de grasa en la región abdominal y tiene un mayor riesgo de desarrollar complicaciones metabólicas y vasculares.
  a) Obesidad androide con disposición de grasa preferentemente subcutánea, en la que el exceso de tejido adiposo se localiza en la zona subcutánea abdominal.
  b) Obesidad androide con disposición de grasa preferentemente intraabdominal visceral, donde existe un exceso de grasa abdominal perivisceral.
- *Obesidad ginoide,* más marcada en el segmento inferior (cinturón escapular < cinturón pelviano), presenta una tendencia mayor a las complicaciones de tipo mecánico (insuficiencia venosa, poliartrosis, etc.) y menor tendencia a las complicaciones metabólicas. El exceso de grasa subcutánea se sitúa en la zona glúteo-femoral.
- *Obesidad de distribución homogénea,* se caracteriza por un exceso de grasa corporal, sin que ésta predomine en ninguna área anatómica concreta.

su relación con la cadera, como indicador indirecto de grasa visceral.

Los depósitos de TA se clasifican según su localización topográfica en tres grandes grupos en el abdomen: TA subcutáneo y TA interno, subdividido en visceral y muscular.

TA subcutáneo

El TA subcutáneo se ha estudiado clásicamente a través de las técnicas antropométricas (pliegues cutáneos). Las diferencias de distribución del TA según el sexo son insignificantes desde la lactancia, durante la niñez y hasta el comienzo de la adolescencia. Con el tiempo, los varones acumulan más grasa subcutánea en el tronco que en las extremidades. Esto sucede de forma desproporcionada durante la adolescencia y más lentamente hasta los 50 años aproximadamente. Por el contrario, las mujeres, acumulan cantidades de grasa similares en el tronco y las extremidades hasta los 40 años de edad, aproximadamente. Con el tiempo, en la mujer, el grosor de los pliegues cutáneos del tronco aumenta proporcionalmente más que el de las extremidades. La variación étnica en la distribución de la grasa subcutánea es también superior en mujeres que en varones[22].

En el abdomen, la grasa subcutánea puede subdividirse en dos compartimentos distintos[23,24] (fig. 2):

1) *Tejido adiposo subcutáneo superficial (TASS):* una capa superficial de TA distribuida bajo la piel abdominal, que presenta un grosor relativamente constante en toda la región, dentro de la variación entre los distintos individuos. Esta grasa es compacta y uniforme y está soportada por septos próximos que conectan la dermis con la fascia subcutánea circunferencial. El grosor de esta capa es lo que normalmente se mide utilizando los lipocalibres y combinando los datos obtenidos de los distintos pliegues antropométricos, da idea aproximada de la grasa subcutánea total.

2) *Tejido adiposo subcutáneo profundo (TASP):* otro compartimento tisular adiposo más profundo, localizado bajo la capa superficial anterior y separado de ella por una fascia subcutánea circunferencial que se fusiona con la pared muscular en regiones anatómicas determinadas, como la línea alba anteriormente o las apófisis espinosas posteriormente. Esta capa grasa subcutánea profunda es la más susceptible de aumentar en grosor en casos de obesidad, principalmente en las regiones periumbilical, paralumbar, glútea y caderas, quedando más delgada lateralmente al ombligo, en los costados. La grasa de este compartimento tiene una estructura de septos mucho más escasos y desordenados, que conectan la fascia subcutánea con la que cubre la musculatura de la pared abdominal de forma incompleta.

La razón fundamental para la división de la grasa subcutánea en profunda y superficial, proviene de los estudios en animales que indican que los lípidos se depositan a mayor velocidad en la capa profunda haciendo que sea un tejido más activo en términos metabólicos y que actuaría más como aislante térmico o capa de reserva[25,26]. Monzon y cols.[27] confirmaron en humanos que la actividad lipolítica era mayor en adipocitos provenientes del tejido graso subcutáneo profundo que en los procedentes del compartimiento superficial.

Existen diferencias entre las proporciones de ambos compartimentos subcutáneos en función del sexo. Así, un estudio reciente realizado sobre imágenes de tomografía computarizada en L4-L5, muestra que en mujeres ambas grasas subcutáneas, superficial y profunda, se presentan en una proporción semejante. En los hombres, por el contrario, la grasa profunda corresponde al 60% de la grasa subcutánea total y el índice de tejido adiposo subcutáneo profundo/tejido adiposo subcutáneo total (TASP/TAST) es significativamente superior. Otro dato interesante es que la grasa subcutánea ventral, la de alrededor del ombligo, es superior en el hombre que en la mujer y además se correlaciona positivamente con al Índice de Masa Corporal (IMC) en este sexo, lo que significa que en el hombre, la grasa subcutánea abdominal aumenta con el grado de obesidad, de forma paralela, situación que no siempre sucede en la mujer[28].

TA subcutáneo y riesgo metabólico

Algunos autores han sugerido que el TA subcutáneo de la región abdominal es el que mejor se correlaciona con los valores de insulina plasmáticos[29,30] y de triglicéridos[31], aunque no existe consenso sobre si la subdivi-

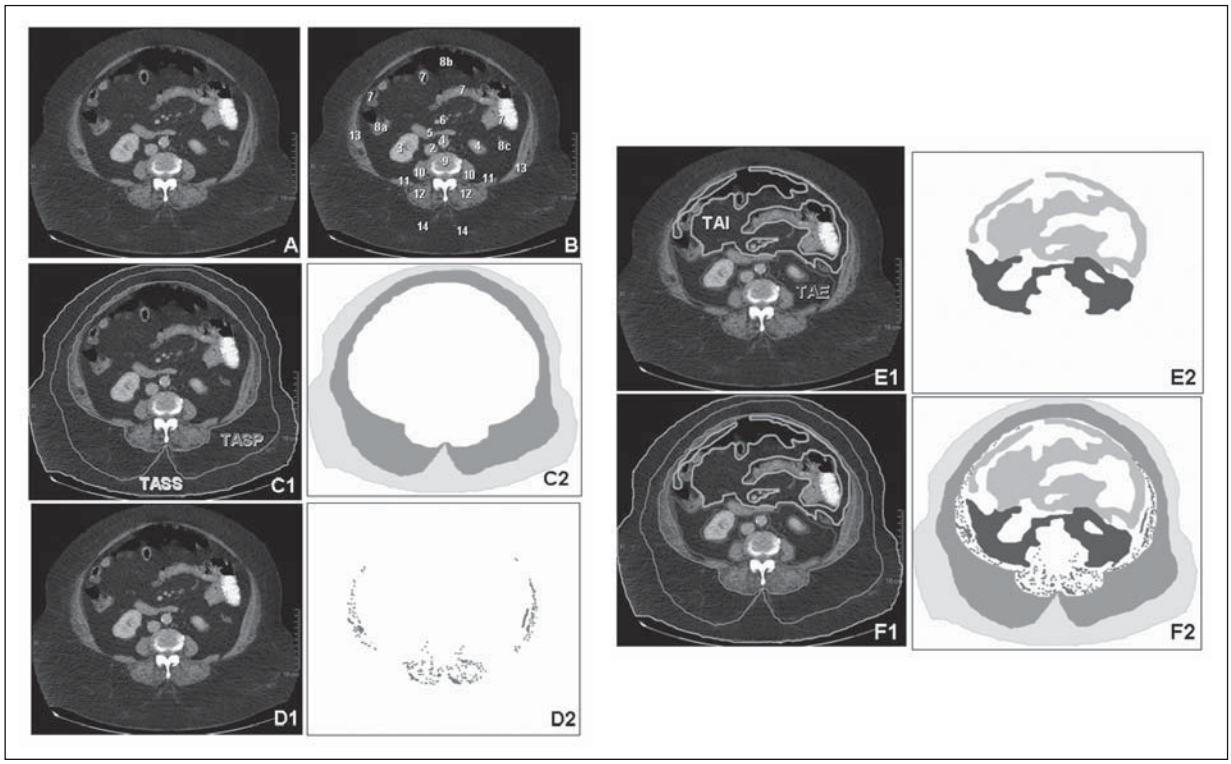

Fig. 2.—Distribución del tejido adiposo blanco a nivel abdominal (L1-L2). A: TC de abdomen a nivel del disco intervertebral entre la primera y segunda vértebra lumbar (L1-L2). La espalda corresponde a la parte inferior de la imagen, el lado derecho está señalado con una R, la escala corresponde a 10 cm. B: identificación de las distintas estructuras: 1- arteria aorta, 2- vena cava inferior, 3- riñón derecho, 4- riñón izquierdo, 5- duodeno, 6- vasos mesentérico superiores, 7- intestino delgado, 8a- colon ascendente, 8b- colon trasverso, 8c- colon descendente, 9-cuerpo y disco intervertebrales, 10- músculo psoas , 11- músculo cuadrado de los lomos , 12- músculos erectores de la columna, 13- músculos anchos del abdomen, 14- fascia en el tejido adiposo subcutáneo. C: Se ha delimitado el tejido adiposo subcutáneo profundo (TASP) y superficial (TASS) en la imagen radiológica (C1), rellenando en su trasformación informática las celdas de color verde oscuro y claro respectivamente (C2). D: El color rojo representa la localización del tejido adiposo muscular extramiocitario en los músculos presentes a ese nivel (D1) y su trasformación informática (D2). E: la grasa visceral se ha separado en dos compartimentos en base a las estructuras que se observan, el tejido adiposo intraperitoneal (TAI) representa la suma del depósito omental y mesentérico, de color azul claro, el tejido adiposo extraperitoneal (TAE) concierne a los depósitos perirrenales y retroperitoneales, representados de azul oscuro (E1), al transformar la imagen, estos depósitos aparecen rellenos (E2). F: se representan conjuntamente los depósitos de tejido adiposo visibles mediante esta técnica en la imagen radiológica (F1) y su transformación informática (F2).

sión de TA subcutáneo abdominal está relacionada con el riesgo metabólico. Así, para Kelley y cols.[32] y Piernas y colaboradores[28], la grasa subcutánea posterior representa en mayor medida a la grasa subcutánea profunda y, por tanto, podría tener un mayor impacto sobre la resistencia a la insulina que la cantidad de grasa que pueda existir en la región anterior del abdomen. Por el contrario, Ross y cols.[33] defienden que la cantidad de grasa subcutánea profunda del abdomen no es un factor pronóstico independiente de la resistencia a la insulina.

Otros trabajos indican que no es la grasa subcutánea en si misma o sus diferentes compartimentos lo que determina el riesgo metabólico, sino su relación con el área visceral. Así, se ha propuesto un nuevo índice entre el área del tejido adiposo subcutáneo profundo y del tejido adiposo visceral (TASP/TAV) que cuando es mayor de 3,65 en la mujer o menor de 1,01 en el hombre, los sujetos presentan un mayor riesgo metabólico[28]. En este trabajo, realizado en 85 pacientes a partir de imágenes de tomografías computarizadas, se demuestra que este nuevo índice (TASP/TAV), es un buen predictor de riesgo metabólico. En particular es un indicativo de la variabilidad de HDL-C en el hombre y de HOMA en la mujer.

Estos resultados tan dispares sobre el impacto metabólico de los tejidos subcutáneos superficial y profundo, podrían deberse al diferente grado de obesidad entre los sujetos de los diferentes estudios. Recientemente se ha postulado que la grasa subcutánea superficial es la de mayor impacto metabólico mientras que no se alcancen valores significativamente elevados de grasa visceral y subcutánea profunda. Es entonces, cuando se alcanza este límite, cuando los compartimentos subcutáneo profundo y visceral, alcanzan la verdadera relevancia metabólica y esto sucede tanto en hombres como en mujeres, en la edad adulta[28].

Grasa intraabdominal, visceral o perivisceral

La denominada grasa intraabdominal, visceral o perivisceral se encuentra dentro de las paredes óseas y

musculares del abdomen, por tanto, para su medición no es posible el uso de las técnicas antropométricas de pliegues cutáneos o el perímetro de cintura, sino que es necesario un estudio con técnicas de imagen o diámetros. Esta región de TA forma parte del TA interno visceral de Shen y colaboradores[20], y se refiriere exclusivamente a la región abdominal que sería visible con técnicas de imagen. La grasa intaabdominal se puede subdividir en (fig. 2):

1) *TA intraperitoneal (TAI):* corresponde al territorio tributario de la vena porta-hepática.

– *Grasa omental,* se encuentra en el omento o epiplon mayor, cuatro hojas de peritoneo que cuelgan a modo de delantal desde la curvatura mayor del estómago y el colon transverso, entre las asas delgadas y la pared anterior del abdomen.

– *Grasa mesentérica,* se deposita en el mesenterio o doble hoja de peritoneo que une el yeyuno-íleon a la pared posterior del abdomen.

2) *TA extraperitoneal (TAE):* corresponde al territorio tributario de las venas cavas

– *Retroperitoneal,* se encuentra entre el peritoneo y la fascia transversal que cubre la cara profunda de los músculos del abdomen, y que incluye la grasa pararrenal, grasa que se encuentra entre la aorta abdominal y la vena cava inferior, delante de los cuerpos vertebrales, y la grasa perirrenal que rodea los riñones, separada del TA retroperitoneal por una celda incompleta.

En general, las personas obesas tienen más grasa visceral que las delgadas. Además el TA visceral difiere entre sexos, mientras que los varones tienen mayor cantidad de grasa visceral que las mujeres, estas últimas presentan un aumento marcado de la grasa visceral principalmente durante la menopausia. Además, en el varón existe una correlación positiva entre la grasa visceral y el índice de masa corporal (IMC), indicando que la grasa intraabdominal se acumula en proporción al grado de obesidad. Sin embargo, en la mujer esta situación no se presenta. Hay que tener en cuenta que en el sexo femenino el aumento de grasa visceral está limitado por barreras anatómicas[28]. Además, la mujer se protege a sí misma de un aumento de grasa visceral, incrementando la grasa subcutánea hasta que se alcanza un cierto grado de obesidad, a partir del cual comienza el aumento de grasa visceral[34]. Durante la vejez, las cantidades absolutas de grasa visceral pueden permanecer más o menos estables, aunque la grasa visceral puede aumentar en mayor medida que la grasa corporal total, ya que ésta disminuye durante la senectud y se redistribuye[35]. Sin embargo, en el adulto, la cantidad de grasa visceral está relacionada sólo de forma moderada con la grasa corporal total, con una varianza que va desde alrededor de 30 a 50%[36,37].

Por el contrario, algunos autores consideran que el sexo no es una variable predictora de la grasa visceral, siendo la edad el factor fundamental responsable del incremento de los depósitos grasos viscerales que se producen con el envejecimiento, estableciendo que cada año más de edad está asociado con un incremento del área grasa visceral de 3,30 cm[238].

TA visceral y riesgo metabólico

Numerosos estudios han mostrado, usando técnicas de imagen, que el tamaño del compartimento adiposo visceral se asocia con factores de riesgo de enfermedad cardiovascular[39-41], con variables de comorbilidad asociadas a la obesidad, tales como elevadas concentraciones plasmáticas de triglicéridos y apolipoproteína B, mayor proporción de partículas LDL, aumento en la relación colesterol total/HDL colesterol, valores inferiores de HDL-colesterol, resistencia a la insulina e hiperinsulinemia, y cambios en las concentraciones séricas de leptina, TNF-alfa, y distintas hormonas sexuales[33,42-54].

Los desórdenes en la distribución de la grasa, especialmente con la acumulación de grasa visceral en la parte superior del tronco y las complicaciones metabólicas asociadas, han hecho que algunos autores denominen al síndrome metabólico como "síndrome de grasa visceral" que correspondería a la suma de la intolerancia a la glucosa, hiperlipidemia, hipertensión y la acumulación de grasa visceral.

Existen numerosos estudios que relacionan la disposición de la grasa corporal con los valores de insulina. En general, se considera el acúmulo de grasa visceral como factor fundamental en la resistencia a la insulina[33,55], incluso con una correlación más fuerte que otros factores de riesgo como las alteraciones de la relación lípidos-proteínas[56]. Sin embargo, para algunos autores, las medidas del compartimento graso subcutáneo profundo serían mejores predictores de resistencia a la insulina que el propio tejido visceral[32,57-59]. Algunos investigadores consideran que la importancia de la grasa visceral radica en los compartimentos mesentérico y omental exclusivamente, los denominados depósitos portales o intraperitoneales frente a los extraperitoneales. Estos autores, se fundamentan en que los ácidos grasos de estas zonas se liberan a un ritmo mayor y drenan directamente en la vena porta. La exposición continua del hígado a elevadas concentraciones de ácidos grasos daría como resultado los desórdenes metabólicos asociados con la acumulación de grasa visceral[41,60,61].

La heterogeneidad metabólica del TA de los distintos compartimentos, particularmente las diferencias entre los depósitos adiposos subcutáneos y los denominados *portales* (grasa mesentérica y omental), puede acompañar a anomalías metabólicas severas. Existen autores que defienden que esta grasa está directamente relacionada con las alteraciones cardiovasculares que se observan en individuos no obesos, como el aumento del grosor de la íntima en la pared de la arteria carótida común, lo que demostraría que el TA portal juega un papel fundamental en el desarrollo potencial de la arte-

riosclerosis propia de la obesidad[41]. Además, se ha sugerido por Enevoldsen y cols.[62] y por nuestro propio grupo[63], que el determinante más importante en el impacto metabólico es la masa relativa de los diferentes compartimentos de grasa, y no su tamaño absoluto. Así, el clásico índice de grasa visceral respecto al subcutáneo (TAV/TAST) se ha propuesto como un criterio adecuado de diagnóstico de alteraciones metabólicas[64].

El exceso de grasa visceral es por tanto un marcador de la incapacidad del tejido adipose subcutáneo de actuar como un protector metabólico, por lipodistrofia o por hipertrofia y por tanto resistencia a la insulina. En esta situación, los individuos sedentarios que no pueden almacenar su exceso de energía en el tejido adiposo subcutáneo depositarán está grasa en lugares "indeseables" como son el hígado, el corazón, el páncreas y finalmente, el músculo esquelético[65].

TA muscular

La grasa muscular comienza a considerarse como un "nuevo" compartimento graso[66] y se refiere a distintos depósitos de almacenamiento de lípidos en el tejido del músculo esquelético: por un lado, los lípidos que están dentro de los adipocitos localizados entre las fibras musculares, los llamados lípidos extramiocelulares o extramiocitarios; por otro lado, los lípidos localizados dentro de las fibras musculares en forma de triacilgliceroles citosólicos, en el sarcoplasma, generalmente en contacto directo con las mitocondrias, también llamados lípidos intramiocelulares o intramiocitarios. La grasa intermuscular, por su parte, se refiere a los depósitos localizados entre los distintos músculos, visibles mediante tomografía computarizada (TC, fig. 2) o resonancia magnética (RM).

Desde el punto de vista fisiológico, se ha sugerido que los lípidos intramiocelulares son una fuente energética durante el ejercicio, puesto que este tipo de lípidos decrece durante el ejercicio prolongado, y del mismo modo que el glucógeno, aumenta durante el entrenamiento. Además, los lípidos intramiocitarios son más abundantes en las fibras musculares tipo 1, lo que sugiere que aumentarían hasta alcanzar el punto óptimo de capacidad oxidativa de grasa, resultando un combustible ventajoso. Sin embargo, cuando se elevan los valores de ácidos grasos en el plasma o aumenta el contenido de grasa en la dieta, también aumentan los lípidos intramiocelulares, sugiriendo que las fibras del músculo esquelético sirven de almacén de ácidos grasos si la disponibilidad es alta[67]. Con el estilo de vida actual en los paises occidentalizados, de baja actividad física y consumo excesivo de alimentos grasos, la capacidad de utilizar los lípidos almacenados como fuente de energía ha quedado reducida, teniendo efectos muy negativos sobre la sensibilidad a la insulina.

Los lípidos intramiocitarios pueden ser cuantificados mediante Resonancia Magnética Espectroscópica (RMS), de forma no invasiva y repetitiva en un determinado músculo a lo largo del tiempo, y en el mismo paciente, aportando datos de un volúmen muscular proporcionalmente mayor que una biopsia. Dentro del músculo, las pequeñas gotas de lípidos están rodeadas por una fase acuosa (el sarcoplasma), diferente a la de los lípidos rodeados por otros lípidos (en el TA) y a la de los lípidos extramiocelulares (capas de lípidos entre fibras musculares), lo que proporciona distintas señales dentro de un campo magnético.

El mayor inconveniente de esta técnica es que aunque el espectro que se obtiene proporciona dos picos separados que corresponden a los lípidos intra y extramiocitarios, éstos se superponen parcialmente, y se necesita un sofisticado programa informático que ajuste y cuantifique los picos por separado. Especialmente en sujetos obesos, la gran cantidad de lípidos extramiocitarios dificulta la localización de un área libre de ellos, obteniéndose un gran pico que se superpone en gran medida con el pico correspondiente a los lípidos intramiocitarios. Se ha estimado que el coeficiente de variación en la cuantificación de lípidos intramiocitarios por RMS está entre 6% y 14%[68].

La mayoría de los estudios sobre lípidos intramiocitarios se limita a un número reducido de músculos. La pierna ha sido ampliamente analizada, debido al alineamiento paralelo de las fibras y de las capas de lípidos que las rodean respecto al campo magnético estático. El mayor contenido de grasa se encuentra en la parte interna del músculo sóleo, mientras que los tibiales anterior y posterior y los gemelos presentan valores dos o tres veces más reducidos[69,70]. Esta diferencia concuerda con los distintos tipos de fibras musculares y los sustratos que utilizan. El sóleo tiene un alto porcentaje de fibras tipo 1 caracterizadas por mayor contenido en grasa y mitocondrias, dependiendo más de la oxidación de los lípidos que los otros músculos.

La sarcopenia o disminución de la masa muscular es un tema de gran interés, por la pérdida de fuerza que puede implicar, limitación funcional y discapacidad, así como aumento del riesgo de caídas y fracturas óseas. La causa principal puede ser el envejecimiento, aunque también puede sumarse un nuevo factor que es el aumento de lípidos del músculo esquelético, tanto intramiocelular como total, y este contenido influye negativamente en la fuerza y la función muscular[71,72].

Los cambios en el músculo esquelético dependientes de la edad están relacionados con cambios en otros componentes de la composición corporal. Forbes[73] observó que los cambios en masa grasa y masa libre de grasa están relacionados, y en general ocurren, de forma proporcional y constante con el cambio de peso: 70% de grasa a 30% de la masa libre de grasa, pero la regulación de esta relación se pierde durante la senectud produciéndose cambios discordantes en los componentes de tejido magro y blando, lo que lleva a una composición corporal caracterizada por una masa muscular reducida en presencia de exceso de peso corporal, esta forma "desordenada" de composición corporal se ha denominado obesidad sarcopénica[74,75].

La obesidad sarcopénica se desarrolla cada vez más en personas mayores a medida que aumenta su edad, y se considera una consecuencia tardía de la obesidad prolongada que puede acelerar la pérdida muscular en la vejez. Se ha estimado que la prevalencia de este nuevo tipo de composición corporal puede aumentar del 2 al 10% de los 65 a los 85 años de edad, estando fuertemente asociada con limitaciones funcionales: trastornos del equilibrio/marcha, discapacidad, etc.[76]

TA muscular y riesgo metabólico

En su conjunto, cuando la adiposidad es baja, la cantidad de TA intermuscular no difiere significativamente entre afroamericanos, asiáticos y blancos. Sin embargo, cuando aumenta, la cantidad de grasa intramuscular crece más rápidamente en mujeres afroamericanas, constituyéndose un depósito que puede llegar a ser de tamaño similar al TA visceral[66]. La relevancia de la localización de estos depósitos radica en que los lípidos intramiocelulares, y no los extramiocelulares, están relacionados con la resistencia a la insulina[77]. Aunque es el hígado el órgano que mayor cantidad de ácidos grasos recibe, los músculos y el páncreas también están sometidos a un flujo incrementado de ácidos grasos en la obesidad. En esta situación el músculo esquelético disminuye su captación de glucosa, hecho que contribuye a la hiperglucemia.

El músculo esquelético es el tejido sensible a insulina más abundante del cuerpo humano, capaz de captar el 40% de la glucosa postprandial, a la vez que consume el 20% de la energía corporal. Su incapacidad para almacenar energía y para transformar la grasa a glucosa, se ha denominado inflexibilidad metabólica. Investigaciones recientes han identificado defectos específicos en la señalización posterior a la unión de la insulina al receptor que se acompañan con una disminución de la capacidad oxidativa de la mitocondria, un aumento del acúmulo de la grasa intramuscular, un incremento de la generación de especies reactivas a oxígeno, y una estimulación de las vías de inflamación lo que finalmente conlleva un riesgo metabólico aumentado[78].

Técnicas de imagen: Tomografía Computarizada (TC) y Resonancia Magnética (RM)

La determinación de la distribución regional de la grasa es cada vez más importante en la valoración de la composición corporal.

La antropometría ha sido utilizada desde hace décadas, es un método barato y sin demasiadas complicaciones técnicas que debe complementar toda valoración de la composición corporal. Así, la determinación del peso, talla y perímetro de cintura son imprescindibles en cualquier exploración clínica. En concreto, el perímetro de cintura es un parámetro de medida imprescindible por su relación con el riesgo cardiovascular asociado a la obesidad y al síndrome metabólico, independientemente del índice de masa corporal[79].

Las técnicas de imagen como la TC o la RM son de referencia para estimar el área grasa abdominal, proporcionando información acerca de la composición corporal a nivel tisular. En cualquier caso, estos métodos tienen aplicaciones clínicas limitadas en el estudio de la composición corporal de cuerpo entero y en el estudio de modelos compartimentales, pero tienen cada vez más interés para estudios de la distribución regional de la grasa corporal, no sólo en obesidad sino también en la detección de estados de desnutrición como la caquexia.

En la tabla III se analizan brevemente los puntos fuertes y débiles de estas técnicas.

Comparación entre ambas técnicas. Ventajas y desventajas

Cualquiera de las dos técnicas permite distinguir entre tejido graso subcutáneo y visceral, dando idea de la relación entre el fenotipo obeso y el riesgo de salud, pero la contribución independiente de cada uno de los depósitos descritos sigue siendo motivo de controversia[80,81].

Los fundamentos de cada técnica son distintos. La TC se basa en rayos X que se atenúan al atravesar las distintas estructuras corporales antes de llegar a los receptores que generarán una imagen digital, proporcionando distintas tonalidades de gris para los distintos tejidos. Por su parte, la RM no utiliza radiaciones ionizantes, se basa en un campo magnético externo que orienta el protón del núcleo de hidrógeno, se aplica un pulso de radiofrecuencia a los tejidos corporales, la energía absorbida por algunos protones se libera al terminar el pulso y volver a la posición original. La variación es detectada por un receptor.

El avance de la medicina nuclear ha permitido generar imágenes mediante el uso de trazadores radioactivos que se fijan con diferente afinidad a los distintos tipos de tejidos, la informática ha proporcionado herramientas que hacen reconstrucciones tridimensionales instantáneas del cuerpo entero o de una determinada estructura, con preparación o sin ella. Ya hemos mencionado la técnica de PET que utiliza isótopos radiactivos que se introducen en moléculas orgánicas o radiofármacos que son inyectadas al paciente y posteriormente se analiza la emisión radiactiva de los diferentes tejidos según la captación del radiofármaco que presenten. Generalmente se utiliza glucosa marcada con Flúor-18, por lo que existe mayor afinidad por parte de las lesiones tumorales o inflamatorias. Los estudios combinando TAC y PET permiten mayor resolución espacial junto con imágenes funcionales, han sido fundamentales en el estudios del TA pardo.

La ventaja de la RM sobre la TC reside en que en esta última, la intensidad de la señal producida por la

Tabla III
Comparación de TC y RM

	Hueso	*Tejido adiposo*	*Ventajas*		*Inconvenientes*	
Tomografía Computarizada (TC)	Color blanco	Hipotenso			– Irradiación del paciente	– Gran complejidad técnica
Resonancia Magnética (RM)	De color negro la parte periférica	Hiperintenso	– Valoración exacta de los compartimentos de TASP, TASS, TAV total, a partir de un único corte a nivel de la 4º vértebra lumbar (L4) o de L4/L5 (4º/5º vértebra lumbar) – Se pueden usar imágenes obtenidas de forma rutinaria	– No irradia al paciente, permitiendo su uso en niños o durante el embarazo – RM espectroscópica proporciona datos sobre grasa corporal	- Precaución en personas con implantes metálicos que puedan desplazarse por el imán - dificultades para distinguir claramente el peritoneo o la fascia del tejido adiposo subcutáneo	– Elevado coste – Mucho tiempo de exploración - artefactos que distorsionan la imagen: movimientos respiratorio, cardíacos o tatuajes. - algunos pacientes con obesidad mórbida no caben en el campo de visión del instrumento de análisis.

grasa es muy baja, mientras que en la RM aparece hiperintensa y el resto de los tejidos tienen distinto grado de hipointensidad. Esta característica permite aplicar técnicas digitales de segmentación para fragmentar en dos compartimentos la grasa subcutánea y visceral de forma automática, reduciendo enormemente el tiempo de estudio empleado[82] y usando imágenes que se obtienen durante la RM rutinaria. Por todo ello, la RM es una técnica muy interesante, no sólo en caso de obesidad sino también de patologías como el cáncer, para prevenir o detectar estados de desnutrición y permitir la intervención nutricional antes de que comiencen a manifestarse los signos clínicos[82].

Una vez determinadas las áreas de grasa abdominal visceral (AV) y la grasa abdominal subcutánea (AS) se calcula un índice AV/AS, que cuando es superior a 0,4 indicaría obesidad visceral[83]. Para la obtención del índice grasa visceral/grasa subcutánea es suficiente con la realización de un único corte, a nivel de L4, la cuarta vértebra lumbar, que generalmente coincide con el ombligo[24,82], y que se considera de referencia. Aunque algunos autores realizan esta medición entre la cuarta y quinta vértebra lumbar (L4-L5, fig. 3)[84]. El índice AV/AS es el que mejor refleja la distribución de la grasa corporal y se relaciona con la presencia de alteraciones metabólicas en mayor medida que el índice cintura/cadera[85].

Es importante que la imagen que se va a estudiar corresponda realmente al nivel L4. En personas con obesidad mórbida, el abdomen presenta gran cantidad de grasa subcutánea, produciendo un pliegue que hace que el ombligo se desplace caudalmente, incluso cuando el individuo está tumbado, dejando de corresponder al nivel vertebral de referencia. Las diferencias del valor de la grasa visceral pueden ser muy grandes en cada nivel[20]. La figura 4 pertenece a una persona con obesidad mórbida, en la que el ombligo está desplazado hasta el nivel de la tercera vértebra sacra, en esta persona, si se compara el valor de la grasa visceral real en L4 (360,37 cm^2) con el obtenido en S3 (221,62 cm^2), la diferencia es del 38,50%. Además, si el estudio se hace con métodos automáticos, es muy importante comprobar y delimitar correctamente los territorios de estudio, ya que la grasa de otro depósito, como puede ser el muscular, o artefactos como el disco intervertebral, pueden añadirse al TA visceral debido a que la fascia o envuelta que los separa no se aprecia bien en la imagen, o los tejidos presentan parecida intensidad.

Para los estudios comparativos de grasa abdominal entre distintos sujetos, lo ideal es realizar cuatro secciones entre las vértebras lumbares segunda y cuarta[86-88] debido a la enorme variabilidad de la disposición de la grasa intrabdominal que existe entre los distintos sujetos a un mismo nivel, lo que para algunos autores[89], cuestiona los resultados obtenidos mediante un único corte. Si a ello añadimos las considerables variaciones entre los protocolos usados, podemos explicar, al menos en parte, las grandes diferencias de los resultados obtenidos en poblaciones aparentemente similares.

Tanto la TC como la RM son herramientas que proporcionan a los investigadores la oportunidad de evaluar los componentes del nivel tejido-órgano en los individuos vivos, pudiendo proporcionar información fundamental para comprender las diferencias sexuales

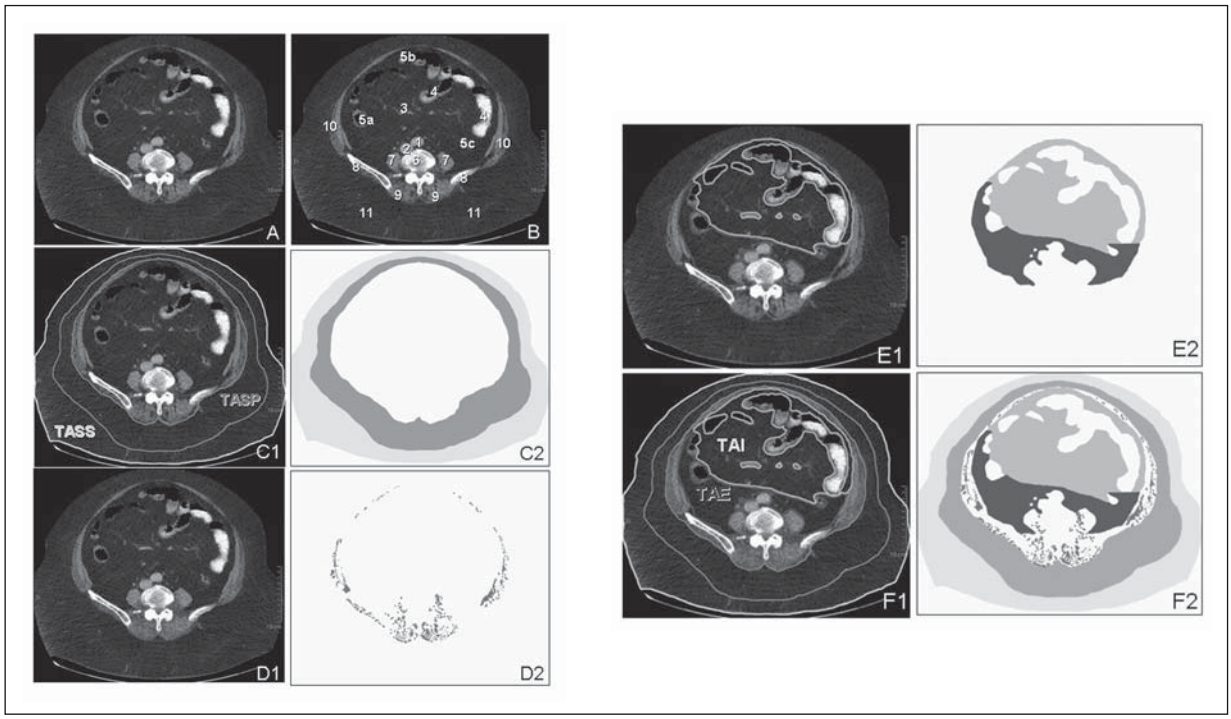

Fig. 3.—Distribución del tejido adiposo blanco a nivel abdominal (L4). A: Tomografía axial computarizada del abdomen a nivel de la articulación entre la cuarta y quinta vértebra lumbar (L4-L5), de la misma persona que la imagen 2. B: identificación de las distintas estructuras visibles a este nivel: 1- arteria aorta, 2- vena cava inferior, 3- vasos mesentérico superiores, 4- intestino delgado, 5a- colon ascendente, 5b- colon trasverso, 5c- colon descendente, 6- cuerpo y disco intervertebrales, 7- músculo psoas, 8- crestas ilíacas, 9- músculos erectores de la columna, 10- músculos anchos del abdomen, 11- fascia en el tejido adiposo subcutáneo. C: Se ha delimitado el tejido adiposo subcutáneo profundo (TASP) y superficial (TASS) en la imagen radiológica (C1), rellenando en su trasformación informática las celdas de color verde oscuro y claro respectivamente (C2). D: El color rojo representa la localización del tejido adiposo muscular extramiocitario en los músculos presentes a ese nivel (D1) y su trasformación informática (D2). E: la grasa visceral se ha separado en dos compartimentos en base a las estructuras que se observan, el tejido adiposo intraperitoneal (TAI) representa la suma del depósito omental y mesentérico, de color azul claro, el tejido adiposo extraperitoneal (TAE) concierne a los depósitos perirrenales y retroperitoneales, representados de azul oscuro (E1), al transformar la imagen, estos depósitos aparecen rellenos (E2). F: se representan conjuntamente los depósitos de tejido adiposo visibles mediante esta técnica en la imagen radiológica (F1) y su transformación informática (F2).

y étnicas en la distribución del TA, incluso antes del nacimiento, pues la RM es el único método aplicable que no perjudica ni a la madre ni al feto[90].

La calidad de imagen de la RM es extraordinaria, proporcionando valores de grasa muscular que posteriormente han sido validados mediante disección[66,91], con pequeñas diferencias de entre el 2 y 6% para el TA subcutáneo o visceral, y hasta del 20% en el músculo esquelético del adulto, pero con gran correlación entre las medidas con TC y RM[85,92-94]. Sin embargo, se han descrito variaciones en las estimaciones de TA en lactantes de hasta el 40%[95].

Limitaciones de las técnicas de imagen

Una limitación muy importante, común a las dos técnicas, es que los obesos, debido a sus dimensiones, a veces no caben en el aparato de medida, sobretodo cuando son cerrados, pudiendo quedar parte del cuerpo fuera del campo de análisis, o en caso de obesidades móbidas, la camilla sobre la que tiene que situarse no puede aguantar el peso del individuo, aunque estos problemas técnicos están comenzando a resolverse.

Dentro del compartimento subcutáneo, la fascia superficial no es fácilmente distinguible en las imágenes de RM, lo que impide determinar los depósitos de grasa profundos y superficiales de forma similar a la TC, pero como las tres cuartas partes de la capa profunda están localizadas en la mitad posterior del abdomen, se puede trazar una línea imaginaria que separe estos depósitos y que permita asumir la analogía de las medidas realizadas por las dos técnicas[57-58].

La subdivisión del TA visceral en depósitos intraperitoneal y extraperitoneal en las imágenes de TC y RM no es clara, ya que el peritoneo no es fácilmente visible con ninguno de los dos métodos, por lo que se trazarían líneas imaginarias que unen detalles anatómicos claros como el borde anterior del disco de las vértebras lumbares L4 y L5, los músculos psoas, el colon ascendente y descendente, los riñones, la arteria aorta o la vena cava inferior, con las paredes del abdomen, para segmentar la grasa visceral. De esta forma, entre el 60 y 75% del TA visceral abdominal se encuentra por

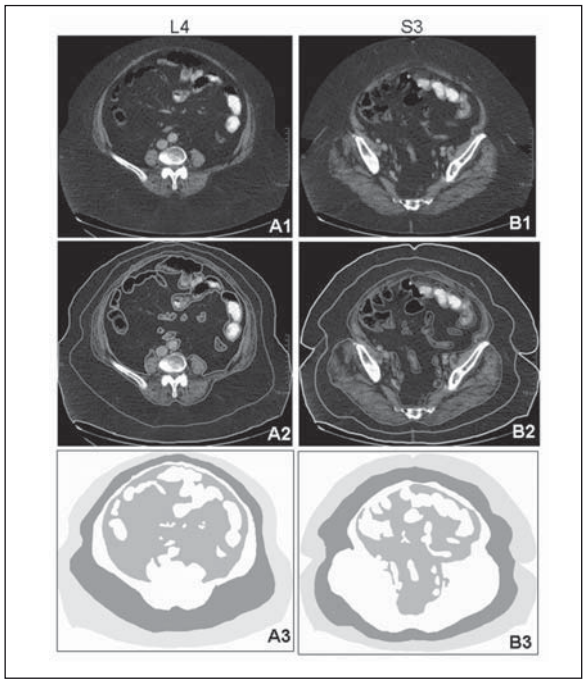

Fig. 4.—Comparación de la distribución del tejido adiposo blanco entre los niveles S3 y L4. En personas con obesidad mórbida, el ombligo puede estar desplazado caudalmente, y no servir como referencia del nivel vertebral. En las imágenes de TAC, las figuras de la izquierda corresponde al nivel L4 (4ª vértebra lumbar), y las de la derecha corresponden al nivel S3 (3ª vértebra sacra). En la imagen radiológica de L4 (A1) no se aprecia el ombligo, que está desplazado caudalmente hasta S3 (B1). Si se dibujan los compartimentos de tejido adiposo visceral, subcutáneo profundo y superficial (A2 y B2), la transformación informática de la imagen en cm2 (A3 y B3) muestra que la grasa visceral tendría un valor casi un 40% más bajo que el real (360,37 cm2 en A3 frente a 221,62 cm2 en B3, un 38,50% menor).

delante de estas líneas y se considera TA portal[92,96], aunque no existe consenso sobre si esta división mejora o no la relación observada entre el tejido graso visceral por sí mismo y la acción de la insulina[29,33,95,97,98].

A pesar de todos los inconvenientes propios de estas técnicas, se están realizando estudios con gran número de personas con TC y RM que deben ayudar a comprender las repercusiones de la distribución del TA en la salud[71,72,99-103].

Modelos antropométricos derivados de las técnicas de imagen

Una de las prioridades de la investigación del TA es la mejora en la identificación de individuos de riesgo. Se trata de definir medidas antropométricas simples que se asocien con alteraciones metabólicas. Tal y como se ha comentado a lo largo de esta revisión, estas alteraciones se relacionan con mayor frecuencia con la grasa visceral. La determinación del TAV no es fácil, y aunque las técnicas de imagen lo hacen de forma precisa y fiable, en numerosos casos su aplicación es inviable por su elevado coste. Este es el caso de los estudios epidemiológicos o de la práctica clínica diaria. Sin embargo, las técnicas de imagen de RM y TC son de gran utilidad como técnicas de referencia para definir nuevos índices o ecuaciones antropométricas. A partir de ellas, numerosos autores han definido medidas rápidas de estimación del área visceral, y como consecuencia de riesgo metabólico, que no requieren importantes gastos y que se pueden utilizar en estudios epidemiológicos.

No existe consenso entre los distintos autores sobre cuáles son las medidas antropométricas más indicativas del TAV.

La circunferencia de la cintura es la más utilizada, entre los diversos índices propuestos, ya que algunos autores defienden que esta medición es mejor para la estimación de grasa visceral que el uso del índice cintura-cadera (ICC)[103]. Sin embargo, la medición de la circunferencia de cintura conlleva algunos problemas, ya que no siempre se siguen definiciones estándares, y la medición varía en función del criterio utilizado[104]. Por ejemplo, se puede determinar el perímetro de cintura a la altura del ombligo, en la línea media entre la cresta suprailíaca y la última costilla, o en la zona más estrecha del tronco. Además, la medición también varía en función del sujeto, de la localización de los huesos, del músculo o del TA. Diversos estudios defienden que el diámetro sagital (fig. 5) presenta numerosas ventajas sobre las circunferencias de cintura y sobre el ICC105. Aún así, tanto las mediciones de circunferencias como las de diámetros son variables unidimensionales y por tanto no son modelos comple-

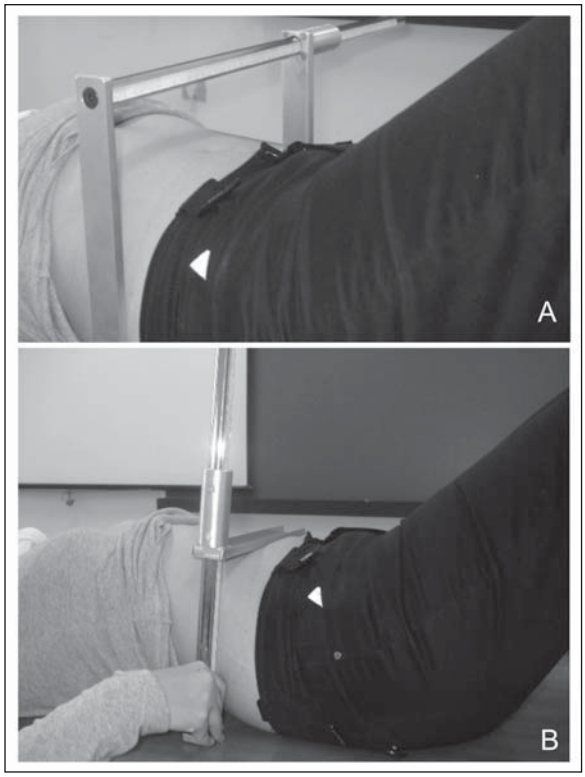

Fig. 5.—Medición antropométrica de los diámetros coronal (A) y sagital (B).

tos para determinar una variable bidimensional como es el área visceral.

Para resolver este problema se ha desarrollado un modelo circular en el que el área visceral (AV) se calcula como si fuera el área de un círculo con la siguiente ecuación[104]:

Área visceral (AV) = π (Cintura (m)1/2 π – pliegue abdominal)^2

Diversos autores consideran que el área del compartimiento visceral del abdomen se asemeja más a la de una elipse que a la del círculo, incluso en sujetos obesos. Basándose en este supuesto, He y colaboradores[106], han desarrollado un modelo elíptico para estimar el área visceral. Sin embargo este modelo presenta problemas en el individuo obeso ya que implica la medición de pliegues de grasa subcutánea de difícil medición. Recientemente, se ha desarrollado un modelo elíptico para clasificar la obesidad visceral en la práctica clínica[107]. Este modelo incluye la medición de dos diámetros, sagital y coronal (fig. 5), y un solo pliegue, el pliegue tricipital, de fácil medición por su accesibilidad, incluso en individuos obesos. A partir de estas medidas se determina el índice de área visceral y subcutánea (AV/AS). Cuando este índice es > 0,42 se considera que el individuo presenta obesidad visceral[107]:

AV/AS = 0,868 + 0,064 _ diámetro sagital – 0,036 x diámetro coronal– 0,022 x tríceps.

Para Soto González y cols.[108] y Bouza y cols.[38], habría que añadir otras variables de efecto independiente sobre la grasa visceral, como la edad, el sexo y el diámetro intrabdominal determinado por DEXA.

Conclusión general

El TA se ha revelado como un órgano endocrino que presenta un importante papel metabólico. Si tenemos en cuenta, además, el gran problema de salud pública que constituye hoy en día la obesidad, comprenderemos el interés creciente que presentan la ciencia y la medicina actual, en el conocimiento de la distribución anatómica, topográfica y funcional del tejido adiposo. Los avances recientes en la metodología de estudio de la distribución del TA, principalmente la TC y RM, en sus diversas modalidades, nos aportan las herramientas necesarias para evaluar el verdadero impacto de la compartimentalización de la grasa sobre los factores de riesgo metabólicos. El ideal sería identificar un compartimiento de TA mórbido y poder actuar sobre él, pues las causas y consecuencias metabólicas de la distribución regional de la grasa tienen particular importancia clínica. Estas observaciones pueden ayudar a diseñar mejores estrategias terapéuticas preventivas y de intervención dirigidas hacia los depósitos regionales de grasa y sus implicaciones metabólicas.

Agradecimientos

Al Servicio de Diagnóstico por Imagen del Hospital Rúber Internacional de Madrid por las imágenes de TC.

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):224-230
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisiones

Physical activity and energy expenditure measurements using accelerometers in older adults

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Abstract

The purpose of this review is to address methodological issues related to accelerometer-based assessments of physical activity (PA) in older individuals. Special interest is also put on recently updated technology. No definitive evidence exists currently to indicate which are the more valid and reliable accelerometer models for use with older people. When it comes to selecting an accelerometer, issues of affordability, product reliability, monitor size, technical support, and comparability with other studies may be equally as important as the relative validity and reliability of an instrument. The accelerometer should be attached as close as possible to the body's center of mass, and in the case of elders using walking aids, it should be placed on the same body side. Variability due to positioning can be reduced with careful training and supervision. Typically, the sampling period is between 3 and 7 days and it is not yet clear if variability exists between weekdays and weekend in the elderly. It is possible that aging effects on physical and cognitive health may limit the ability of an older adult to be compliant with an accelerometer protocol; in this line many methods have been suggested for increasing compliance to protocols for research studies. Accelerometers can provide reliable information on mobility and objective measurement of PA. These activity monitors have significant advantages when compared with other quantitative methods for measurement of energy expenditure. Accelerometers are currently used mainly in a research setting; however, with recent advances, incorporation into clinical and fitness practice is possible and increasing.

(*Nutr Hosp.* 2010;25:224-230)

DOI:10.3305/nh.2010.25.2.4439

Key words: *Accelerometer. Elderly. Physical activity. Energy expenditure.*

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Recibido: 9-VII-2009.
Aceptado: 9-VII-2009.

UTILIZACIÓN DE LOS ACELERÓMETROS PARA LA MEDIDA DE LA ACTIVIDAD FÍSICA Y EL GASTO ENERGÉTICO EN PERSONAS MAYORES

Resumen

El objetivo de esta revisión se centra en cuestiones metodológicas relacionadas con la medición de la actividad física mediante acelerómetros en personas mayores. Se pone un especial énfasis en la tecnología más reciente. Actualmente no existen pruebas definitivas que indiquen que un modelo es más válido y fiable que otro para su utilización con los ancianos. Al seleccionar un acelerómetro, la comodidad, la fiabilidad del producto, el tamaño, el apoyo técnico y la comparación con otros estudios pueden ser tan importantes como la validez y la fiabilidad del instrumento. Los acelerómetros deben colocarse lo más cerca posible del centro de masas del cuerpo y en el caso de que los ancianos utilicen ayudas técnicas para caminar se deben situar en el mismo lado del cuerpo. La variabilidad debida a la colocación puede reducirse con un cuidadoso entrenamiento y supervisión. Normalmente el periodo de registro es entre 3 y 7 días y todavía no está claro si existe suficiente variabilidad entre días de la semana y de fin de semana en ancianos. Es posible que los efectos del envejecimiento sobre la salud física y cognitiva puedan limitar la capacidad de un anciano de adaptarse al protocolo de utilización de un acelerómetro; en esta línea se han sugerido métodos para incrementar el cumplimiento de los protocolos en estudios de investigación. Los acelerómetros pueden aportar información fiable sobre la movilidad y medidas objetivas de actividad física. Estos monitores presentan ventajas significativas cuando se comparan con otros métodos cuantitativos utilizados en la actualidad para la medida de la actividad física habitual. Actualmente los acelerómetros se utilizan principalmente en investigación; sin embargo, con la incorporación de avances recientes, su empleo es posible y se está incrementando en clínica y para la mejora de la forma física.

(*Nutr Hosp.* 2010;25:224-230)

DOI:10.3305/nh.2010.25.2.4439

Palabras clave: *Acelerómetro. Ancianos. Actividad física. Gasto energético.*

Introduction

Older individuals typically experience impairments in physical functioning and increasing incidence of chronic health problems such as cardiovascular disease or osteoporosis. Although some declines with age are inevitable, considerable evidence indicates that physically active older individuals maintain healthy functioning longer than do sedentary peers,[1] Physical activity (PA), defined as any bodily movement produced by skeletal muscles that results in energy expenditure,[2] has been identified as priority area in general health promotion .[3] In older people, regular PA is important for the increase or preservation of aspects of physical function, which allows performance of more integrated functional tasks,[4] such as muscle strength and power, balance, flexibility, endurance, or mobility,[5] and in consequence for the maintenance of an independent living. Although beneficial effects of PA in older adults have largely been attributed to its impact on physical function, evidence is also emerging for positive effects on aspects of mental health. Accumulating data support the popular belief that PA is associated with psychological benefits,[6] and a large number of studies have begun to document preventive effects for depression or neurodegenerative diseases.[7]

Measurement of physical activity in older adults

Overall, there is a lack of valid and reliable methods available to measure PA in older adults because most of the measurement tools available today were designed to be used in a younger population. Accurate measurement of habitual PA is fundamental to both the epidemiological study of relations between PA and health,[8] and the recommendation of an appropriate pattern of PA to maintain good health.[9] PA is often assessed using self-reported measures. These measures are easily administered and can provide information on the types of activities performed, but there are some disadvantages to the use of self-report measures. They do not capture activity patterns throughout the day,[10] and perceptions of the intensity of any stimulus depend on the experience and the stoicism of the person concerned.[11] In older adults in particular, self-report may also be influenced by fluctuations in health status and mood, depression, or anxiety ability,[12] and by problems with memory and cognition.[13,14] Moreover, the activities older adults tend to engage in most frequently are of light to moderate intensity, such as leisurely walking, housework, and gardening. Unfortunately, these activities are often not assessed in self-report techniques that are age-neutral.[14,15] Furthermore, even when these light to moderate intensity activities are assessed they tend to be difficult to measure reliably.[15] In addition, older adults may engage in PA on a somewhat irregular basis, which complicates their ability to accurately recall PA on a survey or questionnaire.[13] All of these factors make the measurement of PA more complex in the elderly.

To address some of these issues, several surveys have been developed specifically for use in older adults: the Yale Physical Activity Survey,[4] the Physical Activity Scale for the Elderly,[15] or the CHAMPS physical activity questionnaire,[14] between others. However, because these surveys still rely on memory, criterion and objective methods of measuring PA in older adults are generally considered superior to these subjective methods.[16] Objective PA measures have gained much attention lately to overcome limitations of self-report measures. Accelerometers, in particular, provide information on the amount, frequency, duration, and intensity of PA. In general, the use of accelerometers for measuring PA in older adults in epidemiological studies has been relatively uncommon.

This paper is focuses on the use of accelerometers in older population. Despite of the increased use of these monitors, methodological issues related to accelerometer-based assessments of PA in older individuals have not been adequately addressed. Special interest is also put on recently updated technology.

Accelerometers types

Using accelerometers to assess human body movement was first proposed in the 1950s.[17,18] However, these devices were expensive, bulky and unreliable; therefore, unsuitable for ambulatory monitoring techniques. However, in the past decade a revolution has taken place in the fabrication of accelerometers, primarily driven by the automotive industry for use in airbag release systems. This new generation of accelerometers was designed to satisfy the extremely stringent quality and reliability requirements of that industry, as well as meeting the demand for high-volume, low-cost manufacturing.

The most commonly used accelerometers have piezo-electric sensors (fig. 1). Piezo-electric sensors measure acceleration due to movement and there are two main types, the cantilever beam and the integrated circuit chip. The cantilever beam technology is named for the beam that is attached to a support at one side that contains a piezoelectric element and a seismic mass. When acceleration is detected by the seismic mass, it causes the piezoelectric element in the beam to bend and record a voltage signal.[19] The amplitude of the voltage signal is in proportion to the acceleration detected.[20] The integrated chip technology (fig. 1) is in many of the newer generations of activity monitors. It also has a piezoelectric element and seismic mass that detect acceleration, but the sensor is fully enclosed in a package that is directly affixed on an electronic circuit board. This is advantageous in particular because it enhances durability and repeatability of the monitors.

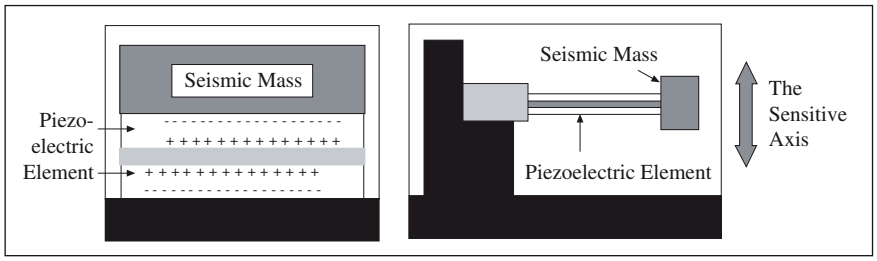

Fig. 1.—Left: Integrated chip sensor. Right: Cantilever beam.

Table I shows the most common accelerometer brands and provides information for some specifications. Although there is a body of literature on the validity and reliability of these monitors, not all have been validated on older persons, despite widespread use of accelerometers to objectively monitor PA among the elderly. Most literature on daytime PA using accelerometry involves the use of the Actigraph (Actigraph LLC) brand monitors, where most literature on nighttime activity and sleep patterns involves the use of Actiwatch (MiniMitter Co) brand.[21]

Table I
Overview of commonly-used accelerometers

Name	*Manufacturer*	*Size and weight*	*Type*	*Placement*	*Epoch length*	*Memory*	*Measurements*
Actical	Mini-Mitter Sunriver, OR	2.8 × 2.7 × 1.0 cm 17.5 G	Uniaxial; Omni-directional	Wrist, ankle or hip	Records epochs from 15 s to 1 min.	Stores up to 45 d using 1 min. epochs	Activity counts Step counts Energy expenditure
Actiwatch AW16 or AW64	Mini-Mitter Sunriver, OR	2.8 × 2.7 × 1.0 cm 16 g	Uniaxial; Omni-directional	Wrist or hip	Records epochs 15 s to 15 min	AW16 records up to 11 d using 1 min. epochs; AW64 up to 45 d	Activity counts Sleep quality
Actiwatch Spectrum	Mini-Mitter Sunriver, OR	4.9 × 3.7 × 1.4 cm 29.8 g	Uniaxial; Omni-directional	Wrist	Records activity in 15 s to 1 min. epochs	Records up to 36 d when using 1 min. epochs	Activity counts Sleep quality
Actiwatch 2	Mini-Mitter Sunriver, OR	4.4 × 2.3 × 1 cm 16.1 g (with band)	Uniaxial; Omni-directional	Wrist	Records activity in 15 s to 1 min. epochs	Records up to 30 d when using 1 min. epochs	Activity counts Sleep quality
Actitrac	IM Systems Baltimore, MD	5.6 × 3.8 × 1.3 cm 34 g	Biaxial	Wrist	Records epochs 2s to 2min	Records up to 44 d when using 1 min. epochs	Activity counts
Biotrainer	IM Systems Baltimore, MD	7.6 × 5 × 2.2 cm 51.1 g	Biaxial	Hip	Records activity in 15 s to 5 min. epochs	Records up to 22 d when using 1 min. epochs	Activity counts Converted into 'g' units or kilocalories expended
Actigraph Model 7164 [formerly CSA, MTI]	Actigraph LLC Pensacola, FL	5.1 × 4.1 × 1.5 cm 45.5 g	Uniaxial	Usually hip, also ankle/ wrist	Records activity in 5 s to 1 min. epochs	Records up to 22 d when using 1 min. epochs	Activity counts Energy expenditure
GT1M Actigraph	Actigraph LLC Pensacola, FL	3.8 × 3.7 × 1.8 cm 27 g	Biaxial	Hip or waist	Records activity in epochs of 1 s to several minutes	Records up to 378 d when using 1 min. epochs	Activity counts Step counts Energy expenditure Sleep quality
GT3X Actigraph	Actigraph LLC Pensacola, FL	3.8 x 3.7 x 1.8 cm 27 g	Triaxial	Wrist or waist	Records activity in epochs of 1/30 s to 4 min	Records up to 1 year when using 1 min epoch.	Activity counts Step counts Energy expenditure
RT3-Triaxial Research Tracker [formerly R3D]	Stayhealthy Inc. Monrovia, CA	7.1 × 5.6 × 2.8 cm 65.2 g 65.2 g	Triaxial	Hip or waist	Records activity in 1 s to 1 min. epochs	Records up to 7 d when using 1 min. epochs	Activity counts for each plane Energy expenditure

Adapted from Murphy[21]

Validity/reliability of accelerometers

There are no studies evaluating all brands and models of accelerometers, and not all brands and models have been validated. Mostly, these kind of studies have putted the attention to determine if accelerometers provide valid assessments of PA and/or energy expenditure in older persons. The results of this research question are summarized below because it is a main factor to select an accelerometer.

Gardner and Poehlman[22] compared PA assessed by Caltrac accelerometer with the criterion method of PA using doubly labeled water in free-living peripheral arterial occlusive disease older patients. The activity value from the accelerometer was highly correlated with energy expenditure of PA calculated by doubly labeled water, yielding a regression equation of energy expenditure of PA (kcal/day) = 81.6 + (0.599 X accelerometer kcal/day); $R = 0.834$, $R^2 = 0.696$, standard error of estimate = 77 kcal/day, $p = 0.001$. None of the PA questionnaires was significantly correlated with energy expenditure of PA, as the correlation coefficients ranged between 0.037 and 0.326.

Although the most relevant studies are those which are validated against doubly labeled water, the high cost of this technique reduces their number. A recent research[23] investigated the reliability and validity of using an accelerometry system (Actiwatch system) to quantify the PA level of elderly subjects against a commonly used PA questionnaire (Minnesota Leisure Time Physical Activity Questionnaire). The accelerometry system was found to be reliable (intraclass correlation coefficient, 0.978). The system was able to differentiate young adults and active elderly from sedentary elderly subjects ($p < 0.001$). The results showed a moderate but significant correlation with scores on the questionnaire ($r = 0.830$; $p < 0.001$). In line with those data it was concluded that the Actiwatch system can be used as an objective tool to quantify the PA level of the elderly.

The validity of the CSA activity monitor has been examined among older adults with chronic disease by Focht and colleagues.[24] In order to assess concurrent validity, 10 volunteers wore both a CSA accelerometer and a Cosmed K4 portable gas-analysis unit during 30 min of rehabilitative exercise. The results revealed significant ($p < 0.01$) positive correlation between CSA activity counts and oxygen uptake ($r = 0.72$). The study concluded that CSA activity monitor is an effective objective measure of PA.

Basset et al.[25] evaluated the relative validity of three accelerometers (Computer Science and Applications [CSA] 7164; Caltrac; and Kenz Select 2) for measuring energy expenditure during moderate intensity PA in field and laboratory setting in 81 participants from 19 to 74 years. Authors selected task from six general categories (yard work, housework, occupation, family care, conditioning, and recreation) listed in the 1993 Compendium of Physical Activities. During each activity, energy expenditure was measured using a portable metabolic measurement system. For the CSA device, three previously developed regression equations were used to convert accelerometer scores to energy expenditure. The mean error scores (indirect calorimetry minus device) across all activities were: CSA1, 0.97 MET; CSA2, 0.47 MET, CSA3, 0.05 MET; Caltrac, 0.83 MET; Kenz, 0.96 MET. The correlation coefficients between indirect calorimetry and motion sensors ranged from $r = 0.33$ to $r = 0.62$. The energy expenditure for power mowing and sweeping/mopping was higher than that listed in the 1993 Compendium of Physical Activities ($p < 0.05$), and the cost for several household and recreational activities was lower ($p < 0.05$). Authors concluded that motion sensors tended to over-predict energy expenditure during walking. However, they under-predicted the energy expenditure of many other activities because of an inability to detect arm movements and external work. These findings illustrate some of the limitations of using motion sensors to predict energy expenditure in field settings.

Choosing an accelerometer

Although many questions on how best to use accelerometers to measure PA remain unanswered, a considerable amount is known about monitor selection, quality, and dependability.[26] The decision to purchase a particular make and model of accelerometer is influenced by a multitude of factors. In general, no one monitor is superior to anothers, and selection depends primarily upon the research interest. However, for most researchers, the relative validity and inter-instrument reliability of a given accelerometry product is of primary importance. According to Trost,[27] evidence indicates that some accelerometers may perform better than others under certain conditions, but the reported differences are not consistent or sufficiently compelling to single out one brand or type of accelerometer as being superior to the others.

Issues of affordability should be considered, because in a study of Conn and coworkers,[28] participants wore the TriTrac units 78% of the requested days and underreported time not wearing the TriTrac. In this case, authors concluded that researchers should provide for the possibility of damaged TriTrac devices. Therefore, when it comes to selecting an accelerometer, issues of affordability, product reliability, monitor size, technical support, and comparability with other studies may be equally as important as the relative validity and reliability of an instrument.

Placements of monitors

The relative position of the accelerometer on the body is another important consideration, given that the

output from an accelerometer is dependent on the positioning on the body[29] and its orientation.[20] Because of this, different acceleration signals are recorded depending on placement as well as the inherent mechanical properties of the sensor.

Monitors record acceleration in different axes or planes of movement. These monitors are often described as uniaxial, biaxial, or triaxial for the axis or plane in which the monitor is most sensitive at detecting acceleration. Most commonly used cantilever beam monitors are usually referred to as "uniaxial" because they are most sensitive in the axis of bending (vertical).[21]

Studies have demonstrated that accelerometers can be calibrated for different positions on the body.[30] Ideally, the accelerometer should be attached as close as possible to body's center of mass.[26] One advantage of the current accelerometer technology is its small, compact size, making it wearable on many body locations (ankle, wrist, hip…). To date, a small number of studies have specifically addressed the issue of monitor placement. Little evidence suggests that one position is better than another. Pragmatic guidelines, such as comfort and ease of use, have taken precedence. However, the trunk location (hip or lower back) has become by far the most common placement for the monitors. When measuring energy expenditure, the hip or waist is the most common site to wear an accelerometer although accelerometer output may vary even with position about the hip.[31] Researchers should consider manufacturer's instructions on how to place the monitors and may recommend wearing the monitor over one hip or anywhere on the waist.

According to a study[32] the accelerometer should be used on the same side of the body. This research aimed to examine the effect of accelerometer placement, use of walking aids, and different types of PA on Stay-Healthy RT3 triaxial accelerometer readings in older people. The authors found significant differences between counts generated by the left and right hip positions. The intraclass correlation coefficient of RT3 counts between left and right hip positions was 0.48, 0.39 and 0.99 for sedentary tasks (standing, sitting and rest), stair and walking tasks respectively. Positioning of the monitor should be an important issue when data are collected over a series of days because of less supervision and guidance on wearing it appropriately. Variability due to positioning can be reduced with careful training and supervision.[29]

Number of days worn

The minimum number of days individuals need to wear an accelerometer has important implications for compliance and overall study costs; in consequence the length of time they are worn should be considered. Researches need to measure for a sufficient number of days so that the average PA reflects a habitual level of PA. Finally, the number of monitoring days will depend on the setting (e.g., occupational or leisure time), the study resources (e.g., low budget vs well funded), and the research questions (e.g., the need for population-level vs individual-level estimates of PA behaviors), although typically the sampling period is between 3 and 7 days.[27] Although Gretebeck and Montoye[33] suggested that weekdays and weekend days need to be sampled, it is not yet clear if sufficient variability between this kind of days exists in the elderly.

Variance partitioning is a commonly-used technique to determine the number of monitoring days required to achieve a desired level of reliability based on the expected between and within subject variance.[27]

Compliance to accelerometer protocols

Accelerometers are reliable and valid tools for measuring PA for research studies, provided that individuals participating in the study are compliant with wearing it as directed by the study protocol. As was indicated previously in this paper, some research has suggested that a minimum number of days of monitoring is needed in order to produce an accurate assessment of the PA patterns of an individual. As a result, participants in research studies who fail to meet the minimum number of valid days of accelerometer wear are excluded from any analysis related to PA, because their PA level cannot be calculated. It is possible that aging effects on physical and cognitive health may limit the ability of an older adult to be compliant with an accelerometer protocol. Unfortunately, no study focused on the factors that predict compliance to accelerometer protocols in older adults has been carried out. It is important, therefore, to identify factors that predict compliance to ensure that older adults with certain characteristics are not consistently excluded from analyses related to PA measured by an accelerometer in research studies.

Many methods have been suggested for increasing compliance to accelerometer protocols.[27] The most important recommendation for improving compliance appears to be education. Table II shows strategies to promote compliance with activity monitoring in field-based studies.

Limitations of accelerometers

The main limitation of accelerometers to approximate energy expenditure is the impossibility to detect the full energy expenditure of certain activities such as walking, carrying a load or walking uphill, because acceleration do not change under these conditions.[34] It is still not clear where the accelerometer should be placed to produce an accurate recording of the activity level of the whole body. In elderly people PA could be underestimated if accelerometer is placed on hip, waist

Table II
Proposed strategies to promote compliance with activity monitoring

Compliance strategies

- Ask to complete an activity monitoring log.
- Display written material/flyers on visible places to prompt wearing the accelerometer.
- Make reminder calls.
- Provide with tips or list of frequently asked questions on how to wear accelerometers correctly.
- Show an example of an output to demonstrate that one can know when they are not wearing the accelerometer.
- Provide rewards for compliance, such as gift certificate, extra credit, coupons…
- Inform on the study in advance to caregivers and educate them about wearing protocols.

Adapted from Trost, McIver and Pate[27]

o lower back. Wrist placement allows to capture the kind of activity that is common in late life, in particular the fine, upper body movements involved in such everyday activities that occur while both sitting (e.g., sewing, playing cards) or standing (e.g., washing dishes).[35] A small number of studies had examined whether additional accelerometers worn on the wrist or ankle can improve the accuracy of energy expenditure predicted with a single accelerometer on the hip or lower back. In a study by Swartz and colleagues[36] in which participated seventy subjects between 19 and 74 years old, the equation based on the results of accelerometer worn on hip explained only 32% of the variance, meanwhile the combination of output from the hip and wrist resulted in an slight increase in explanatory power (an additional 2.6% of the variance in METs).

Other minor limitations include financial cost of monitors and staff time-consuming to process and analyze data.

Conclusions

Recent technological developments have led to the production of inexpensive, miniature accelerometer sensors with potential for use in older people. These sensors can provide reliable information on mobility and objective measurement of PA. Accelerometers have significant advantages when compared with other quantitative methods. Accelerometers are currently used mainly in a research setting, however, with recent advances, incorporation into clinical and fitness practice is possible and is increasing. It is envisaged that the number and type of applications for this technology will increase as its potential is recognized. For instance, the miniature nature of accelerometers has made their incorporation into clothing possible by integrating the sensors into fabric,[37] which would facilitate compliance in long-term mobility monitoring.

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):231-237
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Terapia nutricional en pacientes adultos con quemaduras del tracto gastrointestinal por cáusticos

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Resumen

Objetivos: **Presentar la experiencia del Grupo de Terapia Nutricional del Hospital El Tunal, en el manejo nutricional de pacientes adultos con quemaduras por cáusticos del tracto gastrointestinal.**

Materiales y métodos: **Es un estudio retrospectivo, descriptivo de pacientes manejados por el Grupo de Terapia Nutricional por quemaduras por cáusticos del tracto gastrointestinal en un periodo comprendido entre Enero de 2000 y Diciembre de 2007. Se revisaron las historias clínicas de los pacientes que tenían diagnóstico de quemaduras por cáusticos. Se analizaron los datos pertinentes al manejo nutricional, la evolución y el resultado final de dichos pacientes.**

Resultados: **Se atendieron 30 pacientes, 17 hombres y 13 mujeres con edad promedio 34,4 ± 17,2 años. La ingesta del cáustico fue por intento de suicidio en 22 (73,3%) pacientes y accidental en 8 (26,7%). La mortalidad global fue alta (43,3%). El 46,9% de los pacientes mostró perdida de peso y balance nitrogenado negativo el 62,5%. Diez y siete pacientes (53,12%) recibieron nutrición mixta (enteral y/o parenteral) por un tiempo promedio de 24 ± 22 días. Al comparar dos grupos clasificados como quemadura del TGI Grave vs Moderada se encontró que fue significativamente diferente la mortalidad, la estancia hospitalaria y el valor final de albúmina.**

Conclusiones: **La quemadura del tracto gastrointestinal por cáusticos es una entidad poco frecuente, sucede principalmente en jóvenes por intento de suicidio y se asocia a alta mortalidad, sobre todo en quemaduras graves. Esta agresión lleva a catabolismo importante que produce balance nitrogenado negativo y perdida de peso. Estos pacientes requieren intervención nutricional temprana que puede extenderse por varios meses.**

(*Nutr Hosp*. 2010;25:231-237)

DOI:10.3305/nh.2010.25.2.4269

Palabras clave: *Cáusticos. Ácidos. Álcalis. Ingesta. Terapia Nutricional.*

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Recibido: 10-III-2009.
Aceptado: 30-III-2009.

NUTRITION THERAPY FOR ADULT PATIENTS WITH CAUSTIC INJURIES TO GASTROINTESTINAL TRACT

Abstract

Objectives: **To present here the experience of our Nutrition Therapy Team of the Hospital El Tunal, for the nutritional management of adult patients with caustic injuries to gastrointestinal tract.**

Materials and methods: **This is a retrospective, descriptive study of patients with caustic injuries to gastrointestinal tract managed by our Nutrition Therapy Team between January 2000 and December 2007. We revisited the clinical history of patients with diagnosis of caustic injury. Various nutritional variables, as well as the evolution and outcome were pooled and analyzed.**

Results: **A total of 30 patients, 17 male y 13 female with a mean age of 34.4 ± 17.2 years old were found. The ingestion of caustics was suicidal intent in 22 (73.3%) and accidental in 8 (26.7%). The global mortality was high (43.3%). Weight loss was found in 46.9% of the patients and a negative nitrogen balance in 62.5%. Sixteen patients (53.12%) were managed with mixed nutrition (enteral and/or parenteral) for a mean time of 24 ± 22 days. We compared two groups Moderate *vs* Severe, according to the severity of the caustic injury to gastrointestinal tract and found that mortality, the length of hospital stay and the final albumin value were significantly different among groups.**

Conclusions: **Caustic injuries to gastrointestinal tract are not frequent, they are found mainly in young patients with suicidal intent and are associated with high mortality, especially in severe injuries. This aggression causes important catabolic state leading to a negative nitrogen balance and weight loss. These patients require early nutritional intervention sometimes extended for months.**

(*Nutr Hosp*. 2010;25:231-237)

DOI:10.3305/nh.2010.25.2.4269

Key words: *Caustic. Acids. Alkalis. Ingestion. Treatment. Nutrition therapy.*

Introducción

La quemadura por cáusticos del Tracto Gastro-Intestinal (TGI) es una entidad poco frecuente que puede afectar a pacientes de cualquier edad. puede ser debida a ingesta accidental o con fines suicidas pero sus consecuencias son usualmente graves, principalmente las ocasionadas por intención suicida[1-5]. Las lesiones son producidas por cáusticos, que pueden ser ácidos o álcalis y su mecanismo de lesión es necrosis de coagulación o de licuefacción respectivamente, tendiendo a ser mas graves las causadas por álcalis[1-6]. Los factores causantes de gravedad son múltiples y variados e incluyen el pH de la sustancia, la cantidad, calidad y concentración de la sustancia ingerida, el grado de viscosidad de esta, la duración del contacto y tiempo de tránsito, la presencia o ausencia de comida y la presencia o ausencia de reflujo gastro-esofágico o condiciones pre-mórbidas del TGI[1,3,5-8].

La ingesta puede ocasionar variadas lesiones del TGI desde la boca hasta el yeyuno y/o lesiones de la piel, ojos y vías respiratorias, pero también efectos sistémicos como acidosis metabólica, necrosis tubular, falla renal, síndrome de dificultad respiratoria, etc.[1,6].

Los protocolos de manejo disponibles son incompletos o están escasamente definidos, aún en nuestra institución[1,2,5].

Se debe asegurar una vía aérea permeable, estabilizar hemo-dinámicamente el paciente y descartar abdomen agudo. Se debe tomar una placa de Rx de tórax de pié para evaluar el mediastino y descartar la presencia de neumoperitoneo[1-7]. Se debe realizar una endoscopia de vías digestivas altas en las primeras 12-24 horas de la quemadura[1-8]. El riesgo de perforación por el procedimiento aunque bajo, es menor antes de 48 horas, después de este tiempo es mejor no hacer ningún procedimiento invasivo del TGI alto, hasta después de 15 días, por el riesgo de perforación[1-8].

Algunos autores recomiendan dejar una sonda nasogástrica o nasoenteral que servirá para nutrición y como molde para evitar la estenosis esofágica, pero otros autores desaconsejan esta práctica por la posible estenosis asociada a la sonda[8-12].

Las quemaduras por cáusticos del TGI se pueden clasificar como las quemaduras de la piel en primero, segundo y tercer grado según comprometan las diferentes capas del TGI[6,8]. No hay un criterio uniforme para clasificar endoscopicamente las lesiones, pero la clasificación endoscópica de las quemaduras del TGI modificada por Zargar S. es ampliamente utilizada (tabla I)[7,13].

Las lesiones grado I y II A rara vez producen complicaciones, mientras que del grado II B en adelante se asocian casi invariablemente a estenosis u otras complicaciones[1,6,8,13].

La mayoría de los autores están de acuerdo que en los casos leves (grado I y II A) se pueden manejar con vía oral (VO) tempranamente, pero recomiendan Nutrición Parenteral Total (NPT) por mas de 1 semana en los casos graves o Nutrición Enteral (NE) por gastrostomía o yeyunostomía en casos quirúrgicos[1,4,6-8,14].

Tabla I
Clasificación endoscópica de quemaduras del TGI modificada por Zargar S

Grado I	Edema y eritema
Grado II A	Hemorragia, erosiones, úlceras superficiales, exudado
Grado II B	Lesiones circunferenciales
Grado III A	Pequeñas áreas de necrosis
Grado III B	Necrosis extensa

Aunque hay algunos autores que recomiendan el uso de corticoides y/o antibióticos intravenosos[3,7,16], en general no hay consenso con respecto a usar corticoides o antibióticos para mejorar el resultado o disminuir las complicaciones[1,8,15,17].

Se cree que la lesión esofágica causada por ingesta de cáusticos se asocia al desarrollo de cáncer tardío (carcinoma escamoso) con un riesgo 1000 veces mayor que la población general en lapsos mayores a 25 años[1,4,6-9].

Objetivos

Queremos mostrar a continuación nuestra experiencia en el manejo de la terapia nutricional en este tipo de patología, la cual es infrecuente pero que por sus características afecta principalmente el tracto gastrointestinal, produce un estado catabólico intenso y por ende compromete importantemente el estado nutricional.

Materiales y métodos

El presente es un estudio retrospectivo, descriptivo en un periodo de 7 años (entre Enero 2000 a Diciembre 2007). Se revisaron los registros del Grupo de Terapia Nutricional (GTN) y de los servicios de Cirugía y Gastroenterología. De las historias clínicas se obtuvieron los datos de las hojas de interconsulta, del perfil nutricional del GTN, de la evolución diaria y de los reporte de laboratorios, endoscopias y cirugías. De los 30 pacientes en 3 no se encontró la historia clínica completa y 5 pacientes reingresaron y fueron manejado por el GTN para un total de 27pacientes en quienes se realizaron 32 tratamientos nutricionales. Los datos se tabularon y se analizaron en Epi Info 2000 versión 3.4.3.

Resultados

El promedio de pacientes atendidos por el GTN del hospital El Tunal en los últimos 6 años es de alrededor de 80-90 pacientes por mes. La intervención nutricional se realiza por diferentes causas tanto médicas como

Tabla II
Características demográficas y nutricionales de los pacientes

Nº	*M/F*	*Edad Años*	*Causa*	*Agente*	*Sever.*	*E. H Días*	*Peso kg*	*Pérdida de peso %*	*H-B cal/d*	*Dx Nutric.*	*Alb. Inicial g/dl*	*Alb. Final g/dl*	*Tipo de Soporte*	*Balance N*
1	M	28	S	Ac	G	22	62	-14,5	1.505	NUT	2,94	ND	NE	ND
2	M	48	A	Ac	G	51	60	0,0	1.432	DNT	1,65	2,43	MIX	ND
3	M	60	A	Ac	G	14	60	-18,3	1.305	NUT	ND	2,7	MIX	ND
4	M	72	A	Ac	M	ND								
5	M	23	A	Ac	G	23	60	0,0	1.532	DNT	3,84	3,66	MIX	ND
6	F	28	S	Ac	G					ND				
7	F	20	A	Ac	G	17	55	0,0	1.361	ND	2,93	3,34	MIX	2
8	M	34	S	Al	G	51	70	0,0	1.644	DNT	3,22	3,46	NP	8
9	F	22	S	Ac	G	24	55	-9,1	1.369	DNT	ND	2,04	MIX	-6,9
10	M	29	S	Al	M	64	60	0,0	1.441	DNT	2,6	2,8	MIX	4
11	M	19	S	Al	M	27	50	-6,0	1.447	DNT	3,2	3,1	MIX	-6
12	F	96	A	Al	M	12	48	0,0	928	DNT	2,3	ND	NP	1
13	F	29	S	Al	M	18	48	-18,8	1.235	NUT	ND	3,6	MIX	-1
14	M	31	S	Al	G	8	68	0,0	1.637	NUT	2,2	ND	MIX	-12
15	M	24	S	Al	G	49	50	-18,0	1.438	DNT	4,2	3,39	MIX	-2
16	M	25	A	Al	M	9	62	0,0	1.620	NUT	3,79	3,9	NP	-11
Paciente Anterior Segundo Ingreso						36	55	1,8	1.525	DNT	4,1	3,31	MIX	1
17	M	26	S	Al	M	14	70	0,0	1.708	NUT	3,7	3,7	NP	3
18	F	23	S	Ac	G	17	55	0,0	1.349	NUT	2	2,1	MIX	-20
19	M	24	A	Al	M	11	60	0,0	1.540	NUT	3,3	4,3	MIX	-2
20	F	40	S	Al	M	16	54	-27,8	1.264	NUT	2,7	4	NP	-2
Paciente Anterior Segundo Ingreso						7	39	0,0	1.120	DNT	4,04	3,58	NP	-3
21	F	20	S	Al	M	10	48	0,0	1.294	NUT	4,08	3,6	NP	-7
22	F	28	S	Al	M	13	56	-14,3	1.333	NUT	3,3	3,6	MIX	-15
23	F	26	S	Al	M	6	59	0,0	1.371	NUT	ND	3,98	NE	ND
24	M	49	S	Ac	M	8	70	0,0	1.467	NUT	ND	3,27	NE	ND
25	F	28	S	Ac	M	12	65	-9,2	1.440	NUT	3,15	3,39	NP	2
Paciente Anterior Segundo Ingreso						13	55	0,0	1.344	DNT	3,88	2,94	NP	1
26	M	29	S	Al	G	6	58	-13,8	1.513	DNT	3,3	ND	NE	ND
Paciente Anterior Segundo Ingreso						109	50	-20,0	1.404	DNT	2,1	2,8	MIX	-14
27	F	33	S	Al	M	20	59	-5,1	1.323	NUT	3,34	3,56	NP	-4
Paciente Anterior Segundo Ingreso						28	56	-8,9	1.294	NUT	3,4	3,13	NP	-2
28	F	27	S	Ac	M	ND								
29	M	55	S	Al	M	14	58	-13,8	1.302	DNT	3,06	3,2	MIX	ND
30	M	36	S	Al	G	41	50	-14,0	1.341	DNT	3,25	3,45	MIX	1
Promedio (Mean)						24	57	6,6	1.397		3,2	3,3		-4,0
Desviación Estándar (SD ±)						22	7	8,3	157		0,7	0,5		7

Causa: S: Suicidio, A: Accidental; Agente: Ac: Ácido, Al: Álcali.
Sever.: Severidad: M: Moderado, G: Grave; E.H.: Estancia Hospitalaria; H-B: Harris-Benedict.
Dx Nutric.: Diagnóstico Nutricional: DNT: Desnutrido, NUT: Bien Nutrido.
Alb. : Albúmina; Balance N: Balance Nitrogenado.
Tipo de Soporte: NE: Nutrición Enteral, NP: Nutrición Parenteral, MIX: Nutrición Mixta.
ND: Sin Datos.

quirúrgicas, sin embargo por quemaduras del TGI por cáusticos solo se atendieron 30 pacientes en este periodo de 7 años (tabla II).

En esta serie la distribución por género mostró 13 Mujeres (43,3%) y 17 Hombres (56,7%) con edades entre 19 y 96 años con promedio de 34,4 ± 17,2 años. La causa de la quemadura fue intento suicida en 22 (73,3%) y accidental en 8 (26,7%). Por intento de suicidio la mitad fue en hombres y la mitad en mujeres, por causa accidental el 75% fue en hombres. El tipo de cáustico ingerido fue ácido en 12 (40%) y álcali en 18 (60%). El ácido ingerido con mas frecuencia fue ácido muriático, pero también se reportó ácido sulfúrico y ácido nítrico, a veces mezclado con otras sustancias como aguarrás o alcohol industrial. El álcali ingerido reportado en todos los casos fue soda cáustica. El promedio de estancia hospitalaria fue de 24 ± 22 días, con un máximo de109 días.

En los 30 pacientes se realizaron 17 cirugías. Inicialmente se llevaron a cirugía 11 pacientes por perforación, hemorragia o abdomen agudo y se realizaron tres (3) Esófago-Gastro-Pancreato-Duodenectomias, tres (3) Esofaguectomías, dos (2) Gastrectomías totales, una (1) Gastrectomía subtotal, una (1) Duodenectomía

parcial (bulbo) y en un (1) caso duodenorafia y yeyunorafias.

Tardíamente se realizó reconstrucción del TGI mediante Ascenso gástrico por vía laparoscópica en tres (3) pacientes, Gastro-Yeyunostomía en dos (2) y Ascenso de colon en un (1) paciente.

También se realizaron otras cirugías, algunas conjuntamente con las cirugías anteriores otras como procedimientos aislados. Se hicieron dos (2) Traqueostomías, cinco (5) Yeyunostomías, una (1) Esofagoplastia, dos (2) Esofagostomías y tres (3) Toracotomías de drenaje.

Se reportaron once (11) complicaciones relacionadas con el procedimiento quirúrgico las cuales fueron cuatro (4) Estenosis esofágicas, dos (2) Neumonías, dos (2) Empiemas, una (1) Dehiscencia de la anastomosis esófago-colónica, una (1) Disfunción del tubo gástrico y una (1) Lesión axonal difusa post reanimación cardio-cerebro-pulmonar durante cirugía con recuperación posterior del estado neurológico.

La mortalidad global fue de 13 pacientes (43,3%). De forma temprana (antes de 30 días) en 7 y tardía en 6. Muertes intra-operatorias fueron 4, dos (2) en la cirugía inicial y 2 en la cirugía reconstructiva.

El diagnóstico nutricional al ingreso al GTN mostró 16 pacientes bien nutridos (51%) y 15 pacientes desnutridos (DNT) (49%), encontrando DNT aguda en 10 y crónica en 5 pacientes. La clasificación de desnutrición fue: DNT Aguda Leve en 1, DNT Aguda Moderada en 3 y DNT Aguda Severa en 6; DNT Crónica Leve en 4 y DNT Crónica Moderada en 1.

Con respecto al tipo de nutrición administrada, se usó solamente Nutrición Enteral (NE) en 4 (12,5%), solamente Nutrición Parenteral (NP) incluye Nutrición Parenteral Periférica (NPP) y/o Nutrición Parenteral Total (NPT) en 11 (34,4%) y nutrición Mixta en 17 (53,1%). Se considera nutrición mixta si recibieron dos o mas tipos de nutrición al mismo tiempo (es decir NPP o NPT y NE o VO o si recibieron dos o mas tipos diferentes de nutrición durante la terapia nutricional.

El tipo de nutrición administrada varió según la condición del paciente pasando de NPP inicialmente a NPT o a NE posteriormente. Cuatro (4) pacientes recibieron solamente NPP.

En 10 pacientes se inició con NPT pero luego se cambió a NE o se adicionó VO de forma mixta para mantener trofismo del TGI. Solamente 2 pacientes recibieron NPT exclusivamente durante todo el tiempo.

En 10 pacientes se inició NE pero luego se adicionó NPP para cubrir requerimientos en 6 pacientes. Los otros 4 recibieron NE exclusivamente.

No hubo un tiempo específico en el cambio del tipo de nutrición. La decisión de cambio de tipo de nutrición la dictó personalizadamente la condición del paciente, la vía de acceso disponible y el estado del TGI. Los cambios en detalle se pueden ver en la tabla III.

El promedio de días que recibieron NE fue de 13 ± 18 días con un máximo de 87 días, de NPT fue de 15 ± 11 días con un máximo de 43 días y de mixta fue de 9 ± 11 días con un máximo de 34 días.

Tabla III
Tipo de soporte nutricional según el periodo de administración

Tipo nutrición	*I*	*II*	*III*
NPP	12 pacientes	5 pacientes	
NPT	10 pacientes	4 pacientes	1 pacientes
NE	10 pacientes	7 pacientes	8 pacientes
MIXTA		4 pacientes	1 pacientes
VO		3 pacientes	2 pacientes

NPP: Nutrición Parenteral Periférica; NPT: Nutrición Parenteral Total; NE: Nutrición Enteral; Mixta: Nutrición parenteral combinada con enteral o vía oral; VO: Vía Oral.
I: Periodo Inicial; II: Periodo Intermedio; III: Periodo Final.
(No hay un tiempo específico en días entre un periodo y otro).

Con respecto al acceso venoso, de los 27 pacientes en 16 (59,3%) se colocó un catéter venoso central como acceso inicial y en 11 (40,7%) se colocó una vía venosa periférica.

Con respecto al acceso enteral se utilizaron 17 Sondas Nasoenterales (SNE), 5 yeyunostomías (4 tipo Witzel; 1 Endoscópica percutánea) y solo 1 Sonda Nasogástrica (SNG).

Las complicaciones relacionadas con las vías de acceso de la terapia nutricional fueron reportadas como desalojo de Sonda Nasoenteral (SNE) en 2 pacientes con NE. Relacionadas con la NP se reportaron cinco (5) Flebitis por catéter periférico, un (1) Catéter Central a Periférico Fallido y una (1) infección, dos (2) infecciones por Catéter Venoso Central (CVC) y una (1) embolización de un segmento de un CVC a Vena Cava Superior. No se encontraron complicaciones relacionadas con las yeyunostomías, como tampoco hubo reportes de complicaciones metabólicas causadas por el tipo de nutrición administrada.

El Harris-Benedict (H-B) calculado en promedio fue de 1.397 ± 157 kcal/día y en promedio se necesitó de 5 ± 4 días para alcanzar la meta nutricional, que fue entre 20 y 30% adicional al H-B.

En general el plan nutricional fue administrar inicialmente 20 a 25 cal/kg y 1,5 g/kg de proteína tratando de mantener una relación de calorías no proteicas/ nitrógeno cercana a 80:1. Posteriormente según la evolución clínica y tolerancia metabólica se aumentó hasta 30-35 cal/kg y 1,8 g/kg de proteína. Algunos casos recibieron hasta 2 g/kg de proteína por balance nitrogenado negativo. Solo 2 pacientes en quienes se programó repleción nutricional recibieron 40 a 45 cal/kg y 2 g/kg de proteína.

El tipo de Fórmula Enteral administrada fue: oligomérica en 24% y polimérica en 76%. En nuestro grupo la NE se inicia a un goteo de 10 cc/hora y se aumenta en 10 cc cada 6 horas según la tolerancia hasta alcanzar el volumen que cubra la meta nutricional calculada. El algunos casos fue necesario administrar modulo proteico adicional para cubrir los requerimientos proteicos.

Tabla IV
Clasificación de la severidad de la quemadura según la descripción endoscópica y/o intervención quirúrgica

Leve	Clasificados como lesiones grado I, o hallazgos como esofagitis o gastritis leve en la endoscopia.
Moderada	Clasificados como lesiones grado II A o B, o hallazgos como esofagitis, gastritis o duodenitis moderada en la endoscopia.
Grave	Clasificados como lesiones grado III A o B, o reporte de esofagitis, gastritis o duodenitis severa o grave o reporte de perforación, necrosis, estenosis, o bien fueron llevados a cirugía por complicaciones graves de las lesiones como perforación, necrosis, sangrado de vías digestivas altas, estenosis esofágica o pilórica.

Se encontró pérdida de peso al egreso en 15 pacientes (46,9%), con un promedio de pérdida de -6,6% ± 8,3% y un máximo de -27,8% en un (1) paciente. La comparación de los diferentes tipos de nutrición no mostró ninguna diferencia en el porcentaje de pérdida de peso.

El Balance nitrogenado fue negativo en 62,5% de pacientes. El promedio total fue de -4 ± 7, con un balance negativo máximo de -20 en un paciente llevado inicialmente a esófago-gastro-pancreato-duodenectomia. El promedio del valor global de albúmina al ingreso y al egreso se mantuvo en rangos similares (3,2 ± 0,7g/dl *vs* 3,3 ± 0,5 g/dl).

La causa de egreso del GTN de cada tratamiento nutricional fue: Tolerancia a la VO en 16, salida con NE ambulatoria por Yeyunostomía en 1, Remisión por causas administrativas en 1, sin datos en 1 y muerte en 13.

Como se enunció anteriormente no hay un consenso con respecto a la mejor clasificación endoscópica para quemaduras del TGI. En los reportes de endoscopia (en 25 de los 30 pacientes) no siempre se uso la clasificación de Zargar (13), algunas veces se usaron términos descriptivos vagos, por lo que decidimos clasificar los pacientes como quemadura leve, moderada y severa según los hallazgos endoscópicos o según requirieron manejo quirúrgico por complicaciones tempranas del TGI (tabla IV).

No se encontraron pacientes con clasificación leve que hayan recibido soporte nutricional especializado en esta serie. Los pacientes manejados se dividieron en 2 Grupos: Quemadura Moderada 17 pacientes (56,7%) y Quemadura Grave 13 pacientes (43,3%)

De acuerdo a esta clasificación de Grave *vs* Moderado se compararon los dos grupos y se encontró que presentaban diferencias significativas en la mortalidad RR = 2,18 (1,07-4,47) IC 95%, P = 0,005, en la estancia hospitalaria (33,23 ± 27,79 *vs* 17,78 ± 13,62, p = 0,04) y en el valor final de albúmina sérica (2,93 ± 0,60 *vs* 3,49 ± 0,39, p = 0,006).

Tabla V
Quemaduras del TGI por cáusticos. Comparación entre grupos de acuerdo a la severidad de la quemadura (Grave vs Moderado)

Item	*Grave*	*Moderado*	*Valor p*
Edad (años)	31,31 ± 11,39	34,36 ± 17,56	0,58
Peso inicial (kg)	57,92 ± 6,39	56,42 ± 7,75	0,5
Peso final (kg)	53,38 ± 9,42	53,47 ± 9,30	0,9
Talla (cm)	166,38 ± 5,45	161,94 ± 8,48	0,10
Harris Benedict (cal/kg/día)	1.448,32 ± 110,46	1.368,14 ± 176,79	0,15
NE (días)	16,91 ± 22,71	8,00 ± 2,95	0,25
NP (días)	15,27 ± 13,66	14,58 ± 10,08	0,87
N Mixta (días)	10,50 ± 12,61	5,00 ± 1,41	0,58
Total Días Nutrición	27,92 ± 28,74	16,63 ± 11,89	0,13
Balance N	-5,48 ± 9,40	-2,56 ± 5,13	0,33
Estancia Hospitalaria (días)	33,23 ± 27,79	17,78 ± 13,62	0,04*
Pérdida Peso (%)	-8,28 ± 8,4	-5,3 ± 8,2	0,33
Albúmina inicial (g/dl)	2,87 ± 0,80	3,4 ± 0,54	0,06
Albúmina final (g/dl)	2,93 ± 0,60	3,49 ± 0,39	0,006*
Meta Nutricional (días)	7,09 ± 5,10	4,15 ± 1,95	0,06

NE: Nutrición Enteral; NP: Nutrición Parenteral; N Mixta: Nutrición Mixta; Balance N: Balance Nitrogenado.
* Estadísticamente Significativo (P < 0,05).

En la tabla V, se aprecian las diferencias en los grupos con respecto a los datos demográficos, tipo de nutrición y algunas variables de tipo nutricional, sin encontrar diferencias significativas en la mayoría de las variables.

Discusión

La incidencia de quemaduras del TGI por cáusticos es baja afortunadamente[1,5]. La mayoría de autores solo reportan un número determinado de casos en lapsos de tiempo prolongado como nosotros[1-5,14,18]. El promedio de edad en esta serie muestra que la mayoría fueron pacientes jóvenes y la causa fue por intento de suicido en la mayoría con una distribución igual en hombres y mujeres. En esta serie predomina la ingesta de álcalis que son mucho mas lesivos por la necrosis de coagulación que producen y por la asociación con el intento de suicidio[1-5,8].

La evaluación nutricional mostró que al menos la mitad de los pacientes 49% presentaban algún grado de DNT como ha sido reportado por otros autores en diferentes localizaciones geográficas[18,19,20].

La estancia promedio con soporte nutricional intrahospitalario fue mayor a 20 días aunque hubo un caso de hasta 109 días.

Inicialmente el análisis de todos los pacientes muestra que el 34,4% requirieron NP inicialmente y el 53,1% Nutrición mixta. Se encontró una tendencia a usar NPT o NPP inicialmente, pero NE o Mixta hacia el periodo final. Se utilizó NPP inicialmente en 12 pacientes con adecuado acceso venoso periférico y en quienes se pensó que la terapia nutricional duraría un tiempo menor a 15 días o presentaban inadecuada tolerancia a la vía enteral[21]. Solo 4 pacientes recibieron solamente NPP, los otros pacientes necesitaron cambio a NPT por requerimientos aumentados o toleraron cantidades suficientes de nutrientes por la NE. La flebitis fue la complicación mas frecuente asociada a la NPP[21].

En nuestro hospital los gastroenterólogos suelen dejar una sonda avanzada (SNE) de poliuretano, calibre 12 F en el momento de la endoscopia, para ser usada como vía de nutrición enteral y eventualmente servir de molde para evitar la estenosis completa del esófago. En esta corta serie no es posible evaluar el riesgo de estenosis esofágica secundaria a la colocación de este tipo de sondas, además que por la severidad de las quemaduras en esta serie, la posibilidad de estenosis es muy alta[1,6,8,13]. La colocación de la SNE no siempre es posible, bien por la friabilidad de los tejidos o por que no se puede realizar la endoscopia por ingreso tardío (posterior a 48 horas), en estos casos utilizamos NPT o NPP según el estado nutricional y requerimientos del paciente. Si el paciente es llevado a cirugía, usualmente se realiza una yeyunostomía para nutrición, si las condiciones lo permiten, como se hizo en cuatro (4) pacientes, otro paciente fue llevado a una yeyunostomía endoscópica percutánea de manera programada.

Con la intervención nutricional hubo perdida de peso en poco menos de la mitad de los pacientes (46,9%) y el valor de albúmina sérica final tendió a mantenerse en el mismo rango que la inicial. El balance nitrogenado inicial fue negativo en 62,5%. No hubo diferencias según los diferentes tipos de nutrición administrado, por lo tanto la pérdida de peso no parece relacionarse con el tipo de nutrición administrado y que el balance nitrogenado obedece al estado catabólico intenso ocasionado por la lesión, como ha sido descrito por otros autores[22]. Uno de los pocos autores que ha escrito sobre soporte nutricional en quemaduras por cáusticos reporta la pérdida aumentada de zinc y recomienda medir los niveles de zinc, pero nosotros no pudimos medirlo en nuestros pacientes[22].

La mayoría recibió una fórmula polimérica 76% con buena tolerancia. Las fórmula oligoméricas se reservaron inicialmente para los pacientes con yeyunostomías o en aquellos que se reinició NE luego de un tiempo prolongado (mayor a 7 días) de ayuno o de NPT.

Con respecto a la vía de acceso de NP fue central y periférica inicialmente, pero solo central en el periodo final. Inicialmente si el paciente esta bien nutrido y la quemadura se considera leve o moderada, se puede esperar que reasuma la V.O. antes de 10-15 días por lo que se puede administrar NPP. Si el paciente esta DNT o presenta lesiones graves se coloca un CVC y se administra NPT, si no se ha realizado una yeyunostomía en cirugía. La vía de acceso mas frecuente para NE fue SNE (76,2%) usualmente colocada durante la endoscopia diagnóstica inicial. De las 5 yeyunostomias (23,8%), 4 fueron quirúrgicas tipo Witzel, realizadas en cirugía y una (1) endoscópica percutánea. Esta última fue realizada de manera programada en el paciente que presentó disfunción del tubo gástrico. Las yeyunostomías realizadas sirvieron para su propósito y fue posible administrar NE sin complicaciones. Un (1) paciente con yeyunostomía se manejo ambulatoriamente con formulas caseras en bolos por un periodo de 5 meses. Este paciente presentó recuperación del peso y recuperación adecuada en los parámetros nutricionales, y fue reintervenido al final del periodo de recuperación nutricional con reconstrucción tardía del TGI mediante ascenso gástrico por vía laparoscópica. Luego no necesito soporte especializado pues toleró vía oral adecuadamente en el postoperatorio inmediato y se retiró la yeyunostomía al octavo día postoperatorio.

En esta serie no se encontraron pacientes clasificados como quemadura leve debido a que nuestro hospital es un centro de alta complejidad de atención y se reciben pacientes remitidos de otros hospitales de menor nivel de complejidad.

Al comparar los grupos de acuerdo a la severidad de la lesión se encontró una tendencia a mayor uso de NP en el grupo Grave y mayor NPP-NE en el grupo Moderado, como también una tendencia a recibir por mayor tiempo NE y Nutrición Mixta en el grupo Grave. No hubo diferencias significativas en la mayoría de parámetros nutricionales. Si se encontró diferencia significativa en los grupos de quemadura Grave *vs* Moderada en la Mortalidad, en la estancia hospitalaria y en el valor de final de albúmina que reflejan la mayor severidad de la injuria en el grupo clasificado como Grave. Los pacientes mas graves usualmente requieren manejo mas agresivo en UCI para soporte inotrópico y ventilatorio, y requieren procedimientos quirúrgicos que influyen negativamente para el avance óptimo del soporte nutricional, sin embargo aunque hubo una tendencia a la diferencia en los días para alcanzar la meta nutricional y también en el valor de albúmina inicial no alcanzaron diferencias estadísticamente significativas.

Conclusiones

En nuestro hospital la quemadura del TGI por cáusticos es una entidad poco frecuente. La mayoría de los pacientes que sufrieron quemadura por cáusticos eran jóvenes por intento de suicidio. La lesión por álcalis fue la mas frecuente. La mitad de los pacientes presentaban algún grado de DNT al ingreso. Mas de la mitad de los pacientes se manejaron con nutrición mixta. Con la intervención nutricional se previno la perdida de peso en mas de la mitad de los pacientes y se logro mantener el valor de albúmina sérica. Se realizó el

manejo ambulatorio de 1 paciente con yeyunostomía en quien por las condiciones socioeconómicas del paciente se administró soporte nutricional en bolos de formulas caseras artesanales, con buenos resultados. Esta patología se asocia a estancia hospitalaria prolongada y a una mortalidad alta sobretodo si la lesión es grave. Esta revisión nos ha animado para establecer en nuestro hospital unas guías de manejo mas concretas y mejor definidas.

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):238-244
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Influence of low-protein dietetic foods consumption on quality of life and levels of B vitamins and homocysteine in patients with chronic renal failure

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Abstract

Objective: **The aim of the study was to determine whether the consumption of low protein dietetic foods® improved the quality of life and nutritional status for vitamins B and homocysteine in patients with chronic renal failure.**

Methodology: **This nutritional-intervention involved 28 men and 21 women, divided into two groups. The control-group consumed a low-protein diet prescribed, and the experimental-group consumed a diet in which some commonly used foods were replaced by low-protein dietetic foods. The study lasted 6 months. Food consumption was assessed by 24-h recall. Vitamin B_6 as αEAST was measured in blood. Creatinine, urea, vitamin B_{12}, folate and homocysteine were measured in plasma. The impact on the patients' quality of life from consuming the dietetic foods was assessed via the SF-36 questionnaire.**

Results: **After 6 months, the protein intake among the experimental-group had decreased by 40%, and the urea/creatinine ratio and αEAST activity were also lower. The results of the SF-36 questionnaire show that the patients in the experimental-group obtained higher scores in the categories of general health and physical status.**

Conclusions: **The dietetic foods were very well accepted by all patients and their use allowed a better control of the protein intake, improved B_6 status and a better quality of life.**

(*Nutr Hosp*. 2010;25:238-244)

DOI:10.3305/nh.2010.25.2.4274

Key words: *Chronic renal failure. Vitamins B. Homocysteine. Dietetic foods. Quality of life.*

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Recibido: 25-III-2009.
Aceptado: 15-VI-2009.

INFLUENCIA DEL CONSUMO DE ALIMENTOS DIETÉTICOS BAJOS EN PROTEÍNA SOBRE LA CALIDAD DE VIDA Y LOS NIVELES DE VITAMINAS B Y HOMOCISTEÍNA EN PACIENTES CON INSUFICIENCIA RENAL CRÓNICA

Resumen

Objetivo: **Se estudió si el consumo de productos dietéticos bajos en proteína® mejora la calidad de vida y el estado nutricional en vitaminas B y homocisteína en pacientes con insuficiencia renal crónica (IRC).**

Material y métodos: **La intervención nutricional se llevó a cabo durante 6 meses en un grupo de pacientes con IRC (28 hombres y 21 mujeres) divididos en dos grupos. El grupo control consumió la dieta prescrita para la IRC. El grupo experimental consumió una dieta en donde parte de los alimentos fueron sustituidos por los productos dietéticos bajos en proteína. El consumo de alimentos fue analizado mediante recordatorio de 24 horas. El estatus en Vitamina B_6 se determinó como αEAST en muestras de sangre. En plasma se analizaron los niveles de creatinina, urea, Vitamina B_{12}, folato y homocisteína. El impacto del consumo de los productos dietéticos sobre la calidad de vida de los pacientes se analizó mediante el cuestionario de salud SF-36.**

Resultados: **Tras 6 meses de intervención nutricional, la ingesta proteica en el grupo experimental descendió un 40%. También se redujo la relación urea/creatinina y la actividad αEAST. Los resultados del cuestionario de salud SF-36 mostraron que los pacientes del grupo experimental obtuvieron mejores puntuaciones en las categorías de salud general y estado físico.**

Conclusiones: **Los productos dietéticos bajos en proteína fueron muy bien aceptados por los pacientes y su uso permitió un mejor control de la ingesta proteica, mejorando el estado nutricional del paciente en B_6 y su calidad de vida.**

(*Nutr Hosp*. 2010;25:238-244)

DOI:10.3305/nh.2010.25.2.4274

Palabras clave: *Insuficiencia renal crónica. Vitaminas B. Homocisteína. Estado nutricional. Alimentos dietéticos. Calidad de vida.*

Introduction

Chronic renal failure (CRF) alters the metabolism of and nutritional requirements for a number of vitamins, and can lead to either deficiency or raised levels of these nutrients. Among the causes of these alterations are reduced food intake, the low vitamin content of some low-protein diets, increased endogenous breakdown or clearance of vitamins from the blood, and interference by certain drugs.

Although low-protein diets have often been recommended as a means of slowing the progression of CRF[1,2] adherence to these diets is poor because of the lack of variety in menus and the limits on the consumption of many foods.[3] Moreover, reduced food intake in these patients often worsens the situation and increases the chances that the intake of micronutrients such as folate and vitamins B_6 and B_{12}, abundant in protein-rich foods, will also be inadequate. These vitamins are known to be involved in the metabolism of homocysteine, and deficient levels favour hyperhomocysteinemia. This cardiovascular risk factor is particularly worrisome in patients with CRF. In patients with uraemia the mortality rate attributable to cardiovascular disease is 30% higher than in the general population, and hyperhomocysteinemia is the most prevalent risk factor.[4,5]

This study was designed to discover whether the consumption of manufactured low-protein dietetic foods by patients with CRF enables them to better adjust their protein intake and to maintain their nutritional status for vitamins B_6, B_{12} and folate, and to decrease hyperhomocysteinemia. Moreover, it is important to determine whether the use of these dietetic products might facilitate the manufacture and variety of diets, and thus improve users' quality of life.

Methods

Patients

The participants in this clinical-nutritional intervention were patients with CRF on predialysis. The following criteria were established for inclusion: serum creatinine concentration > 2.5 mg/dL, plasma creatinine clearance between 10 and 45 mL/min, stable clinical condition (stable blood pressure, no special diet, no digestive system or systemic disease, neoplasias, or treatment with corticosteroids or immunosuppressors), corrected metabolic acidosis and lipid alterations, age between 18 and 70 years, and knowing how to read and write. The study was authorized by the Ethics Committee of the Hospital Universitario Virgen de las Nieves (Granada, Spain). All patients provided their consent by signing an Informed Consent form.

The sample was consecutive and nonprobabilistic, since we included all patients who met the inclusion criteria and were seen at the nephrology outpatient clinic of the Hospital Universitario Virgen de las Nieves (Granada, Spain) between November 1999 and June 2006.

The sample of patients initially invited to participate consisted of 64 men and women aged 18 to 70 years. The final sample consisted of 49 persons (28 men, 21 women) with a mean age of 55 (SD 16) years. The final participation rate was 76.6%, and the reasons for dropout, or withdrawal by the investigators were scheduled dialysis (26.7%), nonadherence to the diet (60.0%) or death (13.3%).

The participants were divided randomly into two groups. The 25 control participants (C) remained on the low-protein diet recommended by the hospital. This diet was based on a weekly low-sodium menu that supplied a mean of 46.3 g protein/day, 54.6 g fat/day and 240 g carbohydrates/day. The 24 participants in the experimental group (E) were instructed by a trained dietician to consume a conventional low-protein diet, but with

some of the foods commonly used being replaced by dietetic foods low in protein, amino acids, sodium, potassium and phosphorus, and enriched with certain minerals and vitamins (Harifen®, SanaviSA, Granada, Spain). Harifen manufactures a wide range of dietetic foods especially suitable for the treatment of diseases related to protein metabolism, such as chronic renal disease and metabolic disorders. Further information about the use, composition and manufacture of these foods can be obtained from: http://www.sanavi.com/ing/harifen/harifen.html

The following dietetic foods were supplied to the patients during the study: prebaked bread, milk substitute, Italian pastas, rice substitute, toasted bread, baking and pastry mixture, and various types of biscuits.

The participants were advised by a dietician on how to prepare their meals in accordance with nutritional recommendations for CRF,[6] replacing the foods normally consumed by the special, low-protein dietetic ones supplied. These training sessions were personalized and lasted for 1 week.

The recommended diet contained 0.6 g protein (50% high biological value)/kg bodyweight per day[7,8] and 35 kcal/kg bodyweight per day[9] and was low in sodium, potassium, phosphates, saturated fat and refined sugar.

Participants with obesity (50%) and those older than 60 years (47.3%) were advised to consume a diet that provided 30 kcal/kg ideal weight per day. To adjust the energy content of the low-protein diet, obesity was considered to exist when the participant weighed more than 125% of his or her ideal weight.[10]

On day 0 of the study, all participants received a physical examination, and clinical and nutritional data were recorded. During the 6-month experimental phase, participants in group E consumed the low-protein diets they designed themselves during the initial dietary intervention, while participants in group C continued to consume the low-protein diet recommended by the hospital.

Pharmacological treatment was similar for all participants, and was adjusted depending on individual clini-

cal status. Medications used by participants in this study included calcium-chelated phosphate, calcitriol, oral sodium bicarbonate, ferrous sulphate, antihypertensives (mainly angiotensin-converting enzyme inhibitors), furosemide and subcutaneous erythropoietin (EPO).

At the start of the study and after 6 months, blood samples were taken for biochemical analysis and food consumption was assessed by 24-h recall on 3 different days (including a weekend or holiday).[11] Food consumption data were obtained by a dietician with the aid of an open questionnaire and photographs as a reference for portion size. The pictures showed fresh foods or foods prepared according to usual recipes for dishes that are widely consumed in the area. Food intakes were converted into energy and nutrients with the help of the Spanish Food Composition Table.[12] The composition database was used with AYS44 Diet Analysis software from ASDE, SA (Valencia, Spain).

In order to determine, from the patient's viewpoint, the impact on quality of life from consuming these low-protein dietetic foods, all patients were asked to fill in the SF-36 health status questionnaire[13] at the start and end of the study. This questionnaire consisted of 36 items divided into 8 categories, addressing the patient's perception of his/her health status in general, social function, physical status, limitations caused by physical and/or emotional problems, mental health, vitality and pain. A score for each category was calculated, ranging from 0 to 100. This questionnaire enabled us to detect both positive and negative states of health, and to categorise mental and physical health status, as well as any changes in health status occurring during the treatment period.

Analytical methods

Blood was collected in the morning after the participants had abstained from eating and drinking overnight. Creatinine, urea, uric acid, albumin and total protein concentrations were measured with enzymatic colorimetric tests in a Hitachi Modular P autoanalyzer (Roche Diagnostics, Grenzach, Germany).

Part of the blood (6 mL) was collected in tubes that contained 1 mL ACD-stabilizer (Venoject, Terumo Corporation, Leuven, Belgium). The samples were centrifuged at 3000 × *g* for 15 min at 20 ºC to separate plasma, and erythrocytes were washed with isotonic saline and stored at -80 ºC until analysis.

To assess B_6 nutritional status, we used erythrocyte aspartate aminotransferase activity (EAST) with and without added pyridoxal phosphate (PLP) (Sigma, St Louis, MO). The activation coefficient (a) for erythrocyte aspartate aminotransferase (aEAST) was taken as the ratio of activity with added PLP to activity without PLP.[14] The cutoff points for aEAST were > 1.85 for high risk, 1.85-1.70 for low (moderate) risk, and < 1.70 for acceptable (low) risk.[14,15]

Vitamin B_{12} and folate were measured with an electrochemical luminescence immunoassay (ECLIA, Elecsys 2010 and Modular Analytics E 170, Roche Diagnostics, Germany). The reference value for vitamin B_{12} was 150 μg/L and the reference value for folic acid was 3 pg/L.[15]

Plasma homocysteine concentration was measured with a fluorescence polarization immunoassay (FPIA) (IM® Abbott Laboratories, Abbott Park, IL, USA).

Statistical analysis

All variables and indexes were analyzed with descriptive statistics to report mean values and standard deviations. When the data were distributed normally according to the Kolmogorov-Smirnov test, we used parametric tests, i.e., Student's *t* test for independent or related samples. For variables that required nonparametric testing we used the Wilcoxon test for related samples and the Mann-Whitney test for unrelated samples.

Linear regression analysis was used to find bivariate correlations; Pearson's correlation coefficient was calculated for 95% confidence levels. Multiple logistic regression analysis was used to estimate the degree of association between intake or plasma values (dependent variable) and gender, age, group (control and experimental) and experimental period (day 0 and month 6). The model was adjusted for all variables. All analyses were performed with version 14.0 of the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL). Differences were considered significant at the 5% probability level.

Results

Table I gives the results for the biochemical indicators of renal function. Among the control participants, the glomerular filtration rate (GFR) decreased by 17.2% (4.5 mL/min), whereas for the participants in the experimental group who received nutritional education and lowered their protein intake, the decrease was only 6.9% (1.7 mL/min). In the experimental group, the urea/creatinine ratio was significantly reduced after six months, with respect to the initial values recorded, while no changes were observed among the control group.

Table II summarizes the data for intakes of energy, macronutrients and vitamins, and the percentages of the RDA covered at the start of the experimental period and after 6 months. Energy intakes were below the RDA[9] and tended to decrease with time in both the control and experimental groups. Protein intake in the experimental group (E) decreased significantly and attained the recommended value of 0.6 g protein/kg weight/day.[8] In the former, protein intake decreased by 40% (from 1.0 to 0.6 g protein/kg weight/day). More-

Table I
Functional status of the kidney at the start and at the end of the experimental period

	Day 0				*6 months*			
	Control (n = 25)		*Experimental (n = 24)*		*Control (n = 25)*		*Experimental (n = 24)*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Plasma creatinine (mg/dL)	3.2	0.9	3.2	0.7	3.2	1.2	3.3	0.7
Glomerular filtration rate (mL/min/1,73 m^2)	26.2	7.8	24.5	8.6	21.7	5.6	22.8	9.6
Plasma urea (mg/dL)	110.7	25.5	112.7	35.3	111.8	32.7	107.1	43.3
Urea/creatinine ratio	34.3	9.5	35.2	6.2	33.7	9.8	31.5	5.5‡
Plasma uric acid (mg/dL)	6.0	1.8	7.3	1.7	6.3	1.9	7.3	1.2
Plasma total protein (g/dL)	7.2	0.7	7.0	0.7	7.0	0.4	7.0	0.7
Plasma albumin (g/dL)	4.3	0.2	4.1	0.1	3.9	0.2	4.0	0.2

†Control *vs* Experimental; ‡ $Experimental_{start}$ *vs* Experimental 6 months. $P < 0.05$ in all cases. (% RDA) Percent recommended daily allowance covered.

over, among the experimental group, there was a significant decrease in total fat.

On the other hand, by the end of the study, the intake of vitamin B_6 among the experimental group was significantly higher than among the control group. The intake of vitamin B_{12} decreased among the experimental group, while no significant changes were recorded for the intake of folates.

Table III shows the blood and biochemical parameters for vitamins and homocysteine. After 6 months,

EAST activity among the experimental group was lower ($P < 0.05$) than in the control group.

Values for vitamin B_{12} were below the reference value (150 μg/L) in two control patients, both of whom continued to present similarly low values at the end of the study period.

The results for circulating homocysteine levels indicated moderate hyperhomocysteinemia at the start of the study, which was maintained in both the control and experimental groups during the study period.

Linear regression analysis shows that vitamin B_6 intake correlated with energy intake ($r = 0.49$; $P < 0.01$), protein intake ($r = 0.50$; $P < 0.001$) and vitamin B_{12} intake ($r = 0.60$, $P < 0.001$). Vitamin B_{12} intake cor-

Table II
Energy, macronutrient, vitamins B_6, B_{12} and folate intakes

	Day 0				*6 months*			
	Control (n = 25)		*Experimental (n = 24)*		*Control (n = 25)*		*Experimental (n = 24)*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Energy (kcal/d)	1769	460	1864	531	1687	616	1676	277
kcal/kg weight/day	23.7	6.3	25.7	11.2	22.8	2.2	23.6	7.0
Protein (g/day)	74.5	23.3	74.0	27.4	72.3	20.8	42.8	12.4†,‡
Protein/kg weight/day	1.0	0.3	1.0	0.4	1.0	0.3	0.6	0.2†,‡
Carbohydrates (g/day)	202.9	71.1	220.5	68.2	207.7	44.6	209.0	62.9
Total fat (g/day)	67.9	15.6	75.1	23.2	58.2	25.8	72.7	24.0†
Fiber (g/day)	19.3	8.9	16.1	6.5	16.1	9.4*	14.7	5.2
Vitamin B_6 (mg/day)	1.8	0.4	1.6	0.4	1.2	0.2*	1.5	0.3†
Vitamin B_6 (%RDA)	99.4	18.0	94.8	22.7	71.3	12.1*	87.7	18.1†
Vitamin B_{12} (μg/day)	8.1	10.3	7.8	4.4	7.5	2.2	5.0	4.0†‡
Vitamin B_{12} (%RDA)	405.0	515	390.0	220	277.1	240	250	200
Folates (μg/day)	190.6	86.8	202.7	72.7	156.7	123.0	169.8	79.8
Folic acid (%RDA)	47.6	21.7	50.8	18.2	39.2	20.5	42.5	13.9

†Control *vs* Experimental; * $Control_{start}$ *vs* Control 6 months; ‡ $Experimental_{start}$ *vs* Experimental 6 months. $P < 0.05$ in all cases. (%RDA) Percent recommended daily allowance covered.

Table III
Biochemical parameters

	Control (n = 25)		*Experimental (n = 24)*	
	Mean	*SD*	*Mean*	*SD*
Vitamin B_6 (αEAST)	1.55	0.18	1.40	0.18
Vitamin B_{12} (μg/L)	323.3	154.5	269.0	98.1
Folic acid (pg/L)	2.09	0.61	2.51	0.88
Homocysteine (μmol/L)	14.6	6.30	16.0	5.43
6 months Vitamin B_6 (αEAST)	1.56	0.11	1.39	0.16†
Vitamin B_{12} (μg/L)	310.2	122.5	338.6	129.9
Folic acid (pg/L)	2.10	0.49	2.56	0.54
Homocysteine (μmol/L)	14.7	3.48	16.2	5.82

Values are expressed as the mean ± SD. †Control *vs* Experimental.

related with protein intake ($r = 0.34$; $P < 0.05$). Folate intake correlated with energy intake ($r = 0.44$; $P < 0.01$), protein intake ($r = 0.41$; $P < 0.01$) and vitamin B_6 intake ($r = 0.34$; $P < 0.05$).

Logistic regression analysis did not reveal any significant associations between intake or plasma values (dependent variable) and gender, age, group (control or experimental) or experimental period (day 0 or at 6 months).

The results obtained from the SF-36 health status questionnaire suggest that by the end of the study period, the patients who consumed the low-protein dietetic foods presented higher scores in the categories of general health (Mean, SD) [68, 1.8 (control) *vs* 72, 1.2 (experimental), $P < 0.05$] and physical status [46, 1.2 (control) *vs* 56, 2.0 (experimental), $P < 0.05$].

Discussion

Analysis of the biochemical parameters commonly used in clinical practice to study renal function (Table 1) showed that in the experimental group, a lower protein intake led to a smaller decrease in GFR, as has been reported in other studies.[16] The urea/creatinine ratio in both groups in the present study indicated a slight excess in protein levels (recommended values between 20 and 30 mg/dL). Nevertheless, this was far below the cutoff value for excess protein intake (> 40 mg/dL).[17] The significant decrease in the urea/creatinine ratio observed among the experimental group resulted from the slight fall in circulating levels of urea, a consequence of the consumption of low-protein dietetic products (tables I and II).

Participants in the experimental group received nutritional information to enable them to design a low-protein diet that covered their needs[18] and replace foods commonly consumed with dietetic substitutes. These were very well accepted by all patients.

The results of the food consumption analysis show that energy intake failed to cover 100% of the RDA at the start of the study or after 6 months (table II). This situation might reflect the reduced food intake often seen in patients with CRF.[19]

At the beginning of the study, protein intakes were similar in the control and experimental groups, at approximately 170% of the recommended value, reflecting the fact that high protein intakes are common among the adult population in southern Spain[20]. The nutritional training programme appeared to be an important factor in reducing protein intake, since our participants attained the prescribed value of 0.6 g protein/kg weight/day (table II).

Several studies have reported that vitamin B_6 status worsens in CRF.[21] Low-protein diets can lead to deficient intakes of vitamin B_6, supplied mostly by meat and fish among our population[22]. The decreased vitamin intake may explain why intakes in both groups were close to the RDA at the beginning of the study but were lower after 6 months. This change paralleled the above-described pattern of protein intake. However, although protein intake fell much more sharply among the experimental group than among the control group, the fall in pyroxidine intake was lower among the experimental group (table II). This is because the dietetic products supplied were enriched in this vitamin. In this respect, the mean values measured in our participants were slightly lower than those found by Kopple et al.[23] in adults with advanced CRF.

The greater consumption of vitamin B_6 among the experimental group meant that the average activity of EAST decreased among this group, which indicates an improvement in the status of this vitamin among the patients.

The low-protein diet consumed by the experimental group led to a lower intake of vitamin B_{12} because in southern Spain the main sources of this nutrient are meat and fish[22]. The linear correlation between vitamin B_{12} and protein intake (see Results) supports this hypothesis. Nevertheless, mean intakes were substantially higher than the RDA (table II) in all cases.

Mean plasma concentrations of vitamin B_{12} are usually within the normal range in patients with CRF,[24] and deficiencies are rarely encountered because of the low requirements for this vitamin. However, the plasma mean values were clearly lower than those observed in earlier studies in the healthy adult population residing in the same geographical area.[22]

The relationship between CRF and the RDA for folate is a controversial question. Our results showed that folate intake was low in both groups at the beginning of the study and after 6 months, and that most patients failed to cover 50% of the RDA. This finding appeared to be related to low energy intakes, a hypothesis supported by the linear correlation between folate and energy intake (see Results). Although folate intakes were far below the RDA for the healthy adult population, intakes approached the estimated content (260 μg/day) of different low-protein diets (40 g/day) prescribed to patients with CRF.[1]

A high incidence of folate deficiency has been reported in patients with CRF who are not receiving dialysis. It has also been found, however, that in patients with moderate CRF, serum concentrations of folate are normal.[1] Mean values for folate at the start of the present study and after 6 months were slightly below the reference value (3 pg/L). Most patients (79.6%) had plasma concentrations below this reference value, a situation that may reflect various factors, such as low intake (below 2/3 of the RDA in 87.8% of the patients), altered folate metabolism in uraemia, and decreased intestinal absorption in patients with CRF.[25] Patients with CRF being treated with EPO may have increased folic acid requirements because of the increase in erythropoiesis.[26]

Elevated plasma levels of homocysteine are considered an independent risk factor for vascular disease in nonuraemic patients and those with CRF. Folic acid administration can decrease homocysteine levels by 30-50%, but only some patients attain normal levels of homocysteine in plasma, and treatment has been shown to be more effective when combined with vitamin B_6 and B_{12}.[1]

We found only one patient with vitamin B_6 deficiency, four with vitamin B_{12} deficiency and 39 with folic acid deficiency. These numbers suggest that hyperhomocysteinemia is related to low levels of folate, which would favour an increase in the rate of homocysteine production. However, it has recently been reported that homocysteine levels decrease in malnourished patients with end-stage renal disease, and change according to nutrient intake and various other nutritional parameters, indicating that circulating homocysteine levels can become an expression of nutritional status.[27] Lower homocysteine levels in patients with end-stage renal disease have been associated with a worse clinical outcome.[28] In the light of these considerations, the absence of changes in plasma homocysteine levels in our patients suggests that they maintained or even improved their nutritional status during the study period.

There is currently a consensus that the benefits arising from healthcare interventions should be assessed taking into account the health-related quality of life during the time of survival. The SF-36 questionnaire[13] provides an efficient method for measuring the quality of life from the patient's standpoint, scoring standardized responses to standardized questions. From the application of this questionnaire to our patients, we observed that better results are obtained in the categories of general health and physical state (see Results) among the patients in the experimental group. These results are considered to be the consequence of the fact that the use of these dietetic foods makes it possible to prepare more varied and better balanced meals, and thus fulfil the goal of achieving a low-protein diet.

The results of this study indicate that the consumption of the dietetic products supplied was very well accepted by all patients, who were thus able to better control their protein intake. This improved control was accompanied by an improvement in vitamin B_6 levels and a higher quality of life. These findings, together with the absence of changes in plasma homocysteine levels, indicate that the nutritional intervention had beneficial effects. However, the dietetic products will need to be tested for longer follow-up periods to determine the extent of potential improvements to be attained from low-protein dietetic foods.

Acknowledgments

This research was supported by Plan Nacional I+D project 1FD 1997-0642. All authors have contributed to the experimental work, and to the development and final discussion of the manuscript. We thank Sanavi S.A. for supplying the dietetic products.

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):245-249
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Composición corporal en pacientes con insuficiencia renal crónica y hemodiálisis

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Resumen

Antecedentes: **Las alteraciones en el estado nutricio son un hallazgo frecuente en pacientes con enfermedad renal crónica en etapa 5 de la clasificación NKF K/DOQ sometidos a hemodiálisis. El impacto de la enfermedad renal sobre la composición corporal constituye por si mismo un factor de morbimortalidad en esta población, por lo que la evaluación nutricia constituye una estrategia temprana orientada a mejorar su calidad de vida y pronóstico.**

Objetivo: **Evaluar la composición corporal mediante tres métodos en una población adulta con diagnóstico de insuficiencia renal crónica en hemodiálisis.**

Metodología: **Estudio transversal, prospectivo y descriptivo en el que se evaluó la composición corporal por medición de panículos adiposos (MPA), impedancia bioeléctrica (IBE) y absorciometría de energía dual de rayos X (DEXA). Se calculó la masa grasa (MG) y la masa libre de grasa (MLG).**

Resultados: **Se incluyeron 20 pacientes (12 mujeres y 8 hombres), con edad promedio de 51,9 ± 19,3 años, peso de 59,5 ± 10,5 kg. e índice de masa corporal de 24,9 ± 3,1 Kg/m². Los valores promedio de MLG por cada uno de los métodos fueron de 42,4 ± 8,6 kg (MPA), 43,6 ± 8,9 kg (DEXA) y 42,8 ± 10,2 kg (IBE). Los valores de MG promedio fueron de 17,2 ± 6,2 kg (MPA), 15,9 ± 6,9 kg (DEXA) y 16,9 ± 6,9 kg (IBE). Existió correlación en los resultados derivados de los tres métodos utilizados. Los coeficientes de correlación fueron en MLG 0,982 (MPA *vs* IBE), 0,963 (MPA *vs* DEXA) y 0,947 (IBE *vs* DEXA). Y para MG, 0,975 (MPA *vs* IBE), 0,925 (MPA *vs* DEXA) y 0,898 (IBE *vs* DEXA).**

Conclusión: **Se evidenció un incremento en la cantidad de MG en la población estudiada. La cantidad de MLG se encontró dentro de los rangos de referencia. No existió evidencia de desnutrición proteica. La MPA y el IBE permiten evaluar de manera confiable la composición corporal en pacientes mexicanos con enfermedad renal crónica sometidos a hemodiálisis, los resultados obtenidos son equiparables a los observados con el DEXA.**

(*Nutr Hosp*. 2010;25:245-249)

DOI:10.3305/nh.2010.25.2.4282

Palabras clave: *Enfermedad renal crónica. Hemodiálisis. Composición corporal. Evaluación nutricia. Desnutrición. Impedancia bioeléctrica. Antropometría. Densitometría.*

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Recibido: 31-III-2009.
Aceptado: 27-IV-2009.

BODY COMPOSITION IN CHRONIC KIDNEY DISEASE PATIENTS AND HAEMODIALYSIS

Abstract

Background: **Nutritional alterations are highly prevalent among patients with chronic kidney diseases stage 5 who receive haemodialysis therapy. Body composition alterations are directly related to an increased morbidity and mortality. Nutritional assessment represents a cardinal intervention oriented to improve the outcome and survival in chronic renal patients.**

Objective: **To evaluate body composition in a mexican population with chronic kidney disease stage 5 and haemodialysis therapy.**

Methods: **Prospective, descriptive and transversal study. Free fatty mass (FFM) and fatty mass (FM) were evaluated by means of bioelectric impedance (BIE), anthropometrics measures (MPA) and dual-energy x-ray absorptiometry (DEXA).**

Results: **20 patients were evaluated (12 females and 8 males). Mean age was 51.9 ± 19.3 years. Mean weight was 59.5 ± 10.5 kg and mean body mass index was 24.9 ± 3.1 kg/m². Mean FFM values were 42.4 ± 8.6 kg (MPA), 43.6 ± 8.9 kg (DEXA) y 42.8 ± 10.2 kg (IBE). Mean FM values: 17.2 ± 6.2 kg (MPA), 15.9 ± 6.9 kg (DEXA) and 16.9 ± 6.9 kg (IBE). Correlation coefficients between the three methods were: FFM, 0.982 (MPA *vs* IBE), 0.963 (MPA *vs* DEXA) y 0.947 (IBE *vs* DEXA). Fatty mass: 0.975 (MPA *vs* IBE), 0.925 (MPA *vs* DEXA) y 0.898 (IBE *vs* DEXA).**

Conclusion: **In the studied population, fatty mass was increased and FFM was within the reference ranges. There was not evidence of protein malnutrition. MPA and BIE are practical and useful tools to evaluate body composition in mexican chronic kidney disease patients who receive haemodialysis therapy. The results obtained by means of MPA and BIE correlated with results obtained by DEXA.**

(*Nutr Hosp*. 2010;25:245-249)

DOI:10.3305/nh.2010.25.2.4282

Key words: *Chronic kidney disease. Haemodialysis. Malnutrition. Body composition. Nutritional assessment. Bioelectric impedance. Anthropometrics. Dual-energy x-ray absorptiometry.*

Antecedentes

A lo largo de las últimas décadas se ha observado un incremento en la incidencia y prevalencia de enfermedad renal crónica, destacando particularmente un aumento significativo del número de pacientes con enfermedad renal crónica que requieren terapia sustitutiva[1,2,3].

Por lo anterior, se ha incrementado el costo y el número de recursos requeridos para la atención de la población de enfermos renales[4], en los cuales a pesar de la creciente calidad en la atención médica, la morbilidad y mortalidad continúan siendo elevadas[5,6] estas últimas de manera notable por causas relacionadas a enfermedades cardiovasculares[6] y cuyos factores condicionantes se derivan ya sea de la entidad primaria que condicionó la falla renal o bien de las complicaciones y morbilidades que derivan de la disfunción renal[1].

Dentro de los factores condicionantes de morbimortalidad en pacientes nefrópatas se destacan la presencia de diabetes mellitus, hipertensión, displipidemia, estados inflamatorios crónicos, desnutrición proteico-calórica, disfunción inmune, depleción de masa magra, deficiencia de micronutrimentos y balance nitrogenado negativo, entre otros[1,7,8-22]. La presencia de diabetes mellitus tipo 2 como patología condicionante de falla renal conlleva casi como regla general, la presencia de sobrepeso u obesidad y por ende el consecuente incremento en la cantidad de tejido adiposo y las consecuencias bioquímicas que de este derivan como lo son resistencia a la insulina, disfunción endotelial, efectos aterogénicos y protrombóticos, todas estas condicionantes morbilidad cardiovascular[22].

Otros de los factores que se han descrito como causa significativa de morbimortalidad en esta población es la presencia de desnutrición, cuya prevalencia varía entre el 20 y 50% de los pacientes con enfermedad renal crónica y que se acentúa particularmente una vez que estos requieren del inicio de terapia sustitutiva; su etiología es multifactorial y su presencia por si misma, se constituye como predictor independiente de muerte[11,23].

Por lo anterior, se considera que la evaluación y monitoreo del estado nutricio constituye una estrategia para lograr una disminución de los índices de morbimortalidad[12,20].

Dentro de las herramientas para la evaluación nutricia resultan particularmente útiles aquellas que permiten medir la composición corporal mediante técnicas como lo son la antropometría, la impedancia bioeléctrica (IBE) y la absorción dual de energía de rayos X (DEXA). Diversos autores han señalado la utilidad de BIE y DEXA en pacientes nefrópatas en terapia sustitutiva e incluso se ha propuesto su aplicación rutinaria en la evaluación nutricional de este tipo de población[8-16,21,24-31].

Existen pocos informes en México que describan el empleo de BIE y DEXA en la evaluación nutricional de pacientes con insuficiencia renal[31], por tal motivo, se diseñó el presente estudio con la finalidad de determinar y comparar mediante los métodos de antropometría, BIE y DEXA, la composición corporal de pacientes adultos con enfermedad renal crónica en fase sustitutiva y sometidos a hemodiálisis.

Material y métodos

Tipo de estudio: observacional, prospectivo, transversal y comparativo.

Población: Se incluyeron los pacientes con enfermedad renal crónica estadio 5 de la clasificación NFK-KDOQI[9] sometidos a terapia sustitutiva con hemodiálisis (HD) atendidos durante el periodo de 6 meses en el Servicio de Nefrología del Hospital Central Dr. Ignacio Morones Prieto, San Luís Potosí SLP México y en quienes fue posible alcanzar su peso seco. Se excluyeron los pacientes con contraindicaciones para la realización de BIE, DEXA o aquellos con amputación de algún miembro.

Todos los pacientes firmaron hoja de consentimiento informado y el proyecto fue aprobado por el Comité de Ética de la Institución.

Procedimientos: Previa al inicio del estudio se llevó a cabo la estandarización, capacitación y realización de pruebas piloto por parte de los investigadores para cada uno de los métodos empleados[32-36].

Antropometría: mediante un plicómetro de tipo Lange, se obtuvieron las mediciones de los panículos adiposos mediante medición por triplicado de pliegues subcutáneos tricipital, bicipital, subescapular y suprailiaco; con los datos obtenidos se calculó la cantidad de masa grasa (MG) y masa libre de grasa (MLG) a través de las ecuaciones de Durnin y Womersley[37] y Siri[38].

BIE: se empleó la técnica estándar de una sola frecuencia (50 kHz) y con una resolución de 0,1 hms. Se empleó un impedanciometro Quantum X (RJL Systems, Clinton Township, MI, USA) para la obtención de la la resistencia (R) y la reactancia (Xc), y se utilizó la fórmula de Lukaski[35], para la estimación de la cantidad de MLG, y por diferencia la cantidad de MG.

DEXA: conforme la técnica descrita[39] se realizó la medición de absorciometría de energía dual de rayos X, de cuerpo entero a través de un densitómetro modelo QDR-DELPHI-W (Hologic Inc, Bedford, MA, USA)[39].

Todas las mediciones se realizaron treinta minutos después del tratamiento hemodialítico, y con al menos cuatro horas de ayuno total[8-16,26,27].

Los resultados de las mediciones de los pacientes fueron registrados en una hoja de captura de datos. Los valores de MG y MLG se expresan en medias ± DS. Los coeficientes de correlación entre BIE, DEXA y MPA se obtuvieron mediante el análisis de varianza (ANOVA) por bloques, utilizando el paquete estadístico JMP IN (SAS, Cary NC, USA) versión 4.0.2.

Resultados

Se incluyeron un total de 20 pacientes, cuyas características se muestran en la tabla I.

Los resultados en cuanto a composición corporal expresados en medias en kilogramos de MLG y MG se muestran en la tabla II, no existieron diferencias significativas entre estas según el método de medición empleado.

Tabla I
Características de la muestra

	*n = 20** *Media ± DS*	*Intervalos de confianza*
Edad (años)	51,9 ± 19,3	43,5-60,4
Talla (cm)	154,1 ± 9,9	150-158
Peso seco (kg)	59,5 ± 10,5	54,9-64,2
IMC (kg/m^2)	24,9 ± 3,1	23,6-26,3
MLG (kg)	42,9 ± 3,1	47,0-38,8
(%)	72,2 ± 9,5	76,4-68,1
MG (kg)	16,7 ± 6,8	13,7-19,7
(%)	27,9 ± 9,4	23,8-32,0

*12 mujeres y 8 hombres.

Los coeficientes de correlación entre los tres métodos de medición de MLG y MG se muestran en la tabla III.

Cuando se analizó la composición corporal por sexo existieron diferencias significativas en el porcentaje de MLG (varones 78,8 ± 5,4% *vs* 67.8 ± 9,0% en mujeres, $p < 0,05$) así como en el porcentaje de MG (varones 21,4 ± 5.5 *vs* 32,2 ± 9,0 en mujeres, $p < 0,05$).

No existieron diferencias significativas según el sexo en los coeficientes de correlación conforme los métodos empleados para las mediciones de MG y MLG.

Discusión

La presencia de enfermedad renal terminal en sus diferentes estadios constituye una entidad clínica y bioquímica compleja, con un amplio espectro de alteraciones funcionales y metabólicas a nivel de diversos órganos y sistemas[40]. Su impacto como factor de morbimortalidad en la sociedad moderna ha llevado a los sistemas de salud de diversos países a considerar a la enfermedad renal crónica como un verdadero problema de salud pública[41]. El incremento inexorable en la demanda de servicios médicos y sociales de los pacientes con afección renal ha seguido una curva creciente en los últimos años, siguiendo en forma casi paralela al incremento en la prevalencia de patologías crónico degenerativas como son la diabetes mellitus, hipertensión arterial, dislipidemias y obesidad, y dentro de las cuales, la diabetes mellitus representa el factor causal numero uno como condicionante de enfermedad renal crónica[42].

Tabla II

	Mlg en kg Media ± DS (IC)	*Mg en kg Media ± DS (IC)*
Método		
MPA	42,4 ± 8,6 (38,6-46,1)	17,2 ± 6,2 (14,5-19,9)
DEXA	43,6 ± 8,9 (38,3-47,3)	15,9 ± 6,9 (13,9-19,9)
IBE	42,8 ± 10,2 (39,7-47,5)	16,9 ± 6,9 (12,9-19,0)

MPA: medición de panículos adiposos; DEXA: absortiometría de energía dual por rayos X; IBE: impendacia bioeléctrica; Kg: kilogramos; IC: intervalos de confianza.

Tabla III
Coeficientes de correlación

rMLG	Mapa *vs* IBE 0,982	Mapa *vs* DEXA 0,963	IBE *vs* DEXA 0,947
rMG	Mapa *vs* IBE 0,975	Mapa *vs* DEXA 0,925	IBE *vs* DEXA 0,898

MLG: masa libre de grasa; MG: masa grasa; MPA: medición de panículos adiposos; DEXA: absortiometría de energía dual por rayos X; IBE: impedancia bioeléctrica.

La sobre vida y la calidad de los pacientes con enfermedades condicionantes de daño renal se ve significativamente reducida una vez que desarrollan enfermedad renal crónica[7,43], por lo anterior, es requisito que los servicios de salud implementen estrategias tanto para la prevención de nuevos casos de enfermedad renal crónica así como para elevar la calidad de vida y los estándares de atención medica de los pacientes que ya la presentan. Una de dichas estrategias lo constituye la evaluación y manejo de las alteraciones nutricias que los pacientes con enfermedad renal presentan a lo largo de los diferentes estadios de la enfermedad y que particularmente se agravan una vez que estos requieren terapia sustitutiva[44].

La magnitud del impacto en el estado nutricional en pacientes nefrópatas es variable, informándose que hasta la mitad de estos presentan algún grado de alteración en composición corporal, balance nitrogenado, niveles de micronutrimentos y competencia inmune, todos los cuales en su conjunto se constituyen como factores independientes de morbimortalidad[23,45]. Dado que la etiología de la desnutrición en los pacientes con enfermedad renal es multifactorial se requiere un abordaje sistematizado para la evaluación del estado nutricional de esta población[46].

Existen diversos métodos que permiten la valoración nutricia en pacientes nefrópatas[30], dentro de los cuales se incluyen la historia dietaria, los parámetros bioquímicos, parámetros antropométricos y los métodos que permiten la estimación de la composición corporal en sus compartimientos de MG y MLG. La sensibilidad y especificidad de cada uno de estos métodos varía y dado que muchos de estos indicadores se modifican por causas no nutricias se prefieren aquellos que permiten establecer una cuantificación más precisa de la composición corporal como son la antropometría, IBE y DEXA. Dentro de estos, se ha establecido a DEXA como uno de los métodos de referencia[9-11,30]. Estos métodos se basan en el empleo de ecuaciones derivadas de estudios llevados a cabo en grupos de población particulares y que posteriormente se han validado y utilizado de manera generalizada en diversas poblaciones[15,30,47]. Sus resultados son confiables y permiten establecer posibles marcadores tempranos del inicio las alteraciones nutricias en esta población, y que a su vez, se constituyen como indicadores de factores de riesgo susceptibles de ser potencialmente modificables[5,8-10-12,15,16,25,27-31,48].

En el presente estudio cuando se evaluó a pacientes con enfermedad renal crónica sometidos a HD mediante los métodos de panículos adiposos, BIA y DEXA y en cuyos resultados, al igual que lo descrito en

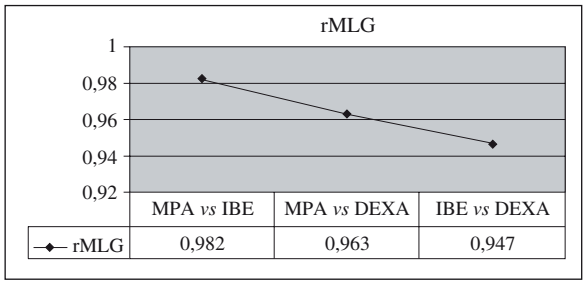

Fig. 1.

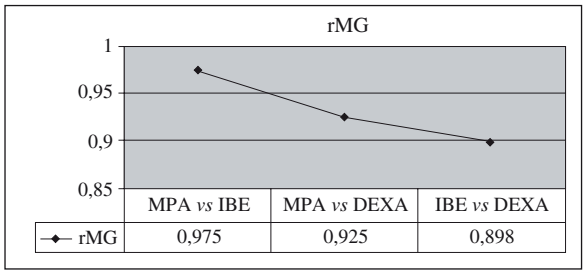

Fig. 2.

la literatura[8-10,16,26], encontramos concordancia en los parámetros de composición corporal entre los tres métodos, sin existir diferencias significativas en cuanto al valor absoluto de MG y MLG expresada en kilogramos o bien en su valor relativo expresada en porcentaje. Lo anterior nos permite establecer su aplicabilidad en nuestra población como mediciones confiables, señalando a su vez que el método de pliegues adiposos resulta útil cuando no se dispone de BIE o DEXA[8,9,11,16].

Respecto a los resultados en la cantidad de MG y MLG estos se encontraron dentro de los marcos de referencia, destacando que las mujeres presentaron una mayor cantidad de MG en relación a los varones; no existió en la población estudiada depleción de MG indicativa de desnutrición proteica. La composición corporal de pacientes nefrópatas sometidos a HD varia entre los diversos informes, ya que mientras unos establecen que esta población se encuentra repletada de masa grasa y masa libre de grasa indicativos de desnutrición[8,11,12,24,16-18,26-29,31], un estudio realizado en población hispana describió que existe un incremento en la cantidad de MG compatible con sobrepeso/obesidad, particularmente en pacientes que también cursaban con diabetes mellitus[25].

Se destaca el hallazgo de que la población estudiada a pesar de encontrarse en rangos de índice de masa corporal dentro de la normalidad, existió una tendencia en que la cantidad de MG se encontró en los límites superiores de normalidad de los valores de referencia[31], lo cual sin considerarse aun sobrepeso u obesidad, potencialmente podría exponer a estos pacientes a un mayor riesgo de enfermedades cardiovasculares derivadas de los efectos mediados por la participación de citocinas y un ambiente metabólico proinflamatorio y aterotrombotico[22,43]. La cantidad de MLG se encontró en rangos de normalidad, lo cual se ha propuesto como un factor que confiere efecto protector en términos de sobrevida, —incluso en aquellos pacientes que a la par presentan incremento en la cantidad de masa grasa—, ya que la preservación de MLG traducida en una mayor cantidad de tejido muscular implica un mejor estado funcional, mayor competencia inmune, mayor independencia y menor morbilidad derivada de desnutrición[49].

Aun y cuando el tamaño de la muestra no permite establecer la comparación entre los tres métodos cuando se aplican a una población del mismo sexo, en este estudio tanto BIE, DEXA y el método de panículos adiposos mantuvieron su coeficiente de correlación para cada uno de los géneros.

La correlación de resultados obtenidos en este estudio mediante BIE permite establecer su utilidad en pacientes sometidos a HD y que han alcanzado su peso seco. No obstante lo anterior, se ha propuesto incluso la posibilidad de emplear BIE multifrecuencia para evaluar cambios tempranos en el estado de hidratación de los pacientes que reciben terapia sustitutiva con HD y de ahí contar con predictores tempranos que permitan optimizar su manejo dialítico[16,26,30,48,50].

En conclusión, de acuerdo a los resultados obtenidos, no se encontraron diferencias en la composición corporal de pacientes nefrópatas sometidos a HD cuando se emplearon MPA e BIE comparados con un estándar de oro como es DEXA, por lo que proponemos que estos métodos pueden ser utilizados en el monitoreo del estado nutricio del paciente en HD, ya que, además de brindar datos confiables resultan métodos más económicos y técnicamente accesibles. Es importante establecer estrategias de valoración y manejo nutricio en pacientes con enfermedad renal crónica a lo largo de sus estadios evolutivos con el fin de disminuir el impacto que deriva de las alteraciones en la composición corporal frecuentemente encontradas en esta población y que se constituyen como factores que contribuyen sustancialmente a la morbimortalidad.

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):250-255
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Exposure to flaxseed during lactation does not alter prostate area or epithelium height but changes lipid profile in rats

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Abstract

Flaxseed intake has increased owing to beneficial effects to health and prevention of diseases. Provided that it's an important source of lignan, a phytoestrogen, the present study aimed at evaluating the possible effect of the intake of this seed during lactation upon prostate, sexual hormones and lipidic profile of the offspring in adult life.

Material and methods: **16 female Wistar rats were used. After delivery, they were divided into two different groups to receive one of the following diets during lactation: Control group (CG), with a casein based diet and Flaxseed group (FG), with a flaxseed based diet containing 25% flaxseed. At weaning, male pups received commercial chow until adult life (170 days old), when they were sacrificed.**

Results: **No differences were perceived concerning offspring food intake and body weight at 170 days. There was a reduction in total cholesterol levels (FG = 45.71 ± 8.96 mg/dL; CG = 63.43 ± 15.69 mg/dL, $p = 0.02$) and triglycerides (FG = 54.29 ± 11.10 mg/dL; CG = 79.86 ± 25.68 mg/dL, $p = 0.03$). Also, no alterations were observed in prostatic morphology, testosterone or estradiol levels in the two groups analyzed.**

Conclusion: **Flaxseed intake during lactation did not produce histological alterations in prostatic alveolus or in sexual hormones, but programmed to a reduction in lipid profile in adult life with decreased cardiovascular risk.**

(*Nutr Hosp*. 2010;25:250-255)

DOI:10.3305/nh.2010.25.2.4289

Key words: *Flaxseed. Lactation. Prostate. Lipid profile. Rats.*

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Recibido: 6-IV-2009.
Aceptado: 27-IV-2009.

EXPOSICIÓN A LA LINAZA DURANTE LA LACTACIÓN NO CAMBIA EL ÁREA O ALTURA EPITELIAL DE LA PRÓSTATA PERO CAMBIA EL PERFIL LIPÍDICO EN RATONES

Resumen

El consumo de la linaza ha aumentado debido a los efectos beneficiosos para la salud y la prevención de enfermedades. Siendo una importante fuente de lignanos, un fitoestrógeno, el presente estudio evaluó los efectos de la administración de esta semilla durante la lactación en la próstata, las hormonas sexuales y perfil lipídico de los hijos en la vida adulta.

Material y métodos: **Fueron utilizados 16 ratones Wistar hembras. Después del parto fueron divididas en dos grupos recibiendo durante la lactación las siguientes dietas: Grupo Control (GC), con ración a base de caseína y Grupo Linaza (GL), con ración a base de caseína conteniendo 25% de semilla de linaza. En el destete, las crías machos pasaron a recibir ración comercial hasta la edad adulta, cuando fueron muertos a los 170 días de vida.**

Resultados: **No fueron verificadas diferencias sobre el consumo alimentario y peso corporal de los animales a los 170 días. Hubo una reducción en los niveles de colesterol total (GL = 45,71 ± 8,96 mg/dL; GC = 63,43 ± 15,69 mg/dL, p = 0,02) y triglicéridos (GL = 54,29 ± 11,10 mg/dL; GC = 79,86 ± 25,68 mg/dL, p = 0,03). Además, no se observaron alteraciones en la morfología de la próstata, la testosterona o los niveles de estradiol en los dos grupos analizados.**

Conclusión: **La administración de la semilla durante la lactación no promueve alteraciones histológicas en los alvéolos de próstata o en las hormonas sexuales, pero programado para una reducción en el perfil lipídico en la vida adulta con una disminución del riesgo cardiovascular.**

(*Nutr Hosp*. 2010;25:250-255)

DOI:10.3305/nh.2010.25.2.4289

Palabras clave: *Linaza. Lactación. Próstata. Perfil lipídico. Ratones.*

Flaxseed *(Linum usitatissimum)* has emerged as a healthy food owing to its beneficial effects and property of acting in the prevention of some diseases.[1] Countless benefits have been associated with the use of flaxseed and its flour, such as: cardiovascular protection through the improvement in lipid profile,[2] reduction in the risk of cancer[3] and prostatic health enhancement.[4]

This seed is made up of 41% lipids (50-55% as alpha linolenic acid, and 15-18% as alpha-linoleic acid), 28% fibers, 21% protein, 4% minerals and 6% carbohydrates distributed among phenolic acids, sugars, lignan and hemicelluloses.[5,6]

Flaxseed is a rich source of dietary lignans, presenting 100 times more of this compound than any other food.[7] The lignans are thought to exert protective effects by interfering with endogenous sex hormone metabolism.[8] The secoisolariciresinol diglycoside (SDG) is the lignan found in flaxseed, precursor of the major mammalian lignans, enterodiol (ED) and enterolactone (EL), which are produced in the presence of bacteria that are naturally present in the colon.[7] ED and EL have chemical structures that are similar to 17-β-estradiol and can bind to estrogen receptors (ER), nevertheless with less affinity than endogenous estrogen.[9]

Flaxseed can exert influence upon prostate growth because this seed acts as a weak estrogen. Prostate growth is a hormone-mediated phenomenon regulated by both androgens and estrogens. Prostate is highly dependent on androgens to grow. Moreover, estrogens can also control normal gland function and may serve to control pathological growth. It has been described that the metabolites from SDG, ED and EL can inhibit the enzyme 5α-reductase, which converts testosterone in dihydrotestosterone, the most potent androgen.[10] Within the prostate, estrogen receptor beta (ERβ) has been shown to be a key component in the regulation of hormone-dependent morphological alterations.[11]

In rats, critical sexual differentiation occurs from gestation day 18 until postnatal day 10,[12] being the initial period of lactation critical to prostate development. The components in flaxseed with potential hormone-like effects can be transferred to nursing offspring via mother's milk,[13] with the risk of provoking some long term effect in many organs systems. This fact can be explained by the term "programming", which can be defined as the process by which a determined factor acts in the beginning of life, during a sensitive or critical period, and promotes long lasting effects in adult health.[14] Extensive human epidemiologic data has indicated that prenatal and early postnatal nutrition influence adult susceptibility to diet related chronic diseases.[15] For these reasons it is important to determine whether maternal consumption of diets rich in flaxseed is safe for infants that suckle breast milk.[13]

Even though many publications focus the use of flaxseed during gestation and lactation, which are critical periods for reproductive system development, few works in the literature describe the use during the lactation exclusively.[13] Furthermore, in other studies, the results are controversial, varying according to the dose used, time of exposition and phase of life.[16,17] Tou et al. (1998) gave 10% flaxseed to rats during gestation and lactation and verified bigger relative prostate weight in the offspring, which increases the risk of cancer.[18] In other study, in rats that consumed 20% flaxseed during gestation and lactation and their offspring were maintained with the same diet for 70 days, a reduction in the prostate weight was found.[17]

The objective of this study was to evaluate if maternal consumption of flaxseed during lactation programs alterations in prostatic morphology, in sexual hormones and lipidic profile of adult male Wistar rats.

Material and methods

Experimental design

Sixteen female wistar rats, with 90 days old and nullipary from the colony kept at the Laboratory of Experimental Nutrition (LabNe) matched in a proportion of 3 females to 1 male receiving commercial chow (Nuvilab®, Nuvital Ltda, Paraná, Brazil). After delivery, mothers were randomly divided in two groups, having access during all lactation period to one of the following diets: Control group (CG), chow made up of casein and flaxseed group (FG), chow with casein and 25% flaxseed. At weaning, 8 male pups from each group (being used only one animal per mother) were weaned onto a commercial chow and this was maintained until 170 days of age, when they were sacrificed. Body weight (BW) and food consumption were recorded three times during the week. All animals were kept under controlled temperature (21-23°C) and dark/light cycle (12/12 h), receiving chow *ad libitum*.

This research project was approved by the Ethics committee in research from Federal Fluminense University (UFF). All procedures were carried out in accordance with the norms from Brazilian College of Animal Experimentation (COBEA).

Experimental diets

The seed was ground in the blender to obtain the flour. The experimental chow prepared at LabNE had the same amount of energy, containing 17% protein and the mix of vitamins and minerals following the recommendations of the *American Institute of Nutrition*-93(AIN-G).[19] The chow that was given to FG had a concentration of 25% of flaxseed, aiming at reach all the recommendation of fibers (AIN-93G). The ingredients of the experimental chows (table I) were weighted and homogenized in industrial blender (Hobart®, São Paulo, SP, Brazil), with heating water to amid gelatinization. The obtained mass was transformed in pellets and dried in ventilated oven (Fabbe-Primar®, São

Table I
Composition of 100 g of chow used in the experiment during lactation phase (17% protein: AIN-G)

Ingredient	*Control (g)*	*Flaxseed (g)*
	g/100g diet	
Casein[1]	20	14.11
Flaxseed[2]	0	25
Cornstarch[3]	52.95	45.84
Sucrose[4]	10	10
Mineral mix AIN 93G[1]	3.50	3.50
Vitamin mix AIN 93G[1]	1	1
Soybean oil[5]	7	0
Cellulose[6]	5	0
Choline bitartrate[1]	0.25	0.25
L-Cystine[1]	0.30	0.30
Tert-Butylhydroquinone[7]	0.0014	0.0014
Total	100	100

The ingredients used in the diets were manufactered by: [1]M. Cassab Comércio e Indústria Ltda (São Paulo, SP, Brazil). [2]Arma Zen Produtos Naturais Ltda (Río de Janeiro, RJ, Brazil). [3]Maisena, Unilever *Bestfoods* Brasil Ltda (Mogi Guaçu, SP, Brazil). [4]União (Rio de Janeiro, RJ, Brazil). [5]Liza, Cargill Agricultura Ltda (Mairinque, SP, Brazil). [6]Microcel, Blanver Ltda (Cotia, SP, Brazil). [7]Vogler Ingredients (Eastman/EUA).

Paulo, SP, Brazil) under 60°C for 24 h, and after identification, kept at refrigeration until being used.

The commercial chow was made up of 23% protein source, 67,7% amid, 4% mineral mix, 0,4%vitamin mix and 5% soy oil.

Biochemical analysis

The animals were anesthetized with intraperitoneal injection of 5% (0,15 ml/100g p.c., i.p.) Thiopental sodic 1G (Cristália pharmaceutical chemical products LTDA, Brazil) in order to collect blood through cardiac punction. The blood samples were centrifuged at 3500 rpm during 15 minutes to obtain serum, which was stored at -20°C. Cholesterol and triglycerides analysis were measured by the colorimetric method with commercial kits (BIOCLIN, Química Básica Ltda/ Belo Horizonte-MG) and the determination of estradiol and testosterone were made through quimioluminescency (Immulite 2000/PPC/H2967, Siemens, Los Angeles, USA), using a specific commercial kit to each hormone (Siemens Medical Solutions Diagnostics, Los Angeles, USA).

Prostate histomorphometric analysis

Prostate was immediately fixated in buffered formalin (10%) per 24 hours. Afterwards, the left lateral lobule was excised and processed following the pattern

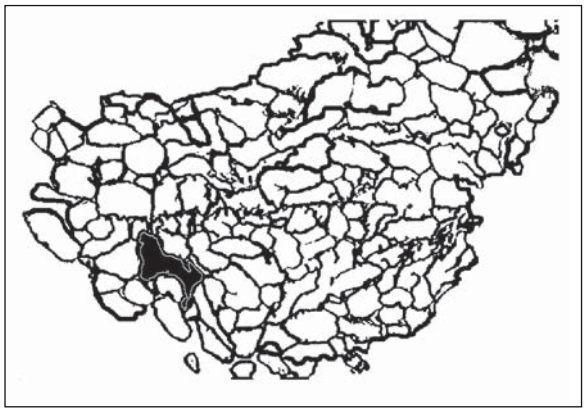

Fig. 1.—Image of binarized area to observe alveolar area.

technique to inclusion in paraffin. Five micrometers thick sections were stained with hematoxylin-eosin.[20] In order to estimate alveolar areas, the images were captured by a stereoscopic microscopy. This procedure made it possible to capture almost the entire area of the section, facilitating the morphometric determinations. The images were binarized (fig. 1) so as to identify the alveolar area in white. Then, 50 alveolos of each prostate (fig. 2) were observed, being the cells measured at four different points in each alveolo. All images were digitalized to produce tiff files. And were analyzed with the software *ImageJ* (National Institutes of Health, USA), by which data from average alveolar area, total area and epithelial height were obtained.

Statistical analysis

Data is presented as average and standard deviation. The normal distribution of the values found was tested through *Shapiro-Wilk test*. Once the normality of data was verified, it was submitted to comparison between groups using Student T test to independent data. In the results that did not follow normal distribution, nonparametric *Mann-Whitney* test was chosen. The established significance level was $p \leq 0.05$. All these analysis were made by *SPSS for Windows 10.0*.

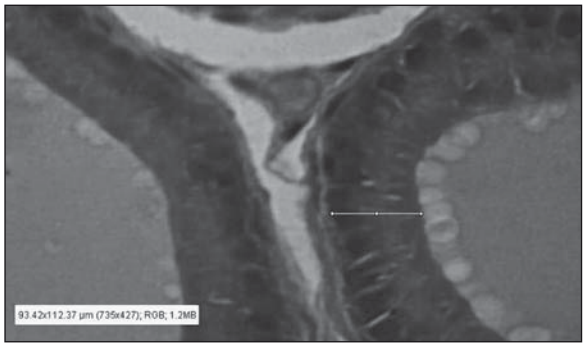

Fig. 2.—Image of prostatic epithelium where cells were measured in four different points per alveolo.

Table II
Mother's intake, offspring's weight at weaning, food intake, body weight (BW) at 170 days of age of rats whose mothers received a diet with 25% flaxseed during lactation

Ingredient	*Control*	*Flaxseed*
Mothers' Food intake (g)	678.40 ± 75.95	642.81 ± 47.60
Offspring's BW at weaning (g)	47.31 ± 4.72	42.69 ± 3.06*
Offspring's food intake (g)	3096.21 ± 281.09	3084.59 ± 243.04
Offspring's BW at 170 days of age (g)	408.07 ± 23.17	379.33 ± 38.04

Results are shown as average and standard deviation. * = indicates statistical difference.

Results

The analysis of mothers' food intake during lactation revealed that there was not difference between the groups. At weaning, it was observed reduction in offspring's body weight ($p = 0.04$). At 170 days, there were no differences concerning body weight and food intake (table II). However, it's important to highlight that there was a decrease in total cholesterol and triglycerides levels in FG ($p = 0.03$). The estradiol and testosterone concentrations were similar (table III). As for prostatic morphology, there was no difference in average alveolar area (mm^2), in total area (mm^2) and in epithelial height between the groups analyzed (table IV).

Discussion

The intake of phytoestrogens rich foods has increased since its protective effects have been extensively linked to prostatic and breast cancer prevention. A study carried out by Tarpila et al in 2002 recommended the use of 20% of flaxseed in relation to the diary energy intake so as to evaluate the benefits from this seed,[21] reinforcing the increasing use by the population. This fact has raised questions in relation to possible effects of these components in male reproductive health.[17] According to the literature, caution should be taken concerning the consumption of flaxseed during

Table III
Biochemical analysis of animals at 170 days old whose mothers received a diet with 25% flaxseed during lactation

Ingredient	*Control*	*Flaxseed*
Cholesterol (mg/dL)	63.43 ± 15.69	45.71 ± 8.96*
Tryglicerides (mg/dL)	79.86 ± 25.68	54.29 ± 11.10*
17 β-estradiol (pg/mL)	34.00 ± 7.46	28.33 ± 2.66
Testosterone (ng/dL)	150.67 ± 18.79	154.33 ± 16.69

Results are shown as average and standard deviation. * = indicates statistical difference.

Table IV
Prostate histomorphometric analysis of animals at 170 days old animals

Ingredient	*Control*	*Flaxseed*
Average alveolar area (mm^2)	0.06 ± 0.02	0.05 ± 0.01
Total area (mm^2)	16.50 ± 5.53	16.93 ± 3.41
Epithelial height (μm)	14.43 ± 4.35	14.34 ± 3.82

Results are shown as average and standard deviation. * = indicates statistical difference.

critical periods such as lactation due to the fact that this contains substances that may interfere with male reproductive system development. Hence, this seed can exert protective or adverse effects, depending on the dose, time of exposure and phase of life.[16] The adverse effects can occur by the direct contact with the lignan that is transferred by the mother, yielding changes in the development that can result in endocrine function alterations in the offspring. Some of these changes are not completely expressed until the offspring reach adult life.[22]

Maternal exposure to a diet containing 25% flaxseed yielded reduction in offspring's body weight at weaning. This observation agrees with the one from Collins et al. (2003) after giving flaxseed or fat free flaxseed diet with different concentrations of the seed, this author verified lower body mass in offspring at weaning when compared to control group.[23] The low body mass at weaning can be explained by Rickard et al. (2000), who administered 5% flaxseed or 1.5mg/day of SDG and found reduction in plasmatic concentrations of insulin-like growth factor (IGF-I),[24] which acts as a hormonal mediator of growth (GH), visto que the actions of GH in the promotion of body weight gain are mediated by IGF-I.[25]

Tou et al. (1999) showed that the administration of 10% flaxseed in the diet resulted in increased levels of serum estradiol and testosterone in male offspring.[16] Conversely, our results did not show differences concerning hormonal concentrations in adult animals. These authors demonstrated that this concentration of flaxseed during gestation and lactation periods resulted in reduced postnatal ponderal gain, smaller anogenital distance, and prostatic morphological alterations with increase in its relative weight as well as increase in seminal tubules and testicles, which suggest estrogenic effects.[16,18] On the other hand, 5% flaxseed provoked antiestrogenic effects, with reduction in the relative weight of the prostate.[16]

In the present work was verified that the average alveolar area and prostatic total area were similar between CG and FG, implying that maternal exposure to flaxseed does not alter the gland at 170 days of age. This fact can be explained by the unchanged concentrations of estradiol and testosterone after the use of the seed. These results agree with the ones from Ward et al.

(2001) in which 10% flaxseed during lactation exclusively did not promote alterations in prostatic morphology in the 132 days old offspring[13]. A study carried out in healthy young men revealed that the intake of 13,5g of flaxseed flour during 6 weeks did not modify plasmatic testosterone levels.[26]

Among beneficial effects linked to flaxseed intake, the reduction in cardiovascular risk is well know in women.[27] However, recent studies describe this protective role also in men and male animals.[28,29] Not only have beneficial effects been associated with the intake of the seed, but also with the use of oil, SDG or protein.

The use of 20 g of flaxseed in hyperlipidemic patients for 60 days showed modification in the risk factors for cardiovascular disease, with significant decrease in total cholesterol, LDL and triglycerides.[30] Riediger et al. (2008) offered flaxseed oil together with a diet rich in saturated fatty acids to male mice and verified reduction in plasmatic cholesterol and triglycerides, which can be accounted for the smaller n6: n3 ratio.[31] Prasad, in 2008, showed that 20 mg/kg BW/day of SDG in rabbits associated with a cholesterol rich diet did not decrease serum lipid levels but prevented atherosclerosis progression through a reduction in oxidative stress.[32]

Flaxseed protein intake reduced plasmatic cholesterol as well as triglycerides in rats with normal lipid profile.[33] Our results ensure this finding as FG showed reduced cholesterol and triglycerides levels, suggesting that flaxseed programs for cardiovascular protection in adult male. However, this programming mechanism remains to be elucidated and further studies are utterly necessary.

Conclusion

According to the results found, the consumption of 25% flaxseed in the maternal diet during lactation does not yield histological alterations in prostatic alveolus or sexual hormones. However, it may directly interfere with metabolic programming for reduction in plasmatic lipids with decrease in cardiovascular risk in adult life.

Acknowlegements

The authors would like to thank the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for financial support.

We would like to thank the biomedicine's student Vivian Alves Pereira for the helping with the prostate analisys.

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):256-260
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Postprandial lipaemia and endothelial adhesion molecules in pre- and postmenopausal Spanish women

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Abstract

Background: **Postprandial hyperlipaemia is an independent risk factor for atherosclerosis.**

Objectives: **To compare postprandial lipaemia and fasting adhesion molecules levels in healthy young premenopausal (PrW) and postmenopausal (PoW) Spanish women.**

Subjects and methods: **Twenty healthy PrW and 18 healthy PoW participated in a postprandial 7-hour intervention study. All participants were given a fat-rich standard meal (11.8% saturated, 39.7% monounsaturated, and 6.6% polyunsaturated) after a 12 h fast. Blood samples were taken at baseline and at 60, 120, 240, 360 and 420 min after eating. Triacylglycerols (TAG), total cholesterol (Chol), soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular adhesion molecule-1 (sVCAM-1) were determined in fasting serum samples and TAG and total Chol postprandial levels were measured.**

Results: **Anthropometric data, serum lipid and sICAM-1 presented significant higher values in PoW compared to PrW, but sVCAM-1 did not significantly differ between groups. Postprandial TAG and Chol concentrations in PoW were significantly higher than in PrW ($p < 0.0001$). There was a significant time influence ($p < 0.0001$) in TAG in PrW and PoW, while time to peak and peak concentration were significantly higher in PoW than PrW. Chol concentrations showed a significant reduction after 1 h, to reach values similar to baseline after 6 h in PrW but not in PoW.**

Conclusions: **Lipid postprandial response to a fat rich meal and soluble intercellular adhesion molecules concentrations indicate a higher cardiovascular risk pattern in postmenopausal compared to premenopausal women. Soluble vascular adhesion molecule levels seem to be influenced not only by age and menopause, but also other factors like usual diet.**

(*Nutr Hosp*. 2010;25:256-261)

DOI:10.3305/nh.2010.25.2.4460

Key words: *Premenopause. Postmenopause. Postprandial lipaemia. Adhesion molecules.*

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Recibido: 27-VII-2009.
Aceptado: 9-VIII-2009.

LIPEMIA POSTPRANDIAL Y MOLÉCULAS DE ADHESIÓN ENDOTELIAL EN MUJERES ESPAÑOLAS PREMENOPÁUSICAS Y POSTMENOPÁUSICAS

Resumen

Introducción: **La hiperlipemia postprandial es un factor independiente de riesgo de aterosclerosis.**

Objetivos: **Comparar la lipemia postprandial y concentraciones en ayunas de moléculas de adhesión en mujeres sanas, jóvenes premenopáusicas (PrW) y postmenopáusicas (PoW).**

Sujetos y métodos: **20 PrW y 18 PoW participaron en un estudio de intervención postprandial de 7 horas. Tras 12 horas de ayuno, las participantes tomaron una comida estándar rica en grasa (11,8% saturada, 39,7% monoinsaturada y 6,6% poliinsaturada). Se tomaron muestras de sangre basal y a los 60, 120, 240, 360 y 420 min después de comer. En las muestras en ayunas se determinaron triglicéridos (TAG), colesterol total (Chol), moléculas solubles de adhesión intercelular-1 (sICAM-1) y moléculas solubles de adhesión vascular-1 (sVCAM-1). Asimismo se determinaron TAG y Chol postprandiales.**

Resultados: **Los valores antropométricos, lípidos y sICAM-1 presentaron valores significativamente mayores en PoW frente a PrW, pero sVCAM-1 fueron similares en ambos grupos. Las concentraciones postprandiales de TAG y Chol fueron significativamente mayores en PoW que en PrW ($p < 0,0001$). Hubo un efecto significativo del tiempo en los TAG de PoW y PrW ($p < 0,0001$), mientras que el tiempo para alcanzar la concentración máxima y dicha concentración fueron significativamente mayores en PoW que en PrW. Las concentraciones de Chol mostraron una reducción significativa después de 1 h para recuperar valores similares a los basales después de 6 h en PrW pero no en PoW.**

Conclusiones: **La respuesta lipídica postprandial a una comida rica en grasa y las concentraciones de las moléculas solubles de adhesión intercelular mostraron un patrón de mayor riesgo cardiovascular en las mujeres postmenopáusicas frente a las premenopáusicas. Las moléculas solubles de adhesión vascular parecen influenciadas no sólo por la edad y la menopausia, sino por otros factores como la dieta habitual.**

(*Nutr Hosp*. 2010;25:256-261)

DOI:10.3305/nh.2010.25.2.4460

Palabras clave: *Premenopausia. Postmenopausia. Lipemia postprandial. Moléculas de adhesión.*

Introduction

The aging process is associated with several structural and functional metabolic modifications. In turn, these changes may increase the individual's susceptibility to develop conditions such as atherosclerosis, diabetes, obesity, cardiovascular disease and metabolic syndrome.[1]

Due to successive meal intakes, humans spend a large part of the day in a postprandial state. Fat-rich meals result in an increase in triacylglycerolemia and modifications in lipoprotein pattern. The extent and kinetics of such postprandial changes are highly variable and are modulated by numerous factors. Postprandial lipoprotein metabolism is affected by dietary habits, meal composition (amount and type of fat, carbohydrates, proteins, fibre and alcohol), lifestyle practices (physical activity, tobacco use), physiological factors (age, gender, menopausal status) and pathological conditions (obesity, insulin resistance, diabetes mellitus, etc.).[2-4] Abnormalities during the postprandial state contribute to the development of atherosclerosis and cardiovascular risk.[5]

There are very few studies comparing postprandial lipid metabolism before and after menopause.[6-8] Postprandial lipaemia is generally studied with test meals like fat-rich liquids or creams, which do not reflect the texture of common foods and therefore may be digested differently to usual food. We studied postprandial changes in serum triacylglycerol (TAG) and in total cholesterol (Chol) concentrations after a regular fat-rich meal. The fat content was designed to reflect fatty acid composition of the Spanish Mediterranean Diet.[9] The majority of studies have tested the effects of a fat load rich in saturated fatty acids, but the lipid profile exert a marked influence in postprandial lipaemia, and monounsaturated fatty acids induce a lower increase in chylomicron triacylglycerols.[10,11]

Adhesion molecules are markers of endothelial dysfunction and early stages of atherogenesis. Soluble intercellular adhesion molecules (ICAM-1) and vascular adhesion molecules (VCAM-1) are associated with cardiovascular diseases, cancer and autoimmune disorders[12] and have been shown to decrease after dietary treatment.[13]

This study compared endothelial adhesion molecule levels and postprandial lipaemia response to a high monounsaturated meal of healthy postmenopausal (PoW) and young premenopausal (PrW) Spanish women.

Subjects and methods

Study population and study design

Twenty PrW recruited through flyers distributed throughout the university campus and eighteen PoW recruited from the Menopause Program of the Madrid City Council of the Food and Health Department participated in the study. This study was conducted in accordance with the ethical rules of the Helsinki Declaration (Seoul, Korea, October 2008). All women gave written informed consent to a protocol approved by the Ethics Committee of the Spanish Council for Scientific Research and the Ethics Committee of the Hospital Clinica Puerta de Hierro. None of the women suffered from any digestive or metabolic disease, as verified by medical history and fasting blood indexes.

For the group of young women, individuals selected had to be healthy, between 18 and 45 years old, premenopausal, not pregnant, not obese (BMI < 30 kg/m^2), and could not be taking medication known to affect bone and lipid metabolism or be taking vitamin, mineral or phytoestrogen supplements. Women for the postmenopausal group had to be amenorrheic for at least one year, could not be obese (BMI < 30 kg/m^2), could not be receiving oestrogen replacement therapy or any other medication known to affect bone and lipid metabolism or be taking vitamin, mineral or phytoestrogen supplements. None of the women smoked.

Women visited the laboratory facilities after 12 h overnight fast. In order to unify food intake the evening before the study, all women followed written instructions with regard to dinner composition (lettuce and tomato with olive oil, vinegar and salt; grilled chicken filet; bread and fruit). On the morning of the visit blood pressure, weight and height were measured and compliance with dinner instructions was verified with a questionnaire. After baseline venous blood samples were obtained using a cannula (ABOCATH 20G, Abbott Laboratories, Abbott Park, Illinois, USA).

The study meal (Table 1) provided 4552 kJ and contained 75.3 g of fat, 21.5 g of protein, 86.5 g of carbohydrates 2.1 g of fibre and 289 mg of cholesterol. In this meal, proteins, lipids and carbohydrates contributed 7.9%, 62.3%, and 6.6% of total energy, respectively, while 11.8% of the total energy supplied by lipids came from SFA, 39.7% from MUFA and 6.6% derived from PUFA. Postprandial blood samples were taken 60, 120, 240, 360 and 420 min after the end of the study meal. To maintain hydration throughout the postprandial time, women drank 100 ml of demineralised water after 240 min and 390 min after eating. Blood samples were collected in Venoject tubes with Gel + Clot Activator.

Measurements

Blood samples were chilled, then centrifuged for 15 min at 1500 x g and 4ºC, and subsequently stored at -80ºC. Serum Chol and TAG were determined using automated enzymatic methods (CHOD-PAP and GPO-PAP; Boehringer Mannheim, Germany; RA-XT Technicon, Tarrytown, NY). Soluble serum intercellular adhesion molecules-1 (sICAM-1) and soluble vascular adhesion molecules-1 (sVCAM-1) concentrations

were measured by means of a commercially available ELISA kit (Parameter, R&D Systems).

Data analysis

Statistical analyses of the results were performed using SPSS 14 for Windows XP. Data are presented as mean and standard deviation. Baseline parameters of anthropometric data, serum lipid and endothelial adhesion molecules were compared with a one-way ANOVA. TAG data were log normalized for statistical analysis. Postprandial TAG were adjusted by subtracting baseline values. Correlation between baseline and postprandial parameters was studied by the Spearman's rank test. Total area under the curve (TAUC) for TAG concentrations was calculated and a one-factor repeated measures ANOVA was performed. A one-factor repeated-measures ANOVA with a between subject-factor group was carried out for serum Chol and TAG for time and time x group interaction. When group x time interaction was significant, one-way ANOVA was used to compare serum Chol and TAG concentrations between groups at each time point. A one-factor repeated-measures ANOVA (time) was performed to determine differences in Chol and TAG concentrations within each group of women and to study peak concentrations of serum Chol and TAG. A Bonferroni post hoc analysis was performed except for time to peak, which was calculated and analysed using the Mann-Whitney test. P values < 0.05 were considered statistically significant.

Results

All 20 PrW and 18 PoW, completed the study. Subjects of the premenopausal group were between the ages of 18 and 36 and those from the postmenopausal group were between 51 and 59 years of age. Standard meal composition is shown in table I. Anthropometric data, serum lipid and endothelial adhesion molecule values, shown in table II, present significant differences between PrW and PoW in all parameters except for sVCAM.

Table I
Composition of the standard meal consumed by pre and postmenopausal women

Ingredients	*Weight*
Whole cow's milk (g)	150
Instant coffee (decaffeinated) (g)	2
Avocado (g)	80
Crabsticks (g)	44
Mayonnaise (g)	30
Olive oil (g)	33
Egg (g)	51
Sugar (g)	33
Wheat flour, white (g)	33
White bread, toasted (g)	18
Saccharin (g)	1
Low mineral water (ml)	500

The TAUC of TAG concentration was significantly higher in PoW than in PrW ($p < 0.0001$). There was a significant time effect ($p < 0.0001$) and a significant time x group interaction ($p < 0.0001$) for TAG concentrations (fig. 1). A one-factor (time) repeated-measures ANOVA performed to analyse TAG concentrations in each group of women showed that the significant time effect in both groups was maintained. Differences between time points were more pronounced in PoW than in PrW. Baseline TAG concentrations were significantly lower than those of all other time points in PoW ($p = 0.001$ compared to 1 h, $p < 0,0001$ compared to 2 h, 4 h and 6 h, and $p = 0.02$ compared to 7 h), whereas in PrW, baseline concentrations were only significantly lower than those of the first two time points ($p < 0.0001$ compared to 1 h and $p = 0.002$ compared to 2 h) while no significant differences

Table II
*Anthropometric data and total cholesterol and triacylglycerol baseline values of the study participants**

Parameter	*Premenopausal women (n = 20)*	*Postmenopausal women (n = 18)*	*ANOVA p*
Age (y)	20.9 ± 2.24	55.7 ± 2.4	< 0.0001
Body weight (kg)	58.17 ± 7.34	64.2 ± 6.6	0.012
BMI (kg/m^2)	21.58 ± 2.25	26.89 ± 3.04	< 0.001
Total serum cholesterol (mg/dL)	171.60 ± 24.37	211.61 ± 27.45	< 0.0001
Serum triacylglycerols (mg/dL)	64.85 ± 30.07	96.83 ± 34.87	0.004
sVCAM (μg/L)	561.05 ± 126.25	522.52 ± 229.53	NS
sICAM (μg/L)	212.88 ± 30.93	311.36 ± 48.40	< 0.0001

*Data are presented as mean ± SD.

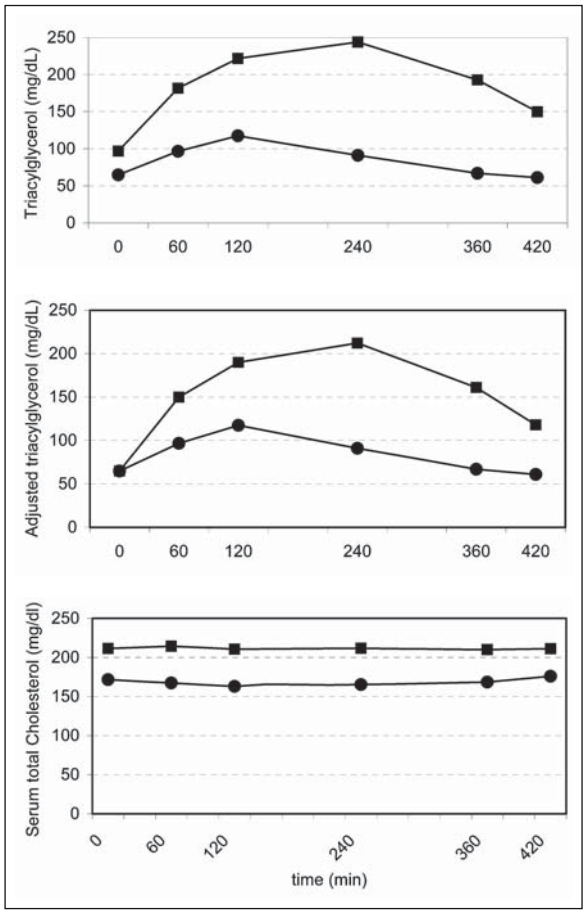

Fig. 1.—Baseline and postprandial serum triacylglycerol and total cholesterol in mg/dL in premenopausal (●) and postmenopausal (■) women after consuming a fat-rich standard area.

between time points 4 h, 6 h, 7 h were observed in PrW. When the postprandial TAG values were adjusted to the baseline data the differences between PrW and PoW remained significant.

Peak concentration and time to peak of serum TAG were significantly higher in PoW than in PrW ($p = 0.024$ and $p = 0.038$ respectively) (fig. 1).

In addition, a significant time effect ($p = 0.001$) and time x group interaction ($p < 0.0001$) were observed for total Chol concentrations. When performed a repeated measures one factor (time) ANOVA of Chol concentrations for each group of women total Chol concentrations of PoW showed no time effect. Those of PrW, on the other hand, displayed a significant time effect ($p < 0.0001$), as concentrations after 1 h, 2 h and 4 h in these females were significantly lower than those obtained after 7 hours ($p < 0.043$, $p = 0.003$ and $p = 0.005$, respectively), while no significant differences were observed between baseline, 6 h and 7 h values (fig. 1).

Discussion

This study clearly shows that PoW display higher postprandial lipaemia than PrW in response to a fat-rich standard meal, and the TAG concentration in PoW is delayed without returning to baseline levels. Even when adjusting for TAG baseline values, these differences were still observed.

To our knowledge this is the first study that compares premenopausal and postmenopausal postprandial response to a meal containing foods with a lipid profile similar to that of the Mediterranean diet. Postprandial lipaemia is influenced by various parameters such as gastric emptying time, intestinal absorption and lipoprotein lipase activity.[6] With age, gastric emptying rate and lipoprotein lipase activity are known to decrease, and a reduction of pancreatic lipase secretion and a delay in the clearance of TAG-rich lipoproteins have also been observed.[6] Bibliographical data on postprandial metabolism in pre and postmenopausal women are scarce and the studies that have been undertaken involve very small numbers of subjects. It is also difficult to compare data due to of the variety of food employed in the different studies. The lower postprandial lipaemia displayed by the PrW in the present study was also found in other studies, with levels of TAG for post- and PrW similar to our data, although in average our PrW were younger.[14] Nabeno et al.[6] reported similar results, but differ in the baseline characteristics of the women studied and in the food consumed, which was given as a fat-rich cream.

Chol levels in the postmenopausal group did not vary during digestion, while in the young PrW Chol levels clearly decreased. Other authors described stable postprandial Chol levels in healthy young men and women.[15-17] Cohn et al.[8] reported that postprandial plasma Chol concentrations can increase, decrease, or remain essentially unchanged, while Nabeno et al.[6] observed that Chol values tended to decrease, although not significantly, during the first hours in young premenopausal women, but not in older premenopausal female which is in agreement with the present results. We found significantly higher fasting HDL-cholesterol levels in PrW than in PoW. In this regard, high fasting baseline HDL-Chol levels relate with lower postprandial lipaemia.[8]

Comparing endothelial function between these women, unexpectedly we observed no differences in the sVCAM-1 concentrations, but sICAM-1 levels were lower in PrW than in PoW. Reports[18,19] indicate that sICAM levels predict better CVD and diabetes risk in healthy subjects and patients. In our healthy PrW and PoW we did not find any association between sICAM-1 levels and fasting insulin concentration (data not shown) which is in accordance with the results obtained by Blüher et al.[20] who found no correlation between these adhesion molecules and fasting insulin and glucose neither in control subjects nor in patients with impaired glucose tolerance or Type II diabetes. Also some authors report a negative correlation between estradiol concentration and sICAM levels,[21,22] which is consistent with these data, presenting PrW lower levels of sICAM than the PoW. We previously observed that postmenopausal women exhibited higher CVD risk and insulin resistance compared with premenopausal young women.[23,24]

Richter et al.[25] compared sVCAM and sICAM values of Dutch vegetarians and non-vegetarians of different ages. These authors state that sICAM levels are influenced by age but not diet. Contrary in sVCAM levels, in older vegetarians they found lower sVCAM levels than those of non-vegetarians of the same age. The PoW of this study consumed a habitual diet, which closely conforms to current nutritional guidelines, eating high quantities of fruits, vegetables and fish and little meat, sugar, sweets and pastry,[26] whereas PrW of this study showed a less favourable dietary intake with lower fruit and vegetables, and higher meat and pastry intake.[27] In this line low sVCAM-1 levels in these PoW could be related to their high antioxidant and fibre intake.

However, the influence of age on adhesion molecules remains controversial. Several authors discuss the influence of age on sICAM and sVCAM levels[25, 28-31] of men and women of different age groups, and rats. Future research regarding the normative data of adhesion molecules in men and women of different ages and on the relations between these biomarkers and risk of chronic diseases, including cardiovascular, diabetes and autoimmune disorders, as well as the influence of diet, are needed.

Conclusion

Postprandial lipaemia after consuming a meal with lipid profile similar to that of the Mediterranean diet show a higher cardiovascular risk pattern in postmenopausal compared to premenopausal women. Intercellular adhesion molecule concentrations also show a higher cardiovascular risk in the postmenopausal women. However, vascular adhesion molecules seem to be influenced not only by age and menopause, but also other factors like usual diet, which was less balanced in the young women.

Acknowledgements

This work was funded by SA Vichy Catalan and two Comunidad de Madrid – European Social Fund FPI Grants. The authors would like to thank the volunteers who participated in this work.

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):262-269
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Standardisation of the Waist Circumference (WC) for each range of Body Mass Index (BMI) in adult outpatients attended to in Endocrinology and Nutrition Departments

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Abstract

By this study we seek the expectable range of waist circumference (WC) for every degree of body mass index (BMI), which will serve to studies targeting ascertaining the health risk. We studied 2,932 patients (39.6% men and 60.4% women, between 18 and 96 years) of the same ethnic group who consecutively attended outpatient departments of our clinics between 2000 and 2004.. BMI correlated linearly with the WC (cc: 0.85; p < 0.001). The men, the obese, and diabetics were older (p < 0.001). BMI was greater in women and WC in men. The women had a greater WC if they had diabetes (p < 0.01), being equal to diabetic males. The men had greater WC when they had diabetes (p < 0.001). Waist at risk was detected (men > = 102 cm and women > = 88 cm) in 94.3% of the obese, in 32.3% of overweight patients, in 3.8% of patients with BMI < 25, in 84.3% of diabetics, and in 72.6% of patients without diabetes. We made graphic standardisation of WC with regard to BMI, and we calculated the percentiles 10, 25, 50, 75 and 90, grouping in ranges of 2 kg/m² of BMI. The diabetic patients are grouped in ranges of 4 kg/m². As conclusion we present a standardisation of the WC measurement of patients attended to in our Endocrinology and Nutrition practices distributed in percentiles as a clinically usable tool to define the ranges of WC for every BMI value.

(*Nutr Hosp*. 2010;25:262-269)

DOI:10.3305/nh.2010.25.2.4520

Key words: *Obesity. Diabetes mellitus. Waist circumference. Body mass index. Standardization.*

ESTANDARIZACIÓN DE LA CIRCUNFERENCIA DE CINTURA (WC), PARA CADA RANGO DE ÍNDICE DE MASA CORPORAL (BMI) EN PACIENTES ADULTOS ATENDIDOS EN UN SERVICIO DE ENDOCRINOLOGÍA Y NUTRICIÓN

Resumen

En este estudio hemos buscado el rango de circunferencia de cintura (WC) para cada grado de índice de masa corporal (BMI), que sirva para estudios que determinen riesgos de salud. Estudiamos 2.932 pacientes (39,6% varones y 60,4% mujeres, entre 18 y 96 años) del mismo grupo étnico que consecutivamente asistieron a consultas externas de nuestras clínicas entre 2000 and 2004. El BMI correlacionó linealmente con la WC (cc: 0,85; p < 0,001). Eran mayores los varones, los obesos y los diabéticos. El BMI era mayor en mujeres y la WC en varones. Las mujeres tenían mayor WC si eran diabéticas (p < 0,01), igualando a los hombres. Los varones tenían mayor WC si eran diabéticos (p < 0,001). La circunferencia de riesgo (varones > = 102 cm y mujeres > = 88 cm) la presentaban el 94,3% de los obesos, el 32,3% de los pacientes con sobrepeso y el 3,8% de pacientes con BMI < 25, el 84,3% de diabéticos y el 72,6% de pacientes sin diabetes. Elaboramos una estandarización gráfica de WC en relación con BMI y calculamos los precentiles 10, 25, 50, 75 y 90, agrupados en rangos de 2 kg/m² de BMI. Como el número de diabeticos es menor, los agrupamos en rangos de 4 kg/m². En conclusión presentamos una estandarización de la WC de pacientes atendidos en nuestra consulta de endocrinología y nutrición distribuidos en percentiles como herramienta utilizable clínicamente para definir rangos de WC para cada valor de BMI.

(*Nutr Hosp*. 2010;25:262-269)

DOI:10.3305/nh.2010.25.2.4520

Palabras clave: *Obesidad. Diabetes mellitus. Circunferencia de cintura. Índice de Masa Corporal. Estandarización.*

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Recibido: 20-IX-2009.
Aceptado: 26-X-2009.

Materials and methods

The study included a total of 2,932 patients (39.6% men and 60.4% women) who consecutively attended outpatient departments of the Endocrinology and Nutrition Services of the Spanish hospitals Virgen de las Nieves (Granada), Juan Canalejo (La Coruña) and Dr. Peset (Valencia) between 2000 and 2004. Patient age was comprised between 18 and 96 years, with no differences by sexes (45.9 ± 12.4 years men and 43.8 ± 14.3 years women).

BMI correlated linearly with the WC (cc: 0.85; $p < 0.001$), whereby the greater the BMI the greater the WC. The age, BMI and WC of the population studied and of the group of obese subjects are presented in table 1. The men were older than the women, the obese (obese 45.4 ± 13.8, non-obese 42.9 ± 13.1 years, $p < 0.001$) and diabetics ($p < 0.001$).

BMI was greater in women and WC in men. The women had a greater WC if they had diabetes ($p < 0.01$), being equal in this parameter to diabetic males The men had greater WC when they had diabetes ($p < 0.001$). Waist at risk was detected (men > = 102 cm and women > = 88 cm) in 94.3% of the obese (men 91.8%, women 95.7%), in 32.3% of overweight patients (men 22.2%, women 43.9%), in 3.8% of patients with BMI < 25 (men 2%, women 5.3%), in 84.3% of diabetics (men 74.6%, women 94%), and in 72.6% of patients without diabetes (men 63.7%, women 78.2%).

To obtain a graphic standardisation of WC with regard to BMI, we calculated the percentiles 10, 25, 50, 75 and 90, grouping in ranges of 2 kg/m^2 of BMI (including patients that exceed a BMI value until the next one). We thus obtain the distribution from table 2 and figures 1, 2 and 3. Due to the difference found in BMI and WC between men and women, and between diabetic and non-diabetic patients, distribution is presented by sexes, and separately for diabetic patients. Since there were no significant differences in terms of WC between diabetic men and women, no different by-sex graphics are provided for them. As the number of these patients is lower, they are grouped in ranges of 4 kg/m^2.

Introduction

Obesity is the most frequent metabolic disease in the western world. Although prevalence data in Europe are variable (from 4% to 28% in males and from 6.2% to 36.5% in women), the prevalence in Spain and Italy is particularly high.[1]

The importance of obesity is derived fundamentally from its relationship with cardiovascular diseases and with type 2 diabetes mellitus, among others, with serious medical and economic consequences for public health, ranging from 0.09% to 0.61% of the gross domestic product of every country.[2]

Obesity is defined by a Body Mass Index (BMI) value of 30 kg/m^2 or greater, calculated as weight/height^2 (BMI),[3] and overweight by a value between 25 and 30 kg/m^2. BMI has been chosen as a surrogate measurement of body fat content because it presents a good correlation with total body fat, and is an indicator of morbidity and mortality, even in the degree of overweight.[4-7] In different works, the rela-

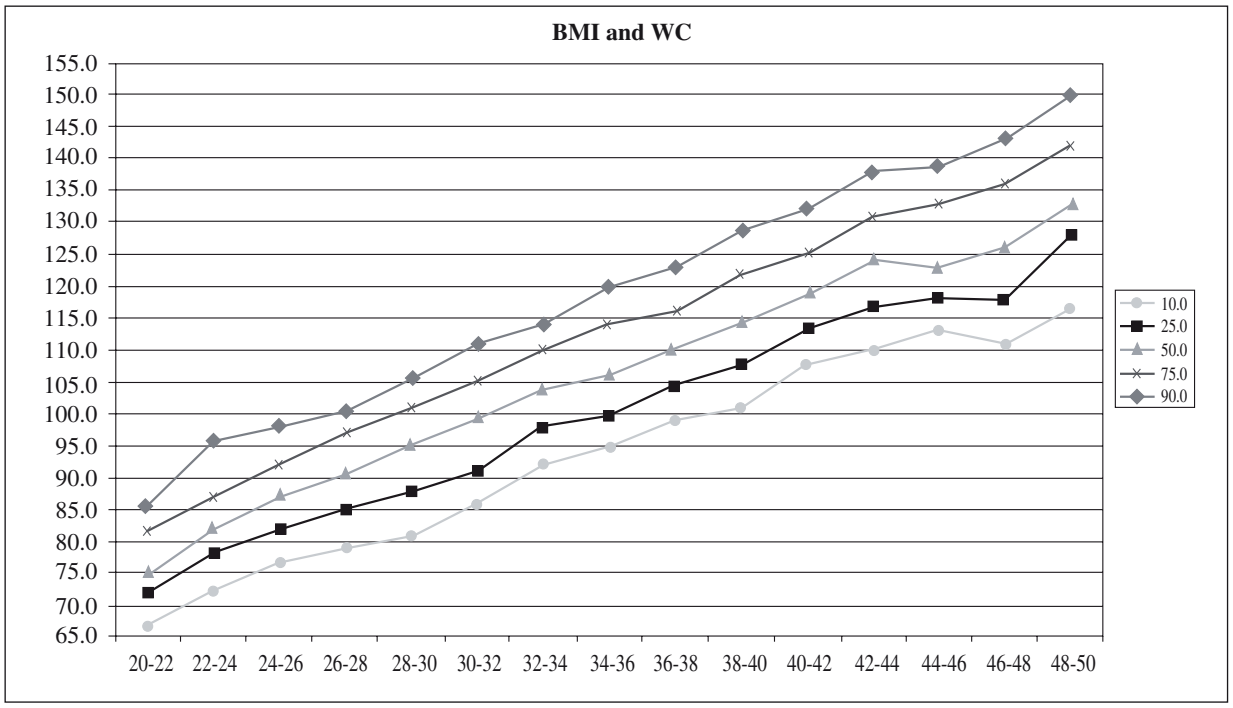

Fig. 1.—Percentiles of WC for each range of BMI in the whole group.

tionship with mortality describes a J curve, increasing progressively as of the degree of overweight.[7,8]

The risk entailed in obesity varies depending on the fat compartment considered, so that the visceral fat compartment is a better predictor of cardiometabolic risk and mortality than accumulated subcutaneous fat, whereby its determination is deserving of increasingly greater interest in clinical practice,[8-17] and it may also be a better indicator of health expenditure than the BMI.[18] The measurement of the waist circumference (WC) is a simple way of deducing a patient's level of visceral fat, and complements the information provided by the BMI.[10,19,20] BMI, WC and the relationship of both of the latter with morbidity and mortality depend on multiple factors, which include age, gender and ethnic group.[21,22]

Thresholds of WC that can be used as markers of morbidity and mortality have been sought with great interest, and a WC equal to or higher than 102 cm in men and 88 cm in women has been proposed as pathological, although the usefulness of these thresholds as predictors as a risk for health is still under debate.[11,17,23]

The definition of a given threshold of WC may be of interest in individuals with a slightly high BMI, but this does not add further information when the BMI is frankly high, since the majority of obese patients have a WC above the risk threshold. It is therefore insufficient to consider a single threshold of WC for all individuals,[11,17] and the information provided by the combined determination of the WC must be associated with the BMI.

Our intention was to progress in this idea, seeking the expectable range of WC for every degree of BMI, which will serve to subsequently address studies targeting ascertaining the health risk. For this purpose we have chosen diabetic and non-diabetic patients that we see in endocrinology and nutrition clinics, which is where cardiometabolic diseases are concentrated. The population considered here is white people, of the same ethnic group, and the results are presented distinguished by gender and type 2 diabetes mellitus.

Materials and methods

The study included a total of 2,932 patients (39.6% men and 60.4% women) who consecutively attended outpatient departments of the Endocrinology and Nutrition Services of the Spanish hospitals Virgen de las Nieves (Granada), Juan Canalejo (La Coruña) and Dr. Peset (Valencia) between 2000 and 2004. Patient age was comprised between 18 and 96 years, with no differences by sexes (45.9 ± 12.4 years men and 43.8 ± 14.3 years women).

Diabetic condition was defined by the American Diabetes Association.[24]

The anthropometric parameters included weight, height, BMI, WC was measured using standard methods. Weight was measured in kilograms, and height was measured in centimetres using stadiometer, both measurements of the subject in light clothing and no shoes. BMI was calculated by dividing the weight in kilograms by the height in square meters. The WC in cm was measured with a tape measure at a point midway between the last rib and the iliac crest, with the patient standing and on expiration.

Statistical analysis: The data were pooled together and managed on an Excel spreadsheet. A descriptive analysis was performed of all the variables collected, and 95% confidence intervals were calculated. Mean and standard deviations summarized the continuous variables. The percentiles of 10, 25, 50, 75 and 90 were calculated for every range of BMI (with patients that exceeded one BMI value being grouped into each range until the next value).

A Student's t-test or a Mann-Whitney test was used to compare between-group numerical parameters, after checking normality with the Kolmogorov-Smirnov test. Values of $p < 0.05$ were considered significant. All the tests were two-sided.

Correlation and linear regression analyses by Pearson's correlation coefficient were performed to study the association of BMI with WC in diabetic and not diabetic patients.

The statistical analysis was carried out with SPSS 12.0 for Windows.

Results

BMI correlated linearly with the WC (cc: 0.85; $p < 0.001$), whereby the greater the BMI the greater the WC. The age, BMI and WC of the population studied and of the group of obese subjects are presented in table 1. The men were older than the women, the obese (obese 45.4 ± 13.8, non-obese 42.9 ± 13.1 years, $p < 0.001$) and diabetics ($p < 0.001$).

BMI was greater in women and WC in men. The women had a greater WC if they had diabetes ($p < 0.01$), being equal in this parameter to diabetic males The men had greater WC when they had diabetes ($p < 0.001$). Waist at risk was detected (men > = 102 cm and women > = 88 cm) in 94.3% of the obese (men 91.8%, women 95.7%), in 32.3% of overweight patients (men 22.2%, women 43.9%), in 3.8% of patients with BMI < 25 (men 2%, women 5.3%), in 84.3% of diabetics (men 74.6%, women 94%), and in 72.6% of patients without diabetes (men 63.7%, women 78.2%).

To obtain a graphic standardisation of WC with regard to BMI, we calculated the percentiles 10, 25, 50, 75 and 90, grouping in ranges of 2 kg/m^2 of BMI (including patients that exceed a BMI value until the next one). We thus obtain the distribution from table I and figures 1, 2 and 3. Due to the difference found in BMI and WC between men and women, and between diabetic and non-diabetic patients, distribution is presented by sexes, and separately for diabetic patients. Since there were no significant differences in terms of WC between diabetic men and women, no different by-

Table I
Distribution of percentiles for each range of BMI

BMI	N	Mean	STD	10.0	25.0	50.0	75.0	90.0
All								
20-22	64.0	76.6	7.4	67.0	72.0	75.0	81.8	85.5
22-24	75.0	82.6	7.8	72.0	78.0	82.0	87.0	95.4
24-26	186.0	86.9	7.9	76.7	82.0	87.0	92.0	98.0
26-28	239.0	90.4	8.55	79.0	85.0	91.0	97.0	100.5
28-30	261.0	94.2	9.0	81.0	87.8	95.0	101.0	105.8
30-32	343.0	98.5	9.6	86.0	91.0	99.0	105.0	111.0
32-34	297.0	103.5	8.9	92.0	97.5	104.0	110.0	114.0
34-36	265.0	107.0	10.7	95.0	99.5	106.5	114.0	120.0
36-38	229.0	110.3	9.5	99.0	104.0	110.0	116.0	123.0
38-40	202.0	114.6	10.0	101.0	108.0	114.3	122.0	128.7
40-42	164.0	119.3	9.6	107.5	113.1	119.0	125.0	132.0
42-44	149.0	123.9	11.0	110.0	117.0	124.0	131.0	138.0
44-46	120.0	125.1	9.7	113.1	118.3	123.0	133.0	139.0
46-48	79.0	127.1	11.1	111.0	118.0	126.0	136.0	143.0
48-50	78.0	133.6	11.6	116.8	128.0	133.0	142.3	150.0
Men								
20-22	16.0	81.3	5.7	72.7	75.3	83.0	85.8	88.3
22-24	38.0	85.6	7.9	76.7	79.8	83.5	92.0	96.1
24-26	113.0	90.0	6.3	82.0	85.0	90.0	94.0	98.5
26-28	131.0	94.6	5.9	87.0	90.0	95.0	98.0	101.8
28-30	118.0	100.3	6.2	91.0	96.8	100.5	105.0	107.0
30-32	140.0	104.5	8.3	95.1	101.0	104.0	109.0	114.9
32-34	127.0	108.5	7.5	99.0	103.0	109.0	113.0	118.0
34-36	87.0	114.5	6.3	107.8	110.0	114.0	120.0	122.2
36-38	77.0	117.1	7.8	106.0	112.0	116.0	123.0	127.0
38-40	76.0	122.4	6.5	115.0	118.0	122.0	127.0	131.0
40-42	51.0	127.7	7.6	118.0	123.0	127.0	133.0	137.0
42-44	44.0	132.5	8.9	120.5	126.0	132.5	138.8	142.0
44-46	35.0	132.3	7.4	120.0	127.0	134.0	137.0	142.0
46-48	25.0	138.0	7.2	127.6	134.0	138.0	144.0	147.0
48-50	24.0	140.0	10.0	125.0	133.5	140.5	148.0	150.0
Women								
20-22	47.0	74.8	7.2	66.8	71.0	74.0	79.0	84.0
22-24	37.0	79.6	6.5	71.6	76.0	79.0	83.0	86.4
24-26	72.0	82.0	7.8	74.0	77.3	82.0	87.0	92.1
26-28	100.0	85.1	8.7	75.0	79.0	85.0	91.0	96.0
28-30	133.0	88.7	7.8	78.4	82.3	88.0	95.0	99.0
30-32	197.0	94.2	7.8	84.0	89.0	94.0	100.0	105.0
32-34	163.0	99.4	7.9	90.2	94.0	99.0	105.0	109.0
34-36	168.0	102.6	9.8	92.9	97.0	102.0	106.9	113.1
36-38	147.0	106.4	7.9	96.0	102.0	107.0	111.0	117.0
38-40	123.0	109.8	8.7	99.0	105.0	109.0	114.0	122.0
40-42	110.0	115.5	7.7	104.1	110.8	116.5	121.0	125.0
42-44	104.0	120.4	9.8	107.5	114.0	121.5	127.8	131.0
44-46	83.0	122.2	9.1	110.7	116.0	122.0	126.0	138.3
46-48	53.0	122.2	8.8	109.4	117.0	123.0	128.0	133.6
48-50	53.0	130.8	11.2	114.2	124.0	132.0	136.8	143.6
Diabetics								
22-26	33.0	89.4	8.3	79.0	82.5	91.0	95.5	100.0
26-30	92.0	98.7	7.1	90.0	94.3	99.0	103.0	107.0
30-34	138.0	104.5	8.7	92.9	99.0	105.5	111.0	115.1
34-38	113.0	112.5	10.9	99.0	106.0	112.0	118.0	125.0
38-42	70.0	119.5	8.8	107.1	114.8	119.0	126.0	131.0
42-46	58.0	126.7	10.6	111.9	118.8	125.0	136.0	142.0
46-50	36.0	128.9	11.8	112.4	121.0	130.0	139.0	145.7

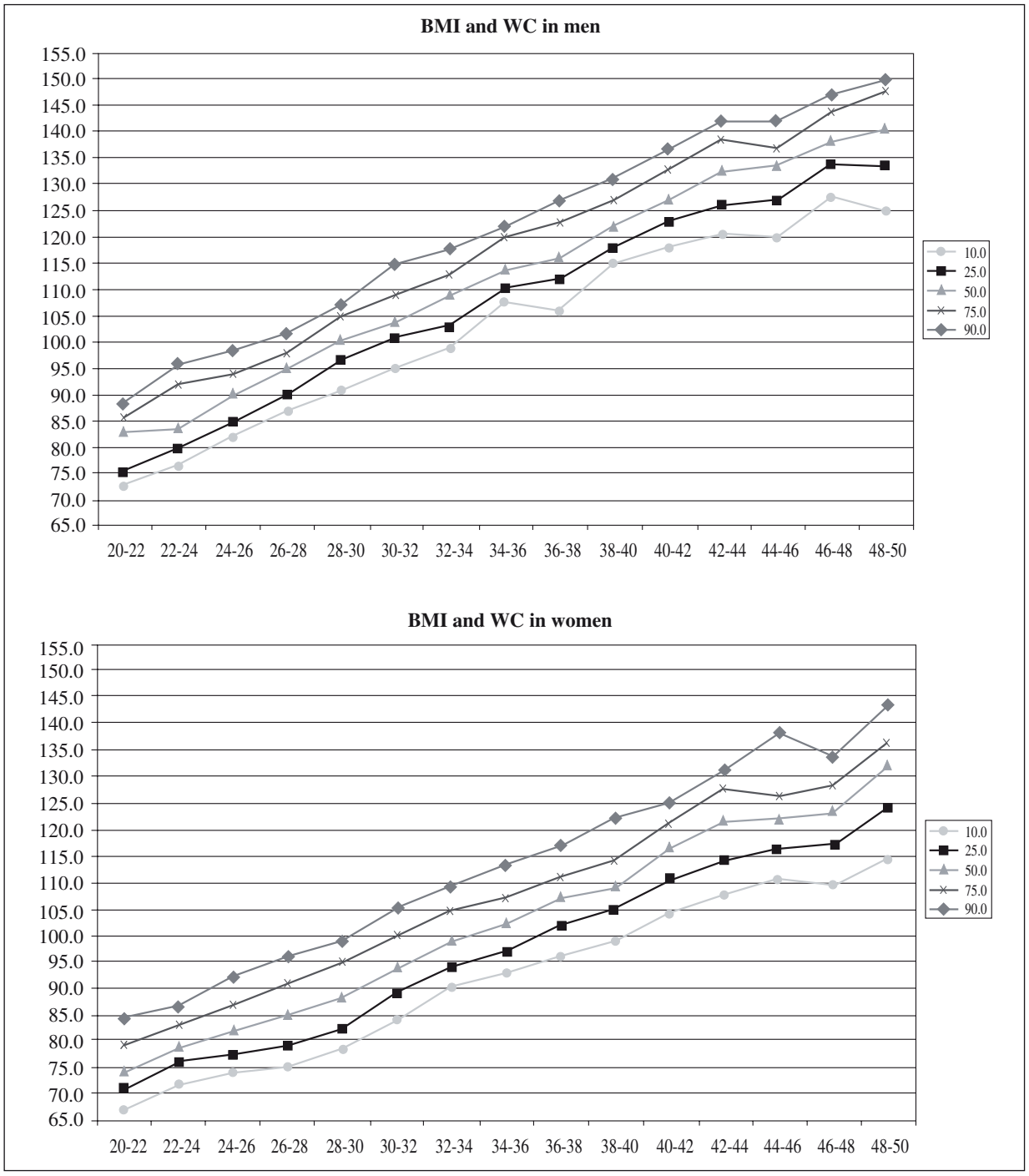

Fig. 2.—Percentiles of WC for each range of BMI in men and women.

sex graphics are provided for them. As the number of these patients is lower, they are grouped in ranges of 4 kg/m^2.

Discussion

The direct relationship between BMI and WC is well-known.[25] The first is an indicator of the degree of corporality and the second of visceral fat. These parameters are measured in routine fashion in clinical practice as they are regarded as independent indicators of body fat content[26] and predictors of cardiovascular risk.[19,27,28] Moreover, both BMI and WC help to predict the risk of developing type 2 diabetes mellitus. BMI is a good predictor of the development of type 2 diabetes mellitus[29] and of insulin resistance.[12] Fat distribution can even predict progression to type 2 diabetes mellitus

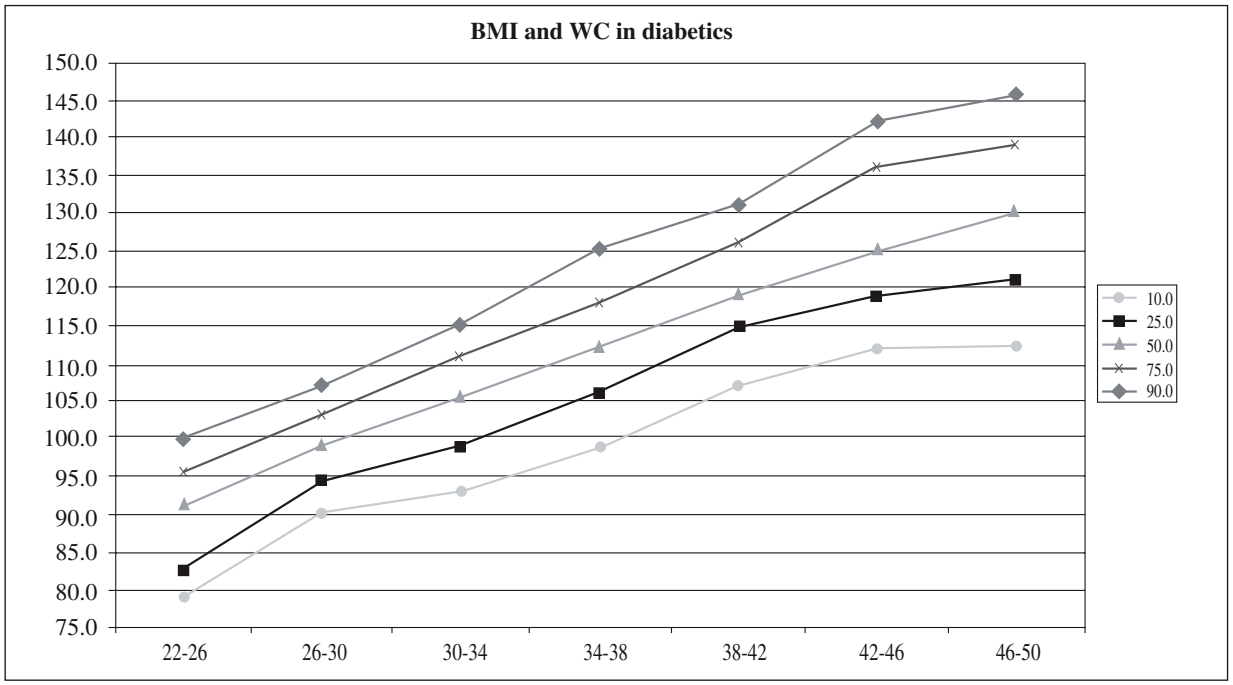

Fig. 3.—Percentiles of WC for each range of BMI in diabetics.

better than BMI.[30] It is assumed that the accumulation of visceral fat plays an important role in the aetiology of this type of diabetes to subject the liver to an excess of free fatty acids, producing insulin resistance and hyperinsulinaemia.[31,32] Our study verified the direct relationship between BMI and WC, both in diabetics and non-diabetics, as well as the relationship between age, BMI and WC and gender and the presence of diabetes mellitus. Our diabetic patients presented greater BMI, WC and age.

Levels of normality, overweight and obesity were established for BMI (BMI less than 25, between 25 and 30, and 30 or above, respectively).[3] These thresholds have been maintained, whereby the different studies have defined a J curve where mortality increases progressively with the different degrees of overweight and obesity.

The interest in establishing these thresholds is derived from the need to detect cardiometabolic risk with their help. In this regard, the thresholds of WC make it possible to define "risk" groups for whom preventive activities can be indicated, even with normal or slightly increased BMI.

The thresholds of normality of WC are the most debated. A WC equal to or higher than 102 cm is regarded as pathological in men and 88 cm in women, as it corresponds to a BMI greater than or equal to 30 (kg/m^2,[33] although others have been proposed.[34,35] In the IDEA study, this value was exceeded by 29% males and 48% women among the 182,970 patients aged between 18 and 80 years who attended primary care facilities in 63 countries.[10] Similarly, in the overweight patients of our group, these thresholds have allowed us to select 32.3% with a greater cardiovascular risk. But the determination of WC is not sensitive enough to detect the risk in the group of obese patients.[11,17,36] In our study, 94.3% of the obese exceeded these values. Had we applied the IDF criteria for European Caucasians (94 cm in men and 80 cm in women) these percentages would have been even greater.

We found a greater WC in men than in women, and in both sexes when they are diabetic. In women with diabetes, WC reaches values similar to diabetic males, whom they surpass in BMI. This relationship of WC with the male sex and with diabetes has been broadly confirmed in other transversal and prospective studies.[4,30,37-40]

These differences justify the definition of different risk thresholds for men and women in non-diabetic individuals (NCEP/ATPIII),[41] but these thresholds could not be extrapolated to the population that is already diabetic, where we found no differences in WC between sexes, and where cardiovascular risk increases with the existence of diabetes. We have therefore offered an individualised standardisation for the diabetic population.

On the other hand, WC and BMI should be considered separately. In the observational studies, the J curve of the mortality study is progressive as BMI and WC increase, from degrees below those considered to be pathological.[7,8,22]

The greater or lesser importance attributed to BMI and WC depends on the approach taken by the studies, the population's circumstances, age, gender and degree of obesity.[13,35,42] The true usefulness lies in combining both determinations, as was demonstrated in the

Nurses Health Study,[28] where the risk of coronary artery disease adjusted for age throughout an 8-year monitoring increases with WC for each tercile of BMI. In this study, the incidence of coronary artery disease was similar in women with lower BMI and greater WC compared to those who had a greater BMI and lower WC. The greater incidence was to be found in the greater levels of BMI and WC. The joint usefulness of BMI and WC in clinical practice was confirmed in subsequent studies. For both parameters, WC cut-off levels have been proposed in the different categories of BMI with regard to cardiovascular risk, with risk determined by the Framingham scale, which predicts the possibility of coronary events after 10 years. Optimal thresholds can be defined as 98, 109 and 124 in men and as of 92, 103 and 115 in women in the categories of overweight, degree 1 obesity and degree 2 obesity or higher, respectively. With these thresholds, Ardern et al.[43] improve sensitivity and specificity to detect patients at risk.

Our work seeks to further develop this idea, defining the expectable range of WC for every degree of BMI, which may serve for subsequent health risk studies. With this purpose in mind, we chose a group of patients with greater frequency of metabolic diseases, obesity and diabetes, who attend Endocrinology and Nutrition clinics, all of them Caucasian. This selection necessarily assumes a limitation, since the results might not be applicable to the general population.

In this study we offer the clinician the measurement of WC graphically by means of WC percentiles for each range of BMI (which may be translated to other dispersion values, such as the SDS). As WC depends on gender and on the patient's diabetic condition, the data must be displayed separately. But WC did not present differences between sexes in diabetics, and for this reason we do not provide a graphic differentiation in this case

The percentiles of WC for each range of BMI inform the clinician as to patients whose abdominal fat (and therefore WC) is above or below the degree expected for their degree of corporality (BMI). The percentile that should be regarded as normal or pathological has yet to be defined, and would be the one that distinguished between patients whose health risks increase, and which will have to be determined in cross-sectional, prospective and predictive studies that may be performed by applying percentiles or other deviation parameters.

In conclusion, we present a standardisation of the WC measurement of patients attended to in our Endocrinology and Nutrition practices distributed in percentiles as a clinically usable tool to define the ranges of WC for every BMI value.

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):270-274
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Study and classification of the abdominal adiposity throughout the application of the two-dimensional predictive equation Garaulet et al., in the clinical practice

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Abstract

Introduction: **The excess of visceral abdominal adipose tissue is one of the major concerns in obesity and its clinical treatment.**

Objective: **To apply the two-dimensional predictive equation proposed by Garaulet *et al.* to determine the abdominal fat distribution and to compare the results with the body composition obtained by multi-frequency bioelectrical impedance analysis (M-BIA).**

Subjects/methods: **We studied 230 women, who underwent anthropometry and M-BIA. The predictive equation was applied. Multivariate lineal and partial correlation analyses were performed with control for BMI and % body fat, using SPSS 15.0 with statistical significance $P < 0.05$.**

Results: **Overall, women were considered as having subcutaneous distribution of abdominal fat. Truncal fat, regional fat and muscular mass were negatively associated with $VA/SA_{predicted}$, while the visceral index obtained by M-BIA was positively correlated with $VA/SA_{predicted}$.**

Discussion/Conclusion: **The predictive equation may be useful in the clinical practice to obtain an accurate, costless and safe classification of abdominal obesity.**

(*Nutr Hosp*. 2010;25:270-274)

DOI:10.3305/nh.2010.25.2.4544

Key words: *Abdominal obesity. Visceral adipose tissue. Multi-frequency bioelectrical impedance analysis. Anthropometry. Truncal fat.*

ESTUDIO Y CLASIFICACIÓN DE LA ADIPOSIDAD ABDOMINAL MEDIANTE LA APLICACIÓN DE LA ECUACIÓN PREDICTIVA BIDIMENSIONAL DE GARAULET ET AL., EN LA PRÁCTICA CLÍNICA

Resumen

Introducción: **El exceso de tejido adiposo abdominal visceral es una de las mayores preocupaciones en la obesidad y su tratamiento clínico.**

Objetivo: **Aplicar la ecuación predictiva bidimensional propuesta por Garaulet et al., para determinar la distribución de la grasa abdominal y comparar los resultados con la composición corporal obtenida mediante el análisis de impedancia bioeléctrica multi-frecuencia (M-BIA).**

Sujetos/métodos: **Estudiamos a 230 mujeres a las que se sometió a antropometría y M-BIA. Se aplicó la ecuación predicitiva. Se realizaron correlaciones lineales multivariadas y parciales controlando el IMC y el % de grasa corporal, utilizando SPSS 15.0 con significación estadística $P < 0,05$.**

Resultados: **En global, se consideró que las mujeres tenían una distribución subcutánea de la grasa abdominal. La grasa troncal, regional y la masa muscular se asociaron negativamente con $VA/SA_{predicha}$, mientras que le índice visceral obtenido mediante M-BIA se correlacionó positivamente con $VA/SA_{predicha}$.**

Discusión/conclusión: **La ecuación predictiva puede ser útil en la práctica clínica para obtener una clasificación segura, barata y precisa de la obesidad abdominal.**

(*Nutr Hosp*. 2010;25:270-274)

DOI:10.3305/nh.2010.25.2.4544

Palabras clave: *Obesidad abdominal. Tejido adiposo visceral. Análisis por impedancia bioeléctrica de multifrecuencia. Antropometría. Grasa troncal.*

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Recibido: 13-X-2009.
Aceptado: 26-X-2009.

Introduction

One the major concerns in the clinical treatment of obesity is the excess of adipose tissue located in the abdominal region and it´s increased associated risk. The visceral adipose tissue (VAT) is considered the clinically relevant type of body fat independently of total body fat,[1] closely linked with increased risk of type 2 diabetes and cardiovascular disease.[2]

Imaging techniques as magnetic resonance imaging (RMI) or computed tomography (CT)[3] ensure an accurate quantification of abdominal fat compartments, but their economic cost and complexity make them not suitable in the clinical practice or in large-scale studies. Although several anthropometric measures have been validated as indicators of VAT or SAT compartments,[4] no single parameters are considered as accurate measures of both fat deposits.[5] Also, it has been suggested that one-dimensional variables are not complete models for estimating two-dimensional parameters such as cross-sectional fat areas,[6] that have been described as ellipses rather than circles, even in obese subjects.[7] Based on this fact, Garaulet et al. have developed a two-dimensional equation,[8] based on the elliptical model, using the classical ratio of visceral area (VA) over subcutaneous area (SA) at the umbilicus level. This equation was validated in obese subjects who underwent computed tomography and anthropometry and was established a cut-off point at the level of 0.42. The classical VA/SA ratio has been used as a diagnostic criterion for classifying obesity into subcutaneous and visceral types[9] and has shown important associations with metabolic disturbances.[10]

Bioelectrical Impedance analysis (BIA) is a popular alternative to assess body composition because is a safe, non-invasive and portable method. Modern multifrequency BIA (M-BIA) technology also includes the ability to provide total body fatness and regional estimates such as truncal fatness.[11] Recent studies have shown good agreement between M-BIA and dual-energy X-ray absorptiometry (DXA) for estimating changes in body composition during weight loss in overweight young women.[12] However, M-BIA may not be widely available in the clinical practice.

The purpose of the present study was to apply a two-dimensional predictive equation proposed by Garaulet et al.[8] to determine the abdominal fat distribution in women included in a cognitive-behavioral therapy for the treatment of obesity,[13] and to compare the results with the body composition obtained by M-BIA, with the purpose to reach a more accurate, costless and easier classification of the abdominal obesity in the clinical practice mainly based in the application of the predictive equation.

Subjects and methods

Subjects

The studied population was composed by 230 women, aged 39 ± 12 years, with BMI 29 ± 5 and % body fat 35.4 ± 5.3, who visited the "Garaulet Nutritional Centers", in Murcia, Spain, and were included in a cognitive-behavioral therapy based on the Mediterranean diet for the treatment of obesity.[13] The Ethics Committee of the University of Murcia approved this study and the informed consent was obtained before the experiments.

Anthropometric measurements

According to SEEDO 2007 Consensus,[14] body weight was measured by a clinical scale with 100 g recess, and body height was measured with a Harpender digital stadiometer (0.7-2.05 m range), in barefooted subjects. BMI was calculated as weight (kilograms) divided by squared height (meters). Body fat distribution was assessed using the waist circumference (WC) at the level of the umbilicus; hip circumference (HC) over the widest part of the greater trocanters; sagittal diameter was measured at the level of the iliac crest (L4-5) using a Holtain Kahn Abdominal Caliper,[15] as the distance between the examination table up to the horizontal level, allowing the caliper arm to touch the abdomen slightly but without compression;[16] and coronal diameter was measured at the level of iliac crest (L4-5), with the patient lying in a supine position in the examination table. The abdominal caliper was perpendicular to the body.[15] The waist to hip ratio (WHR) was also calculated.[17] Skinfold thicknesses (biceps, triceps, subscapular and suprailiac) were measured with a Harpender caliper (Holtain Ltd., Bryberian, Crymmych, Pembrokeshire), on the right side of the body with the subject standing up in a relaxed position. The complete set of anthropometric measurements was performed three times but not consecutively, and were obtained in order and repeated a second and a third time. All these measurements were carried out by the same person. To analyze the abdominal fat distribution, the two-dimensional predictive equation proposed by Garaulet et al.,[8] was calculated with the following formula:

Visceral area (VA)/Subcutaneous area (SA) predicted = 0.868 + (0.064 x sagittal diameter) – (0.036 x coronal diameter) – (0.022 x triceps skinfold).

According to the values obtained by the predictive equation in the present study, we classified individuals into subcutaneous and visceral group using the cut-off point proposed by Garaulet et al. who have classified visceral obese subjects as those individuals with $VA/SA_{predicted} \geq 0.42$.

Multi-frequency bioelectric impedance analysis (M-BIA)

To guarantee the maximum accuracy of the data, all the measurements were performed in bare-footed and

fasting individuals. These measures were obtained by TANITA MC-180 (TANITA Corporation of America, Inc, Arlington Heights, IL, USA), equipped with 8 tactile electrodes: a platform with 2 electrodes for each foot and two handgrips with two electrodes each. We obtained total body measures, excluding the head, such as total body fat (% and kg), muscular mass (kg), fat free mass (kg), total body water (kg); and the regional measures were truncal fat (kg), visceral index, muscular truncal mass (kg), fat leg mass (kg), fat arm mass (kg), muscular leg mass (kg) and muscular arm mass (kg). The visceral index obtained by M-BIA has been previously validated through Computed Tomography and DXA in both spinal-cord injured and healthy patients respectively.

Statistical analysis

Data are expressed as mean ± s.e.d. Statistical differences between means were tested using multivariate lineal analyses controlled for BMI and total body fat (%). Partial correlation coefficients controlled for BMI and total body fat (%) were performed to determine the relations between general characteristics, anthropometrical variables and M-BIA data, with $VA/SA_{predicted}$ by the two-dimensional equation. All statistical procedures were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, USA). Statistical significance was defined with P values < 0.05.

Results

General characteristics, anthropometry and multi-frequency bioelectric impedance data

Clinical and M-BIA data from the total population are presented in Table 1. The studied population presented overweight (BMI = 29 ± 5). The mean value of $VA/SA_{predicted}$ classified females with subcutaneous distribution. Women had mean values of total body fat (%) considered as obesity.[14]

Classification of individuals according to the $VA/SA_{predicted}$

To classify the total population into subcutaneous or visceral abdominal distribution we used the cut-off point proposed by Garaulet et al. (table I). The subcutaneous group presented significantly higher values of weight, coronal diameter, skinfold thicknesses, fat free mass, total body water, truncal fat (% respect to total fat), muscular truncal and leg mass. The visceral group presented significant higher values of sagittal diameter. The visceral index obtained by M-BIA was not significantly different between groups, but it was slightly higher in the visceral group.

Associations between $VA/SA_{predicted}$ and the variables derived from anthropometry and M-BIA analysis

Table II shows the partial correlation coefficients between anthropometric and M-BIA measures and $VA/SA_{predicted}$ values. Regarding the anthropometric variables, hip circumferences (HC) ($P < 0.05$), coronal diameter ($P < 0.001$) and skinfold thicknesses ($P < 0.001$) were significantly and negatively correlated with the predictive equation values. Whereas, sagittal diameter correlated positively. We also observed significant and negative correlations between the equation values and fat free mass, total body water, truncal fat ($P < 0.01$) and muscular truncal ($P < 0.05$) and leg mass ($P < 0.01$). The predictive equation was significantly and positively associated with the visceral index obtained by M-BIA ($P < 0.001$).

Discussion

The present study was designed to show the effectiveness of the two-dimensional predictive equation in the classification of the abdominal obesity in the clinical practice. It has been stated that no single clinical anthropometric measure correlates well with visceral adipose tissue (VAT) in the prediction of the abdominal fat depot.[11] The equation published by Garaulet et al., is composed by coronal and sagittal diameters plus triceps skinfold, having the advantage that can measure two-dimensional variables as cross-sectional areas like VAT.[6] Those three variables were revealed as strong and significant contributors to the explained variance of VA/SA obtained by computed tomography (CT) by multiple regression analysis.[8] This equation showed more accuracy than previous models such as the circular model, the elliptical model using different abdominal and back skinfolds,[7] and even more than the classical visceral obesity classification proposed by Tarui et al.[9]

In the studied population, women presented overweight and had waist circumference and waist-to-hip ratio (WHR) slightly greater than the accepted highly risk cut-off points.[14] Taking into account these variables, women presented little risk of metabolic disturbances associated with obesity.[18] The application of the predictive equation revealed that, overall, women were considered as having a subcutaneous distribution of the abdominal fat. After statistical control for BMI and total body fat (%), a positive correlation between the $VA/SA_{predicted}$ and the visceral index (VI) obtained by M-BIA was found. Considering the VI as an indicator of visceral obesity, we can assume that the equation is classifying the patients adequately. Measures of visceral adiposity through M-BIA have shown important correlations with visceral area determined by CT and DXAThe VI has been validated throughout CT in both healthy individuals and patients with spinal cord injury,[19] and even stronger correlations than the waist circumference.[19,20]

Table I
General characteristics, anthropometric and multi-frequency bioelectric impedance data in the total population and differences between means classifying women according to $VA/SA_{predicted}$

	Total population n = 230	*Subcutaneous group $VA/SA_{predicted} \leq 0.42$ (n = 164)*	*Visceral group $VA/SA_{predicted} > 0.42$ (n = 66)*	*p*
Weight (kg)	75 ± 13	75.56 ± 0.45	73.39 ± 0.72	0.013
Waist (cm)	91.54 ± 11.08	91.66 ± 0.46	90.62 ± 0.75	0.248
Hip (cm)	106.89 ± 10.06	107.33 ± 0.54	105.45 ± 0.87	0.073
WHR	0.86 ± 0.08	0.86 ± 0.01	0.86 ± 0.01	0.699
Coronal diameter (cm)	33.74 ± 4.40	34.52 ± 0.22	31.63 ± 0.36	0.000
Sagittal diameter (cm)	20.92 ± 3.01	20.71 ± 0.12	21.21 ± 0.20	0.039
Biceps skinfold (mm)	15.75 ± 7.48	16.49 ± 0.44	13.05 ± 0.71	0.000
Triceps skinfold (mm)	30.30 ± 8.01	32.59 ± 0.40	23.75 ± 0.65	0.000
Subscapular skinfold (mm)	29.15 ± 9.87	30.01 ± 0.59	26.31 ± 0.95	0.001
Suprailiac skinfold (mm)	31.47 ± 9.56	32.42 ± 0.62	28.98 ± 1.01	0.005
$VA/SA_{predicted}$	0.33 ± 0.19	0.23 ± 0.01	0.56 ± 0.02	0.000
Visceral Index	6,29 ± 2,87	6.20 ± 0.12	6.59 ± 0.20	0.110
Total Body Fat (kg)	26.73 ± 8.45	26.79 ± 0.20	26.43 ± 0.33	0.367
Muscular mass (kg)	45.17 ± 6.79	45.47 ± 0.37	44.08 ± 0.61	0.058
Fat free mass (kg)	47.40 ± 6.20	47.69 ± 0.31	46.25 ± 0.49	0.016
Total body water (kg)	33.91 ± 4.47	34.11 ± 0.22	33.08 ± 0.36	0.017
Truncal fat (kg)	12.60 ± 4.31	12.80 ± 0.13	12.32 ± 0.21	0.057
Truncal fat (% respect to total fat)	46.39 ± 7.54	47.50 ± 0.29	46.38 ± 0.46	0.046
Fat leg mass (kg)	5.52 ± 1.60	5.49 ± 0.04	5.54 ± 0.06	0.553
Fat arm mass (kg)	1.52 ± 0.68	1.52 ± 0.02	1.51 ± 0.03	0.816
Muscular truncal mass (kg)	26.13 ± 3.56	26.27 ± 0.17	25.46 ± 0.28	0.016
Muscular leg mass (kg)	7.31 ± 0.97	7.38 ± 0.06	7.12 ± 0.09	0.020
Muscular arm mass (kg)	2.17 ± 0.32	2.19 ± 0.02	2.13 ± 0.03	0.105

Data are presented as mean ± s.e.d. BMI: body mass index, WHR: waist to hip ratio. VA: visceral area, SA: subcutaneous area. Bold characters indicate significant differences between groups with $P \leq 0.05$. Multivariate lineal analysis was controlled for BMI (body mass index) and total body fat (%).

The partial correlation analysis also revealed negative correlations between $VA/SA_{predicted}$ and truncal fat, regional fat and muscular mass. These results support the fact that women tend to gain more subcutaneous fat in the abdominal region. This observation is consistent with others that states that premenopausal[20] premenopausal[21] and postmenopausal[22] women have more abdominal subcutaneous adipose tissue than men.

The utilization of the predictive equation proposed by Garaulet et al. (2006) may have some advantages over M-BIA, especially if modern equipments of M-BIA are not available in the daily practice. However, some limitations may be taken into account. One of the key issues is how the triceps skinfold, a negative component of the equation, affects the values of $VA/SA_{predicted}$. Our results showed that the visceral group ($VA/SA_{predicted} \geq 0.42$) had significantly less weight and truncal fat (% respect to total fat) than the subcutaneous group. These results could be explained by significantly fewer values of triceps in the women classified as visceral group compared with those classified in the subcutaneous group (Table 2). This skinfold has been shown to be highly correlated to total body fat in different population groups[22,23] groups,[23,24] and was correlated to subcutaneous fat in the previous study of Garaulet et al.[8] In this case, the triceps skinfold is diving women according to the % of body fat. On the other hand, the predictive equation was validated in obese women, while women in the present study presented overweight, although both population had a wide range of BMI and % total body fat. To avoid the influence of obesity degree, the statistical analyses were controlled for both variables.

In summary, the predictive equation proposed by Garaulet et al. (2006) has satisfactorily classified overweight women with a subcutaneous distribution of the abdominal fat, and the results showed good agreement with the visceral index and other variables derived from M-BIA. The predictive equation is useful in the clinical practice and can be applied without any other method or equipment to obtain an accurate, costless and safe classification of the obese patients.

Table II
Partical correlation coefficients for the independent association between VA/SA predicted and total body composition

	Total population
Waist (cm)	NS
Hip (cm)	-0.135*
WHR	NS
Coronal diameter (cm)	-0.515‡
Sagittal diameter (cm)	0.258‡
Biceps skinfold (mm)	-0.316‡
Triceps skinfold (mm)	-0.723‡
Subscapular skinfold (mm)	-0.209†
Suprailiac skinfold (mm)	-0.159*
Total Body Fat (kg)	NS
Muscular mass (kg)	NS
Fat free mass (kg)	-0.181†
Total body water (%)	-0.197†
Truncal fat (kg)	-0.183†
Truncal fat (% respect to total fat)	-0.151*
Visceral Index	0.246‡
Fat leg mass (kg)	NS
Fat arm mass (kg)	NS
Muscular truncal mass (kg)	-0.161*
Muscular leg mass (kg)	-0.171†
Muscular arm mass (kg)	NS

WHR: waist to hip ratio. Partial correlation analysis was controlled for BMI and total body fat (%). *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$. NS: not significant.

Acknowledgements

We thank the Garaulet Centers of Nutrition located in Cartagena, Molina de Segura and Murcia, Spain, and its managers for exceptional assistance and help in the data acquisition. None of the authors has conflict of interests of any type with respect to this manuscript. This work was supported by the Government of Education, Science and Research of Murcia (project BIO/FFA 07/01-0004) and by the Spanish Government of Science and Innovation (projects AGL2008-01655/ALI).

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):275-279
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Effects of telmisartan vs olmesartan on metabolic parameters, insulin resistance and adipocytokines in hypertensive obese patients

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Abstract

Background: **Angiotensin II regulates the production of adipokines. The objective was to study the effect of treatment with telmisartan versus olmesartan in hypertensive obese and overweight patients.**

Subjects: **A sample of 65 overweight and obese patients with mild to moderate hypertension was analyzed in a prospective way with a randomized trial. Patients were randomized to telmisartan (80 mg/day) or olmesartan (40 mg/day) for 3 months. Weight, body mass index, blood pressure, basal glucose, insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, HOMA, QUICKI, leptin and adiponectin were determined at basal time and after 3 months of treatment.**

Results: **Sixty five patients gave informed consent and were enrolled in the study. Patients treated with telmisartan had a significative decrease of glucose 10.53 mg/dl (CI 95%: 2.6-18.5), insulin 2.51 mUI/L (CI 95%: 2.07-7.17) and HOMA 1.08 (CI 95%: 0.39-2.55). Patients treated with olmesartan had a significative decrease of total cholesterol 20.2 mg/dl (CI 95%: 5.8-34.9) and LDL cholesterol 22.6 mg/dl (CI 95%: 9.7-35.6). Only leptin levels have a significant decrease in telmisartan group 7.39 ng/ml (CI 95%: 1.47-13.31).**

Conclusion: **Telmisartan improved blood pressure, glucose, insulin, HOMA and leptin in hypertensive diabetic patients. Olmesartan improved blood pressure and lipid levels.**

(*Nutr Hosp*. 2010;25:275-279)

DOI:10.3305/nh.2010.25.2.4545

Key words: *Adiponectin. Hypertension. Insulin resistance. Leptin. Olmesartan. Telmisartan.*

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Recibido: 15-X-2009.
Aceptado: 26-X-2009.

EFECTOS DE TELMISARTAN VS OLMESARTAN SOBRE PARÁMETROS ANTROPOMÉTRICOS, RESISTENCIA A LA INSULINA Y ADIPOCITOQUINAS EN PACIENTES HIPERTENSOS OBESOS

Resumen

Introducción: **La angiotensina II puede regular la producción de adipocitoquinas. El objetivo de nuestro trabajo fue evalaur el efecto sobre parámetros bioquímicos del tratamiento con telmisartan versus olmesartan en pacientes obesos hipertensos.**

Pacientes: **Se analizó una muestra de 65 pacientes con hipertensión moderada severa y obesidad, mediante un ensayo clínico randomizado. Los pacientes fueron randomizados en dos ramas; telmisartan (80 mg/día) u olmesartan (40 mg/día) durante 3 meses. Se determinaron en el tiempo basal y tras 3 meses los siguientes parámetros; peso, índice de masa corporal, presión arterial, glucosa, insulina, colesterol total, LDL-colesterol, HDL-colesterol, triglicéridos, HOMA, QUICKI, leptina y adiponectina.**

Resultados: **Los pacientes que recibieron telmisartan tuvieron una disminución significativa de los niveles de glucosa 10,53 mg/dl (CI 95%: 2,6-18,5), insulina 2,51 mUI/L (CI 95%: 2,07-7,17) y HOMA 1,08 (CI 95%: 0,39-2,55). Los pacientes tratados con olmesartan presentaron una disminución significativa de colesterol 20,2 mg/dl (CI 95%: 5,8-34,9) y LDL colesterol 22,6 mg/dl (CI 95%: 9,7-35,6). Solo, los niveles de leptina disminuyeron de manera significativa con telmisartan 7,39 ng/ml (CI 95%: 1,47-13,31).**

Conclusion: **Telmisartan mejora los niveles de presión arterial, glucosa, insulina, HOMA y leptina en pacientes hipertensos obesos. Olmesartan mejoró los niveles de presión arterial y el perfil lipídico.**

(*Nutr Hosp*. 2010;25:275-279)

DOI:10.3305/nh.2010.25.2.4545

Palabras clave: *Adiponectina. Hipertensión. Resistencia a la insulina. Leptina. Olmesartan. Telmisartan.*

Introduction

Obesity and insulin resistance are associated with cardiovascular risk factors, including altered levels of adipocytokines.[1] Epidemiologic evidence of this rising tide of obesity and associated pathologies has led, in the last years, to a dramatic increase of research on the role of adipose tissue as an active participant in controlling pathologic processes.[2,3]

The current view of adipose tissue is that of an active secretory organ, sending out and responding to signals that modulate appetite, insulin sensitivity, energy expenditure, inflammation and immunity. Adipocytokines are proteins produced mainly by adipocytes.[4] These molecules have been shown to be involved in the pathogenesis of the metabolic syndrome and cardiovascular disease. Adiponectin is an adipocyte-derived collagen like protein identified through an extensive search of adipose tissue. Hypoadiponectinemia increased risk of coronary artery disease together with the presence of multiple risk factors, indicating that adiponectin is a key factor of the metabolic syndrome.[5] Leptin is a 16 KDa protein secreted primarily from adipocytes. Recent reports suggest that leptin contributes to atheroscleoris and cardiovascular disease in obese patients.[6] Insulin resistance and hyperinsulinemia are characteristics findings of this metabolic syndrome (MetS) and are very common in patients with essential hypertension.[7]

Circulating angiotensin II, the active product of the renin-angiotensin system, is a hormonal regulator of cardiovascular function and electrolyte metabolism. Angiotensin II is also produced by local renin-angiotensin systems in many organs including adipose tissue.[8] In addition, angiotensin II regulates the production of adipokines. Angiotensin II increases the expression and the release of pro-inflammatory cytokines,[9] increases leptin ob gene expression and secretion,[10] and reduces plasma levels and gene expression of adiponectin, and insulin-sensitizing, anti-inflammatory adipokine.[11] In turn, blockade of the renin-angiotensin system with inhibitors of angiotensin II formation or angiotensin II AT1 receptor blockers decreases body weight, improves insulin-sensitivity and prevents development of insulin resistance.[12] Telmisartan and olmesartan are two antagonists of angiotensin II receptors used as antihypertensive drugs.

To clarify the effect of angiotensin II system blockade on adipocytokines, we studied the effect of treatment with telmisartan versus olmesartan in a randomized clinical trial in hypertensive obese and overweight patients.

Subjects and methods

Subjects

A sample of 65 obese and overweight patients with mild to moderate hypertension was analyzed in a prospective way with an open-randomized trial. We used WHO/ISH[13] definitions for hypertension defined as systolic and diastolic blood pressure > 140 or > 90 mmHg, respectively. These patients were studied in an Endocrinology Unit and written informed consent was obtained. The study has been approved by the local ethics committee. Exclusion criteria included a history of cardiovascular disease or stroke during the previous 36 months, total cholesterol > 300 mg/dl, triglycerides > 400 mg/dl, blood pressure > 140/90 mmHg, the use of sulfonylurea, metformine, acarbose, thiazolidinediones, insulin, glucocorticoids, antineoplasic agents, angiotensin-converting enzyme inhibitors, psychoactive medications, drinking and/or smoking habit.

Procedure and calculations

Patients were randomized to telmisartan (80 mg/day) or olmesartan (40 mg/day) for 2 months. Weight, body mass index, blood pressure, basal glucose, insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, leptin and adiponectin levels were measured at basal time and after 3 months of treatment.

Body weight was measured to an accuracy of 0.1 kg and body mass index (BMI) was calculated as follows: BMI = body weight (kg)/(body height (m))^2.

The homeostasis model assessment for insulin sensitivity (HOMA) was calculated as follows: HOMA = (glucose x insulin)/22.5.[14] Quantitative Insulin-Sensitivity Check index (QUICKI), a surrogate index of insulin sensitivity, was calculated as follows: QUICKI = 1/(log (insulin)+ log (glucose)).[15]

Blood pressure was measured twice after a 10 minutes rest with a random zero mercury sphygmomanometer, and averaged.

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 sulphate-magnesium. LDL cholesterol was calculated using Friedewald formula. Plasma glucose levels were determined by using an automated glucose oxidase method (Hitachi 917, Roche Diagnostics, Mannheim, Germany). Insulin was measured by enzymatic colorimetry (Insulin, WAKO Pure-Chemical Industries, Osaka, Japan).

Adipocytokines

Leptin was measured by ELISA (Diagnostic Systems Laboratories, Inc., Texas, USA) with a sensitivity

Table I
Clinical and epidemiological characteristics of study population

Characteristics	Telmisartan n = 34	Olmesartan n = 31	p
Male/female	14/20	12/19	ns
Age(years)	56.2 ± 14.7	59.8 ± 15.7	ns
BMI(kg/m²)	29.2 ± 5.9	29.9 ± 3.6	ns
Weight (kg)	78.9 ± 11.1	77.8 ± 9.6	ns
Systolic BP (mmHg)	150.7 ± 19.1	145.6 ± 15.1	ns
Diastolic BP (mmHg)	85.7 ± 9.4	85.9 ± 9.1	ns

BP: Blood pressure; ns: no significative.

of 0.05 ng/ml and a normal range of 10-100 ng/ml. Adiponectin was measured by ELISA (R&D systems, Inc., Mineapolis, USA) with a sensitivity of 0.246 ng/ml and a normal range of 865-21424 ng/ml. Ratio adiponectin/leptin levels were calculated.

Statistical analysis

A power calculation based on weight improvement was performed. Thirty patients in each group were necessary to detect a change of 6 ng/dl in leptin levels, with an error type I < 0.05 and a statistical power of 80%.

The results were expressed as average ± standard deviation. The distribution of variables was analyzed with Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with a two-tailed, paired Student's-t test and ANOVA test. Non-parametric variables were analyzed with the Friedman and Wilcoxon tests. Qualitative variables were analyzed with the chi-square test, with Yates correction as necessary, and Fisher's test. A p-value under 0.05 was considered statistically significant.

Results

Sixty five patients gave informed consent and were enrolled in the study. Baseline characteristics of patients were presented in table I, without statistical differences.

Table II
Changes in anthropometric variables and blood pressure

Parameters	Telmisartan (n =34)		Olmesartan (n = 31)	
	Baseline	3 months	Baseline	3 months
BMI	29.2 ± 5.9	29.6 ± 8.5	29.9 ± 3.6	29.8 ± 5.2
Weight (kg)	78.9 ± 11.1	79.0 ± 10	77.8 ± 9.6	77.7 ± 9.5
Systolic BP (mmHg)	150.7 ± 19.1	126.3 ± 7.7*	145.6 ± 15.1	124.8 ± 9.6*
Diastolic BP (mmHg)	85.7 ± 9.4	76.2 ± 8.3*	85.9 ± 9.1	80.5 ± 6.6*

BP: Blood pressure.
T Student test and Wilcoxon test were used as statistical methods.
* p < 0.05, in each group with basal values.

Table III
Clasical cardiovascular risk factors

Characteristics	Telmisartan (n =34)		Olmesartan (n = 31)	
	Baseline	3 months	Baseline	3 months
Glucose (mg/dl)	139.6 ± 35	129.1 ± 28*	138.2 ± 36	134.2 ± 41
Total ch. (mg/dl)	198.1 ± 37	200.4 ± 30	214.2 ± 41	193.8 ± 43*
LDL-ch. (mg/dl)	101.1 ± 31	108.4 ± 36	127.4 ± 39	104.7 ± 37*
HDL-ch. (mg/dl)	52.3 ± 9.8	52.4 ± 9.6	51.2 ± 10.7	50.9 ± 12.9
TG (mg/dl)	169 ± 71	181 ± 86	183.5 ± 98	169.9 ± 77
Insulin (mUI/L)	14.1 ± 9.1	11.6 ± 8.2*	15.9 ± 8.9	14.8 ± 8.4
HOMA	4.9 ± 3.7	3.9 ± 3.1*	4.7 ± 4.9	4.5 ± 3.7
QUICKI	0.54 ± 0.11	0.56 ± 0.14	0.51 ± 0.07	0.6 ± 0.07

LDL-ch: low density lipoprotein. HDL: high density lipoprotein. Chol: Cholesterol. TG: Triglycerides.
(HOMA): Homeostasis model assessment, HOMA = (glucose x insulin)/22.5
(QUICKI): Quantitative Insulin-Sensitivity Check index, QUICKI = 1/(log(insulin)+ log(glucose))
T Student test and Wilcoxon test were used as statistical methods.
(*) p < 0.05, in each group with basal values.

Table II shows a significantly decrease in systolic and diastolic blood pressures without changes in weight, with both treatments.

Table III shows the differences in classic cardiovascular risk factors. Patients treated with telmisartan had a significantly decrease of glucose 10.53 mg/dl (CI 95%: 2.6-18.5), insulin 2.51 mUI/L (CI 95%: 2.07-7.17) and HOMA 1.08 (CI 95%: 0.39-2.55). Patients treated with olmesartan had a significantly decrease of total cholesterol 20.2 mg/dl (CI 95%: 5.8-34.9) and LDL cholesterol 22.6 mg/dl (CI 95%: 9.7-35.6).

Table IV shows differences between basal and after treatment levels of adipocytokines. Only leptin levels have a significant decrease in telmisartan group 7.39 ng/ml (CI 95%: 1.47-13.31).

Discussion

The major finding of this study was that telmisartan 80 mg per day significantly improved insulin, HOMA, glucose and leptin levels. However, olmesartan improved lipid levels. Both drugs had the same beneficial effect on blood pressure levels.

Recently, Furuhashi et al.[16] showed that blockade of the renin-angiotensin system by angiotensin-convert-

Table IV
Circulating adypocitokines

Variables	Telmisartan (n =34)		Olmesartan (n = 31)	
	Baseline	3 months	Baseline	3 months
Adiponectin (ng/ml)	13.5 ± 8.5	14.4 ± 15.8	20.2 ± 17.3	21.4 ± 19.5
Leptin (ng/ml)	38.8 ± 30.5	31.4 ± 28.3*	35.8 ± 47	34.2 ± 37.1

T Student test and Wilcoxon test were used as statistical methods.
* p < 0.05, in each group with basal values.

ing enzyme inhibitor (ACEI) and/or angiotensin II receptor blocker (ARB) decreased adipocyte size with improvement in insulin sensitivity. This previous data may partially explain our results with telmisartan. Other study[17] suggests that other ARB (candesartan)-induced decrease in plasma insulin level might be induced an increase in plasma adiponectin in patients with renal dysfunction. In agreement with these results, the blockades of renin-angiotensin system are reported to decrease plasma insulin level and to increase plasma adiponectin level in patients without renal dysfunction, too.[18] Our study did not show modification in levels of adiponectin, but telmisartan decrease leptin levels.

Recently, telmisartan displays the ability to act as partial agonist of PPARgamma,[19] this stimulation induces the differentiation of pre-adipocytes to mature adipocytes, increases the subcutaneous fat and reduces the visceral fat related with insulin resistance. Several are the mechanisms through to explain the increased insulin sensitivity induced by blockade this system. They are represented by 1) vasodilatation, which increases the blood flow in skeletal muscle,[20] 2) inhibition of the impairment of insulin signaling induced by angiotensin II,[21] decrease of tumor necrosis factor (TNF-alpha in skeletal muscle,[22] increase in the ratio of insulin-sensitive type 1 fiber in muscle fiber composition.[23] In summary, the effect of ARB on adiponectin levels may be mediated by the decrease in insulin levels, which is due to the effect of ARB on enhancing insulin sensitivity[24]. Moreover, RAS blockade may stimulate phosphatidylinositol-3-kinase activity, which regulates insulin-stimulated adiponectin exocytosis.[25]

In our study, two characteristics differentiated telmisartan from olmesartan 1) telmisartan showed a reduction of blood pressure and leptin levels while olmesartan did not decrease leptin and 2) a greater impact of telmisartan on the glucose control.

Physiological increase in plasma leptin has been shown to significantly inhibit glucose-stimulated insulin secretion in vivo and to determine insulin resistance.[26] Serum leptin concentrations reflects the total amount of fat present in the body, and lower plasma leptin levels have been reported consistently among weight losing patients.[27] The results of our study show that significant reduction in leptin levels after telmisartan treatment occur when weight is unchanged. The decrease of leptin levels, which may reflect a drug induced improvement of leptin sensitivity, may play a role, indirectly or directly, in the induction of diabetes control. Telmisartan improved glucose tolerance and it can be due to a possible insulin-independent mechanism, possibly acting through an enhanced uptake and utilization of glucose by tissues mediated by leptin without changes in insulin sensitivity measured as HOMA (homeostasis model assessment).

As above-mentioned, there is a general consensus that angiotensin II has a trophic role in adipose tissue. However the effects of angiotensin II on adipocyte metabolism and differentiation are not conclusive, while others show that angiotensin II promotes it. Leptin gene expression is under the control of PPARgamma. PPARgama represses the expression of leptin ob gene.[28] In animal models, angiotensin II AT1 receptor blockers enhanced insulin sensitivity and improved the serum lipid profile in obese.[29]

In summary, the administration of telmisartan improved blood pressure, glucose, insulin, HOMA and leptin in hypertensive obese patients. Olmesartan improved blood pressure and lipid levels. These results suggest that telmisartan could be more useful in preventing atherosclerosis in these patients than olmesartan.

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):280-289
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Conductas de salud en escolares de la provincia de Cádiz

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Resumen

Objetivo: **El objetivo del estudio ha sido analizar algunas características de las conductas relacionadas con la salud en escolares de la provincia de Cádiz, centrándose en la práctica de deporte y actividad física y en los hábitos alimenticios.**

Metodología: **Participaron 738 alumnos, con una media de edad de 12,2 años que cursaban desde primero de educación primaria hasta segundo de bachillerato. La muestra estaba compuesta por un 50,9% de chicos y un 49,1% de chicas, a los que se aplicó la versión española del Inventario de Conductas de Salud en Escolares.**

Resultados: **Existían diferencias entre ambos sexos en cuanto al porcentaje de aquellos que afirmaban no practicar nunca deporte, mayor en el caso de las chicas. Los chicos practicaban deporte y realizaban actividad física de mayor intensidad que las chicas, siendo también mayor la duración de dicha práctica. Un porcentaje elevado consideraba su forma física buena o normal y solo regular en una pequeña parte. Más de la mitad de los sujetos percibían un apoyo para la práctica por parte de padres y madres, siendo menor el apoyo de hermanos y amigos. Una parte importante de los alumnos no desayunaba todos los días de la semana y algunos no realizaban esta primera comida del día. Un porcentaje muy alto de los sujetos consumía golosinas o dulces de forma habitual, siendo también elevado el consumo de patatas fritas, de frutos secos y de hamburguesas o salchichas. Cerca de una cuarta parte reconocía no consumir nunca verduras u hortalizas.**

Conclusiones: **Los resultado obtenidos confirman la necesidad de una adecuada educación sobre hábitos de vida saludable y el desarrollo de programas de intervención en niños y jóvenes, aconsejando sobre dieta y actividad física y prestando especial interés a las chicas, que constituyen el grupo menos físico activamente y con mayor riesgo de padecer trastornos.**

(*Nutr Hosp*. 2010;25:280-289)

DOI:10.3305/nh.2010.25.2.4579

Palabras clave: Salud. Actividad física. Deportes. Dieta. Niños y adolescentes.

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Recibido: 24-X-2009.
Aceptado: 26-X-2009.

HEALTH BEHAVIOUR OF SCHOOL CHILDREN AT THE PROVINCE OF CÁDIZ

Abstract

Objective: **The aim of this study was to analyze some characteristics of health-related behaviour in school children at the province of Cadiz, centering on engagement in sports and physical activity, and on dietary habits.**

Methodology: **Participants were 738 students, mean age 12.2 years, from primary school o high school. 50.9% were boys and 49.1% girls, who responded a Spanish adaptation of the Health Behavior in Schoolchildren Inventory.**

Results: **Sex differences were observed in the percentage of subjects not engaged in sports, which was higher in girls. Boys practiced sports and physical activity at a higher intensity and more time than girls. A large number of subjects considered good or normal their physical fitness, with only and small percentage describing it as regular. More than half of participants felt a support by parents, and to a smaller extent by brothers and friends. An important part of the subjects did not have breakfast every day, and some even never. A high percentage of the sample ate candies 1 to 3 days per week, being also high the intake of chips, nuts, hamburgers and sausages. Near a quarter of subjects reported not to consume vegetables.**

Conclusions: **Results obtained confirm the necessity of an adequate lifestyle habits education and the development of intervention programs in children and youth, counseling on diet and physical activity and targeting on girls, who are less physically active and on risk of serious disorders.**

(*Nutr Hosp.* 2010;25:280-289)

DOI:10.3305/nh.2010.25.2.4579

Key words: Health. Physical activity. Sports. Diet. Children and adolescents.

Introducción

La infancia y la adolescencia constituyen etapas clave en la adquisición del estilo de vida. Niños y adolescentes se enfrentan a conductas y experiencias, fruto de la extensión de sus relaciones y de la acción de los agentes de socialización, que tendrán una importancia primordial en la formación de los hábitos de conductas saludables y en la adquisición de hábitos positivos que tengan continuidad en la vida adulta[1]. El desarrollo de patrones de conducta no saludables en estas edades en un fenómeno relativamente generalizado y es en ellas cuando han de adoptarse medidas adecuadas para la prevención de patologías que inciden en la calidad de vida de la población[2].

Dentro de las conductas saludables resaltan la alimentación correcta y los hábitos de práctica de actividad física y deportiva. Esta última es una variable fundamental en el estilo de vida saludable y la literatura actual señala un gran número de beneficios fisiológicos y psicológicos como consecuencia de la práctica regular de actividades físico-deportivas[2,3]. Por otra parte, la práctica de actividad física está positivamente relacionada con conductas que mejoran la salud, tales como la alimentación equilibrada y asociada negativamente con conductas no saludables tales como el consumo de tabaco o las malas prácticas alimentarias[4,5].

El ejercicio físico en el tiempo libre no es un hábito de la mayoría de la población infantil y juvenil en España y en otros países desarrollados, siendo numerosos los estudios que indican la tendencia actual hacia un descenso de los niveles de actividad física, que comienza a ser significativo precisamente a partir de la adolescencia[6]. La mayoría de las investigaciones indican que la práctica de ejercicio es menor de lo que resultaría conveniente y se sabe que una parte importante de los niños y adolescentes españoles y europeos no realizan actividad física regular en su tiempo libre, especialmente las chicas[7], produciéndose además una reducción significativa de la práctica con la edad[8,9].

En lo que se refiere a la alimentación hay que considerar las necesidades energéticas y de nutrientes características de la infancia y la adolescencia. Los profundos cambios que se producen en estas edades, especialmente en adolescentes, hacen que haya que considerarlos como un grupo de riesgo nutricional, con aparición de nuevos hábitos alimentarios que pueden llevar a desequilibrios y trastornos nutricionales[10].

Las conductas sedentarias y los hábitos alimentarios inadecuados pueden representar una carga para la salud pública[11]. En consecuencia, resulta de extrema importancia el desarrollo de estudios que incidan sobre el análisis del estado de salud y los hábitos de alimentación y actividad física en la edad infantil y juvenil, haciendo posible el diseño de campañas educativas y la realización de programas específicos de intervención en niños y adolescentes, con el objeto de mejorar su estado de salud y de reducir el riesgo de patologías crónicas[12,13]. A este respecto son esenciales abordajes como la Estrategia para la Nutrición, Actividad Física y Prevención de la Obesidad (Estrategia NAOS) desarrollada por el Ministerio de Sanidad en España[2].

El objeto de la presente investigación ha sido analizar algunas características de las conductas relacionadas con la salud en escolares de la provincia de Cádiz, centrándose en la práctica de deporte y actividad física y en los hábitos alimenticios.

Metodología

Sujetos

Se llevó a cabo un estudio transversal y descriptivo. La muestra es representativa de los estudiantes escolarizados de la provincia de Cádiz y se seleccionó mediante un criterio aleatorio estratificado proporcional. Los participantes en el estudio fueron 738 estudiantes, con una media de edad de 12,2 años (DT = 2,8, rango 6-18) y correspondían a los cursos comprendidos entre primero de educación primaria y segundo de bachillerato. La muestra estaba compuesta por un 50,9% de chicos (N = 376; M edad = 12,0; DT = 2,9) y un 49,1% de chicas (N = 362, M edad = 12,4; DT = 2,7).

Instrumento

El instrumento utilizado fue la versión española del "Inventario de Conductas de Salud en Escolares" (The Health Behavior in Schoolchildren (1985/86: A WHO cross-national survey; HBSC)[14,15]. Se trata de un instrumento diseñado para evaluar las variables del estilo de vida saludable que fue creado por la oficina regional europea de la Organización Mundial de la Salud. El cuestionario está compuesto por 29 items con preguntas que hacen referencia a variables psicosociales y del estilo de vida. Las principales secciones que se recogen en el instrumento son las siguientes: a) actividad, física y deporte; b) hábitos de alimentación; c) tabaco; d) alcohol; e) drogas; f) higiene dental; h) consumo de vitaminas y hierro; i) conductas de riesgo y seguridad; j) hábitos de descanso; k) consumo de medicamentos; y l) tiempo libre. La versión española utilizada muestra una adecuada estructura factorial[16].

Procedimiento

Tanto a los padres como a los alumnos y profesores se les ha explicado en que consistía el estudio y se ha contado con su consentimiento expreso. La recogida de datos se realizó mediante un cuestionario anónimo que se autocumplimentaba voluntariamente por los alumnos en la propia clase y durante un período aproximadamente de una hora. Durante dicha administración estuvo presente al meno uno de los investigadores.

Tabla I
Frecuencia, intensidad y duración del deporte realizado

Variable	*Opciones*	*Varón*	*Mujer*
Frecuencia del deporte	Nunca	14,8%	32,6%
	Menos de una vez a la semana	3,2%	3,4%
	1 vez por semana	6,1%	6,9%
	2-3 veces por semana	43,1%	40,1%
	4-5 veces por semana	20,2%	9,9%
	6-7 veces por semana	9,0%	1,7%
	NS/NC	3,5%	5,8%
Intensidad del deporte	Muy intenso	16,5%	5,5%
	Intenso	29,0%	15,5%
	Moderado	29,8%	32,9%
	Ligero	5,8%	6,9%
	NS/NC	18,9%	39,2%
Duración del deporte	Más de 45 min.	63,3%	42,7%
	De 35 a 45 min.	8,0%	6,3%
	De 25 a 35 min.	5,8%	4,42%
	De 15 a 25 min.	2,1%	1,9%
	De 5 a 15 min.	1,6%	1,9%
	Menos de 5 min.	0,5%	0,3%
	NS/NC	18,6%	38,4%

Análisis de los datos

El análisis estadístico consistió en el cálculo de porcentajes e intervalos de confianza por el método exacto. La comparación de proporciones se llevó a cabo mediante la prueba χ^2. Se consideraron significativos valores de $p < 0,05$.

Resultados

Aunque las variables que se obtienen con el Inventario de Conductas de Salud en Escolares son muchas más de las que se muestran en el presente artículo, aquí nos centramos en los aspectos más directamente relacionados con los estilos de vida saludables, presen-

Tabla II
Frecuencia, intensidad y duración de la actividad física realizada

Variable	*Opciones*	*Varón*	*Mujer*
Frecuencia de actividad física	Nunca	16,5%	11,3%
	Menos de una vez a la semana	5,9%	4,7%
	1 vez por semana	29,0%	13,0%
	2-3 veces por semana	31,9%	36,2%
	4-5 veces por semana	19,2%	16,6%
	6-7 veces por semana	17,6%	13,8%
	NS/NC	4,5%	4,4%
Intensidad de actividad física	Muy intenso	10,1%	5,8%
	Intenso	19,4%	16,3%
	Moderado	50,8%	49,4%
	Ligero	9,3%	10,8%
	NS/NC	10,4%	17,4%
Duración de actividad física	Más de 45 min.	41,8%	32,9%
	De 35 a 45 min.	16,8%	14,6%
	De 25 a 35 min.	17,0%	16,0%
	De 15 a 25 min.	9,3%	12,7%
	De 5 a 15 min.	3,5%	5,3%
	Menos de 5 min.	0,5%	1,4%
	NS/NC	10,9%	16,8%

Tabla III
Pertenencia a clubes o equipos deportivos y participación en competiciones

Variable	*Opciones*	*Varón*	*Mujer*
Miembro de un club deportivo	No	47,6%	73,5%
	Sí	48,4%	23,2%
	Si pero no participo	3,5%	2,8%
	NS/NC	0,5%	0,6%
Miembro de equipo escolar	No	65,7%	78,2%
	Sí	31,1%	18,8%
	Sí pero no participo	2,4%	2,5%
	NS/NC	0,8%	0,6%
Competiciones deportivas	Sí	66,5%	42,3%
	No	22,3%	42,8%
	Lo hacía, pero ya no lo hago	10,9%	14,4%
	NS/NC	0,3%	0,6%
¿Con quién haces ejercicio?	Solo	5,1%	8,6%
	Con otros	69,1%	59,4%
	A veces solo y a veces con otros	25%	29,6%
	NS/NC	0,8%	2,5%

tando los resultados obtenidos sobre la práctica de deporte y actividad física y los hábitos alimenticios.

Actividad física y deporte

Las tablas I y II muestran la frecuencia, intensidad y duración de la práctica de deporte y actividad física. El perfil, tanto en el caso del deporte como en el de la actividad física, es el de un individuo que practica 2 ó 3 veces por semana con una intensidad moderada durante más de 45 minutos. Existen diferencias entre ambos sexos en cuanto al porcentaje de aquellos que afirman no practicar nunca deporte, mayor en el caso de las chicas ($p < 0,01$). Por otro lado, es mayor el porcentaje de chicos que practican deporte 4-5 veces por semana en comparación con las chicas ($p < 0,05$), así como el porcentaje de los que practican deporte intenso o muy intenso ($p < 0,05$). En el caso de la actividad física, se reducen las diferencias entre ambos sexos en el porcentaje de sujetos que reconocen no practicar nunca ($p < 0,05$). Los chicos realizan actividad física de mayor intensidad que las chicas y la duración de dicha práctica es también mayor ($p < 0,05$).

En lo que se refiere a los resultados relacionados con la pertenencia de los alumnos a clubes o equipos deportivos y su participación en competiciones (tabla III), aproximadamente dos tercios de los sujetos son miembros de clubes deportivos y es aún mayor el porcentaje de alumnos que pertenecen a un equipo escolar. En cuanto a las competiciones deportivas, poco más de la mitad de la muestra compite y algo más de la décima parte reconoce que lo hacían pero ya lo han abandonado. Si nos centramos en las diferencias que existen en estos datos según el sexo, vemos que el porcentaje de niñas que no pertenecen a ningún club deportivo es mucho mayor que el de niños ($p < 0,01$). Además, también son ellos los que participan en competiciones deportivas en mayor proporción ($p < 0,05$). En el caso de la compañía a la hora de realizar ejercicio, tanto los chicos como las chicas prefieren mayoritariamente hacerlo con otras personas en lugar de solos.

En cuanto al tipo de deporte o actividad física practicados (tabla IV), predominan el correr y la bicicleta, siendo el fútbol/fútbol el deporte más practicado. Las razones por las que a los individuos les gusta el deporte son diversas y semejantes en chicos y chicas (fig. 1). Tanto ellos como ellas, consideran muy importante practicar deporte por divertirse, tener hábitos saludables, preservar su forma física y hacer amigos. En el caso de la población femenina se presta más atención a tener buen aspecto a través de la práctica de actividad

Tabla IV
Actividades físico-deportivas regulares realizadas

Deporte o actividad física	*N.º sujetos*	*Porcentaje*
Fútbol o fútbol sala	319	43,2%
Deportes de raqueta	110	14,9%
Jugar al escondite o a pillar	288	39,0%
Bailar	222	30,1%
Montañismo	34	4,6%
Patines o monopatín	147	19,9%
Esquí	14	1,9%
Natación	158	21,4%
Correr	381	51,6%
Baloncesto	137	18,6%
Balonmano	44	6,0%
Bicicleta	337	45,7%
Atletismo	46	6,2%
Gimnasia	99	13,4%
Aeróbic	49	6,6%
Artes marciales	46	6,2%
Otros	65	8,8%

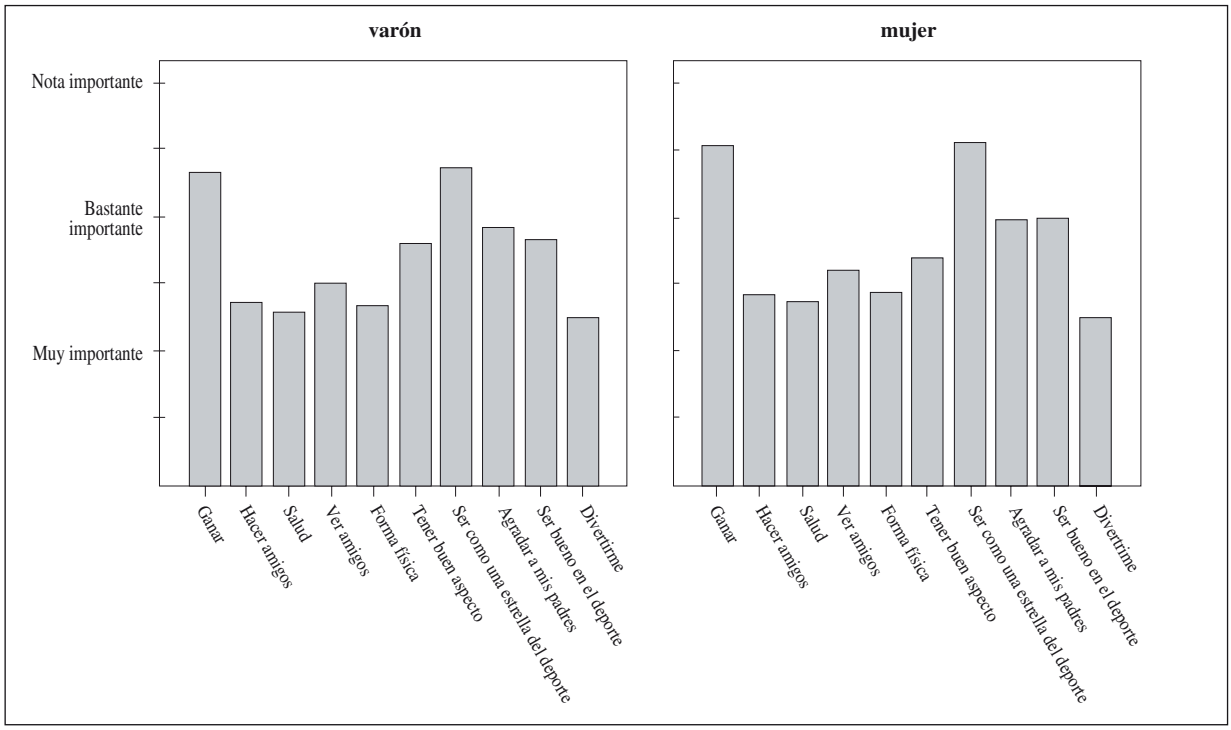

Fig. 1.—Razones para la práctica del deporte.

física que los hombres, que a pesar de ello, también lo consideran bastante relevante. Ambos sexos dan bastante importancia a razones como agradar a sus padres o ser buenos en el deporte y, por el contrario, apenas consideran ganar o llegar a ser una estrella en el deporte.

En la figura 2 mostramos los resultados en respuesta a la pregunta "¿Cómo consideras tu forma física?". No existen grandes diferencias en las opiniones de chicas y chicos, con un porcentaje importante considerando su forma física buena o normal y solo regular en una pequeña parte. Al margen de la actividad física y deporte que los alumnos/as practican fuera del horario escolar, el cuestionario administrado incluye ítems relacionados con las clases de educación física que los sujetos reciben en la escuela (fig. 3). Los resultados no difieren según el sexo. A la mayoría le gustan mucho las clases de educación física y solamente un porcentaje muy pequeño afirma que les gusta poco o nada.

A través de los cuestionarios administrados hemos querido obtener información no sólo de los hábitos de actividad física de los sujetos de la muestra, sino tam-

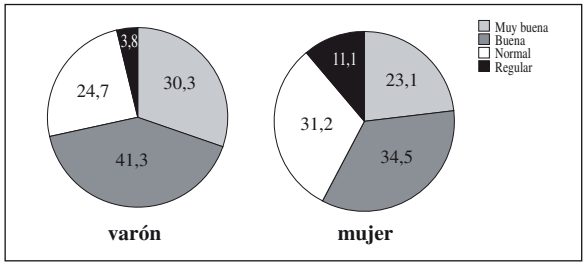

Fig. 2.—Forma física percibida.

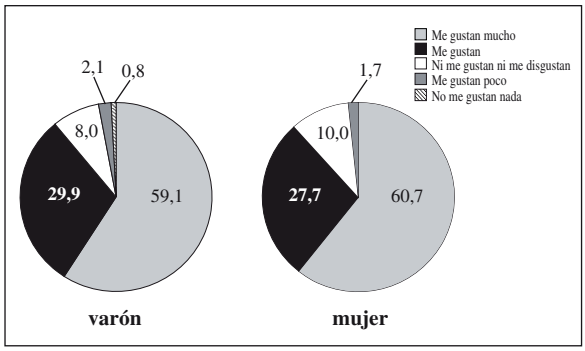

Fig. 3.—Gusto por las clases de educación física en la escuela.

bién de las personas que les rodean, como son la familia cercana y los mejores amigos. Dichos datos están recogidos en la tabla V, en la que se muestra como un tercio de padres y madres nunca practican, porcentaje que se reduce en el caso de los hermanos mayores o menores. En lo que se refiere a los hábitos de los amigos, la mitad de los jóvenes de la muestra sostienen que sus mejores amigos practican deporte todos los días de la semana en su tiempo libre y tan sólo una mínima parte afirma que no lo realizan nunca.

La tabla VI se refiere al apoyo que los jóvenes de la muestra poseen por parte de las personas cercanas a la hora de la realización de deporte. Más del 50% de los alumnos/as se sienten animados por su padre todas las semanas a la hora de practicar deporte, siendo algo mayor el porcentaje de sujetos que perciben por parte de su madre ánimos todas las semanas. El porcentaje de apoyo se reduce marcadamente por parte de los herma-

Tabla V
Práctica deportiva de las personas del entorno

Persona	*Frecuencia*	*Porcentaje*
Padre	Todas las semanas	37,3%
	Menos de una vez a la semana	17,3%
	Nunca	30,1%
	No lo sé	13,1%
	No tengo	2,2%
Madre	Todas las semanas	30,8%
	Menos de una vez a la semana	19,4%
	Nunca	35,4%
	No lo sé	13,8%
	No tengo	0,7%
Hermano mayor	Todas las semanas	29,1%
	Menos de una vez a la semana	8,8%
	Nunca	12,1%
	No lo sé	13,7%
	No tengo	36,3%
Hermano menor	Todas las semanas	24,8%
	Menos de una vez a la semana	8,1%
	Nunca	12,7%
	No lo sé	13,5%
	No tengo	40,8%
Mejor amigo	Todas las semanas	53,4%
	Menos de una vez a la semana	12,3%
	Nunca	6,2%
	No lo sé	24,7%
	No tengo	3,4%

Tabla VI
Apoyo a los sujetos en la práctica deportiva por parte de sus personas cercanas

Persona	*Frecuencia*	*Varón*	*Mujer*
Padre	Todas las semanas	58,8	53,6
	Menos de una vez a la semana	14,1	14,7
	Nunca	14,4	19,1
	No lo sé	11,7	10,5
	No tengo	1,6	2,2
Madre	Todas las semanas	63,8	59,1
	Menos de una vez a la semana	14,6	17,4
	Nunca	12,5	14,1
	No lo sé	8,3	9,4
	No tengo	0,8	0
Hermano mayor	Todas las semanas	22,6	21,0
	Menos de una vez a la semana	9,0	8,8
	Nunca	17,3	15,5
	No lo sé	15,4	18,8
	No tengo	35,6	35,9
Hermano menor	Todas las semanas	13,0	11,3
	Menos de una vez a la semana	5,6	6,4
	Nunca	21,8	25,7
	No lo sé	18,4	20,2
	No tengo	41,2	36,5
Mejor amigo	Todas las semanas	39,1	32,0
	Menos de una vez a la semana	15,7	14,9
	Nunca	17,8	20,2
	No lo sé	25,0	28,7
	No tengo	2,3	4,1

nos mayores y de los amigos. No se detectan diferencias importantes entre chicos y chicas.

Hábitos alimenticios

El siguiente apartado de la investigación está destinado al conocimiento de los hábitos de alimentación de los jóvenes participantes. En la tabla VII reflejamos la frecuencia con la que los sujetos realizan las diferentes comidas a lo largo del día, desde el desayuno hasta la cena. Como podemos observar, una parte importante de los alumnos no desayuna todos los días de la semana y algunos no realizan esta primera comida del día. Sin embargo, el porcentaje de participantes que almuerzan a media mañana es más elevado, con casi un 90%. A la hora de comer, diferenciamos la comida con sándwich o bocadillo de la comida caliente. La mitad de los sujetos de la muestra nunca comen bocadillos y por otro lado, en torno a una cuarta parte lo hacen entre 1 y 3 días a la semana. Son más frecuentes los estudiantes que optan por la comida caliente, con más de dos tercios del total. Este es también el porcentaje de los que merienda, siendo mínima la cuantía de los que no lo hacen. Al igual que en la comida, para la cena también hacemos distinción entre la cena con sándwich o bocadillo y la caliente. El tanto por ciento de sujetos que cenan caliente todos los días es muy superior al que lo hace con bocadillo; sin embargo, sí existe un porcentaje considerable de individuos que cenan sándwich o bocadillo entre 1 y 3 días a la semana.

La tabla VIII muestra la periodicidad con la que se consumen ciertos alimentos específicos. Aunque una gran mayoría de los alumnos no suelen tomar café o té nunca o casi nunca, si hay un pequeño porcentaje que afirma hacerlo entre 1 y 3 días a la semana. Cerca de una cuarta parte consumen diariamente bebidas con gas y más del 80% comen golosinas o dulces al menos 1 a 3 días a la semana. El consumo de bolsas de patatas fritas, de frutos secos y de hamburguesas o salchichas es también elevado y en torno a un 70% de los sujetos reconocen tomarlas al menos 1 a 3 días a la semana.

La fruta es un alimento que se consume todos los días por en torno a la mitad de la muestra, existiendo un 9% de la misma que afirma no consumirla nunca. Las verduras y hortalizas no son de los alimentos más frecuentemente consumidos y cerca de una cuarta parte reconocen no consumirlas nunca o casi nunca. Las legumbres son consumidas por la mitad de los sujetos entre 1 y 3 días a la semana y por más del 30% entre 4 y 6 días. Tan sólo una pequeña parte de la muestra sostiene que nunca o casi nunca ingiere este tipo de alimentos.

Tabla VII
Hábitos alimenticios

Comidas	*Frecuencia*	*Porcentaje (%)*
Desayuno	Todos los días	59,1%
	4-6 días por semana	9,6%
	1-3 días por semana	16,9%
	Nunca o casi nunca	14,1%
	NS/NC	0,3%
Almuerzo	Todos los días	89,3%
	4-6 días por semana	3,9%
	1-3 días por semana	2,2%
	Nunca o casi nunca	2,4%
	NS/NC	2,2%
Comida con sandwich o bocadillo	Todos los días	13,1%
	4-6 días por semana	6,9%
	1-3 días por semana	27,0%
	Nunca o casi nunca	50,0%
	NS/NC	3%
Comida caliente	Todos los días	69%
	4-6 días por semana	17,5%
	1-3 días por semana	9,9%
	Nunca o casi nunca	1,8%
	NS/NC	1,9%
Merienda	Todos los días	67,8%
	4-6 días por semana	14,2%
	1-3 días por semana	8,9%
	Nunca o casi nunca	6,5%
	NS/NC	2,6%
Cena con sandwich o bocadillo	Todos los días	9,3%
	4-6 días por semana	11%
	1-3 días por semana	44,3%
	Nunca o casi nunca	32,2%
	NS/NC	3,1%
Cena caliente	Todos los días	43,2%
	4-6 días por semana	27,4%
	1-3 días por semana	16,1%
	Nunca o casi nunca	11,4%
	NS/NC	1,9%

El 16% nunca o casi nunca comen embutidos, mientras que una cuarta parte dice tomarlos todos los días. En torno a la mita de la muestra suele consumir ternera o cerdo y pollo o pavo entre 1 y 3 veces a la semana. La ingesta de pescado y huevos tiene unas proporciones muy similares a las de la carne. En lo que se refiere a los productos lácteos, mas de la mitad de los sujetos toman yogures a diario y sin embargo, en el caso del queso, el porcentaje es bastante más reducido y hasta una cuarta parte afirman no consumirlo nunca. La frecuencia de ingesta de mantequilla es algo superior a la de la margarina, aunque ambos productos no alcanzan porcentajes altos de consumo.

Una vez conocidos los hábitos alimenticios de los sujetos que toman parte en la investigación, les preguntamos si creían que dichas costumbres de alimentación eran más o menos sanas comparadas con las de los jóvenes de su edad (fig. 4). Los resultados son similares

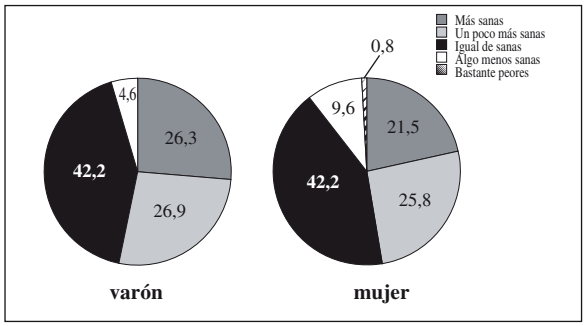

Fig. 4.—Opinión sobre las costumbres alimenticias comparadas con las de jóvenes de la misma edad.

en ambo sexos. El mismo porcentaje de chicas y de chicos opinan que sus costumbres alimenticias son igual de sanas que las del resto de los jóvenes, hasta una cuarta parte apuntan que poseen hábitos de alimentación más sanos y más de un cuarto sostienen que dichas costumbres son un poco más sanas.

En lo que se refiere al consumo de complementos alimenticios tales como las vitaminas y el hierro (fig. 5), tanto los chicos como las chicas alegan en un gran porcentaje que no han tomado vitaminas durante el pasado mes. Dicho porcentaje es aún mayor en lo que se refiere consumo de suplementos de hierro.

Discusión

El estudio de la relación entre práctica deportiva y salud por parte de diferentes autores ha puesto de manifiesto que en los niños y adolescentes es importante considerar la práctica deportiva extraescolar, pues la actividad realizada en la escuela es generalmente insuficiente para generar efectos beneficiosos sobre la

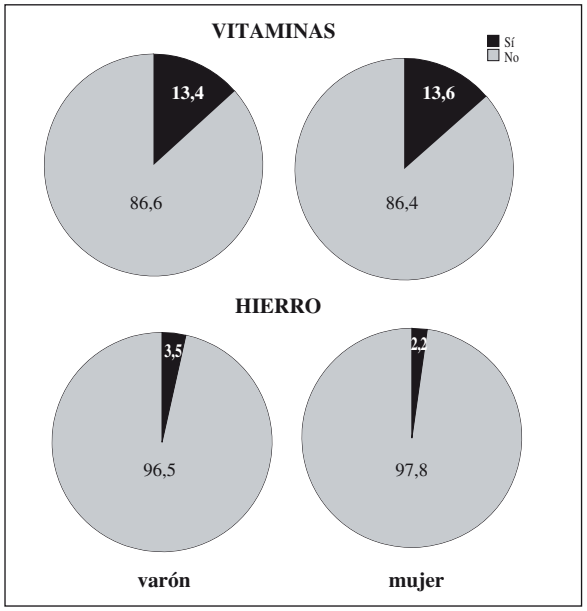

Fig. 5.—Ingestión de complementos alimenticios.

Tabla VIII
Frecuencia del consumo de alimentos

Alimento	*Todos los días*	*4-6 días por semana*	*1-3 días por semana*	*Nunca o casi nunca*
Café, té	3,5%	1,8 %	6,8%	88%
Frutas	45,7%	20,2 %	25,4%	8,7%
Bebidas con gas	24,5%	12,3 %	32,6%	30,6%
Dulces y golosinas	18,6%	23,4 %	43,5%	14,5%
Verduras y hortalizas	16,3%	27,4 %	34,3%	22%
Frutos secos	8,3%	16 %	44,1%	31,6%
Patatas fritas caseras	11,9%	22,9 %	50,3%	14,8%
Bolsa de patatas chips	9,7%	12,3 %	47,3%	30,8%
Hamburguesas o salchichas	4,5%	9 %	51,2%	35,3%
Pan integral o de centeno	13,6%	8,7 %	11,1%	66,6%
Zumo natural	27,3%	18,7 %	30,9%	23,1%
Embutidos	24,4%	25,7 %	33,9%	16%
Legumbres	12%	30,8 %	48,8%	8,3%
Margarina	10,3%	11,6 %	26,5%	51,6%
Mantequilla	13%	14,1 %	32,6%	40,3%
Yogur	54%	23,9 %	16,7%	5,3%
Queso	14%	28 %	35%	23%
Carne	13,4%	36,8 %	45,1%	4,7%
Carne de ave	9,0%	33,2 %	52%	5,8%
Pescado	10,5%	27,5 %	54,5%	7,6%
Huevos	10,5%	27,2 %	55,7%	6,6%

salud[14,17]. El cuestionario utilizado en nuestra investigación permite distinguir entre la práctica de deporte reglado y la realización de actividades tales como montar en bicicleta o correr, que requieren esfuerzo físico. Los resultados del estudio ponen de manifiesto que los participantes invierten la mayor parte de su tiempo en actividades ligeras o moderadas y que una parte apreciable nunca práctica actividades físico-deportivas, confirmando datos previos en diferentes países desarrollados. Así, comportamientos sedentarios y actividades ligeras predominan en muchos adolescentes norteamericanos[18], británicos[19] o australianos[20]. En adolescentes españoles con edades comprendidas entre los 12 y 16 años se ha indicado recientemente que más de dos tercios de las actividades diarias son de tipo sedentario y que las actividades ligeras suponen en torno a un 17%[21]. Los datos referentes a la frecuencia de práctica ponen de manifiesto que la práctica de actividad física y deporte al menos dos o tres veces por semana alcanza porcentajes superiores al 70% en chicos y menores, sobre todo en lo que a deporte se refiere, en chicas. Estos resultados son similares a los obtenidos en el estudio AVENA de adolescentes españoles[22] o en investigaciones realizadas en Estados Unidos, con valores en torno al 70% en varones y al 50% en mujeres[23]. El deporte más practicado es el fútbol, al igual que ya se ha observado en otros estudios llevados a cabo en nuestro país[24], mientras que la actividad física mayoritaria es el correr.

Nuestro estudio pone de manifiesto que los chicos realizan mayor actividad que las chicas, especialmente en lo que se refiere a la práctica de deportes, y que en éstas últimas es más elevado el porcentaje de las que reconocen una ausencia total de práctica. Está ampliamente descrito que en la población infantil y juvenil los chicos son físicamente más activos que las chicas y los presentes resultados son consistentes con los obtenidos en estudios previos que analizan la práctica deportiva diferenciada por géneros, tanto en España[26], como en otros países desarrollados[27]. Muy recientemente la información procedente de autoinformes se ha confirmado en adolescentes españoles mediante el uso de acelerómetros[28]. Según algunos autores el mayor grado de sedentarismo en las chicas podría deberse predominantemente a diferencias en el tiempo empleado en actividades moderadas y muy intensas[29], y se ha indicado que los hombres tienden a informar de la realización de más actividad física en su tiempo libre, tanto ligera como moderada o intensa, que las mujeres[30]. Nuestro propio grupo ha descrito con anterioridad resultados muy similares en la población escolar de Educación Secundaria Obligatoria de distintos municipios asturianos[31,32].

Entre los factores predictores de la práctica de actividad física se encuentran factores de tipo personal y social. Desde el punto de vista de los primeros, es conocida que la percepción de competencia física o deportiva o la forma física percibida se asocian positivamente con la práctica en niños y adolescentes[33] y tienen, además una influencia positiva en un menor consumo de sustancias nocivas y un mayor consumo de alimentos sanos[34]. Los individuos que se perciben más sanos y con mejor forma física perciben además menos

barreras para la práctica del ejercicio físico que aquello que se consideran en peores condiciones físicas[17]. En la presente investigación, un porcentaje importante de los sujetos encuestados considera su forma física buena o normal y solo una pequeña parte la define como regular. Es interesante que, a pesar del mayor porcentaje de sedentarismo en las chicas, no existan diferencias apreciables de género en la percepción de la forma física, es decir, no se presenta una correspondencia entre una dimensión específica del autoconcepto y una determinada conducta de salud, efecto que ha sido atribuido por diversos autores a los valores y actitudes dispares que imprime el proceso de socialización en chicos y chicas[34].

Entre los factores sociales destaca la práctica de la actividad física por parte de los otros significativos y se observa que una parte importante de la muestra indica pertenecer a clubes deportivos o escolares y reconoce el hacer amigos como una de las razones fundamentales para la práctica de actividades físico-deportivas. Por otra parte, existe una relación directa entre la práctica de actividad física de niños y adolescentes y la práctica y el estímulo por parte de padres, hermanos y amigos[35]. Nuestros datos ponen de manifiesto el hecho preocupante de que un tercio de padres y madres nunca practican actividades físico-deportivas, a pesar de los escolares reconocen encontrar un apoyo por parte de los mismos, y también, aunque en menor medida por parte de amigos y hermanos mayores. La influencia de los hermanos mayores sobre la práctica deportiva y de ejercicio intenso ya ha sido descrita previamente en adolescentes valencianos[17]. Aunque algunas investigaciones han puesto de manifiesto la importancia de considerar diferencias de género en las influencias sociales[36], en nuestra muestra no se detectan diferencias significativas entre chicos y chicas en el apoyo encontrado por parte de los padres, hermanos o amigos.

Otra variable importante en lo que se refiere a conductas de salud que hemos analizado en el presente estudio se refiere a la alimentación. Una tendencia preocupante en nuestro país está siendo el progresivo abandono de la dieta mediterránea adoptándose una adhesión a patrones dietéticos menos saludables, especialmente en la infancia y en la adolescencia, que están repercutiendo en un incremento de la obesidad y en mayores tasas de enfermedades crónicas[2].

Resulta interesante considerar los resultados obtenidos respecto a las comidas diarias, observándose que un porcentaje muy importante de sujetos reconocen no desayunar de forma habitual. El desayuno debe considerarse como una de las ingestas más importantes por su contribución al mantenimiento de una actividad física e intelectual durante la mañana y el poder constituirse en un factor determinante en el condicionamiento de una dieta inadecuada[37]. Sin embargo, los nuevos estilos de vida están contribuyendo a cambiar los hábitos alimentarios y son diversos los estudios realizados en España que confirman como una parte de los niños y adolescentes acuden a los colegios e institutos sin haber realizado su primer desayuno, caso de estudiantes navarros y valencianos de educación secundaria[38,39] o adolescentes escolarizados de Santander[40].

La alimentación de los jóvenes gaditanos también muestra algunas otras tendencias que sería deseable corregir. Por ejemplo, menos de la mitad consumen fruta todos los días o verduras y hortalizas de forma habitual. Se trata de resultados similares a estudios previos, por ejemplo los realizados en una población de jóvenes de Guadalajara[24], o en adolescentes de Santander[10]. Como aspecto positivo habría que destacar el que dos tercios de los sujetos encuestados ingieren comidas calientes en el almuerzo todos los días, mientras que solo una pequeña parte lo hace en forma de sandwiches o bocadillos. En un estudio realizado en alumnos de Educación Secundaria Obligatoria de Navarra se había descrito con anterioridad que una parte muy importante de los jóvenes tomaban un bocadillo en el almuerzo[38]. Por último, hay que resaltar que, a pesar de la tendencia al consumo creciente de suplementos por parte de los adolescentes[41], lo sujetos encuestados no reconocen una utilización reciente de suplementos de vitaminas y hierro.

Nuestros resultados indican que la práctica de conductas saludables por parte de los niños y adolescentes gaditanos es mejorable, tanto a lo que se refiere a los hábitos alimenticios como a la práctica de actividades físico-deportivas. Los datos obtenidos, junto con los publicados en los últimos años por diversos autores, confirman la necesidad de una adecuada educación sobre hábitos de vida saludable y el desarrollo de programas de intervención en niños y jóvenes, aconsejando sobre dieta y actividad física y prestando especial interés a las chicas, que constituyen el grupo menos físico activamente y con mayor riesgo de padecer trastornos. Nuestro objetivo debería ser que cuando lleguen a la edad adulta sean capaces de mantener hábitos de vida saludables que les hagan posible prevenir la enfermedad y mantenerse en un estado de salud óptimo.

Agradecimientos

Este estudio ha sido financiado por el Centro Andaluz de Medicina del Deporte.

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):290-298
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

The effect of prostaglandin synthase inhibitor, aspirin on the rat intestinal membrane structure and function

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Abstract

Aspirin at a dose of 50 mg/kg body weight was found to decrease the activity of the rat intestinal brush border membrane (BBM) - associated enzymes such as the sucrase, lactase, maltase and alkaline phosphatase. Aspirin treatment also led to a decrease in the microviscosity in the native as well as the benzyl alcohol treated membrane which might be due to the lipid peroxidative damage in the membrane. Physical correlation of the membrane oxidative damage was evident as the Fourier Transformation Infra Red (FTIR) study of the Aspirin treated membrane, which include an increased proportion of gauche to trans conformer, shift in the methylene C-H asymmetric and symmetric stretching frequencies, C = O double bond stretching, NH bending, antisymmetric (N)-CH_3 bending, C-N stretching and antisymmetric CNC stretching while there was no change in the CH_2 wagging and twisting as well as in NH-bending amide bond I and II. Aspirin treatment also caused an alteration in the glucose and histidine transport, as evident by a decreased V_{max} value while the apparent K_m remaining unchanged in the control and Aspirin-treated animals confirming that there was no change in the substrate affinity constant of the membrane transport proteins for the glucose and the basic amino acid, although the rate of transport decreased considerably. There was a decrease noted in the energy of activation of glucose and histidine transport when studied at different temperature but no change in the temperature of phase transition in the BBM with Aspirin treatment, thus implying that perhaps the thermotropic phase transition in the membrane may have relatively little effect on the transport processes. The result suggests an underlying molecular mechanism indicating the implied membrane damage by Aspirin, an important member of the non-steroidal anti-inflammatory drug (NSAID) family which could possibly through an oxidative damage may lead to an altered molecular structure, physical state and biological functions of the intestinal membrane.

(*Nutr Hosp*. 2010;25:290-298)

DOI:10.3305/nh.2010.25.2.4598

Key words: *Aspirin. Transport studies. FTIR. Disaccharidases. Pyrene fluorescence.*

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Recibido: 17-XI-2009.
Aceptado: 22-XI-2009.

EL EFECTO DEL INHIBIDOR DE LA SINTASA DE PROSTAGLANDINA, ASPIRINA, SOBRE LA ESTRUCTURA Y FUNCIÓN DE LA MEMBRANA INTESTINAL DE LA RATA

Resumen

Se encontró que la aspirina a una dosis de 50 mg/kg de peso corporal disminuye la actividad de las enzimas asociadas a la membrana con borde en cepillo (MBC) del intestino de la rata como la sucrasa, lactasa, maltasa y fosfata alcalina. El tratamiento con aspirina también produjo una disminución de la microviscosidad en la membrana nativa así como en la membrana tratada con alcohol bencílico, lo que podría deberse a la lesión de peroxidación lipídica de la membrana. La correlación física de la lesión oxidativa de la membrana fue evidente como mostró el estudio Fourier Transformation Infra Red (FTIR) de la membrana tratada con aspirina, que incluía un aumento en la proporción de la conformación levo a trans, un cambio en las frecuencias de estiramiento metileno C-H asimétrico y simétrico, el estiramiento de los dobles enlaces C = O, la curvatura NH, la curvatura anti-simétrica (N)-CH3, el estiramiento C-N y el estiramiento anti-simétrico CNC, mientras que no hubo cambios en el movimiento y retorcimiento CH2 ni en la curvatura NH del enlace amida I y II. El tratamiento con aspirina también produjo una alteración en el transporte de glucosa e histidina, como se evidenció por una disminución del valor de la Vmax mientras que la Km aparente permaneció inalterada en los animales control y tratados con aspirina, lo que confirma que no hubo cambios en la constante de afinidad por el sustrato de las proteínas transportadoras de membrana para la glucosa y el aminoácido básico, si bien la tasa de transporte disminuyó considerablemente. Se apreció un descenso en la energía de activación del transporte de glucosa e histidina cuando se estudiaron a temperaturas distintas, pero no hubo cambios en la temperatura de la fase de transición de la MBC con el tratamiento con aspirina, lo que implica que quizás la fase de transición termotrópica en la membrana pudiera tener un efecto relativamente pequeño sobre los procesos de transporte. El resultado sugiere un mecanismo molecular subyacente lo que indica el daño implícito de la membrana por la aspirina, un miembro importante de la familia de fármacos antiinflamatorios no esteroideos (AINE), que posiblemente a través de un daño oxidativo podría producir una alteración de la estructura molecular, del estado físico y de las funciones biológicas de la membrana intestinal.

(*Nutr Hosp*. 2010;25:290-298)

DOI:10.3305/nh.2010.25.2.4598

Palabras clave: *Aspirina. Estudios de transporte. FTIR. Disacaridasas. Fluorescencia pireno.*

Introduction

Despite the introduction of many new drugs, aspirin (acetyl salicylic acid) the first among the non-steroidal anti-inflammatory drugs (NASIDs) is still the most widely prescribed analgesic, antipyretic and anti-inflammatory agent.[1,2] Recent studies have shown that the long-term intake of aspirin in humans leads to protection against the development of colorectal cancer as well as malignancies in other tissues.[3-6] In addition, aspirin has been demonstrated to inhibit chemically induced carcinogenesis in various animal models.[7-9] The protective effects of aspirin against carcinogenesis have been presumably attributed to its ability to inhibit inflammation.[6] The anti-inflammatory action of aspirin is believed to result from its non-specific inhibition of cycloxygenase (COX)[2,6] by acetylating the amino terminal of serine on the active site of the enzyme thereby reducing the level of prostaglandin production. Moreover, it has got the ability of scavenging free radicals which further increases its anti-inflammatory efficacy.[10] Also, salicylic acid the metabolite of aspirin exhibits anti-inflammatory action by inhibiting the migration of leucocytes besides the aggregation of human neutrophils which is induced by some chemoattractants. Aspirin has been reported to inhibit the growth and size of intestinal tumor, probably by inhibiting the activation of NF-κB, a transcription factor critically involved in the production of inflammatory cytokines and the subsequent inflammatory response.[11,12] The most spectacular effect of aspirin is to cause inhibition of platelet aggregation and therefore, the drug of choice for patients suffering from cardiovascular diseases, such as angina pectoris, coronary artery diseases, myocardial infarction and stroke.[13-16]

Besides its wide range of uses, it has certain adverse effects however, probably arising out of the deficient cytoprotective role of the prostaglandins, such as the stomach irritation, gastrointestinal disturbances, ulcerative alteration of certain enzyme levels and other biochemical parameters.[17,18] Keeping in view the above, therefore, in the present study the intestinal membrane structure and function have been studied in rats in aspirin treatment.

Materials and methods

Animals and drug treatment: Male Wistar rats weighing between 100-125 g were procured from the central animal house, Panjab University. They were housed in individual cages and maintained on rat pellet diet and water *ad libitum*. The animals were kept individually in polypropylene cages under hygienic conditions, and ambient light and temperature, strictly in conformation with the guidelines as laid down by the institutional ethics committee. After acclimatization for one week, the animals were divided into two groups, control and treated, comprising six animals each. Treated group of animals were given aspirin dissolved in water orally at the dose of 50mg/5 ml H_2O/kg body weight while the control received water only. The treatment was discontinued after 28 days and on 29th day after overnight fasting, the animals were sacrificed under an overdose of ether anesthesia. In order to avoid diurnal variation in the biochemical parameters, nutrient uptake and enzymatic analysis, the animals were sacrificed uniformly around 9AM throughout the study. From each animal the intestine was removed, divided into duodenum, jejunum, ileum and colon, washed with chilled normal saline, wet weight of the tissue recorded and proceeded for the above mentioned parameters.

Preparation of intestinal brush border membrane (BBM): Intestinal BBM of different segments, i.e., duodenum, jejunum, ileum and colon were isolated following the method of Schmitz et al. (1973).[19] The 10% (w/v) homogenate of the tissue in 1mM Tris-50mM Mannitol buffer (pH 7.4) at 4°C was passed through two layers of cheese cloth. To the filtrate, anhydrous $CaCl_2$ was added with constant stirring on a magnetic stirrer to a final concentration of 10 mM and left for 10-15 min in cold. Later it was centrifuged at 2,000 x g for 10 min at 4°C. The supernatant was recentrifuged at 42,000 x g for 20 min. The pellet was suspended in 20 vol of 50mM sodium maleate buffer (pH 6.5-6.8) and recentrifuged at 42,000 x g for 20 min, the final pellet obtained was suspended in 50 mM sodium maleate buffer containing 0.02% sodium azide. The final membrane preparation obtained was similar to the P_2 fraction of Schimtz et al. (1973)[19] and essentially free from mitochondria, microsomes, lysosomes, basolateral membranes and nuclei as assessed by marker enzyme assays. Also, purity of the isolated BBM was assessed by enrichment of the marker enzymes that showed 20-25 fold purification in the activity of alkaline phosphatase and the disaccharidases.

Assay of Disaccharidases: Sucrase, lactase and maltase activity were determined by measuring the D-glucose liberated from the respective sugar substrates and then using a glucose oxidase-peroxidase enzymatic system (GOD-POD) as described earlier.[20]

Assay of alkaline phosphatase: Alkaline phosphatase acitivity was assayed according to the method of Bergmeyer (1963)[21] by measuring the liberated *p*-nitrophenol from the phosphate mono-ester substrate, *p*-nitrophenyl phosphate.

Protein estimation: Protein concentration was determined by the method of Lowry et al. (1951)[22], using bovine serum albumin as the standard.

Measurement of membrane microviscosity using pyrene as an extrinsic fluorophore: Pyrene fluorescence excimer (dimer) formation was used to study the lateral diffusion in the membrane as described by us earlier.[23] A 100 µl of membrane preparation was taken and added 1ml stock solution (5 mM in acetone) of pyrene and 100 µl of sodium maleate buffer. The tubes were incubated at 37°C for 1 h, vortexed in between and then centrifuged at 10,000 x g for 1 h. To the pellet was added sodium maleate buffer till the solution was clear. Finally, the flu-

orescence intensity was read in a fluorimeter (ELICO CL 53, Vardhman Scientific Agencies, India) using a primary filter of 365 nm while the secondary filter used were 515 and 475 nm for the excimer and monomer fluorescence, respectively. The viscosity was calculated from the monomer/excimer fluorescence intensity ratio using the following relationship:

E/M (excimer fluorescence)/(monomer fluorescence) = (Pyrene) TK/η

Where T is the absolute temperature in Kelvin, K is the Boltzman constant (1.38062 x 10^{-23}j/k) and η is the microviscosity, while the pyrene concentration was kept at 5 mM.

FTIR studies in the intestinal BBM: A 100 µl aliquot of the membrane preparation was taken, and to it 1 ml of sodium maleate buffer (pH 6.5-6.8) was added. The tubes were centrifuged for 10 min at 10,000 x g. The precipitates were dried and mixed with KBr in the ratio of 5:95. The mixture was passed at a pressure of 10-15 tonnes with the help of a hydraulic pressure machine. The FTIR spectra were recorded in these pellets in the range of 450-4,000 cm^{-1} in a Perkin-Elmer instrument.[17]

Transport studies: Everted sac technique[24] was used to study the intestinal transport. A section of the intestine is turned inside out and tied at each end. This everted sac is immersed in buffered ionic medium containing the metabolite and change in the concentration of the molecule is measured after incubation. By turning the intestine inside out transport is now from a large volume of the incubation medium into a small volume inside the everted gut.[25] This thus magnifies the absorption that occurs and is more sensitive preparation than using the opened intestine tissue as such (e.g., the intestinal ring preparation).

Preparation of everted sac: After dissecting, the intestine was recovered and flushed with chilled saline to remove the residual faecal matter and undigested food etc. The everted sac was prepared by sliding a glass rod as described by Mizuma et al. (1992).[24] One end of the everted sac was ligated carefully; a syringe filled with Krebs-Ringer Phosphate (KRB) buffer (pH 7.4) was inserted into the sac. The sac thus prepared was then incubated with the metabolites (L-histidine or D-glucose) to be studied. Care was taken in tying the open ends of the sacs such that all ligatures were firm and tight enough to prevent leakage but not too tight to damage the tissue.

Glucose transport and estimation: An increase in the rate of appearance of glucose from the medium in the sacs is taken as an indication of glucose transport across the membrane, which can be measured spectrophotometrically using the GOD-POD enzymatic system.[25] One ml of KRP buffer was injected into all the sacs and 2 ml of acetic acid was added. It was kept in boiling water bath for 10 min to deproteinize the solution and then centrifuged to obtain the clear supernatant solution. Four ml of GOD-POD reagent was added into all the tubes and after 30 min the OD was taken. Blank and standard glucose samples were also run simultaneously. To study the effect of temperature, sacs were immersed in KRP containing 5 mM glucose for 30 min at 4, 20, 37 and 50°C, respectively. At the end of the incubation time, the sacs were punctured and analyzed for glucose.

Histidine transport and estimation: An increase in the appearance of histidine from the medium in the sac is taken as an indication of amino acid transport across the membrane[25]. Injected was 1 ml of KRB buffer into all the sacs and they were placed in KRB containing 10, 20, 30, 40 and 50 mM histidine for 30 min. The solution was taken out of the sacs after the designated time interval in a standard assay system and 2ml of acetic acid was added. It was kept in boiling water bath for 10min to deproteinize the solution. To this was added 0.4ml sulphanilic acid, mixed thoroughly and 0.4 ml of sodium nitrite added to the tubes. Tubes were shaken and left for 5 min and 0.6 ml of sodium carbonate added into all the tubes and incubated for 30 min. L-histidine was measured by reducing it with diazotized sulphanilic acid, producing a colored compound that is read at 498 nm. Blank and standard histidine samples were also run simultaneously. The effect of temperature was studied by immersing the sacs in KRP containing 40 mM L-histidine for 30 min at 4, 20, 37 and 50°C. To study the effect of time, sacs were immersed in the medium containing 40 mM L-histidine for different time intervals: 30, 45, 60 and 120 min.

Statistical Analysis: Data is expressed as mean ± S. D. of six independent observations. Differences between different groups was tested using Student's 't' test.

Results and discussion

The present study was carried out to investigate the effects of aspirin on the intestinal functions of rats such as the brush border membrane disaccharidases and alkaline phosphatase activities as well as the intestinal transport of D-glucose and L-histidine. The functional changes of the intestinal membrane were correlated with the physical characteristics such as the membrane fluidity study by pyrene excimer formation and the analysis of the functional groups by FTIR study.

Changes in specific activity of the enzyme: Table I shows the results of the effect of aspirin administration orally for 28 days in duodenal, jejunal, ileal and colonic homogenates, which demonstrate a significant alteration in the specific activities of the sucrase, lactase, maltase and alkaline phosphatase in the treated animals as compared to the control. Aspirin treatment resulted in a highly significant decrease ($p < 0.001$) in the sucrase activity in duodenal, jejunal and colonic homogenates and a significant decrease in ileal homogenate ($p < 0.01$). Lactase showed a highly significant decrease ($p < 0.001$) in jejunal and significant decrease in the duodenal homogenate ($p < 0.01$), and fairly significant decrease ($p < 0.05$) in ileal and colonic homogenates. For maltase, a

Table I
Effect of aspirin on enzymes in intestinal homogenates and the isolated brush border membrane

Intestinal segment		Enzymes (μmoles/mg protein)							
		Sucrase		Lactase		Maltase		Alkaline phosphatase	
		Control	Treated	Control	Treated	Control	Treated	Control	Treated
Duodenum	Homogenate	0.076 ± 0.002	0.049 ± 0.003***	0.032 ± 0.001	0.021 ± 0.004**	0.108 ± 0.003	0.083 ± 0.005***	0.064 ± 0.001	0.043 ± 0.001***
	BBM	2.006 ± 0.109	0.579 ± 0.078***	0.476 ± 0.111	0.084 ± 0.010***	4.39 ± 0.022	0.987 ± 0.136***	2.096 ± 0.039	0.479 ± 0.061***
Jejunum	Homogenate	0.131 ± 0.013	0.066 ± 0.002***	0.063 ± 0.006	0.033 ± 0.002***	0.144 ± 0.013	0.086 ± 0.002***	0.069 ± 0.006	0.040 ± 0.001***
	BBM	0.146 ± 0.019	0.128 ± 0.012	0.110 ± 0.013	0.107 ± 0.010	0.159 ± 0.020	0.138 ± 0.012	0.087 ± 0.011	0.048 ± 0.004**
Ileum	Homogenate	0.100 ± 0.020	0.048 ± 0.006***	0.034 ± 0.006	0.02 ± 0.005*	0.127 ± 0.025	0.097 ± 0.013	0.064 ± 0.013	0.035 ± 0.005*
	BBM	0.345 ± 0.028	0.73 ± 0.093***	0.145 ± 0.008	0.257 ± 0.033**	0.4 ± 0.021	1.030 ± 0.132***	0.21 ± 0.011	0.417 ± 0.089**
Colon	Homogenate	0.026 ± 0.003	0.006 ± 0.0005***	0.026 ± 0.003	0.016 ± 0.004*	0.095 ± 0.006	0.047 ± 0.004***	0.041 ± 0.004	0.014 ± 0.001***
	BBM	0.139 ± 0.014	0.111 ± 0.018	0.034 ± 0.003	0.027 ± 0.004	0.489 ± 0.051	0.306 ± 0.060**	0.195 ± 0.021	0.140 ± 0.023*

Values are expressed as mean ± SD of four observations. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, represents the comparison between the control and treated groups.

highly significant decrease ($p < 0.001$) was recorded in duodenal, jejunal and colonic homogenates whereas in ileum, the enzyme activity showed a decrease which was not statistically significant. A highly significant decrease ($p < 0.001$), in the activity of alkaline phosphatase was observed in duodenal, jejunal and colonic homogenates while the ileal tissue showed a fairly significant decrease ($p < 0.05$).

Aspirin treatment also produced changes in the specific activities of various enzymes in the brush border membranes (BBM) of various intestinal segments. The result shows that it significantly decreased the sucrase activity in duodenal BBM ($p < 0.001$) and also a decrease in jejunal and colonic BBM which was however not statistically significant. In ileal BBM a highly significant elevation in sucrase activity ($p < 0.001$) was observed. Similarly lactase activity showed a highly significant decrease ($p < 0.001$) in duodenal BBM and a much significant decrease in jejunum and colon. Lactase level was found to be significantly increased ($p < 0.01$) in ileal BBM. Aspirin treatment to animals significantly inhibited the activity of maltase in duodenal and colonic BBM ($p < 0.01$). The decrease in jejunum was found to be statistically non-significant, while the ileal BBM showed a highly significant increase in maltase activity ($p < 0.001$). The alkaline phosphatase activity was found to be decreased in duodenum ($p < 0.001$), jejunum ($p < 0.01$) and also in colon ($p < 0.05$), while the enzyme activity was significantly increased in ileal BBM ($p < 0.01$). The comparison of the data in table I also shows the presence of these enzymes in greater amount in the partially purified brush border membranes as expected which shows considerable enrichment of the activity. The enzyme activities also showed similar pattern of alteration in BBM as observed in the homogenates after aspirin treatment. The observed decrease in the activity of the enzymes might be due to either reduced substrate affinity (kinetic effect)[26] or specific modulation in protein molecules number or activity (metabolic effect).[27] On the other hand a rise in BBM enzyme in the ileum may indicate to a metabolic shift in absorption and digestive activities in preference to jejunum as earlier kinetic evidences suggest a close functional link between the carrier mediated sugar transport system and the disaccharide hydrolases,[28] as these are more enriched in the jejunum.

Studies on the pyrene fluorescence excimer formation in the intestinal BBM: The fluorescent aromatic hydrocarbon, pyrene has been solubilized and incorporated in the biological membranes, which appears to be located in the hydrocarbon core of the membrane. Steady state fluorescence measurements were performed at 27°C at an angle of 90° to the exciting beam in the fluorimeter and E/M ratios were calculated by comparing the fluorescence intensity at 515 nm to that 475 nm using 360 nm as the exciting wavelength. Microviscosity of the membrane was calculated from thereon and the inverse of microviscosity is taken as the fluidity. In a membrane suspension, the dimer (excimer) formation is independent of total pyrene concentration in the sample.

Table II shows the E/M ratios in native membranes of control and treated rats, and benzyl alcohol treated membranes in control and treated rats, respectively. Native membrane of treated rats showed an increase in E/M ratio in all the intestinal segments except in the jejunum. The increased value of E/M ratio leads to a decrease in microviscosity which in turn indicates to an elevation in membrane fluidity. Similarly in case of benzyl alcohol treated membranes, BBM of aspirin treated rats showed an increased E/M ratio except in jejunum. A decrease in microviscosity was observed in all the intestinal segments except jejunum resulting from an elevation in E/M ratios. In ileum and colon fluidity was highly increased. However, a small decrease and large reduction in fluidity was observed in duodenum and jejunum, respectively.

Table II

Relationship of the pyrene fluorescence excimer/monomer ratio and the resultant microviscosity in the isolated brush border membrane of intestinal segments in the control and the aspirin treated rats

Intestinal segment	Native membrane						Benzyl alcohol treated membrane					
	Excimer/monomer (E/M)		Microviscosity (η)		Fluidity (1/η)		Excimer/monomer (E/M)		Microviscosity (η)		Fluidity (1/η)	
	Control	Treated	Control	Treated	Control	Treated	Control	Treated	Control	Treated	Control	Treated
Duodenum	1.154	1.572	1.367	1.316	0.731	0.759	3.452	3.489	0.599	0.593	1.699	1.686
Jejunum	1.587	2.196	1.304	0.942	0.766	1.061	5.100	3.273	0.405	0.632	2.469	1.582
Ileum	1.657	1.757	1.249	1.178	0.800	0.848	4.237	5.463	0.488	0.378	2.049	2.645
Colon	1.794	1.875	1.153	1.104	0.867	0.905	0.480	3.964	0.594	0.522	1.683	1.915

The results are mean of two independent observations run in duplicate and $\eta = X \times 10^{-23}$

Considerable evidence exists that many function of biological membranes are influenced by composition and physical state of membrane lipids and the resultant membrane fluidity.[28,29] Lipid protein interaction of BBM of rat small intestinal epithelial cells has also been examined by Brasitus et al. (1979),[30] where the membrane fluidity has been characterized as the rotational motional freedom of the lipid molecules or substitute thereof in the bilayer. Moreover a number of studies have revealed that a large number of plasma membrane activity including certain transmembrane transport processes such as the sodium dependent D-glucose which transport appears to be influenced by the lipid composition and fluidity of the membrane.[31]

In study with benzyl alcohol treated membranes, increased lateral diffusion of pyrene in the membranes might have resulted due to partial lipid removal and thus more motional freedom of the probe in the hydrocarbon phase. Aliphatic as well as aromatic alcohols can modify some properties of lipid bilayer as phase transition temperature and certain structural and mobility parameters as shown by ESR and NMR measurements.[32] Effects of benzyl alcohol and some short chain alkanols in altering lipid phase fluidity in the biological membrane have also been demonstrated earlier. Similarly, the efficiency of pyrene excimer formation has been shown to increase linearly with the increase of isoamyl alcohol concentration in the membrane upto approximately 50 mM.[33]

Infrared spectroscopy study of the BBM: Infrared spectroscopy is a method of physicochemical analysis which had been employed here to study the macromolecular composition and organization in the biomembranes. The IR spectra may give unequivocal structural information; quite often the absence of band is as informative as the presence of a particular one. The instruction which may exist between membrane lipids and intrinsic proteins and the degree to which the intrinsic proteins can perturb a lipid bilayer have been the subject of many studies.[34-36] Infrared spectroscopy, both difference infrared and Fourier transform provide new powerful non-perturbing tool operating on an entirely different time scale than NMR spectroscopy for studying the conformation of membranes. The IR measurements were carried out using a Perkin Elmer spectrophotometer and scans were computer averaged in the region of 400-3,500 cm^{-1}. In all the cases the maximum noise suppression of the instrument was used together with the wide slit-width to reduce the scanning time.

The IR spectra of the different intestinal BBM of the control animals are shown in figure 1 (a-h). Administration of aspirin caused the appearance of new peaks or disappearance of the peaks which were present in the control animals. Also, change in the peak height and shifting in the wave numbers have been observed. Aspirin treated duodenal BBM showed 32 peaks as compared to 26 in the control. Jejunal BBM of the treated animals exhibited 28 peaks against 22 in the control group. Ileal BBM showed 21 peaks in the treated groups while 25 peaks in the control. In colonic BBM, 26 peaks were noticed in the treated animals as compared to the 29 in the control group.

In duodenal BBM of aspirin treated rats changes in wave number were noticed as compared to the control at 3,395cm^{-1} to 3,397cm^{-1} which corresponds to OH-stretching (R-OH), NH_2- stretching (R-NH_2) and NH-stretching (R-NH-R). Similarly, changes in wave number were noticed at 2923 cm^{-1} due to anti symmetry stretching $(-CH_2-)_n$, changes in wave number 1,921 cm^{-1} due to C = X stretching (X = C, N, O) and for wave number 1,702 cm^{-1} due to C = O double bond stretching (R-CO-OH). Shifting in the wave number was also noticed at 1,684 cm^{-1} (C = C stretching, $R_2C = CR^1H$), 1,653 cm^{-1} (C = C stretching $R_2C = CR^1H$, NH_2 bending R-NH_2, NH- bending amide I Bond R_2NH), 1,560 cm^{-1} (anti symmetry and symmetry C = O double bond stretching R-CO-O, NH-bending amide II bond R_2NH) and 1,523 cm^{-1} (symmetry NH_3^+- bending R- NH_3^+, NH-bending R_2NH). Changes in wave number 1,421 cm^{-1} were due to CH_2-bending of α-methylene group –CH_2-CO-O-R, and asymmetry and symmetry C=O double stretching R-CO-O, while symmetry bending C-CH_3, antisymmetry and symmetry C = O double stretching R-CO-O and OH- bending R-OH were responsible for change in wave number 1374. Also, changes in the wave number at 1,220 cm^{-1} resulted due to CH_2- wagging and CH_2-twisting $(-CH_2-)_n$, OH-bending (R-CO-OH, R-OH) and

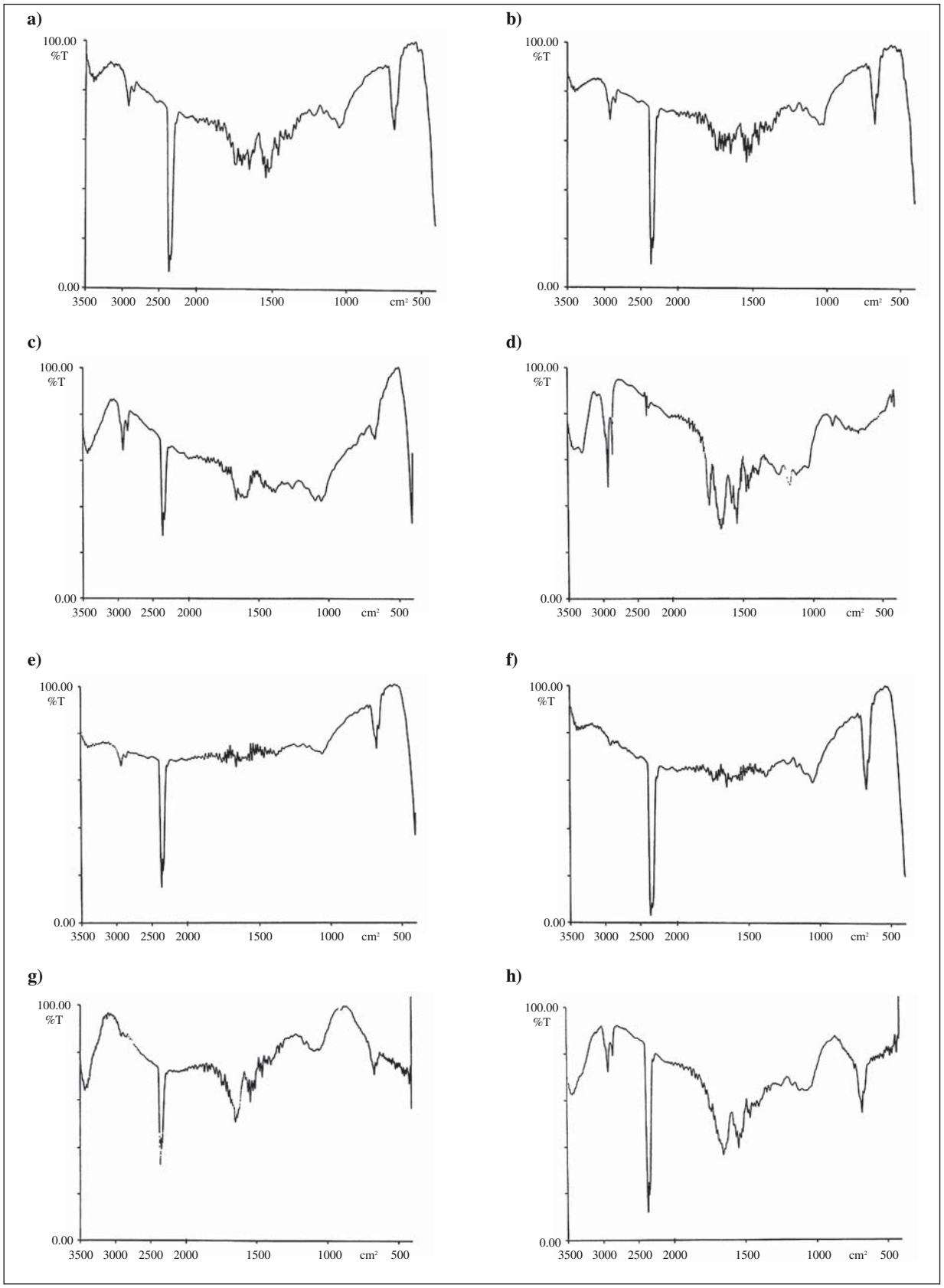

Fig. 1.—The Fourier Transform Infra red spectra (FTIR) of intestinal brush border membranes of control and aspirin treated rats. Control duodenum (a), aspirin duodenum (b); control jejunum (c), aspirin jejunum (d); control ileum (e), aspirin ileum (f); control colon (g) and aspirin colon (h).

antisymmetry PO_2^- double bond stretching (R-O-PO_2-O-R). Besides changes in the wave number , aspirin treatment also resulted in the change in the peak height at the following: 3,395 cm^{-1}, 2,923 cm^{-1}, 2,853 cm^{-1} [$(-CH_2-)_n$ symmetry stretching], 2,361 and 2,359 cm^{-1} (C X stretching, X = C or N) 1,921, 1,830, 1,795 and 1,773 cm^{-1} (C = X, stretching, X = C, N, O), 1,718 & 1,702 cm^{-1} (C = O double bond stretching R-CO-OH), 1,684, 1,653cm^{-1}, 1,560 cm^{-1}, 1,542 cm^{-1} (NH-bending amide II bond R_2NH), 1,523 cm^{-1}, 1,458cm^{-1} [antisymmetry bending C-CH_3, CH_2- bending $(-CH_2-)_n$] 1,421 cm^{-1}, 374 cm^{-1} and 670 cm^{-1} (totally, symmetrical C-N- stretching, gauche dq-isotope).

In jejunal BBM, after aspirin treatment the changes in the different numbers observed were at 2,922, 2,853, 1,656 and 671 cm^{-1} while the peak height showed considerable alteration at 2,922, 2,852, 1,656 and 671 cm^{-1}. Ileal BBM showed changes in wave number at 3,395, 2,340, 1,752, 1,721, 1,705, 1,687, 1,656, 1,625, 1,477, 1,461, 1,377, 1,053 cm^{-1} while noticeable alteration in the peak height at 3,395, 2,361, 2,340, 1,752, 1,721, 1,705, 1,687, 1,656, 1,652, 1,545, 1,526, 1,510, 1,477, 1,461, 1,377, 1,053 and 670 cm^{-1}.

Colonic BBM showed marked alterations in the wave number shift at 34,334, 2,341, 1,868, 1,793, 1,772, 1,651, 1,558, 1,457, 1,397, 520, 469 & 419 cm^{-1} while the peak height changed were discernable at 2,361, 2,341, 1,845, 1,793, 1,772, 1,651, 1,558, 1,542, 1,523, 1,339, 669, 520, 469 and 419 cm^{-1}.

The proportion of gauche to trans conformations and therefore the static order of lipid acyl chains can be measured by shifts in the methylene C-H asymmetric and symmetric stretching frequencies.[37] The presence of high intrinsic protein concentrations within the lipid bilayer structure introduces considerable amino acid side chain contribution to the –C-H bonds. High frequency shoulder on the C-H stretching bonds is attributed to the high levels of intrinsic proteins present.[38]

Uptake of end-product nutrients: The uptake studies of end products of digestion such as glucose and amino acid like histidine were carried out in jejunal segments in both the control and aspirin treated animals. Orally

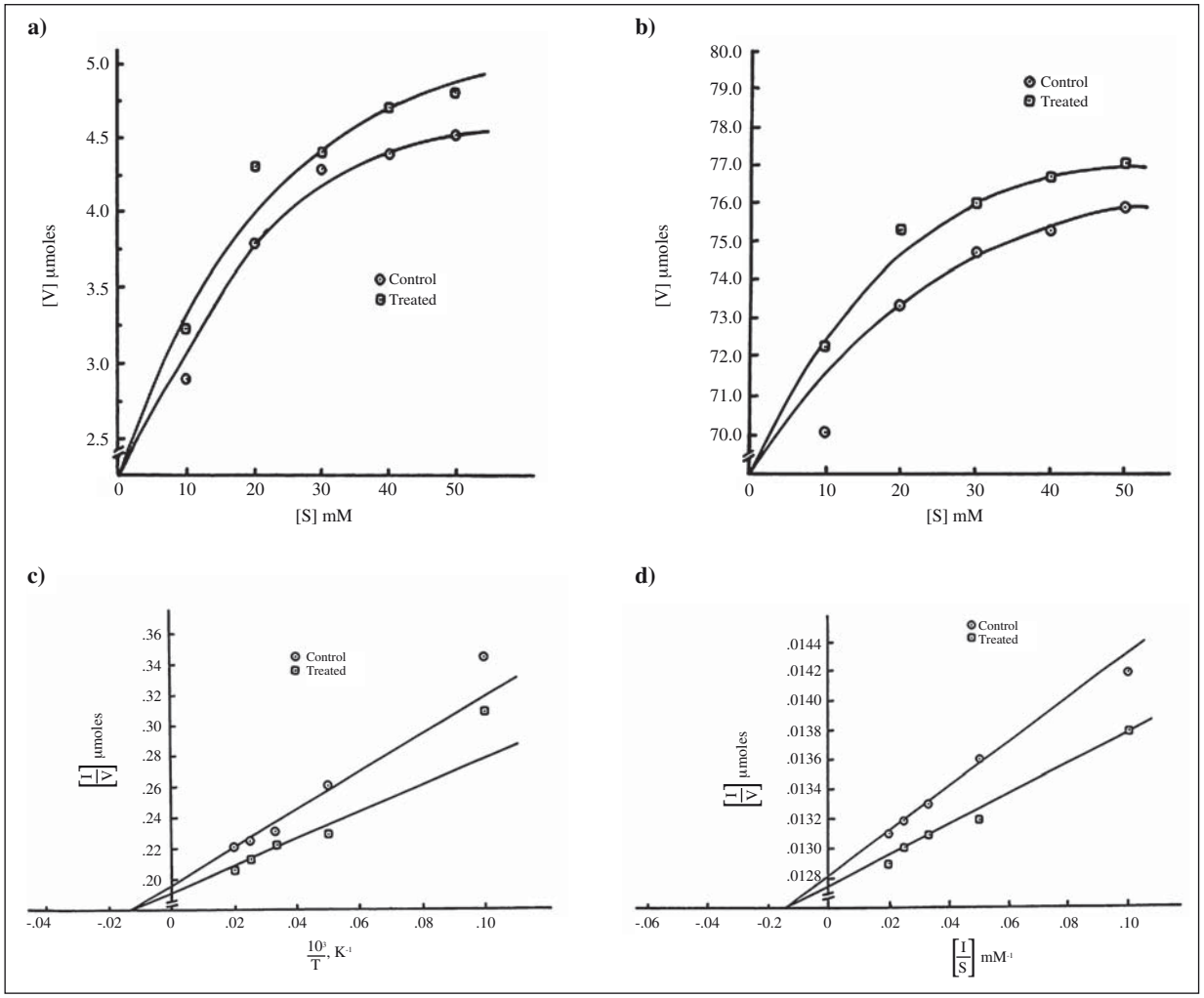

Fig. 2.—Effect of substrate concentration on D-glucose (a) and L-histidine (b) uptake by rat intestine. Lineweaver burk plot of D-glucose (a) and L-histidine (b) uptake by rat intestine.

administered aspirin at a dose level of 50 mg/kg body weight for 28 days resulted in an increase in the uptake of end product nutrients. Moreover, there was an increase in the uptake of glucose and histidine when studied at an increasing substrate concentration in the treated animals as compared to the control (fig. 2a, b).

The uphill movement of these nutrients particularly across the BBM depends heavily on the carrier molecules (transport proteins) and the increase in the uptake could be attributed to the substrate affinity constant (K_m) of the protein. To probe such possibility the Michaili's-Menten parameters (K_m and V_{max}) were studied and the Lineweaver-Burk plot clearly showed that there was no change in K_m and V_{max} value between the control and aspirin treatment (fig. 2 c, d) which may lead to the speculation of other reason for such metabolic increase, such as the uptake of glucose and histidine, possibly due to membrane lipid effect.

Uptake of nutrients in the intestinal segments showed the dependence on temperature of incubation. Though there was an increase in glucose and histidine transport in the treated animals with every temperature (4, 20, 37 & 50 °C) but the optimum temperature (37°C) reflected no change in both the transport processes even after aspirin administration. Moreover, uptake also undergoes changes in relation to temperature resulting in the non-linearity (break) of the Arrhenius plot in control as well as treated groups, although showing close parallelism and near proximity of these lines (fig. 3 a, b).

Ducis and Koepsell (1983)[39] concentrated on the lipid composition required for sodium dependent D-glucose transport in the reconstituted liposomes and concluded that in addition to cholesterol the presence of PE and sphingomyelin enhanced the transport activity further.[39] This observation seems to be in tandem with our results, as aspirin treatment increases the fluidity, causes partial lipid removal or removal of cholesterol which enhances the glucose and histidine transport. Moreover, studies have suggested that alteration of membrane fluidity may influence the uptake of sodium dependent D-glucose into rat small intestine[40] and renal BBM vesicle.[41] Increase in transport can be the consequences of increase in cell number or ability of aspirin to enhance the absorption capacity of the enterocytes by induction of specific carrier proteins.

It has been established that a temperature dependent change in the physical state of the lipid can influence certain membrane activities carried on by the proteins.[42] Since Arrhenius plots reveal a proximity between the control and aspirin treated animals in glucose and histidine transport, a close similarity is therefore expected in the transport process in the two membranes. Non-linearity in Arrhenius plots indicates that the proteins involved in both kinds of transport may experience temperature induced changes in the membrane, namely fluidity and therefore may be termed as the membrane intrinsic proteins.[43] Break in the Arrhenius plot was observed at the same temperature, which rules out the possibility of any effective denaturation of the enzymes involved between

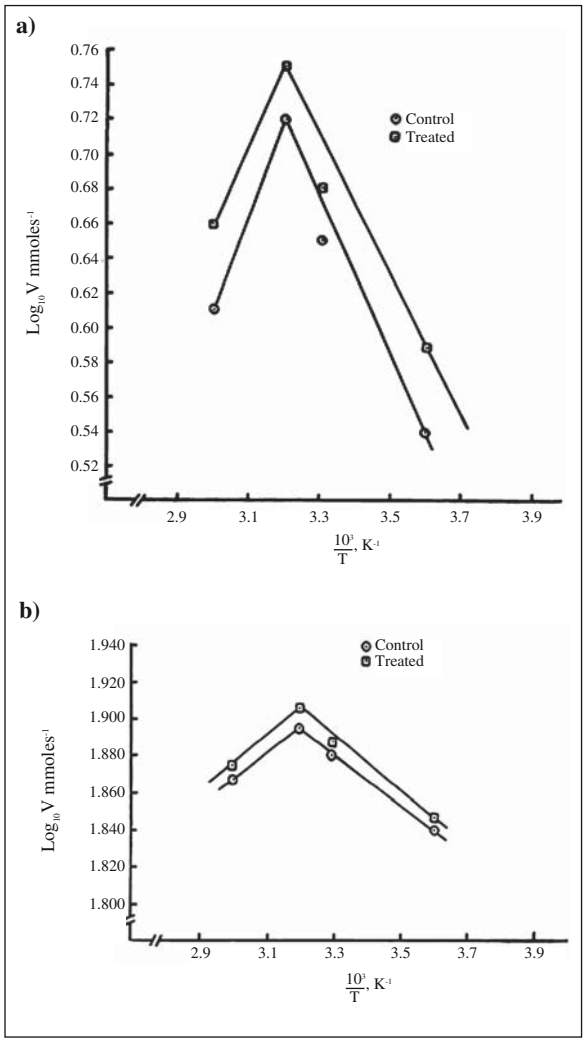

Fig. 3.—Arrhenius plot of D-glucose uptake (a) and L-histidine uptake (b) by rat intestine.

the fluid and ordered lipid domains of the membrane.[44] Also no change in transition temperature (T_c) was observed which evaded any chance of aspirin binding to the membrane lipid bilayer but possibly altering the phase transition or melting process of the membrane lipids. In addition, the unaltered transition temperature and a negligible decrease in activation energy (E_a) in the aspirin treated animals reflects only small alteration in the energy requirements of carrier proteins for binding of substrate molecules.

The treatment of aspirin for 28 days in male Wistar rats has caused structural and functional changes in intestine as evident by alteration in the enzyme levels, increase in E/M ratio leading to enhanced fluidity, physical changes as determined by IR spectra along with changes in glucose and histidine uptake. Discontinuities in Arrhenius plots represent several phenomena such as lipid phase transition from gel to liquid crystalline state, a lateral lipid phase separation and the interaction between the boundary lipid phase associated with membrane protein and the bulk lipid phase.

Phase transition in small intestine and colonocyte membranes have also been examined by assessing the temperature dependence of enzymatic and transport activities where it is suggestive that the breakpoint temperature is determined by the lipid immediately surrounding the protein called the annular lipid rather than by the bulk lipid phase of the membrane.

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):299-303
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Polymorphism Trp64Arg of beta 3 adrenoreceptor gene: allelic frequencies and influence on insulin resistance in a multicenter study of Castilla-León

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Abstract

Background and objective: **The genetic variant (Trp64Arg) is a missense mutation located within the beta3 adrenoreceptor (Beta3AR). The aim of our study was to investigate the influence of Trp64Arg polymorphism in the Beta3AR gene on insulin resistance in obese patients and the allelic distribution of this polymorphism in a geographic area of Spain.**

Design: **A population of 264 obese patients was analyzed. A bioimpedance, blood pressure, an assessment of nutritional intake, and biochemical parameters were measured. The beta 3 adrenoreceptor gene polymorphism (Trp64Arg) was genotyped.**

Results: **Two hundred and twenty six patients (77 males/149 females) (85.6%) had the genotype Trp64/Trp64 (wild type group) with and average age of 41.12 ± 13.1 years and 38 patients (16 males/22 females) Trp64/Arg64 (14.4%) (mutant type group) with an average age of 40.5 ± 12.7 years. High frequencies of Arg64 allele were observed in Salamanca and Valladolid. In the mutant type group, HOMA (3.75 ± 2.77 *vs* 5.27 ± 5.4; p < 0.05) was higher than wild type group.**

Conclusion: **The finding of this study is the association of the Trp64/Arg64 Beta3AR with higher levels of HOMA. Frequencies of this polymorphism are different among geographic areas.**

(*Nutr Hosp*. 2010;25:299-303)

DOI:10.3305/nh.2010.25.2.4599

Key words: *Castilla-León. Obesity. Trp64Arg beta 3 adrenoreceptor.*

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Recibido: 17-XI-2009.
Aceptado: 22-XI-2009.

POLIMORFISMO TRP64ARG DEL GEN RECEPTOR BETA 3: FRECUENCIA ALÉLICA E INFLUENCIA EN LA RESISTENCIA A LA INSULINA EN UN ESTUDIO MULTICÉNTRICO DE CASTILLA Y LEÓN

Resumen

Introducción y objetivos: **La variante genética (Trp64Arg) es una mutación localizada en el adrenoreceptor Beta 3 (Beta3AR). El objetivo de nuestro trabajo es evaluar la influencia de el polimorfismo Trp64Arg del gen de Beta3AR sobre la resistencia a la insulina en pacientes obesos, así como la distribución alélica de este polimorfismo en un área geográfica de España. Diseño: Una muestra de 264 pacientes obesos fue analizada. Se realizó una bioimpedancia, evaluación nutricional y análisis bioquímico. Se genotiparon a los pacientes en función del polimorfismos Tr64Arg del gen adrenoreceptor-beta 3.**

Resultados: **Un total de 227 pacientes (77 varones/149 mujeres) (85,6%) presentaron el genotipo Trp64/Trp64 (grupo genotipo salvaje), con una media de edad de 41,12 ± 13,1 años y un total de 38 pacientes (16 varones/22 mujeres) Trp64/Arg64 (14,4%) (grupo genotipo mutante) con una edad media de 40,5 ± 12,7 años. Se detectó una alta frecuencia alélica (Arg64) en las áreas de Salamanca y Valladolid. En el grupo mutante, la resistencia a la insulina (HOMA) (3,75 ± 2,77 *vs* 5,27 ± 5.4; p < 0,05) fue más alta que en grupo con genotipo salvaje.**

Conclusion: **Existe una asociación entre el genotipo mutante del polimorfismo Trp64/Arg64. Las frecuencias alélicas del polimorfismo son diferentes en función de la áreas de salud.**

(*Nutr Hosp*. 2010;25:299-303)

DOI:10.3305/nh.2010.25.2.4599

Palabras clave: *Castilla y León. Obesidad. Trp64Arg beta 3 adrenoreceptor.*

Introduction

Obesity has multiple causes, and it is determined by the interaction between genetic and environmental factors.[1] Especially, gene defects showing no or only minor effect when expressed alone might influence on the phenotype. Genetic background of these patients could influence in follow up and outcomes.[2,3]

A genetic variant is the tryptophan-to-arginine (Trp64Arg) missense mutation in the beta3 adrenoreceptor (Beta3AR). Beta3-AR is the principle mediator of cathecolamine-stimulated thermogenesis and lipolysis.[4] Trp64Arg variant in this receptor has been reported to be associated with increased body weight and insulin resistance.[5] Since the publication of this polymorphism, numerous studies have been conducted to investigate the relationship of this common variant with various phenotypes of obesity. However, such findings have not been consistent among the studies subsequently undertaken raising questions about the significance of a possible relationship between the Trp64Arg polymorphism and these clinical features. Adipose tissue is considered an active secretory organ, sending out and responding to signals that modulate appetite, insulin sensitivity, energy expenditure, and inflammation.

The aim of our study was to investigate the influence of Trp64Arg polymorphism in the Beta3 adrenoreceptor gene on obesity anthropometric parameters and insulin resistance in obese patients and the allelic distribution of this polymorphism in a geographic area of Spain (Castilla-León).

Subjects and methods

Subjects

A population of 264 obesity (body mass index > 30) patients was analyzed in a prospective way (research protocol accepted by ethical committee). These patients were studied in the Nutrition Clinic Units and signed an informed consent. The recruitment of subjects was a non probabilistic method of sampling among patients send from Primary Care Physicians with obesity to each Unit of Nutrition of each Health Area of Castilla Leon in the Northwest of Spain (Avila (n = 156,535 habitants), Burgos (n = 350,122 habitants), Leon (n = 473,407 habitants), Palencia (n = 165,740 habitants), Salamanca (n = 335,407 habitants), Segovia (n = 141,750 habitants), Soria (n = 90,521 habitants), Valladolid (n = 507,297 habitants), Zamora (n = 182,710 habitants)). Exclusion criteria included history of cardiovascular disease or stroke during the previous 36 months, total cholesterol > 300 mg/dl, triglycerides > 400 mg/dl, blood pressure > 140/90 mmHg, fasting plasma glucose > 110 mg/dl, as well as the use of sulfonylurea, thiazolidinedionas, insulin, glucocorticoids, antineoplastic agents, angiotensin receptor blocker, angiotensin converting enzyme inhibitors, psychoactive medications, drinking and/or smoking habit.

Procedure

All patients with a 2 weeks weight-stabilization period before recruitment were enrolled. Weight, blood pressure, basal glucose, c-reactive protein (CRP), insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides blood levels were measured. Genotype of beta 3 adrenoreceptor gene polymorphism was studied.

Genotyping of Beta3 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 95ºC for 3 min; this was followed by 50 cycles of denaturation at 95ºC for 15 s, and annealing at 59.3º 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.[6] CRP was measured by immunoturbimetry (Roche Diagnostcis GmbH, Mannheim, Germany), with a normal range of (0-7 mg/dl) and analytical sensitivity 0.5 mg/dl.

Anthropometric measurements

Body weight was measured to an accuracy of 0.5 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. Tetrapolar body electrical bioimpedance was used to determine body composition.[7] An electric current of 0.8 mA and 50 kHz was produced by a calibrated signal generator (Biodynamics Model 310e, Seattle, WA, USA) and applied to the skin using adhesive electrodes placed on right-side limbs. Resistance and reactance were used to calculate total body water, fat and fat-free mass.

Blood pressure was measured twice after a 10 minutes rest with a random zero mercury sphygmomanometer, and averaged.

Dietary intake and habits

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. Handling of the dietary data was by means of a personal computer equipped with personal software, incorporating use of food scales and models to enhance portion size accuracy. Records were reviewed by a registered dietitian and analyzed with a computer-based data evaluation system. National composition food tables were used as reference.[8] Regular aerobic physical activity (walking was allowed, no other exercises) was maintained during the period of study (2-3 hours per week).

Statistical analysis

Sample size was calculated to detect differences over 1 point of HOMA with 90% power and 5% significance. The results were expressed as average ± standard deviation. The distribution of variables was analyzed with Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with a two-tailed, Student's-t test. Non-parametric variables were analyzed with the U-Mann Whitney test. Qualitative variables were analyzed with the chi-square test, with Yates correction as necessary, and Fisher's test. Correlation analysis was realized with Pearson test and Spearman test. The statistical analysis was performed for the combined *Trp64*/*Arg64* and *Arg64*/*Arg64* as a mutant group and type *Trp64*/*Trp64* as wild group with a dominant model. Hardy Weinberger equilibrium was assessed. A p-value under 0.05 was considered statistically significant.

Results

Two hundred and sixty four patients gave informed consent and were enrolled in the study. The mean age was 41.1 ± 13.1 years and the mean BMI 36.5 ± 5.9, with 94 males (35.6%) and 170 females (74.4%).

Two hundred and twenty six patients (77 males/149 females) (85.6%) had the genotype *Trp64*/*Trp64* (wild type group) with and average age of 41.12±13.1 years and 38 patients (16 males/22 females) *Trp64*/*Arg64* (14.4%) (mutant type group) with an average age of 40.5 ± 12.7 years.

Table I shows distribution of genotypes and allelic frequencies in different Health Areas. High frequencies of Arg64 allele were observed in Salamanca and Valladolid.

Table II shows the anthropometric variables. No statistical differences were detected between genotypes.

Table III shows the differences in cardiovascular risk factors. In mutant type group, HOMA was higher than wild type group.

Table IV shows nutritional intake with 3 days written food records. No statistical differences were detected in calorie, carbohydrate, fat, and protein intakes.

Table I
Genotype and allelic distribution in different health areas

Areas	*Trp64/Trp64*	*Trp64/Arg64*	*Trp64*	*Arg64*
Avila (n = 12)	86.4%	13.6%	0.93	0.07
Burgos (n = 35)	91.4%	8.6%	0.95	0.05
Leon (n = 61)	86.3%	13.7%	0.94	0.06
Palencia (n = 12)	91.7%	8.3%	0.95	0.05
Salamanca (n = 7)	71.4%*	28.6%*	0.85+	0.15
Segovia (n = 21)	100%	0%	1.00	0.00
Soria (n = 18)	88.9%	11.1%	0.94	0.06
Valladolid (n = 64)	77.7%*	22.3%*	0.88+	0.12
Zamora (n = 24)	83.3%	16.7%	0.92	0.08

(*) $P < 0.05$, statistical differences in the same genotype among different Health Areas.
(+) $P < 0.05$, statistical differences in the same allele among different Health Areas.

Table II
Differences in anthropometric variables

Characteristics	*Trp64/Trp64 n = 226*	*Trp64/Arg64 n = 38*
BMI	36.6 ± 5.6	36.1 ± 7.4
Weight (kg)	98.3 ± 19.2	96.8 ± 20.4
Fat free mass (kg)	56.3 ± 13.1	54.2 ± 13.7
Fat mass (kg)	39.6 ± 12.4	40.5 ± 16.4
Waist circumference(cm)	111.8 ± 14.3	110.6 ± 15.2
Waist to hip ratio	0.93 ± 0.09	0.92 ± 0.07
Systolic BP (mmHg)	126.9 ± 16.6	130.1 ± 18.1
Diastolic BP (mmHg)	79.2 ± 12.1	80.9 ± 7.8

BMI: body mass index. BP: Blood pressure. No statistical differences between genotypes.

Discussion

In the mutant group of beta3 adrenoreceptor gene *(Trp64/Arg64)* patients have higher HOMA than wild type group. Two Health Areas (Salamanca and Valladolid) have a high frequency of this polymorphism compared with others of Castilla León.

Our present finding that the global frequency of the Arg64 allele in Castilla-León was 14.4% in obese patients agrees with previous reports.[9-11] The results of a meta-analysis assessing quantitative phenotypes in relation to a genetic polymorphism, and the result support the association of Trp64Arg polymorphism with BMI across diverse populations.[12] However, other meta-analysis did not find evidence of this association,[13] as our multi center study shows.

Other controversial area is the relationship of this polymorphism and glucose metabolism disorders. Mice with knockout of the Beta 3 adrenoreceptor gene showed marked reductions in lipolysis stimulated by Beta 3 agonists,[14] and omental adipocyte Beta 3 adrenoreceptor sensitivity was related to waist to hip ratio and insulin resistance.[15] Perhaps, defects in beta 3 adrenoreceptor signal transduction, binding, or regulatory mechanism may result in a diminished lipolytic response in visceral adipose tissue, aggravating insulin resistance. However, other authors have detected an inverse relation between visceral obesity in Trp64Arg mutation patients and serum triglyceride.[16] Our data showed higher insulin resistance in mutant type group than wild type group. This relationship with a lack of association with body mass index has been detected in a middle-aged white population from Denmark,[17] too. In this study the Trp64Arg polymorphism was not associated with obesity. However the Arg allele was associated with an increased insulin resistance estimated by HOMA. Bracale et al have demonstrated similar results in a population from Italy.[18]

Table III
Clasical cardio vascular risk factors

Characteristics	*Trp64/Trp64 n = 226*	*Trp64/Arg64 n = 38*
Glucose (mg/dl)	98.2 ± 24.7	102.9 ± 34.1
Total ch. (mg/dl)	188.0 ± 37.2	185.6 ± 38.6
LDL-ch. (mg/dl)	107.9 ± 42.4	102.8 ± 42.8
HDL-ch. (mg/dl)	66.1 ± 36.2	63.4 ± 32.8
TG (mg/dl)	122.6 ± 67.4	116.5 ± 55.2
Insulin (mUI/L)	16.3 ± 13.3	21.6 ± 22.9
HOMA	3.75 ± 2.77	5.27 ± 5.4*
CRP (mg/dl)	4.90 ± 7.30	4.86 ± 10.4

Chol: Cholesterol. TG: Triglycerides. HOMA: homeostasis model assessment. (*$p < 0.05$) statistical differences between genotypes.

Table IV
Dietary intake

Characteristics	*Trp64/Trp64*	*Trp64/Arg64*
Energy (kcal/day)	2023 ± 817	1979 ± 649
CH (g/day)	200.6 ± 64.4	197.1 ± 75.3
Fat (g/day)	91.5 ± 51.5	79.3 ± 33.1
Protein (g/day)	94.8 ± 40.3	87.6 ± 31.8

No statistical differences between groups. CH: Carbohydrate.

The mechanism through which the Arg64 variant alters insulin sensitivity could be explained by adipocytokine actions. Resistin and adiponectin appear to be important in regulating insulin sensitivity.[19] Perhaps, these unclear results in the literature[20] may partially be explained by differences in ethnic background, baseline BMI, gender distribution, previous weight loss, experimental design (early stage or late stage type 2 diabetes mellitus) and basal adipocytokines levels of participants. Therefore, interaction between gene and ambient could explain these differences with bias in previous studies. Perhaps these differences could be explained by a dietary bias. Gene-environment interaction studies would require composition analysis of the diet to determine whether dietary components could be responsible for the lipid differences. In our study dietary intake did not show statistical differences between groups, in this way our dates have controlled by dietary intake and previous discrepancies could be explain by this uncontrolled factor (dietary intake). Geographic area of the populations could be other factor to take account.

Geographic variations of prevalence have been described in other single nucleotide polymorphism such as Ala54Thr of Fatty acid binding protein.[20] Other results are consistent with the idea that climate has been an important selective pressure acting on candidate genes for common metabolic disorders such as LEPR polymorphisms.[21] In one study with hypertensive obese patients from China, the allele frequency of 64ARg was 0.18.[22] Other study from Japan showed an allele frequency of Arg64 of 18%.[23] Both studies

showed higher frequencies than our global area (Castilla Leon) but similar that two Health Areas (Valladolid and Salamanca).

This association could have therapeutically implications. Interventional studies with this polymorphism are limited.[24] This study showed that the beneficial effect of mild weight reduction by a low caloric diet and exercise program is the greatest in subjects with normal homozygotes beta 3 adrenoreceptor gene. In other study, after obese children were subjected to a low-fat diet for 3 months, the increased range in body weight in obese children without the mutation was less than that in obese with mutation and the control group.[25]

The finding of this study is the association of the Trp64/Arg64 Beta3AR with higher levels of HOMA. Frequencies of this polymorphism are different among geographic areas.

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):304-310
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Lycopene mediated modulation of 7,12 dimethlybenz (A) anthracene induced hepatic clastogenicity in male Balb/c mice

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Abstract

The present study was designed to evaluate the modulatory effects of lycopene against 7, 12 Dimethylbenz (a) anthracene induced clastogenicity and oxidative stress in male Balb/c mice. The animals were divided into four groups; group I served as control (vehicle treated). Animals of group III and IV were administered lycopene orally at a dose of 4 mg/kg body weight for 10 weeks. Groups II and IV were administered DMBA, i.p., at a dose level of 40mg/kg body weight, 48hrs before the sacrifice of animals. Exposure to DMBA clearly induced hepatic cell injury as was evident by an increase in micronucleated cell score, lactate dehydrogenase and alkaline phosphatase activities, and Lipid Peroxidation levels. When the lycopene pre-treated animals were challenged with DMBA, a decrease in micronucleated cell score was observed, which was in corroboration with the observed decrease in LDH and ALP activities and LPO levels. DMBA treatment caused an increase in the oxidative stress with consequent alterations in enzymatic antioxidant defense system. Lycopene pre-treatment boosted the antioxidant defense in group IV. Thus, the antioxidant role of lycopene could be plausible in the protective action conferred by lycopene, enabling it to be used an effective natural free radical scavenger.

(*Nutr Hosp*. 2010;25:304-310)

DOI:10.3305/nh.2010.25.2.4607

Key words: *Oxidative stress. Carotenoids. Micronucleus. Antioxidants.*

MODULACIÓN MEDIADA POR LICOPENO DE LA CLASTOGENICIDAD HEPÁTICA INDUCIDA POR 7,12 DIMETILBENZ (A) ANTRACENO EN RATONES MACHO BALB/C

Resumen

El presente estudio se diseñó para evaluar los efectos moduladores del licopeno frente a la clastogenicidad y el estrés oxidativo inducidos por 7,12 dimetilbenz(A) antraceno en los ratones macho Balb/c. Se dividió a los animales en cuatro grupos; el grupo I sirvió de control (tratado con vehículo). A los animales de los grupos III y IV se les administró licopeno por vía oral a una dosis de 4 mg/kg de peso corporal durante 10 semanas. Los grupos II y IV recibieron DMBA, i.p., a una dosis de 40 mg/kg de peso corporal, 48 horas antes de ser sacrificados. La exposición a DMBA indujo claramente una lesión de los hepatocitos como se hizo patente por el aumento de la puntuación de células micronucleadas, y las actividades de la lactato deshidrogenasa y la fosfatasa alcalina, así como por los niveles de peroxidación lipídica. Cuando a los animales pre-tratados con licopeno se les expuso a DMBA, se observó un descenso de la puntuación de células micronucleadas, lo que corroboraba el descenso observado de las actividades LDH y ALP y de los niveles de LPO. El tratamiento con DMBA produjo un aumento del estrés oxidativo con las consiguientes alteraciones del sistema de defensa antioxidante. El pre-tratamiento con licopeno aumentó notablemente la defensa antioxidante en el grupo IV. Así pues, el papel antioxidante del licopeno podría ser plausible en la acción protectora conferida por el licopeno, permitiendo usarlo como un eliminador natural eficaz de los radicales libres.

(*Nutr Hosp*. 2010;25:304-310)

DOI:10.3305/nh.2010.25.2.4607

Palabras clave: *Estrés oxidativo. Carotinoides. Micronúcleo. Antioxidante.*

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Recibido: 27-XI-2009.
Aceptado: 30-XI-2009.

Introduction

Environmental factors are recognized to play a major role in the etiology of various diseases, including cancer.[1] Exposure to environmental pollutants such as polycyclic aromatic hydrocarbons (PAHs) is one of the major risk factors responsible for the onset of various diseases associated with oxidative stress.[2] PAHs are a large group of organic compounds with two or more fused aromatic rings that are formed during the incomplete combustion of organic materials such as wood, coal and mineral oil and products derived from them. They are also found in motor vehicle exhaust and tobacco smoke and can be produced by pyrolysis of amino acids, fatty acids and carbohydrates during the cooking process.[3] PAHs are indirect acting carcinogens that require metabolic activation to form electrophilic moieties capable of binding to cellular nucleophilic target to initiate their carcinogenic action.[4] DMBA, a prototype of PAHs is a potent pro-carcinogen, which on metabolism forms epoxides and other toxic reactive oxygen species consequently leading to chromosomal damage and formation of micronuclei.

For the last couple of decades, natural products derived from plants, fruits, spices, herbs etc have been the main focus of research to ameliorate the threat posed by harmful chemicals, toxins etc from endogenous and exogenous sources.[5,6,7] Overwhelming evidence from epidemiological studies indicates that diets rich in fruits and vegetables can be associated with a lower risk of numerous diseases.[8,9] Natural products like fruits, vegetables, herbs etc contain several promising chemopreventive compounds such as vitamins, minerals, carotenoids and an array of other phytochemicals.

Tomato *(lycopersicon esculentum),* a member of Solananaceae family, is consumed widely as a vegetable and as processed tomato products (juice, sauce, soup and ketchup). The active compounds isolated from tomatoes that have antioxidative and anticarcinogenic properties include chlorogenic acid, eugenol, quercetin, rutin, kaempferol, naringenin, alpha and beta carotenes, phytotene, neurosporene and lycopene.[10] The prominent carotenoid present in tomato is lycopene. Lycopene has received particular attention as a chemopreventive agent because of its highly efficient free radical scavenging activity.[11,12,13]

The chemopreventive action of lycopene against several diseases can be attributed to its antioxidant activity. Lycopene adminstration to rats subjected to gentamicin-induced oxidative stress exhibited a protective effect on kidney owing to its antioxidant properties.[14] Lycopene supplementation to cigarette smoke exposed ferrets led to inhibition of lung squamous metaplasia and also induced apoptosis.[15] In a study conducted on murine keratinocyte cell lines, it was reported that lycopene supplementation to the tumor cell line caused a marked decrease in the growth properties of the cell line.[16] Velmurugan and co-workers in their study have demonstrated that tomato protects against the clastogenic effects of MNNG by decreasing the micronucleated cell score, lipid peroxidation and by enhancing the antioxidant status.[17]

Keeping in view the above mentioned facts, the present study was designed to evaluate the long term modulatory effects of lycopene on DMBA induced hepatic clastogenicity in male balb/c mice.

Materials and methods

Experimental design

Chemicals: 5,5-dithiobis-2-nitrobenzoic acid (DTNB), reduced glutathione (GSH), oxidized glutathione (GSSG), Bovine Serum Albumin (BSA), Thiobarbituric Acid (TBA), reduced nicotinamide adenine dinucleotide (NADH), reduced nicotinamide adenine dinucleotide phosphate (NADPH) were obtained Sigma Chemical Co. (St Louis, MO,USA). Capsules containing Lycopene were obtained from a recognized pharmaceutical company Gelnova, India. The contents of the capsule were reconstituted in olive oil immediately before oral administration to the animals in order to attain the required dose. Rests of the chemicals were obtained from local firms (India) and were of analytical grade.

Animal model and experimental conditions

Male Balb/c mice (6-8 week old) were procured from the Central animal house of Panjab University, Chandigarh. The animals were housed in polypropylene cages bedded with sterilized rice husk. The animals were given free access to clean drinking water (tap water) and standard animal pellet diet (Ashirwad Industries Kharar, Punjab, India), throughout the experiment. The experimental protocols were approved by the Institutional Ethics Committee and conducted according to the Indian National Science Academy Guidelines for the use and care of experimental animals. After acclimatization to the experimental conditions for one week, the animals were randomly divided into four groups of 6-8 animal each and were administered the following treatments.

Treatment of animals: Group I animals served as the control group and was vehicle treated (olive oil). Group II mice were administered with DMBA (i.p.) at a dose of 40 mg/kg body weight, 48 hrs before sacrifice. Group III animals were administered lycopene orally at a dose of 4 mg/kg body wt, daily for 10 weeks.[18] Group IV mice were pre-treated with lycopene orally at a dose of 4 mg/kg body wt daily for ten weeks and were administered DMBA (i.p.) at a dose of 40 mg/kg body wt, 48 hours before sacrificing the animals. Lycopene was dissolved in olive oil. Weekly alterations in the body weight, diet and water consump-

tion were observed for the mice in all groups throughout the experiment. After 48 h of the DMBA injection, the mice were sacrificed and hepatic tissue was obtained.

Micronucleus assay

The micronucleus assay was carried out according to the method described by Schmid, 1975.[19] For this, the tissue was washed with chilled homogenizing buffer (24mM Na_2-EDTA buffer pH 7.5, containing 75 mM of NaCl), and then homogenized at 500 to 800 rpm. The homogenates were then centrifuged at 7000 rpm for 10 min. The supernatant was removed and fresh homogenizing buffer was poured to re-suspend the pellet. A drop of the suspension was put at one end of precleaned, grease free microscopic slide and was spread using cover slip held at an angle of 45° into a smooth layer. The slides were then air dried in dust free environment for at least 12 h before staining. The hepatocytes were then stained with May & Grunwald for 1-2 min followed by staining with Giemsa for 10 min. The slides were rinsed twice in distilled water dried and then rinsed in methanol. The slides were then cleared in xylene and mounted in DPX. Minimum of 300 cells were counted per mice for the presence of micronuclei using light microscope at 45X.

Biochemical assays

After the completion of the respective treatments the mice were sacrificed by cervical dislocation under light ether anesthesia. The hepatic tissue was obtained and perfused with cold normal saline (0.9% NaCl solution), blotted and then weighed carefully. The hepatic tissue was homogenized in 100mM potassium phosphate buffer (pH 7.4) containing 150 mM KCl to obtain 10% homogenate (w/v). The homogenate was subjected to cold centrifuge at 10,000 x g for 30 minutes and the supernatant (PMS) thus obtained was used for various biochemical estimations. Aliquots of 10% homogenate were kept for estimation of reduced glutathione and lipid peroxidation levels.

Lactate dehydrogenase (LDH) - LDH activity was estimated by determining the rate of oxidation of NADH at 340 nm by the method of Bergmeyer and Bernt *et al*., (1971).[20]

Alkaline phosphatase (ALP) - ALP activity was assayed using p-nitrophenyl phosphate as a substrate to yield p-nitro phenol phosphate, whose absorbance is determined at 420 nm by the method of Bermeyer, (1963).[21]

Reduced glutathione (GSH) - GSH was estimated as the total non-protein sulphydryl group by the method described by Moron et al. (1979).[22] Homogenates were immediately precipitated with 0.1 ml of 25% trichloroacetic acid and the precipitate was removed after centrifugation at 1500 × g for 10 min. The free-SH groups were assayed in a total 3 ml volume by adding 2 ml of 0.6 mM DTNB prepared in 0.2 M sodium phosphate buffer (pH 8.0), to 0.1 ml of the supernatant and the absorbance was read 412 nm using a Shimadzu UV-160 spectrometer. GSH was used as a standard to calculate micromole of GSH contents/mg protein.

Glutathione-S-transferase (GST) - GST activity was determined spectrophotometrically according to the procedure described by Habig et al., 1974.[23] The reaction mixture (3 ml) contained 2.7 ml of 100 mM potassium phosphate buffer (pH 6.5), 0.1 ml of 30 mM CDNB and 0.1 ml of 30 mM GSH. After pre-incubating the reaction mixture at 37°C for 2 min, the reaction was started by the addition of an appropriate amount of the supernatant. The absorbance was followed for 3 min at 340 nm. The specific activity of GST was expressed as µmol of GSH-CDNB conjugates formed/min/mg protein using an extinction coefficient of 9.6 $mM^{-1}cm^{-1}$.

Lipid peroxidation (LPO) - The assay for lipid peroxidation was performed according to the method of Wills, 1966.[24] 0.5 ml of 10% tissue homogenate was diluted to 1 ml using Tris-HCl buffer. The samples were then incubated at 37ºC for 2 h. At the end of the incubation period, 1 ml of cold TCA was added and after thorough mixing the reaction mixture was centrifuged at 800 x g for 10 minutes. To 1 ml of supernatant was added 1ml of TBA and the reaction mixture was boiled at 100ºC for 15 minutes. The pink colored complex was formed whose absorbance was read at 532 nm. The amount of MDA formed (index of lipid peroxidation) was calculated using an extinction coefficient of 1.56 x 10^5 M^{-1} $cm^{-1}$for MDA-TBA chromophore and the results are expressed as nanomole of MDA formed /mg of protein.

Catalase - The catalase activity was estimated by measuring the breakdown of hydrogen peroxide at 240 nm according to the method of Luck, 1971.[25] To 1.5 ml of the H_2O_2 buffer added an appropriate amount of PMS (5-20 µl).The blank lacking H_2O_2 buffer (containing only phosphate buffer) was also run simultaneously. The decrease in OD is monitored at 240 nm for 3 minutes. The catalase activity is expressed as millimole of H_2O_2 decomposed/min/mg of protein using an extinction coefficient of 0.0394 $M^{-1}cm^{-1}$.

Superoxide Dismutase (SOD) - Superoxide dismutase activity was estimated according to the method described by Kono, 1978, wherein reduction of nitroblue tetrazolium mediated by superoxide anions generated by photo oxidation of hydroxylamine hydrochloride to blue formazon was measured at 560 nm.[26] The activity of superoxide dismutase was expressed as International Units per mg protein (IU/mg protein), where 1 IU is defined as the amount of enzyme inhibiting the increase in optical density by 50%.

Protein content - Protein content of various samples was estimated by the method of Lowry et al., 1951 using BSA as standard.[27]

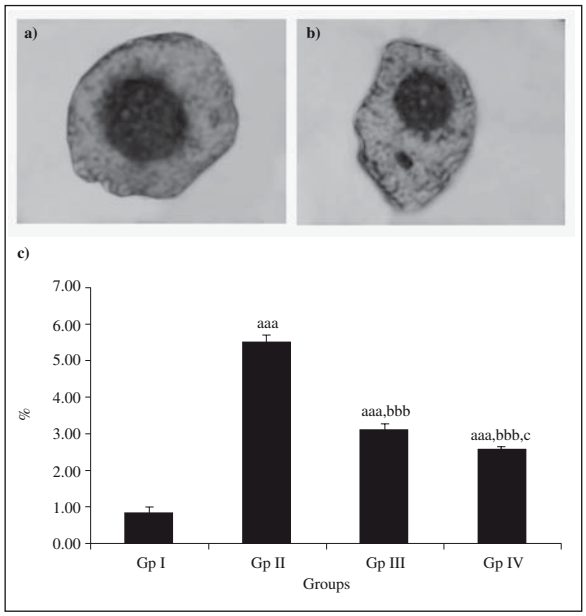

Fig. 1—a) Photomicrograph of Normal hepatic cell at 400X; b) Photomicrograph of Micronucleated hepatic cell at 400X; c) Effect of DMBA and/or lycopene on percentage of micronucleated cells.

Statistical analysis: The data is expressed as Mean ± SD. Statistical significance was analysed by one-way ANOVA followed by Student's Newman Keul Test.

Results

The mice were observed for changes in body weight, diet and water consumption throughout the experiment. Non significant changes were observed in the diet and water consumption by the mice in all the groups studied (Data not shown).

Micronucleus Assay (fig. 1, a, b, c): A significant increase ($p < 0.001$) in the micronucleated cell score was observed in DMBA treated group when compared to the control group. The micronucleated cell score also increased significantly ($p < 0.001$) in the lycopene *per se* group when compared to the control group. A significant decrease ($p < 0.001$) in micronucleated cell score was observed in Group IV when compared with Group II i.e. when lycopene pre-treated animals were challenged with DMBA exposure. However, a significant increase ($p < 0.001$) in the micronucleated cell score of Group IV was observed when compared to Group I (control). When group IV was compared with group III a significant decrease ($p < 0.01$) was observed.

Liver marker enzymes

Alkaline phosphatase and Lactate Dehydrogenase (table I): The activity of liver marker enzymes ALP and LDH increased significantly ($p < 0.01$; $p < 0.001$) in DMBA treated animals (Group II) when compared to control animals. No significant changes in ALP and LDH levels were observed in the lycopene *per se* group and control animals. A significant decrease in ALP ($p < 0.01$) and LDH ($p < 0.001$) activities of Group IV (lycopene + DMBA) was observed when compared to Group II animals.

Table I
Effects of DMBA and/or lycopene on hepatic lactate dehydrogenase (LDH) and alkaline phosphatase (ALP)

Treatment	*Group I*	*Group II*	*Group III*	*Group IV*
LDH	19.0 ± 2.3	39.8 ± 1.8^{aaa}	19.2 ± 0.2	22.4 ± 2.0^{bbb}
ALP	35.4 ± 5.8	57.9 ± 5.5^{aa}	35.7 ± 2.1	40.3 ± 5.9^{bb}

Values expressed as: LDH- µmol of NADH oxidized/min/mg protein; ALP- µmol/mg protein.
Data is expressed as Mean ± SD (n = 6-8). Statistical significance is analysed by One way ANOVA, followed by Student's Newman Keul test.
Statistical significance:
aa, aaa: $p < 0.01$, $p < 0.001$ respectively when compared to Group I.
bb, bbb: $p < 0.01$, $p < 0.001$ respectively when compared to Group II.

Antioxidant Defense System

Lipid Peroxidation (table II): A significant increase ($p < 0.001$) in hepatic LPO level was observed in the DMBA treated animals when compared to the control animals. When lycopene pre-treated animals were challenged with DMBA, a significant decrease ($p < 0.001$) in hepatic LPO levels was observed when compared to the only DMBA treated group. No significant alteration was observed in the hepatic LPO levels of lycopene *per se* group and control group.

Reduced Glutathione (table II): DMBA adminstration to animals caused a significant decrease ($p < 0.001$) in hepatic GSH levels when compared to the control animals. Lycopene *per se* group exhibited a significant increase ($p < 0.001$) in hepatic GSH levels when compared to the control group. Group IV animals

Table II
Effects of DMBA and/or lycopene on antioxidant defense system

Treatment	*Group I*	*Group II*	*Group III*	*Group IV*
LPO	0.331 ± 0.07	0.795 ± 0.08^{aaa}	0.432 ± 0.06	0.490 ± 0.11^{bbb}
GSH	0.738 ± 0.07	0.473 ± 0.03^{aaa}	1.030 ± 0.05^{aaa}	0.724 ± 0.06^{bbb}
GST	30.2 ± 2.4	12.2 ± 2.9^{aaa}	25.9 ± 5.4	34.9 ± 7.6^{bbb}
Catalase	30.5 ± 2.9	22.8 ± 2.3^{aa}	37.5 ± 5.2^{aa}	27.7 ± 2.2^{b,ccc}
SOD	3.16 ± 0.3	1.37 ± 0.5^{aaa}	2.95 ± 0.5	2.81 ± 0.2^{bbb}

Values expressed as: LPO- nmol/min/mg protein, GSH and GST- µmol/mg protein, Catalase- mmol/min/mg protein, SOD- IU/ mg protein.
Data is expressed as Mean ± SD (n = 6-8). Statistical significance is analysed by One way ANOVA, followed by Student's Newman Keul test.
Statistical significance:
aa, aaa: $p < 0.01$, $p < 0.001$ respectively when compared to Group I.
b, bbb: $p < 0.05$, $p < 0.001$ respectively when compared to Group II.
ccc: $p < 0.001$ when compared to Group III.

(lycopene + DMBA) also exhibited a significant increase ($p < 0.001$) in GSH levels when compared to Group II animals (DMBA).

Glutathione-s-Transferase (table II): GST activity decreased significantly ($p < 0.001$) in the DMBA treated animals when compared to the control animals. A non significant decrease in GST levels of lycopene *per se* group was observed when compared to the control animals. However, when lycopene pre-treated animals were challenged with DMBA (Group IV), a significant increase ($p < 0.001$) in hepatic GST activity was observed when compared to animals treated with DMBA only (Group II).

Catalase and Superoxide Dismutase (table II): DMBA treatment caused a significant decrease in hepatic catalase ($p < 0.01$) and SOD ($p < 0.001$) activity when compared to the control animals. Animals of the lycopene *per se* group exhibited a significant increase ($p < 0.01$) in catalase activity when compared to the control animals. A significant increase in catalase ($p < 0.05$) and SOD ($p < 0.001$) activity in Group IV animals (lycopene + DMBA) was observed when compared to the Group II animals (DMBA). A non-significant change was observed in hepatic SOD activity in the lycopene *per se* group when compared to the control group.

Discussion

DMBA, a member of PAH class of carcinogens, is present in the environment as a product of incomplete combustion of complex hydrocarbons. Being an indirect carcinogen, DMBA requires metabolic activation to exert its carcinogenic potential. DMBA is metabolized by cytochrome P450 enzymes in the liver to form diol epoxides and other toxic reactive oxygen species. The toxic metabolites of DMBA including diol epoxides, are capable of binding to adenine residues of DNA causing chromosomal damage, thus leading to formation of micronuclei. The micronucleus formed in liver cells is the hall mark of genotoxicity.[28]

In the present investigation, micronucleus assay was carried out in order to explore the extent of nuclear damage induced during hepatotoxicity caused by DMBA exposure. DMBA exposure to mice caused a significant increase in the hepatic micronucleated cell score when compared to the control group. These results are in corroboration with previous investigations.[29] Mice administered with lycopene also exhibited a marked increase in micro nucleated cell score when compared to the control group. When the lycopene pretreated animals are challenged with DMBA exposure, a significant drop in micronucleated cell score was observed when compared to the group exposed to DMBA only and to the group exposed to lycopene only.

The increase in score of micronucleated cells in lycopene *per se* group could be attributed to the production of pro-oxidant species of lycopene, resulting from the chronic exposure to lycopene in otherwise normal animals. In the present investigation the observations of potential adverse effects from administration of pure lycopene, with regard to the formation of micronucleus is in line with several human intervention studies, in which adverse effects were induced by pure preparations of carotenoids and phytochemicals at high doses administrated for extended time periods.[30,31,32] Breinholt et al, 2003 have reported that prolonged exposure to lycopene induced DNA damage in lymphocytes.[33] The deleterious effects of lycopene could be a dose related phenomenon, suggesting that chronic treatment of lycopene should be followed at a low dose level.

In group IV, when animals were challenged with DMBA, after a chronic treatment regime of lycopene, the number of micronucleated cells decreased as compared to group II, which indicates that lycopene exhibited a protective effect when animals are exposed to a carcinogen/genotoxin. Several investigations have revealed that lycopene, was found to be protective against DNA strand breakage induced in wistar rats by the resistant hepatocytes model of hepato-carcinogenesis.[34] Bhuvaneswari et al., 2004, in their study on hepatic genotoxicity caused by DMBA, have shown that consumption of tomato extract decreased the micronucleated cell score in DMBA exposed animals relative to the only DMBA treated animals.[35] Lycopene is a potent antioxidant because it scavenges free radicals and ROS, consequently offering protection to the cells against carcinogen/genotoxin induced genetic damage.

Lactate dehydrogenase and Alkaline phosphatase are cytotoxic markers that serve as very useful indicators of tissue damage induced by xenobiotics, radiation etc.[36] Enhanced activity of ALP and LDH in liver indicates damage to hepatic cells. In the present investigation, damage to hepatocytes by DMBA is reflected by a significant increase in the activities of ALP and LDH in group II when compared to the control animals. Several previous studies support the present observation of carcinogen induced cell damage, with a consequent increase in ALP and LDH activities.[37,38] Animals of the lycopene per se group did not exhibit any changes in the ALP and LDH activities when compared to the control group. Pre-treatment of the DMBA challenged animals with lycopene was able to bring down the elevated levels of hepatic ALP and LDH. Some investigations also reported that lycopene was able to reduce the toxicity in liver cells.[39]

Reactive oxygen species formed during DMBA metabolism can diffuse from the site of generation to other targets within the cells or even propagate the injury outside the cells. Lipid peroxidation causes alterations in membrane integrity, thereby causing impairment of major metabolic functions, which are dependent on membrane structure and integrity.[40] Lipid peroxides also causes damage to cellular macromole-

cules by generating reactive oxygen species that further enhance carcinogenesis.[41,42] DMBA exposure significantly elevated the MDA levels in group II animals (about 2 fold) when compared to the control group. Koul et al., 2006 in their study on skin tumor bearing mice have reported that DMBA exposure enhanced the hepatic LPO levels.[37] DMBA insult to lycopene pretreated animals showed a marked decline in MDA levels when compared to the only DMBA treated group. Evidences are accumulating in support of the protective role of lycopene.[43,44] Among the various defense strategies adopted by lycopene in conferring protection, its antioxidant action seems to be the most plausible one. Likely as other antioxidants, lycopene scavenges reactive oxygen species, singlet molecular oxygen ($^1O_2$), and peroxyl radical.[12]

Glutathione is a ubiquitous tri-peptide which in its reduced state serves to detoxify electrophiles, maintains the essential thiol states of proteins by preventing the oxidation of SH- groups or by reducing disulphide bonds induced by oxidative stress.[45]

A noticeable decrease (nearly two fold) in GSH content was observed on DMBA exposure that could be well correlated with the increased levels of lipid peroxidation observed in group II mice. Accumulating literature over the years has made it evidently clear that exposure to carcinogens such as PAH causes a decrease in the GSH levels in the target organs.

A marked increase in hepatic GSH levels was observed in the animals that were on a chronic treatment regime of lycopene. Lycopene pre-treatment to the DMBA exposed animals caused a considerable increase in the hepatic GSH levels, which is in absolute correlation with a drop in MDA levels in the same group. This suggests the ability of lycopene to detoxify cells by up regulating the GSH mediated detoxification process. Administration of tomato alone and in combination with garlic enhanced the GSH levels in liver and stomach of MNNG treated animals, when compared to the animals treated with MNNG only.[46]

Conjugation reactions in metabolic degradation of xenobiotics are chiefly done by glutathione-S-transferase (GST) in assistance with GSH. GST catalyzes a wide range of reactions in which GSH replaces an easily displaced group in xenobiotic and thus prevents subsequent toxic reactions.[47] A significant decrease (more than two folds) in hepatic GST activity was observed in DMBA exposed animals, when compared to the control group. No significant alterations were observed in the hepatic GST activity of lycopene per se group. Lycopene treatment followed by DMBA exposure increased the activity of GST in group IV when compared to group II. Tomato, a rich source of naturally occurring carotenoids has proved to be an effective phase II detoxifier by up regulating the activity of GST under conditions of exposure to carcinogens/ genotoxins.[33,35]

In the present investigation, DMBA induced oxidative stress was associated with decreased activities of catalase and SOD in hepatic tissue. Several studies have repeatedly developed a relation between low levels of antioxidant defense system and exposure to toxins, carcinogens etc. Lycopene treatment to the otherwise normal animals boosted the antioxidant defense system which is evident from an increase in the hepatic catalase activity when compared to the control group, the SOD activity remained unchanged. An increase in the catalase and SOD activities was observed in the lycopene pre-treated and DMBA challenged animals when compared to the animals exposed to DMBA only. Lycopene has been shown to exhibit the highest physical quenching rate constant with ROS.[48,13] Reifen et al., 2004 suggested that lycopene as well as 5-aminsalicyclic acid act as antioxidant in oxidative stress against colitis induced iron in rats.[49] Srinivasan (2007) reported that lycopene is very efficient ROS scavenging and also has the potential to increase the activity of SOD and catalase.[50] Moreira et al., 2005 reported that lycopene rich diet is beneficial in prevention of oxidative damage related to ROS.[51]

Overall, the present data provides evidence that prolonged exposure to pure lycopene to the normal animals does not affect the liver marker enzymes, LPO and selected antioxidant enzymes in liver. On the other hand this compound was found to increase the number of micronucleated cells in normal animals, which suggested that pure compounds may not prove to be beneficial when given for long duration at this dose. However, pure lycopene had the potential to reduce the number of micronucleated cells when animals were challenged with DMBA, which indicates that it shows some protective role on DMBA exposure. The role of lycopene needs to be investigated further with regard to its dose level.

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):311-316
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Comunicaciones breves

Socioeconomic status influences physical fitness in European adolescents independently of body fat and physical activity: the HELENA Study

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Abstract

Introduction: **The influence of socioeconomic status on health-related fitness is not clear.**

Aim: **To examine the influence of socioeconomic status on health-related fitness in adolescents.**

Methods: **A total of 3,259 adolescents (15.0 ± 1.3 y) from the Healthy Lifestyle in Europe by Nutrition in Adolescence Cross-Sectional Study (HELENA-CSS) participated in the study. Socioeconomic status was assessed by the family affluence scale (FAS). Speed-agility, muscular strength and cardiorespiratory fitness were assessed. Covariates included total body fat, physical activity and pubertal status.**

Results: **Adolescents with high FAS had significantly higher fitness levels than their peers of lower FAS categories except for speed-agility and handgrip in boys. Overall, the associations observed presented a medium to large effect size.**

Conclusion: **These results suggest that socioeconomic status is positively associated with physical fitness in European adolescents independently of total body fat and habitual physical activity.**

(*Nutr Hosp*. 2010;25:311-316)

DOI:10.3305/nh.2010.25.2.4596

Key words: *Socioeconomic status. Physical fitness. Physical activity. Total body fat.*

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Recibido: 14-XI-2009.
Aceptado: 22-XI-2009.

EL ESTATUS SOCIOECONÓMICO INFLUENCIA LA CONDICIÓN FÍSICA EN ADOLESCENTES EUROPEOS. EL ESTUDIO HELENA

Resumen

Introducción: **La influencia del estatus socioeconómico sobre la condición física en relación con la salud no está clara.**

Objetivo: **Examinar la influencia del estatus socioeconómico sobre la condición física en relación con la salud en adolescentes.**

Metodología: **Un total de 3259 adolescentes (15,0 ± 1,3 años) del "Healthy Lifestyle in Europe by Nutrition in Adolescence Cross-Sectional Study" (HELENA-CSS) participaron en el estudio. El estatus socioeconómico fue medido con una escala de riqueza familiar "family affluence scale (FAS)". Se midieron velocidad-agilidad, fuerza muscular y capacidad aeróbica. Las covariables incluidas fueron grasa corporal total, actividad física y estadio madurativo.**

Resultados: **Los adolescentes con alto FAS tuvieron significativamente mayores niveles de condición física que aquellos con bajo FAS exceptuando los tests de velocidad-agilidad y fuerza de prensión manual en chicos. En general, las asociaciones observadas presentaron un efecto del tamaño de la muestra (effect size) entre medio y largo.**

Conclusión: **Estos resultados sugieren que el estatus socioeconómico esta positivamente asociado con la condición física en adolescentes Europeos independientemente de la grasa corporal total y el nivel de actividad física.**

(*Nutr Hosp*. 2010;25:311-316)

DOI:10.3305/nh.2010.25.2.4596

Palabras clave: *Estatus socioeconómico. Condición física. Actividad física y grasa corporal total.*

Introduction

Speed-agility, muscular fitness, and cardiorespiratory fitness (CRF) are considered important health-related markers already in youth.[1,2] Genetics greatly determines physical fitness[3], but there is little doubt that environmental factors also play an important role. Socioeconomic status is associated with several health outcomes (e.g., birth weight, obesity, diet, etc.)[4,5] and with mortality.[6] To better understand the specific role of different indicators of socioeconomic status on health-related fitness markers will enable a more efficient physical fitness promotion. In this regard, the association between socioeconomic status and fitness was investigated in Portuguese[7] and Irish[8] youth with contradictory results. In Portuguese adolescents, the socioeconomic status was inversely associated with fitness in boys but positively in girls.[7] However, in Irish youth there was a positive association of socioeconomic status with fitness.[8] These previous findings highlight that both social and cultural contexts are often country-specific, so studies from a widespread vision and including populations from different countries are required to facilitate a better understanding.

The Healthy Lifestyle in Europe by Nutrition in Adolescence Cross-Sectional Study (HELENA-CSS) used harmonised and well standardised methods of measurement in nine European countries and previous workshops were organised in order to guarantee this process. Therefore the HELENA-CSS provides a good opportunity to explore the relationship between socioeconomic status and physical fitness in European adolescents (see annex 2). The aim of this study was to examine the influence of socioeconomic status on health-related physical fitness (speed-agility, muscular fitness, and CRF) in urban European adolescents.

Methods

The HELENA-CSS study is a multi-centre study aiming to obtain reliable data from European adolescents aged 12.5 to 17.5 years about nutritional habits and patterns, body composition and levels of physical activity and fitness (see annex 2). The total sample of the HELENA-CSS was 3,528 adolescents and the present work comprised 3,259 (1,558 boys and 1,701 girls) adolescents with valid data on socioeconomic status and at least one physical fitness test. More details about the sampling procedures, preparation of the field teams, pilot study and reliability of the data can be found elsewhere (see annex 2).

Ten cities in nine different European countries were chosen due to an existing network of research groups and a rough geographical balance across Europe; Stockholm (Sweden), Athens (Greece), Heraklion (Greece), Rome (Italy), Zaragoza (Spain), Pecs (Hungary), Ghent (Belgium) Lille (France), Dortmund (Germany) and Vienna (Austria). Signed informed consent was obtained from all participants and their parents, and the protocol was approved by the Human Research Review Committees of the involved centres (see annex 2).

Socioeconomic status

The Family Affluence Scale (FAS) is based on the concept of material conditions in the family to base the selection of items. Currie et al.[9] chose a set of items which reflected family expenditure and consumption that were relevant to family circumstances. Possessing these items was considered to reflect affluence and their lack, on the other hand, material deprivation. FAS was used in the present study as an index of socioeconomic status,[10] which includes 4 questions answered by the adolescent: Do you have your own bedroom?; How many cars are there in your family?; How many PCs are there in your home?; Do you have internet access at home? We defined low, medium and high socioeconomic status based on the final score obtained from the four questions. That is, we give a numerical value to each possible answer in the four questions. Then we summed the final score from all the questions being ranged from 0 to 8. Finally, we grouped these scores in three levels: low (from 0 to 2), medium (from 3 to 5) and high (from 6 to 8).

Physical fitness

Speed-agility was assessed with the 4 x 10 m shuttle run test. Upper-body muscular strength was assessed with the handgrip strength and the bent arm hang tests. Lower-body muscular strength was assessed with the standing long jump, the squat jump, the counter movement jump and the Abalakov jump tests. The Infrared Platform ERGO JUMP Plus-BOSCO SYSTEM (Byomedic, S.C.P., Barcelona, Spain) was used for the jump assessment. CRF was assessed by the 20 m shuttle run test. More detailed information about the fitness testing protocol has been published elsewhere (see annex 2).

Covariates

Following standard procedures (see annex 2), weight was measured in underwear and without shoes with an electronic scale (Type SECA 861) to the nearest 0.05 kg, and height was measured barefoot in the Frankfort plane with a telescopic height measuring instrument (Type SECA 225) to the nearest 0.1 cm. Skinfold thickness was measured to the nearest 0.2 mm in triplicate in the left side at biceps, triceps, subscapular, suprailiac, thigh, and medial calf with a Holtain Caliper (Crymmych, UK).[11] The Actigraph accelerometer (Actigraph MTI, model GT1M, Manufacturing

Technology Inc., Fort Walton Beach, FL, USA) was used to assess physical activity and expressed as counts/min.[12] Adolescents were asked to wear the accelerometer during the daytime for 7 consecutive days, except during water based activities. The criterion for inclusion was to record at least 8 h per day, for at least 3 days.[13] A total of 2,208 (68% of the total) adolescents (1,192 girls) reported valid data of accelerometry. Pubertal status was assessed by a medical doctor according to Tanner stages.[14]

Statistical analysis

The data are presented as means (standard deviation). To achieve normality in the residuals, handgrip, bent arm hang, squat jump, counter movement jump, Abalakov jump, and sum of skinfold thickness were transformed to the natural logarithm. The associations between FAS and physical fitness were assessed by one-way analysis of covariance with FAS entered as fixed factor and the fitness tests as dependent variables. Age, height, total body fat and physical activity were entered as covariates. Effect size statistics is a measure of the magnitude of effect and in this study was assessed using Cohen's *d* (standardized mean difference) and 95% confidence interval.[15] Taking into account the cut-off established by Cohen, the effect size (Cohen'd) can be small (~0.2), medium (~0.5) or large (~0.8). We analysed possible differences in age, weight, height and BMI (variables available for the whole study sample) between adolescents with complete valid data (1,411) and missing data. No differences were observed in the variables studied. The analyses were performed using the Statistical Package for Social Science (SPSS, v. 15.0 for Windows; SPSS Inc., Chicago, IL) and the level of significance was set at 0.05.

Results

Table I shows the associations between FAS and physical fitness by sex. In boys, those with high FAS performed better in bent arm hang, standing long jump, squat jump, counter movement jump, Abalakov jump or 20 m shuttle run test (all $P \leq 0.05$). FAS was not associated with the 4 x 10 m shuttle run test or handgrip strength. Small effect sizes were observed for the standing long jump test in boys with high FAS compared to those with low FAS, whereas medium to large effect sizes were observed for the bent arm hang, squat jump, Abalakov jump, counter movement jump and 20m shuttle run tests.

Table I
Association between family affluence scale and physical fitness, after adjusting for age, height, skinfold thickness and physical activity

		Family afluence scale				*Effect size*		
Fitness Tests	*n*	*Low (L)*	*Medium (M)*	*High (H)*	*P*	*L-M*	*M-H*	*L-H*
Boys								
4 x 10 m shuttle run test (s)	921	11.6 (0.9)	11.4 (0.9)	11.4 (0.9)	0.207	0.2 (0.04; 0.45)	0.0 (-0.14; 0.14)	0.2 (0.01; 0.39)
Handgrip (kg)[a]	942	69.6 (12.0)	70.8 (12.0)	70.7 (12.0)	0.352	0.1 (-0.05; 0.26)	0.1 (-0.04; 0.23)	0.0 (-0.18; 0.21)
Bent arm hang (s)[a]	902	18.4 (16.0)	21.9 (15.9)	24.8[†§] (16.0)	< 0.001	0.4 (0.23; 0.55)	0.1 (-0.02; 0.25)	0.5 (0.31; 0.71)
Standing long jump (cm)	933	179.1 (26.2)	185.1 (26.1)	186.5[†] (26.2)	0.05	0.2 (0.02; 0.38)	0.1(-0.08; 0.19)	0.3 (0.09; 0.48)
Squat Jump (cm)[a]	868	22.5 (7.0)	24.9* (7.0)	26.9[†§] (7.0)	< 0.001	0.3 (0.19; 0.51)	0.3 (0.13; 0.41)	0.6 (0.41; 0.83)
Counter Movement Jump (cm)[a]	868	24.5 (6.7)	28.0* (6.7)	29.8[†§] (6.7)	< 0.001	0.5 (0.35; 0.68)	0.3 (0.13; 0.41)	0.8 (0.56; 0.99)
Abalakov Jump (cm)[a]	867	30.6 (7.1)	34.2* (7.0)	35.0[†§] (7.0)	< 0.001	0.4 (0.21; 0.54)	0.3 (0.12; 0.40)	0.6 (0.43; 0.85)
20m shuttle run (stage)	820	5.8 (2.6)	6.8* (2.6)	7.2[†§] (2.6)	< 0.001	0.4 (0.24; 0.48)	0.2 (0.01; 0.30)	0.6 (0.35; 0.78)
Girls								
4 x 10 m shuttle run test (s)	1060	13.4 (1.2)	12.8* (1.2)	12.8[†§] (1.2)	< 0.001	0.5 (0.33; 0.62)	0.3 (-0.13; 0.39)	0.7 (0.55; 0.92)
Handgrip (kg)[a]	1093	51.3 (8.5)	50.8 (8.4)	52.3[§] (8.5)	< 0.05	0.1 (-0.08; 0.20)	0.2 (-0.05; 0.31)	0.1 (-0.06; 0.30)
Bent arm hang (s)[a]	1048	7.3 (14.5)	8.5 (14.4)	9.8 (14.5)	< 0.001	0.3 (0.16; 0.46)	0.3 (0.16; 0.43)	0.6 (0.42; 0.79)
Standing long jump (cm)	1085	139.1 (25.0)	144.4 (24.8)	153.1[†§] (25.1)	< 0.001	0.2 (0.07; 0.36)	0.3(-0.23; 0.48)	0.6 (0.38; 0.74)
Squat Jump (cm)[a]	974	16.0 (5.6)	18.8* (5.5)	21.2[†§] (5.6)	< 0.001	0.5 (0.35; 0.65)	0.4 (0.29; 0.57)	0.9 (0.73; 1.12)
Counter Movement Jump (cm)[a]	971	19.3 (6.1)	21.1* (6.0)	23.7[†§] (6.1)	< 0.001	0.3 (0.15; 0.45)	0.4 (0.28; 0.56)	0.7 (0.52; 0.91)
Abalakov Jump (cm)[a]	967	23.2 (5.6)	24.9* (5.5)	27.2[†§] (5.6)	< 0.001	0.3 (0.17; 0.47)	0.4 (0.28; 0.55)	0.7 (0.53; 0.92)
20 m shuttle run (stage)	942	3.1 (1.9)	3.8* (1.9)	4.6[†§] (1.9)	< 0.001	0.4 (0.22; 0.53)	0.4 (0.29; 0.57)	0.8 (0.61; 1.00)

Values are mean (standard deviation). Effects size statistics are expressed as *Cohen's d* (95% Confidence interval).
*P < 0.01 for differences in Medium vs Low. [§]P<0.01 for differences in High vs Medium. [†]P < 0.01 for differences in High *vs* Low. [a]Non-transformed data are presented in the table, but analyses were performed on log-transformed data.

Girls with high FAS performed significantly better in all fitness tests (all $P < 0.05$) compared to their peers of lower FAS level. Medium effect sizes were found for the bent arm hang, 4 x 10 m shuttle run test, standing long jump, counter movement jump and Abalakov jump in girls with high FAS compared to those with low FAS. We observed large effect sizes for the squat jump and 20m shuttle run tests. Additional adjustments for pubertal status instead of age did not modify the results (data not shown). The result did not change when body mass index or waist circumference was used instead of skinfold thickness. Likewise, the results remained the same when parental educational level was used instead of FAS (data not shown).

Discussion

The results from the present study suggest that there is a strong positive association between socioeconomic status and physical fitness in European adolescents independently of total body fat and objectively assessed physical activity. Overall, the associations observed presented a medium to large effect size. These findings could be interpreted as an overall influence of socioeconomic status on the physical fitness performance. A higher socioeconomic status could allow the adolescents to have more facilities to practice exercise in terms of sport equipments acquisition, extracurricular sport sessions as well as a major awareness of their parents regarding the importance of having a healthy fitness.

These findings do not concur with a previous study[7] in which negative associations were observed between socioeconomic status and CRF (12 min walk-run) and muscular strength (standing long jump and bent arm hang) in boys.[7] Moreover, Freitas et al. reported a positive association between socioeconomic status and speed-agility performance (5 x 10 m shuttle run test). They also reported a higher upper-body muscular strength (handgrip) in those boys with medium socioeconomic status compared to those with lower socioeconomic status.[7] In contrast, our findings showed positive associations between socioeconomic status and CRF (20 m shuttle run test), lower-body muscular strength (standing long jump, squat jump, counter movement jump, Abalakov jump) and one upper-body muscular strength test (bent arm hang), while no associations for speed-agility (4 x 10 m shuttle run test) and other upper-body muscular strength (handgrip) were found. In girls, Freitas et al. found positive associations between socioeconomic status and lower-body muscular strength and speed-agility performance, but no association for CRF and upper-body muscular strength,[7] which partially concur with our results. However, we also found positive associations for CRF and upper-body muscular strength. Our data also concur with the results observed by Mutunga et al.[8] They reported higher CRF (20 m shuttle run test) in boys and girls with higher socioeconomic status compared to those with lower socioeconomic status.[8] Discrepancies among studies could be due to the specific social and cultural contexts of each country, together with the different methodologies used to assess socioeconomic status and physical fitness.

The direction of the associations cannot be established from cross-sectional designs. However, in the current study, it is not likely that adolescent physical fitness level determines the affluence of their families. The relatively large sample of adolescents studied from nine European countries (ten cities) provides a good overview of the relationships between socioeconomic status and physical fitness in European adolescent population.

In conclusion, these results suggest that high socioeconomic status, as assessed by family affluence, positively influences physical fitness in urban European adolescents independently of total body fat and habitual physical activity.

Annex

Annex 1: HELENA Study Group

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Acknowledgements

We gratefully acknowledge all participating children and adolescents, and their parents and teachers for their collaboration. We also acknowledge all the members involved in the field work for their efforts and great enthusiasm. The HELENA study takes place with the financial support of the European Community Sixth RTD Framework Programme (Contract FOOD-CT-2005-007034). This analysis was also supported by grants from the Spanish Ministry of Education (AP-2005-3827, AP-2005-4358, EX-2007-1124, EX-2008-0641), the Swedish Council for Working Life and Social Research, and the ALPHA study, an European Union-funded study, in the framework of the Public Health Programme (Ref: 2006120). This study was also supported by a Grant from the Spanish Ministry of Health: Maternal, Child Health and Development Network (number RD08/0072) (LAM) and Science-FEDER funds (Acciones Complementarias DEP2007-29933-E).

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):317-126
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

DOI:10.3305/nh.2010.25.2.4631

Cartas científicas

Ketogenic diet in epileptic children: clinical and laboratory assessment

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Introduction

Epilepsy is the most frequent neurological pathology in children, and in some cases it has no adequate control with drug treatments[1]. The improvement of epilepsy control observed during starvation periods triggered the development of a diet that simulates its alterations, allowing its use to treat difficult to control epileptic patients. Many researchers have been demonstrating the efficacy of the ketogenic diet (KD) on controlling epileptic children[2]. The mechanisms involved still remain unknown, though[3].

Objective

Assess clinical and laboratorial aspects of difficult to control epileptic children submitted to KD for a period of 18 to 24 months.

Material and methods

20 patients (10 boys and 10 girls) with median age of 6 years and 2 months were assessed three times: assessment 1 – inpatient service to start the diet; assessment 2 - 6 to 12 months and assessment 3 - 18 to 24 months after beginning the treatment. Weight and height measurements, and serum lipids and triacylglycerol dosages were assessed. A vitamin and mineral supplementation was prescribed. The ANOVA statistical test was used to compare the analyzed parameters.

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Recibido: 16-XII-2009.
Aceptado: 25-XII-2009.

Results

Clinical and neurological improvements were observed in all patients. Significant decrease occurred for the medium values for weight/age (W/A) and height/age (H/A) Z scores ($p < 0.05$), which didn't occur with the BMI/age. Significant increase on the medium values for the serum total cholesterol and LDL-cholesterol ($p < 0.05$) had also been observed. The medium values for serum triacylglycerol had decreased, but it was not statistically significant (table I).

Discussion

KD can provide a better control for epileptic children. Considering all the nutritional restrictions involved, it is possible that alterations on growth and nutritional status may occur[4]. The decrease on the W/A and H/A outcomes was probably consequent to the low caloric amount offered by the KD. The stability of the BMI/A shows a proportional growth stop (table 1). The higher amount of saturated fats ingested during the study caused an increase on serum lipids. The individual ability to metabolize fats contributed to normalize them (or not). The serum lipids dosage had evidenced a significant increase in the medium values of total cholesterol, consequent to an increase of LDL-cholesterol.

Table I
Results

	I	*II*	*III*
Z BMI/A	-0.51 ± 1.7	-0.9 ± 1.2	-0.7 ± 1.6
Z W/A*	-0.41 ± 1.9	-0.95 ± 1.5	-1.2 ± 2.0
Z H/A*	-0.41 ± 1.5	-0.6 ± 1.4	-1.05 ± 1.3
Total Cholesterol	177.7 ± 35.1	203 ± 46.2	213.4 ± 43.7
Triacylglycerol	107.6 ± 54.9	94.8 ± 47.8	85.8 ± 28.8
LDL-cholesterol	123 ± 26.2	135.6 ± 48.0	151.7 ± 45.7

* $p < 0.05$.

Conclusions

The growth velocity reduction observed in these patients, as well as the increase on the concentrations of serum lipids, indicate that the use of KD for longer periods should be discussed with rigorous criteria. Despite the clinical benefit, evidenced by the neurological improvement, there's the need of follow-up, even after stopping the diet. The catch-up of growth must be assured to guarantee the nutritional safety of the diet.

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DOI:10.3305/nh.2010.25.2.4641

Cartas científicas

Evolution of mesenteric artery blood flow in healthy premature neonates

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This study aims to analyze the superior artery blood flow in healthy premature neonates with birth weight between 1,000 g and 1,500 g, on the first and seventh days of live.

It is a prospective cohort study, including 15 premature neonates with mean weight of 1,243g ± 173.6 (ranging from 1,000 to 1,495 g). Exclusion criteria were: unstable hemodynamic conditions; assisted ventilation with high parameters; large deformations or clinical syndromes; feeding intolerance; necrotizing enterocolitis; and conditions those alter the mesenteric flow: phototherapy, umbilical catheters, patient ductus arteriosus and sepsis.

The Doppler velocimetric examination was done by a 8 MHz imaging transducer, and the pulsed color Doppler readings were obtained by sonographic waves at 4 MHz. The neonate was kept in a supine position, with the transducer positioned in the epigastric region, immediately below the xyphoid appendix, obtaining two dimensional images of the celiac trunk and of the superior mesenteric artery, a few millimeters after its emergence from the aorta in the sagital plane.

The flux measurements were obtained in the longitudinal direction of the vessel and at an isonation angle between 0 and 20 degrees. The blood flow curves were recorded after a sequence of five stable measurements, with respect to the quality of the waves, and their audible characteristics. The following measurements were obtained: Peak Systolic Velocity (PSV), End Diastolic Velocity (EDV), Resistance Index (RI), and Pulsatility Index (PI).

The values obtained were expressed in means and standard deviations. The measurements were done prior to feeding (up to 30 minutes) and after feeding (between 15 and 60 minutes). The measurements were done on the first day (between the 6th and the 24th hours of life), and on the 7th day of life. The comparison of means and standard deviations was carried out by ANOVA.

Table I lists the values of RI, PI, PVS, and EDV, prior and after feeding, on the first and 7th days of life, in means and standard deviations.

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Recibido: 27-XII-2009.
Aceptado: 28-XII-2009.

Table I
Resistance Index (RI), Pulsatility Index (PI), Peak Systolic Velocity (PVS), End Diastolic Velocity (EDV) prior and after feeding, on the first and on the seventh days of life

	First day	*Seventh day*
RI prior to feeding	0.69 ± 0.07	0.78 ± 0.05
RI after feeding	0.66 ± 0.07	0.73 ± 0.08
PI prior to feeding	1.45 ± 0.20	1.81 ± 0.27*
PI after feeding	1.35 ± 0.39	1.6 ± 0.2
PVS (cm/s) prior to feeding	60.1 ± 23.4	95.3 ± 28.0*
PVS (cm/s) after feeding	57.2 ± 21.5	112.3 ± 38.0*
EDV (cm/s) prior to feeding	18.5 ± 6.2	20.0 ± 5.7*
EDV (cm/s) after feeding	20.3 ± 13.4	31.5 ± 19.5*

* $p < 0.05$.

In conclusion, these studied neonates showed a significant evolution of the blood flow of superior mesenteric artery on the 7th day of life, represented by the Peak Systolic Velocity and the End Diastolic Velocity improve, and a better vasodilatation response after feeding.

These results suggest for the Doppler velocimetry as a specific evaluation method for feeding introduction and progression, in order to reduce the prevalence of gastrointestinal inflammatory diseases in neonates, and to improve the neonatal survive[1-5].

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DOI:10.3305/nh.2010.25.2.4714

Cartas científicas

Análisis de los sustitutos de comida comercializados de uso habitual en nuestro entorno y su adaptación a la legislación vigente

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Los "sustitutos de comida" (SC) son productos empleados para reemplazar una o varias comidas diarias en dietas de bajo valor energético y pueden constituir una opción más frente a una dieta hipocalórica convencional como estrategia para el tratamiento y prevención de la Obesidad.

La composición nutricional de los SC debe ser la adecuada para satisfacer las exigencias diarias de nutrientes esenciales o, cuando son pensados para sustituir parte de la dieta diaria deben proporcionar una parte significativa de dichos elementos a las personas a las que aquellos van destinados.

Forma parte de los llamados "alimentos destinados a ser utilizados en dietas de bajo valor energético para reducción de peso" y están regulados por diferentes normas legislativas vigentes[1-3].

En base al estudio realizado por M. Cabanillas y cols., 2009[4] se realizó un análisis de los treinta y dos sustitutos de comida estudiados y su adaptación a la legislación que los regula.

Tabla I
Composición nutricional de los treinta y dos productos analizados y los valores fijados según la legislación vigente

	Mínimo	*Máximo*	*Media*	*Desv. típ.*	*%*	*Valores según legislación*
kcal	160,9	357,3	266	54		200-400
g proteínas	7,7	23,8	17,9	3,7	26	25-50 %
g carbohidratos	15,1	40,5	30,6	5,6	45	
g grasas	2,9	16	8,8	3,1	29	< 30%
g fifra	1,2	13	4,4	2,5		
% RDA de calcio	13,1	50	26,4	8,6		30%
% RDA de fósforo	18,8	60	37,9	13,4		30%
% RDA de hierro	23	76,6	43,3	12		30%
% RDA de magnesio	11	32,4	15,1	5,1		30%
% RDA de zinc	23,4	56,8	34,4	8,7		30%
% RDA vit A	21,4	56	39,3	11		30%
% RDA vit D	29,4	59,8	41,6	11,9		30%
% RDA vit E	13,2	129,9	34,1	22,4		30%
% RDA vit B6	33,8	74,3	51,4	12,5		30%
% RDA vit B12	13,7	41,6	25,6	9,5		30%
% RDA vit C	15,2	145,4	39,1	41,1		30%
% RDA fólico	10,5	48,3	21,8	7,8		30%

* % RDA calculado como la media de las RDA para varones y mujeres de 31 a 50 años

En cuanto a la distribución global de macronutrientes (valores medios por comida) fueron 26% del VCT en forma de proteínas, un 45% de carbohidratos y una media del 29% como grasas, con un aporte medio de fibra de 4,45 gramos por comida y un aporte energético medio de 266 kcal/comida. Todos estos valores medios pueden considerarse adaptados a la legislación, sin embargo, si tenemos en cuenta los valores máximos y mínimos obtenidos puede observarse una gran variabilidad y que varios de los analizados no se adaptan a dichas normas. Respecto a los micronutrientes, aunque también existen marcadas diferen-

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Recibido: 13-I-2010.
Aceptado: 4-II-2010.

cias entre los productos (máximos y mínimos), se supera el aporte medio global establecido del 30% de las RDA por comida sobretodo para el hierro y las vitaminas B1, B6 y D. Sin embargo para otros micronutrientes como el calcio, el magnesio, el ácido fólico y la vitamina B12 y no llega a alcanzarse el 30% de las RDA (tabla I).

Los planes de sustitución parcial de comidas son una opción más a tener en cuenta en el tratamiento de la obesidad, especialmente por tratarse de dietas de más fácil comprensión y manejo y con más altas tasas de seguimiento a largo plazo. Al analizar un grupo de sustitutos de comida comercializados de uso habitual en nuestro entorno y su adaptación a la legislación vigente, si bien en la mayor parte de los productos se cumple con la misma tanto en el caso del valor energético como en el aporte de micronutrientes, no siempre es así, por lo que resultará fundamental tenerlo en cuenta a la hora de realizar su recomendación.

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(2):322-323
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

DOI:10.3305/nh.2010.25.2.4715

Cartas al director

Uric acid is associated with features of insulin resistance syndrome in obese children at prepubertal stage

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Recientemente he leído el artículo de M. Gil-Campos y cols., *Uric acid is associated with features of insulin resistance syndrome in obese children at prepubertal stage*[1]. Sin dudas un trabajo interesante considerando que la hiperuricemia es un potencial factor de riesgo para la mortalidad y morbilidad por enfermedad cardiovascular[2].

No obstante proponer un mecanismo fisiopatogénico que relacione a la obesidad con la hiperuricemia, si bien es necesario, no es nada sencillo.

La hiperuricemia predice de modo independiente el surgimiento de diabetes mellitus tipo 2, la hipertensión arterial y el actualmente discutido síndrome metabólico (condiciones relacionadas con altos índices de resistencia a la insulina y obesidad)[2].

El estrés oxidativo en el tejido adiposo parece ser uno de los elementos clave en el desarrollo de insulinorresistencia[3]. El ácido úrico (AU) es captado por los adipocitos en los que provoca un desbalance redox dependiente de la NADPH oxidasa[4]. Durante la diferenciación de estas células, la expresión de dicha enzima se relaciona con la acumulación de lípidos y con la desregulación de la expresión genética de las adipoquinas TNFα y adiponectina[3]. Es conocido que el TNFα estimula la lipólisis y favorece la resistencia a la insulina, mientras que la adiponectina se asocia a lo opuesto.

Gil-Campos propone que los ácidos grasos libres ocasionan un incremento de la adenosina extracelular por alteraciones en el metabolismo lipídico. Sin embargo, no dan argumentos de cómo se convierte la adenosina extracelular en AU. Tampoco queda claro de dónde se obtienen los ácidos grasos libres.

La dieta es un factor que puede modular de forma importante las concentraciones séricas de AU[5]. Sin embargo, pocos estudios epidemiológicos controlan esta variable confusora.

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Recibido: 9-I-2010.
Aceptado: 4-II-2010.

Le propongo así, de forma muy resumida, otro posible mecanismo fisiopatogénico integrador: una dieta hiperuricemiante y obesogénica pudiera provocar un desbalance redox en tejido adiposo que conduzca a una resistencia a la insulina (con incremento de TNFα y la reducción de adiponectina), con una consecuente elevación de las concentraciones séricas de ácidos grasos libres. Estos ácidos grasos libres pueden contribuir también a un incremento del catabolismo intracelular de nucleóticos purínicos generándose así un círculo vicioso.

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Replica de los autores

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Estimado Sr. Director:

En relación con nuestro artículo titulado *Uric acid is associated with features of insulin resistance syndrome in obese children at prepubertal stage*[1] y la carta del

Dr. Daniel Díaz Arce, nos gustaría hacer algunas consideraciones.

Efectivamente, tal y como indica, proponer un mecanismo fisiopatogénico que relacione la obesidad con la hiperuricemia es complicado y, probablemente existan diversas causas que actúan de forma paralela o sinérgica, especialmente si se considera la población infantil. No obstante en los resultados de otros trabajos de nuestro grupo en niños con obesidad[2,3] y en los datos de otros autores[4] y, creemos que puede haber un acercamiento a una hipótesis posible para explicar no la hiperuricemia sino la elevación relativa de las concentraciones circulantes de urato en los niños obesos respecto de los niños sanos.

Es cierto que pueden existir mecanismos independientes de generación de hiperuricemia en relación con la resistencia a la insulina, la hipertensión arterial o el estrés oxidativo y en particular en relación con una dieta hiperuricemiante. No obstante, en nuestros trabajos en niños prepúberes, la evaluación de la dieta no ha indicado grandes diferencias entre la dieta de niños obesos en edad prepuberal y la de niños con normopeso, sobre todo entre aquéllos obesos que desarrollan síndrome metabólico y aquéllos que no lo originan[2]. Por tanto, no parece probable que en nuestro caso una dieta con elevado contenido en nucleótidos purínicos sea la causa de la elevación de los niveles plasmáticos de urato respecto a niños controles con normopeso.

Por otra parte, al contrario de lo que está descrito en adultos y en niños en edad puberal y adolescentes, nuestro grupo ha observado y publicado niveles similares en ayuno e incluso disminuidos tras la ingesta de TNF-α, probablemente debido a que la edad prepuberal representa una primera etapa de la obesidad en la que hay mecanismos compensadores. No obstante, en esta etapa, como en otras etapas de la vida la adiponectina ya está disminuida. Aún cuando las concentraciones de TNFα no están alteradas en los niños en edad prepuberal no es descartable que en el tejido adiposo exista una producción aumentada de este factor. Así, la disminución de la adiponectina, al menos en parte, puede explicarse, por un aumento de la producción tisular de TNFα que estimula la lipólisis, favorece la resistencia a la insulina, y disminuye la expresión génica de adiponectina. A través de este mecanismo pueden aumentar las concentraciones séricas de ácidos grasos libres. No obstante, tampoco los ácidos grasos libres circulantes en niños obesos prepúberes están muy aumentados[2,3]. Sin embargo la aclaración es mucho más lenta por lo que el efecto es similar[3].

En nuestro trabajo se propone la hipótesis que el menor aclaramiento de los ácidos grasos libres ocasionaría un incremento de los ácidos grasos intracelulares y como consecuencia de la adenosina extracelular (Ado) y del ácido úrico circulante. La Ado elevada parece convertirse en ácido úrico a través del translocador mitocondrial de nucleótidos de la adenina (ANT) que sirve para suministrar a la matriz mitocondrial de los tejidos y también para facilitar el paso al citoplasma del ATP, producido desde el ADP en la matriz mitocondrial[4]. Por tanto, los niveles elevados intracelulales de acil-Coa, derivados de la menor aclaración o niveles aumentados de ácidos grasos libres en el estado de obesidad, hipotéticamente pueden dar lugar a un exceso de ADP, y paralelamente una disminución de ATP en el citoplasma. El aumento de las concentraciones de AMP en el citoplasma da lugar a un aumento en la desfosforilación de AMP a Ado[4]. Este aumento ocasiona un desequilibrio en el transporte desde el espacio extracelular porque hay un menor gradiente y por ello, aumentan en plasma los niveles de Ado y consecuentemente, las concentraciones de ácido úrico[5]. Además, por otra parte, si hay una elevada síntesis de ácidos grasos-acil-CoA en los tejidos periféricos, esto ocasiona una mayor síntesis de AMP y de nuevo da lugar a mayores niveles de ácido úrico[5,6].

Esta hipótesis, por supuesto necesita comprobación en la edad pediátrica, aspecto complicado de solucionar, si se considera que el acceso a tejido adiposo no es factible excepto en condiciones especiales. No obstante, la posibilidad de tomar muestras de tejido adiposo durante intervenciones quirúrgicas programadas como la solución de hernias, y la determinación de la expresión génica del gen ANT y de las concentraciones intracelulares de acil-CoA, TNFα y adiponectina, abre una posibilidad a la aclaración de la hipótesis sugerida por nuestro grupo para explicar la elevación del ácido úrico en niños obesos en edades tempranas.

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Nutrición Hospitalaria

Nutr Hosp. 2010;25(1):324-325
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

DOI:10.3305/nh.2010.25.2.4716

Crítica de libros

Un planeta de gordos y hambrientos: la industria alimentaria al desnudo

A world of fat and hungry people: the food industry without secrets

L. de Sebastián. Editorial: Ariel.
Año de edición: 2009. 358 páginas. ISBN: 978-84-344-8789-5.

Existen alrededor de mil personas que padecen hambre en el mundo y aproximadamente otras tantas sufren sobrepeso. Tanto el hambre como la obesidad son problemas relativos a la malnutrición, que vienen determinados por diferentes causas y consecuencias sobre la salud. Su conocimiento permite crear medidas para combatir las carencias y excesos. Sin embargo, la realidad es muy compleja, siendo necesario utilizar diferentes enfoques para generar un conocimiento dirigido a la formulación de medidas adecuadas. Además, existen razones estructurales en torno a ambos problemas así como otras cuestiones más dinámicas, recientes y polémicas en las tendencias de la alimentación. Entre estas cuestiones cabe citar la elaboración de biocombustibles a partir de alimentos básicos, el cultivo y consumo de alimentos genéticamente modificados, y la influencia del cambio climático en el hambre mundial.

Con el fin de enfrentarse a los retos aludidos anteriormente, Luis de Sebastián analiza el hambre y la obesidad desde una perspectiva multidisciplinar (es licenciado en Economía, Filosofía, Ciencias Sociales y Teología, además de doctor en Ciencias Políticas), de forma divulgativa y sencilla, partiendo de una extensa documentación y con una gran completitud. Las perspectivas en las que analiza los problemas del hambre y la obesidad son principalmente de tipo económico y político en cuanto a sus causas, y nutricional en cuanto a sus consecuencias. Resulta difícil destacar todos los temas tratados, ya que su abanico es muy amplio. Cabría destacar en el libro cuestiones tales como el papel de la estructura del mercado de la industria de alimentos en torno al hambre y la obesidad. El autor argumenta que la excesiva concentración de la producción y el comercio de alimentos en un número pequeño de empresas, contribuye a los malos hábitos nutricionales y a la escasez de alimentos. Todo ello en un contexto de mercado en el que las empresas alimentarias tienen como objetivo la maximización de beneficios en lugar de fomentar hábitos nutricionales sanos o el acceso a los mismos hacia los más desfavorecidos y donde la regulación gubernamental escasea.

Dentro del objetivo de maximizar beneficios, las empresas alimentarias tratarán de que el consumidor ingiera la mayor cantidad de alimentos, así como de innovar en su oferta alimentaria para atraer a los clientes. El fomento de la ingesta de una cantidad de alimento mayor de las necesidades individuales y en una composición poco saludable, así como la innovación de nuevos alimentos a través de ingredientes artificiales, son razones que contribuyen a explicar la obesidad. Además, los excesos de publicidad de alimentos y la falta de educación nutricional son motivos de la generación de malos hábitos alimentarios. El fomento de una alimentación sana y el ejercicio, a través de un entorno adecuado para reducir el exceso de peso, y el incentivo de los individuos afectados o en riesgo para que se sientan capaces de bajar de peso, son soluciones hacia el combate de la obesidad.

Sobre el hambre, en el libro se argumentan diversas cuestiones que pueden resultar incluso paradójicas. Por ejemplo, el hecho de que los agricultores pobres no puedan vender su producción al mercado, mientras que las bebidas y dulces de marcas internacionales llegan a los rincones más remotos del mundo. Otra cuestión digna de atención es la comparación de la revolución verde con la nueva revolución de los alimentos modificados genéticamente. La revolución verde generó grandes aumentos de la productividad agrícola, permitiendo contradecir los supuestos malthusianos sobre la falta de alimentos para toda la población. Esta revolución afectó positivamente a los agricultores pobres, ya que fue dirigida por instituciones oficiales, ministerios de agricultura y organismos de ayuda internacional, y sus frutos fueron repartidos equitativamente. Por otro lado, la posible revolución genética es obra de empresas multinacionales, que protegen mediante patentes las semillas fruto de sus investigaciones, diseñadas exclusivamente para maximizar el beneficio de las empresas que las idean. Este motivo y otros analizados en este trabajo dificultan que las pequeñas explotaciones agrícolas puedan permitir alimentar a las familias de las personas que las trabajan.

Sin duda, el libro de Luis de Sebastián, profesor de Economía de ESADE recientemente fallecido, proporciona una imagen fiel de la dualidad del hambre y la obesidad en el mundo, desde un rigor científico pero de forma divulgativa y accesible para cualquier disciplina; generando además un bien común mediante el impulso de una conciencia civil sobre estos problemas, y realizando recomendaciones para llevar una vida más

sana desde un punto de vista nutricional. Es precisamente el enfoque social el que prima en este libro, de ahí que se haga gran hincapié en los mercados de alimentos, que son creados, regulados e incorporados a la sociedad por la acción de los seres humanos. El hecho de que la responsabilidad caiga en el ser humano le capacita para modificarlos o transformarlos, de tal forma que se creen mercados más justos y más eficientes, garantizando el acceso a suficiente alimento inocuo para la población más necesitada, y contribuyendo a generar hábitos de alimentación saludables en las sociedades más opulentas.

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DOI:10.3305/nh.2010.25.2.4717

A primer for the exercise and nutrition sciences
Primer ensayo sobre las ciencias de ejercicio y de la nutrición

C. B. Scott. Editorial: Humana Press.
Año de edición: 2008. 166 páginas. ISBN: 978-1-60327-382-4.

En este libro se realiza una aproximación al estudio del consumo energético introduciendo los conceptos mas recientes sobre los sistemas abiertos de termodinámica y el intercambio de la célula y el organismo en su conjunto.

El libro realiza un transito a lo largo de distintos conceptos, empezando con la energía, donde se localiza en la glucosa y terminando en los conceptos de ejercicios de alta intensidad versus baja intensidad y su relación con los cambios de peso.

Se describen los intercambios de energía entre las moléculas de los alimentos ingeridos y los requerimientos en situación de reposo y ejercicio.

El libro consta de tres partes con un total de 16 capítulos. La primera parte se refiere a termodinámica, la segunda a la bioenergética y la tercera al metabolismo.

Jesús Culebras

DOI:10.3305/nh.2010.25.2.4718

European nutrition and health report 2009
Informe 2009 sobre nutrición y salud en Europa

I. Elmadfa. Editorial: KARGER.
Año de edición: 2009. 412 páginas. ISBN: 978-3-8055-9296-3.

El objetivo principal de este libro es proporcionar información fiable, tanto publicada como inédita, sobre el estado nutricional y de salud en los países de la Unión europea. El primer informe realizado en 2004 incluía tres miembros de la Unión Europea y Noruega. En la edición de 2009 se incluyen 24 miembros de la EU y Noruega.

Para la recopilación de datos los investigadores se concentraron en los siguientes puntos: Descripción de tendencias de suministro alimenticio en la Comunidad Europea; comparación de la disponibilidad diaria e individual de comida en los domicilios; evaluación del consumo individual de comida, energía y nutrientes; descripción de datos sobre indicadores de salud relacionados con la dieta; análisis de las políticas de nutrición en los distintos países de la Comunidad Europea.

Se ha tenido también en consideración el impacto del sexo y de la edad, y se hace un análisis comparativo entre las distintas regiones de la comunidad Europea.

El capitulo correspondiente a España ha sido realizado por Serrá Majem y Col.

El libro contiene un total de 87 figuras y 172 tablas distribuidas en 11 capitulos que ocupan un total de 410 paginas.

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